National Institute for Public Health
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Ministry of Health, Welfare and Sport

The *National* Immunisation *Programme* in *the Netherlands*

Surveillance and developments in 2021-2022

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Editors:
A.J.M. Pluijmaekers, H.E. de Melker

Authors:
A. Afrian, S.P. Andeweg, J.A. Backer, M.J.C. van de Beld, E. Benincà, K.S.M. Benschop, D.S.F. Berry, R.S. van Binnendijk, S. Blomont-Frederick, R. Bodewes, P. de Boer, M.C. Boer, M. van Boven, J.G.M. Brouwer, J. Brummelman, A. Buisman, M. Carpay, E. op de Coul, J. Cremer, E. Duizer, K. van Eer, D. Eggink, C.A.C.M. van Els, C. van den Ende, C.E. van Ewijk, K. van Ewijk, W. Freudenburg-de Graaf, I.H.M. Friesema, B. de Gier, T. Gordon, C.C.E. van Hagen, S.J.M. Hahné, G. den Hartog, F. van Heiningen, M.M. Henry, A. Huiberts, C. Hoeve, S. van den Hof, L.L. van den Hoogen, M. Hooiveld, A. Huiberts, M.M. Immink, F. Jongenotter, P. Kaaijk, C. Kampshoff, J. van de Kassteele, P.B. van Kasteren, J.M. Kemmeren, A.J. King, F.R.M. van der Klis, M.J. Knol, H. Korthals Altes, J.M.A. Kusters, S.J. Lanooij, E.A. van Lier, T. van der Maaden, N.A.T. van der Maas, R. Mariman, A.A.A. Maxwell, S. McDonald, A. Meiberg, A. Meijer, D.L. van Meijeren, H.E. de Melker, M. Middeldorp, W. Miellet, A. Niessen, D.W. Notermans, C. Oostdijk, E. Op de Coul, R. Pijnacker, E. Pinelli Ortiz, N. Plantinga, A.J.M. Pluijmaekers, B.C.L. van der Putten, N.Y. Rots, W.L.M. Ruijs, I. Schreuder, J. van Slobbe, G. Smits, N.M. van Sorge, A. Steens, S. Teelen, A.C. Teirlinck, A. Valk, C. Veerman, I.K. Veldhuijzen, H. Vennema, P. Versteegen, L.J. Visser, P.H. Voskuil, E.R.A. Vos, M. de Vries, C.H. van Werkhoven, A.J. Wijmenga-Monsuur, J. de Wit, D. Wong

Contact:
H.E. de Melker
Centre for Epidemiology and Surveillance of Infectious Diseases
Hester.de.melker@rivm.nl

This is a publication by the National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Contents

Synopsis

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2021-2022

RIVM tracks how many people fall ill due to a disease that is included in the National Immunisation Programme (NIP). In 2021, fewer people got such a disease compared to 2020. This is very likely due to COVID-19 control measures such as social distancing and handwashing. There were especially fewer people with invasive pneumococcal disease (about 1,205 people), pertussis (74), and mumps (1). The number of notifications for meningococcal disease caused by serotype W (4) decreased further, after introduction of the vaccine for adolescents into the NIP in 2020. There were no notifications of diphtheria, tetanus, measles, rubella, or polio in 2021.

The number of chronic hepatitis B notifications (743) was about the same as in 2020. Between 2014 and 2019 there were many more notifications, with about 1,000 to 1,100 people being made aware they had this disease. The decrease is probably the result of a decrease in doctors' visits and therefore diagnoses during the COVID-19 pandemic.

Only *Haemophilus influenzae* type b (Hib) occurred more frequently than before the COVID-19 pandemic. In 2020 and 2021 there were 68 notifications per year, compared to 39 in 2019. RIVM currently investigates the cause. The vaccine seems to be as effective as in previous years.

In 2021, 1,703,102 children were vaccinated as part of the NIP. They received a total of 2,219,341 vaccinations. Also, 115,886 pregnant women received a vaccination that protects their baby immediately after birth against, amongst others, whooping cough. Vaccination coverage in the Netherlands is slightly lower than last year. This is partly because of the COVID-19 pandemic, which caused some vaccinations to be given later than normally planned.

The Health Council of the Netherlands recommended in June 2021 to offer rotavirus vaccination to young babies. In September 2021, the Health Council recommended inviting more risk groups for flu vaccination, including pregnant women. The ministry of Health, Welfare and Sport adopted both recommendations in 2022.

Vaccination against COVID-19 works well to prevent severe illness and death, but the protection slowly decreases. Booster vaccinations increase protection again.

Keywords: *Haemophilus influenzae* type b, hepatitis B, human papillomavirus (HPV), measles, meningococcal disease, mumps, pertussis, pneumococcal disease, rotavirus, COVID-19

Publiekssamenvatting

Het Rijksvaccinatieprogramma in Nederland

Surveillance en ontwikkelingen in 2021-2022

Het RIVM houdt elk jaar bij hoeveel mensen een ziekte krijgen waartegen vanuit het Rijksvaccinatieprogramma (RVP) wordt gevaccineerd. In 2021 kregen minder mensen zo'n ziekte dan in 2020. Dit komt waarschijnlijk door de coronamaatregelen, zoals afstand houden en handen wassen. Er waren vooral minder mensen met invasieve pneumokokkenziekte (ongeveer 1.250 personen), kinkhoest (74) en bof (1). Ook is het aantal meningokokkenziekte type W ziektegevallen (4) verder gedaald nadat deze vaccinatie in 2020 voor tieners is toegevoegd aan het RVP. Er waren in 2021 geen mensen met difterie, tetanus, mazelen, rodehond of polio.

Het aantal meldingen van chronische hepatitis B (743) was ongeveer hetzelfde als in 2020. Tussen 2014 en 2019 waren dat er veel meer, toen per jaar zo'n 1.000 tot 1.100 mensen te horen kregen dat ze deze ziekte hebben. De daling komt waarschijnlijk doordat mensen tijdens de coronapandemie minder vaak naar een dokter gingen.

Alleen *Haemophilus influenza* type B (Hib) komt vaker voor dan vóór de coronapandemie. In 2020 en 2021 waren er 68 meldingen per jaar, vergeleken met 39 in 2019. Het RIVM onderzoekt de oorzaak. Het vaccin lijkt even effectief te zijn als in eerdere jaren.

In 2021 zijn 1.703.102 kinderen gevaccineerd via het RVP. Zij kregen in totaal 2.219.341 vaccinaties. Ook hebben 115.886 zwangere vrouwen een vaccinatie gekregen die hun baby vanaf de geboorte beschermt tegen onder andere kinkhoest. Dit is de 22 wekenprik. De vaccinatiegraad in Nederland is iets lager dan vorig jaar. Dit komt voor een deel door de coronapandemie, waardoor sommige vaccinaties later zijn gegeven dan normaal.

De Gezondheidsraad adviseerde in juni 2021 om jonge baby's tegen het rotavirus te vaccineren. In september 2021 adviseerde de Gezondheidsraad om meer risicogroepen uit te nodigen voor de griepvaccinatie, waaronder zwangere vrouwen. Het ministerie van VWS heeft in 2022 beide adviezen overgenomen.

Vaccineren tegen de ziekte COVID-19 werkt goed om ernstige ziekte en sterfte te voorkomen, maar de bescherming neemt langzaam af. De booster- en herhaalvaccinaties zorgen ervoor dat de bescherming weer toeneemt.

Kernwoorden: *Haemophilus influenzae* type b, hepatitis B, humaan papillomavirus (HPV), mazelen, meningokokkenziekte, bof, kinkhoest, pneumokokkenziekte, rotavirus, COVID-19

Preface

This report presents an overview of surveillance data and developments in 2021 and the first four to six months of 2022 that are relevant for the Netherlands with respect to diseases included in the current National Immunisation Programme (NIP): diphtheria, *Haemophilus influenzae* serotype b (Hib) disease, hepatitis B, human papillomavirus (HPV) infection, measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella, and tetanus. It also describes surveillance data for potential target diseases: hepatitis A, respiratory syncytial virus (RSV), rotavirus, varicella zoster virus (VZV) infection. Furthermore, it presents information on COVID-19[1]. In addition, the report presents an overview of vaccines against infectious diseases undergoing clinical trials that are relevant for the Netherlands, including new COVID-19 vaccines.

For developments with regard to influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the Health Council, and the KNCV Tuberculosis Foundation. (See the Introduction for these references.)

The report is structured as follows:
Chapter 1 contains a summary introduction of the NIP organisation, new recommendations from the Health Council of the Netherlands, and new decisions issued by the Ministry of Health, Welfare and Sports. Recent data regarding vaccination coverage are discussed in Chapter 2. Chapter 3 focuses on public acceptance of vaccination and NIP communication. The burden of diseases covered by the NIP are described in Chapter 4, whilst information on adverse events following immunisation (AEFIs) is given in Chapter 5. Chapter 6 focuses on current NIP target diseases. For each disease, the section starts with key points outlining the most prominent findings followed by figures and tables. An update of information on epidemiology, the pathogen, the outcome of recent and ongoing studies, and international developments is provided. Vaccination coverage and developments in relation to current NIP target diseases in the Dutch overseas territories, including the Dutch Caribbean islands, are presented in Chapter 7. Chapter 8 describes potential new target diseases that are under consideration for (future) vaccination. Chapter 9 discusses COVID-19 epidemiology, Health Council recommendations, the COVID-19 vaccination programme and coverage and its effect on the pandemic, seroepidemiology and pathogen surveillance, and lastly a section on the side effects experienced after COVID-19 vaccination. Chapter 10, finally, presents an overview of vaccines against infectious diseases that are undergoing clinical trials and are potentially relevant for the Netherlands.

Appendix 1 describes the surveillance methods used to monitor the NIP. Appendix 2 reports on mortality and morbidity figures from 2001 onwards based on various data sources. Appendix 3 provides an overview of changes in the NIP since 2000, whilst Appendix 4 presents the composition of the vaccines used in the period 2020/2021. Appendix 5 offers an overview of recent publications by the National Institute for Public Health and the Environment (RIVM), and Appendix 6 lists relevant websites.

[1] While COVID-19 vaccination has been placed within the Dutch NIP, this has only been done in judicial terms; when the NIP is mentioned in this report, this refers to the structural childhood vaccinations only.

Comprehensive summary

Current vaccination schedule

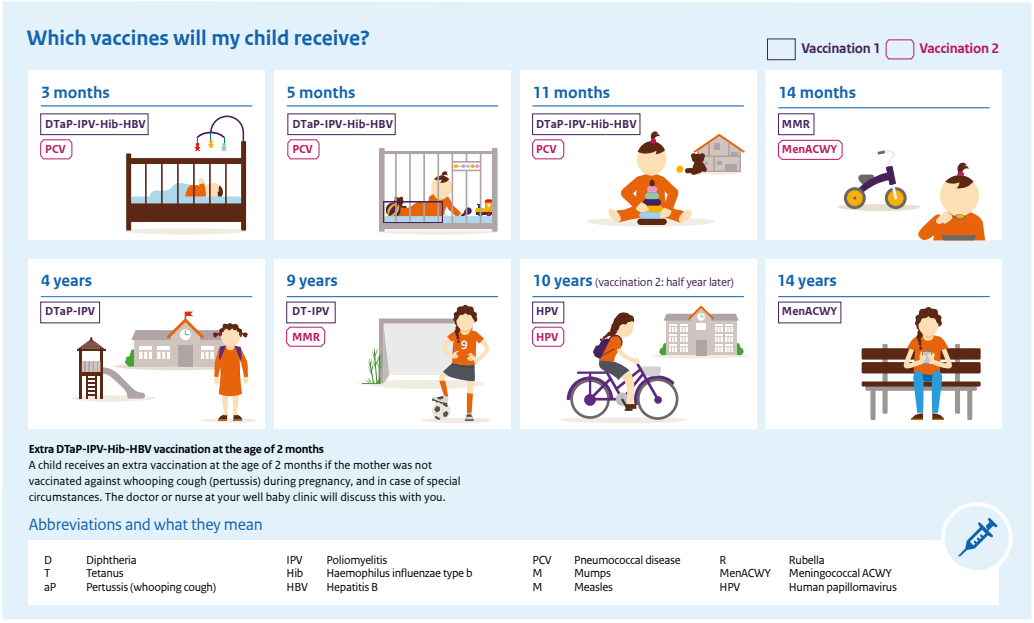


Figure 1 The NIP vaccination schedule in 2022, including universal HPV vaccination in the year children turn 10 years old.
Source: *https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-english*

Vaccination coverage

The vaccination coverage of almost all NIP vaccinations as determined and reported in 2022 was slightly lower (1-2 percentage points) than the year before. This was partly because some vaccinations were given later than usual, due to the COVID-19 pandemic. In the Netherlands, the consequences of the COVID-19 pandemic for participation in NIP vaccinations appear to be limited. However, should the decline continue, possible causes need to be researched and measures should be taken.

The large share of anonymous vaccinations (about 12 percent), caused by the introduction of informed consent for data exchange with the RIVM in January 2022, is a concern. These vaccinations cannot be included in the vaccination coverage. Therefore, from 2022 onwards RIVM can no longer determine with certainty whether the vaccination coverage changes. This not only hampers the monitoring of participation in the NIP, but also of vaccine effectiveness and adverse events. Furthermore, this also limits the ability to advise on political decisions and measures, based on vaccination coverage data.

Acceptance of vaccination

A study among pregnant women showed that predictors for acceptance of maternal pertussis vaccination (MPV) were similar for the second and third trimester. The predictors most positively associated with vaccine acceptance were vaccination intent, attitude, perceived safety, risk perception of the severity of and susceptibility to side effects, and moral responsibility. Another study among pregnant women showed that vaccination intent for maternal influenza vaccination (MIV) increases with duration of pregnancy. About half of the women were unaware of the increased risks of influenza during pregnancy.

Two studies regarding intent for HPV vaccination showed that the most important reason for boys to get vaccinated is the importance of protecting others, while girls appear to primarily want to protect themselves. Most reasons parents cite to not have their children vaccinated, relate to the perceived young age of vaccination. The chance of getting infected with HPV and the effectiveness of the vaccine are underestimated, while the risk of developing HPV-associated cancer is overestimated.

Offering HPV vaccination one year earlier than currently scheduled while combining it with the then scheduled DT-IPV and MMR vaccinations, does not appear to result in higher vaccine uptake. Offering vaccinations during well-child appointments, however, does appear to positively impact vaccine uptake.

In the elderly, intent to vaccinate against pneumococcal disease was found to relate to perceptions of own health and risks of the disease, and to general vaccine-related preferences. Receiving an invitation for vaccination, confers importance of vaccination and leads to re-evaluation of the risks of the disease, especially when complemented by official advice from RIVM, thus potentially boosting intent to get vaccinated.

A study into the acceptance of COVID-19 vaccinations shows the importance of anticipating public perception and response after a vaccine safety scare. Another study found that three different informational videos about COVID-19 vaccines did not influence vaccine intent or confidence, informed decision-making, or recognition and sharing of content presenting misinformation or disinformation.

Burden of disease

For the year 2021, the estimated total burden of disease caused by (partially) vaccine-preventable diseases was highest for HPV (17,200 disability adjusted life years (DALYs); 78% among women), invasive pneumococcal disease (5,200 DALYs), rotavirus infection (920 DALYs), and invasive *Haemophilus influenzae* disease (890 DALYs). For most vaccine-preventable diseases the estimated burden in 2021 (and 2020) was considerably lower compared to 2019. This was probably due to the implementation of various COVID-19 response measures, e.g., social distancing and hand hygiene. Recently implemented additional vaccination of elderly people against pneumococcal disease and adolescents against meningococcal disease also played a part.

The burden of invasive *H. influenzae* disease type b was higher in 2021 and 2020 than in 2019.

The burden of COVID-19 is estimated to be at least 219,000 DALYs for 2021 (excluding long-term consequences of the disease). For COVID-19, the burden was higher in 2021 than in 2020.

Adverse events after vaccination within the national immunisation programme

In 2021, Lareb received 1,462 reports, representing a total of 4,636 adverse events following immunisation (AEFI) with NIP vaccinations (excluding COVID-19 vaccination). This number is similar to the number of reports received in 2020 (n=1,475). The number of reported AEFIs per report was between 3 to 4, which is equal to earlier years. No new signals of disturbing adverse events were found in children, adolescents or pregnant women.

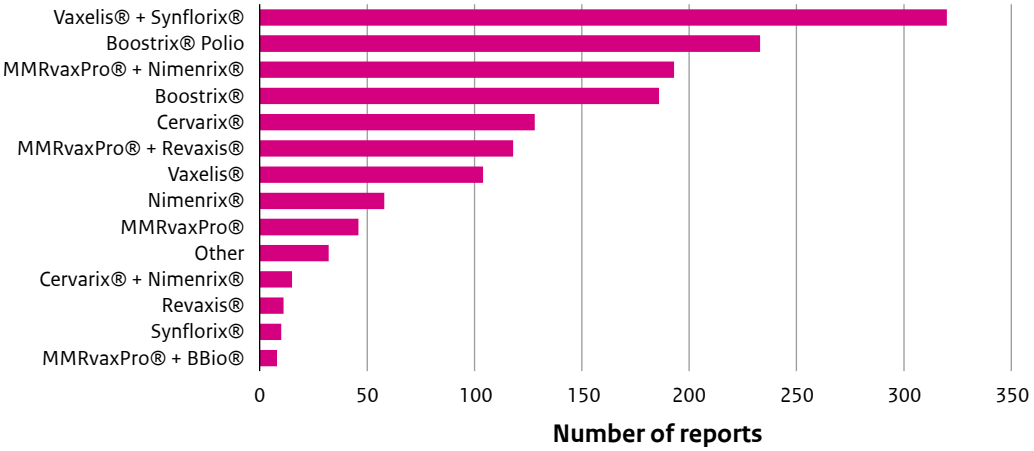


Figure 2 Number of adverse event reports per suspected vaccine(s) in 2021.
Source: Lareb

Current NIP

For developments regarding influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the Health Council, and the KNCV Tuberculosis Foundation. (See the Introduction for these references.)

Diphtheria

No diphtheria cases were reported in The Netherlands in 2021 and 2022 up to and including April. In the same period, RIVM received 11 (9 in 2021 and 2 in 2022) *C. diphtheriae* or *C. ulcerans* strains for confirmation testing. None of these strains tested positive for exotoxin production, which is in line with the fact that no cases were reported.

Internationally, the COVID-19 pandemic has negatively impacted the quality and timeliness of both the epidemiologic and laboratory surveillance of diphtheria in the Region of the Americas, which contributed to the occurrence of outbreaks. In 2021 up to and including week 42, four countries in the region reported a total of 38 confirmed diphtheria cases, of which 16 fatal. All cases for which vaccination data was reported had an incomplete vaccination history.

Haemophilus influenzae (Hi) disease

The incidence of invasive disease caused by *Haemophilus influenzae* type b (Hib) is still low, but had increased in 2020. In 2021, a similar incidence was observed as in 2020, with an incidence of 0.39 per 100,000 inhabitants in both years. The increased incidence in 2020-2021 was seen in all age groups. In the first four months of 2022, 21 cases already occurred, compared to 13 in 2020 and 18 in 2021. The incidence among children <5 years old has been increasing since 2012 and continued to rise in 2021. Out of 79 Hib cases with known outcome from 2021 until May 2022, three died (one <5 years old; vaccine failure).

The increase does not appear to be caused by a decrease in vaccine effectiveness (VE) against disease; the VE estimate is still higher than 90%, even for a recently emerging subclade. Also, little antibiotic resistance/decreased susceptibility was observed in 2020-2021. And while there has been a schedule change from 3+1 to 2+1 in 2020, none of the cases up to and including April 2022 that were vaccinated with the 2+1 schedule could have been prevented if vaccinated with the 3+1 schedule.

Invasive disease caused by non-typeable *Haemophilus influenzae* (NTHi) or other non-b serotypes is still lower than before the COVID-19 pandemic, except for serotype f disease. In the first four months of 2022, 18 Hif cases were reported, all in older adults. Generally, this serotype is uncommon (<20 yearly pre-COVID). Genetic data showed that the Hif cases were not related to each other.

Hepatitis B

The reported incidence of acute hepatitis B (n=72) decreased in 2021 with 24% to 0.4 per 100,000 population. Sexual contact was the most frequently reported risk factor for acute HBV infection. In 2021, genotype A continued to be the dominant genotype among acute HBV cases, with 60% of 45 genotyped cases.

The number of newly diagnosed chronic HBV infections in 2021 (n=743) was 4.2 per 100,000 population, comparable to 2020 (n=722). The decrease in chronic hepatitis B notifications in 2020 and 2021 compared to 2014-2019 (about 1,000 to 1,100 notifications per year) is likely related to the COVID-19 pandemic.

Human Papillomavirus (HPV)

The incidence of cervical cancer increased to 10.41 per 100,000 in 2021 (n=947) compared to 8.68 per 100,000 (n=802) in 2020, while the number of deaths caused by cervical cancer remained relatively stable (n=213 compared to 230 in 2020). The incidence and mortality

of other HPV-related cancers was relatively stable as well. In a prospective cohort study (HAVANA), a high vaccine effectiveness (VE) against HPV types 16/18 was found for persistent cervicovaginal infections up to eleven years post-vaccination after three-times bivalent vaccination. Similarly, a high VE against incident HPV types 16/18 cervicovaginal infections was observed up until six years after vaccination in girls who received two doses of the bivalent vaccine in a prospective cohort study (HAVANA2). Moreover, evidence of cross protection against HPV31/33/45 cervicovaginal infections was observed in both studies. Regarding viral load, the mean viral load of incident clearing infections with HPV types 16, 18 or 31 was lower in women who were vaccinated three times compared to unvaccinated women, while no difference was observed for women who were vaccinated twice vs. unvaccinated women. However, numbers of infection remained low in two-dose vaccinated women, likely because compared with three-dose vaccinated women, their younger age may have limited the exposure to HPV. For persistent infections, type-specific HPV viral loads were similar in women who received two or three doses and in unvaccinated women. In a repeated cross-sectional study (PASSYON), risk factors for type-specific concordance of genital and anal HPV for women were explored. A genital chlamydia infection was the only factor associated with concordance. Since February 2022, gender neutral vaccination was implemented in the Netherlands, along with a catch-up campaign for boys and unvaccinated or partially vaccinated girls up to and including the age of 18 years.

Measles

No measles cases were reported in 2021 and the first 6 months of 2022, probably as a result of the COVID-19 measures.

Meningococcal disease

Since the introduction of MenACWY vaccination, the accompanying catch-up vaccination campaign, and the COVID pandemic, the incidence of invasive meningococcal disease (IMD) has decreased further, from 1.2 per 100,000 in 2018 to 0.21 per 100,000 in 2021.

In 2021 and the first four months of 2022 only four IMD-W cases have occurred. No vaccine failure occurred in this period. From 2020 until March 2022, no IMD-C cases occurred, but in April 2022, two (unrelated) IMD-C cases were reported. One of them had been vaccinated with the MenC vaccine through the national immunisation programme. In 2021-2022, one IMD-Y case occurred. No information on vaccine status was available for this case. The incidence of IMD-B has decreased further, from around 0.45 per 100,000 between 2011 and 2019 to 0.15 per 100,000 in 2021. Two deaths were reported among IMD-B cases in 2021-22 (5%).

The predicted vaccine strain coverage by the licenced MenB vaccine during 2019-2021 for 4CMenB was 77-79% for those <5 years old, 75-92% for those aged 5-14 years, and 87-91% for 15-24 year olds. For MenB-fHbp the strain coverage was 69% for those aged 10-17 and 85% for the 18-25 year olds (the licensed age groups). If corrected for uncertainty in the manner this is done for 4CMenB, coverage was 85% and 92% respectively.

Mumps

In 2021, only one case of the mumps was reported, whereas in the first 6 months of 2022, two cases were reported. These small numbers are probably the result of the COVID-19 measures.

Pertussis

The decreasing trend in the number of notifications that was observed after the introduction of the COVID-19 measures in March 2020, has continued in 2021. In 2021, the overall number of pertussis notifications and the incidence rate were 74 and 0.4 per 100,000 respectively. The pertussis notifications in 0-5 month old babies in 2021 were found to be due to a pseudo-outbreak of *B. parapertussis*, resulting from contaminated swabs. In the first four months of 2022, no increase in the number of pertussis notifications was observed yet. Apart from a reduction of circulation of *B. pertussis* due to the COVID-19 measures, other reasons may have partly caused the decrease in notifications, for example changed care-seeking behaviour for complaints that are consistent with a pertussis infection.

It is as of yet very difficult to distinguish a potential effect of the maternal pertussis vaccination, which was introduced in the NIP in December 2019, from the effect of the COVID-19 measures on the pertussis incidence among 0-5 month old infants. Using an estimated maternal vaccination coverage of 70%, vaccine effectiveness of the maternal pertussis vaccination was estimated at 74% (95% CI: -32 to 96%) for the time period April 2020 to May 2022. This estimate, however, is based on only eight *B. pertussis* cases in 0-3 month old infants.

Results from a study among pregnant women and their infants (the PIMPI study), showed that in 2 month olds whose mothers received the Tdap vaccination between 20-24 weeks of gestational age, geometric mean concentrations of IgG antibodies were comparable between terms and late preterms for all antigens in Tdap vaccination; diphtheria toxoid (DT), pertussis toxoid (PTx), filamentous hemagglutinin (FHA), pertactin (Prn) and tetanus toxoid (TT). Statistically, IgG GMCs against PTx did not differ significantly between early preterms, late preterms and terms. However, in early preterms, significantly lower concentrations of IgG specific for FHA, Prn, TT were found.

Research showed that antibodies in sera from (ex)pertussis patients can opsonize *B. pertussis* and induce reactive oxygen species (ROS) production by human neutrophils, which is essential for killing this bacterium. It is proposed to further investigate ROS production by human neutrophils in response to opsonized *B. pertussis* as a correlate of protection.

Pneumococcal disease

The incidence of invasive pneumococcal disease (IPD) increased from 5.0 per 100,000 in 2020-2021 to 8.9 per 100,000 in 2021-2022, likely as a result of the gradual reopening of society and relaxing of the COVID-19 measures. An increase was seen across all age groups. The incidence is still lower than the average pre-COVID-19 incidence of 15.0 per 100,000 per year. The incidence in children <5 years increased in 2021-2022, to the highest in more than a decade (8.8 per 100,000). This increase was mainly due to an increase in (PCV13-10) serotypes 19A and 3; serotype 19A is now the most common serotype in children <5 years.

One vaccine failure (19F) occurred in a child without known underlying medical risk-conditions who had received PCV7.

The PCV13 serotypes not included in PCV10 (serotypes 3, 6A and 19A), together with the PCV13-associated serotype 6C (cross-protection of serotype 6A in PCV13/15/20) covered 37% of all cases in 2021-2022. This was lower than 2020-2021 (39%), but higher than 2019-2020 (31%). For people >65 years, 77% of IPD was caused by a serotype included in the 23-valent pneumococcal polysaccharide vaccine (PPV23). The newly licensed PCV15 and PCV20 covered 46% and 75%, respectively (note: cross-reacting serotype 6C is included).

Since the autumn of 2020 PPV23 is offered to individuals born in 1941-1947 and since the autumn of 2021 to those born in 1948-1952. The estimated impact of PPV23 on vaccine-type IPD in these age groups was 31% (95% CI 1.0–50.1).

Poliomyelitis

In 2021 and 2022 up to and including April 20th, no cases of poliomyelitis were reported in the Netherlands.

Nationwide coverage of enterovirus surveillance (EV) was obtained in 2021 and no poliovirus was found in any sequenced sample. In 2021, five poliovirus detections were reported from the environmental surveillance at Utrecht Science Park (Sabin 1 (n=2), Sabin 3 (n=2), and wild type poliovirus 1 (n=1)). The detections were likely direct releases from one of the facilities at the Utrecht Science Park, seeing as none of the screened employees showed any sign of recent exposure to poliovirus. None of these incidents have led to introduction of poliovirus into the Dutch population. Before June 2022, no poliovirus was detected at this site.

Between February and June 2022, poliovirus was detected during surveillance in several samples of sewage in London (UK), resulting in the advice to offer all children aged 1 to 9 in all London boroughs an IPV booster dose. In New York State (NYS, US), a polio case (VDVP2) in an unvaccinated person was confirmed in July 2022, after which poliovirus was also found in NYS sewage surveillance samples. The strains found in London and NYS were related to each other, as well as to strains found in Jerusalem (Israel) sewage.

A wild type 1 poliovirus case was reported by Malawi in November 2021, and another case by Mozambique in March 2022. These cases are genetically linked to a strain detected in Pakistan in 2020. The combined number of reported WPV1 cases in Afghanistan and Pakistan was substantially lower in 2021 and 2022 up to and including May 24th compared with 2020 (9 versus 140). The worldwide number of reported vaccine-derived poliovirus 2 cases decreased in 2021 compared with 2020 (675 versus 1079). Two-thirds of the cases in 2021 occurred in Nigeria.

Rubella

In 2021 and the first six months of 2022 no rubella cases were reported, probably as a result of COVID-19 measures.

Tetanus

In 2021 and 2022 up to and including April, no tetanus cases were reported in the Netherlands.

Twelve countries have not yet achieved the maternal and neonatal tetanus elimination (MNTE) status, of which Yemen, South Sudan and Somalia score the lowest.

The immunisation program in the Caribbean Netherlands

In general, vaccination coverage in the Dutch overseas territories, including the Caribbean Netherlands (Bonaire, St. Eustatius, and Saba), is high. In 2021, no NIP diseases were reported in the Caribbean Netherlands.

Recent and upcoming changes to the vaccination schedules in the Dutch overseas territories include the maternal pertussis vaccination (MPV), VZV and MenACWY vaccination for all children, and HPV vaccination for boys.

NIP candidates

Hepatitis A

In 2021, 77 hepatitis A-cases were reported, corresponding to 0.4 cases per 100,000 population. This number of cases is higher than in 2020 (n=55 cases), but similar to 2015 and 2016. In the past few years, infections were mainly seen in 20 to 49 year olds. However, in 2021 a shift was seen, with most cases in the age groups of 10-19 years (36%) and 50 years and older (34%). Eighteen cases (21%) contracted the disease abroad, which is comparable with 2020 (18%), but lower than seen in the previous years (2012-2019; mean: 40%). Travel and person-to-person contact are important transmission routes for hepatitis A. The measures taken since mid-March 2020 to control the coronavirus COVID-19 pandemic appear to still have influenced the incidence of hepatitis A in 2021.

Respiratory syncytial virus (RSV) infection

While hardly any RS-virus circulated in the winter of 2020/2021, an out of season RSV epidemic started in week 23 of 2021, which continued up to the end of this reporting period (week 20/2022). RSV circulation was highest in summer 2021, followed by stable circulation in autumn and winter, a slight decrease in early 2022, and circulation increasing again in spring. In 96 of the 1,289 patients (7.4%) with an acute respiratory infection (ARI), including Influenza-Like Illness (ILI), RSV was detected in nose swabs and throat swabs collected by sentinel GPs from week 21/2021 until week 20/2022. The overall percentage of RSV positive ARI specimens collected by the GPs was highest in children in the age group 0-1 years (36%), followed by age group 2-4 years (15%) and >65 years (7%). The percentage was lowest in the age groups 5-64 years (range 1 – 5%). While in 2021 RSV-A was dominant, this shifted to RSV-B dominance in 2022.

Rotavirus infection

Rotavirus circulation in 2021 had a remarkable seasonal pattern, with a low number of rotavirus detections during the usual rotavirus season in the first half of the year. This was likely due to COVID-19 control measures. In October 2021, however, an increase in rotavirus detections was observed, marking an early start of the 2022 rotavirus season.
G9P8 was the most prevalent genotype in 2021, although a shift towards G3P8 was observed at the end of the year.
In September 2022, the Ministry of Health, Welfare and Sport decided that universal rotavirus vaccination would be offered to all young infants, as part of the NIP.

Varicella zoster virus (VZV) infection (varicella and herpes zoster)

The epidemiology of herpes zoster (incidence of GP consultations, hospitalisations and deaths) in the Netherlands in 2020 was similar to previous years; GPs recorded about 92,000 herpes zoster episodes (530 episodes per 100,000 population). For varicella, however, the incidence of GP consultations and hospitalisations in 2020 was significantly lower. GPs recorded about 23,000 varicella episodes (130 episodes per 100,000 population). The incidence was approximately half of that in previous years. This is probably linked to the COVID-19 measures, which have also limited transmission of VZV.

COVID-19

Since the start of the COVID-19 pandemic, the Netherlands has seen six COVID-19 periods up to week 26 of 2022. While the COVID-19 control measures and vaccination program have slowed down the spread and incidence of COVID-19, and have limited hospitalisation and mortality resulting from SARS-CoV-2 infections, adherence to the measures and increasing vaccination coverage remain important. Throughout the pandemic, different variants of concern have been dominant; Alpha from February to June of 2021, Delta from July to December of 2021, and several Omicron subvariants from January to June 2022.

The COVID-19 vaccination program in the Netherlands started on January 6th, 2021, and currently includes the mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna), the vector vaccine Jcovden® (Janssen), and since recently (week 11, 2022) the protein substitute vaccine Nuvaxovid® (Novavax). Since November 2021, Vaxzevria® (AstraZeneca) is no longer in use in the Netherlands.

Vaccination coverage is in general higher in older age groups and is geographically highest in the east and south east of the Netherlands, and lowest in larger cities and the Bible Belt. Vaccine effectiveness (VE) against hospitalization and ICU admission is high, albeit lower in the elderly and in certain medical risk groups, as well as lower for Omicron compared to Delta. The VE against transmission in case of infection has generally been moderate, and while lower for the Delta variant than the Alpha variant, it was similar when comparing the Delta variant to the Omicron variant. VE decreases over time, but is restored by booster doses and/or exposure to SARS-CoV-2. All SARS-CoV-2 variants except for the Alpha variant have been found to

escape immunity from vaccination, while the Omicron variant has been found to also escape immunity from previous infection.

Data from the PICO study up to November 2021, shows that seroprevalence in the entire Dutch population aged 12 and over was more than 90%. During the pandemic, the group most infected were young adults, while the elderly where infected least often. The number of infections in children of school age increased particularly during the periods that were dominated by the Alpha and Delta variants.

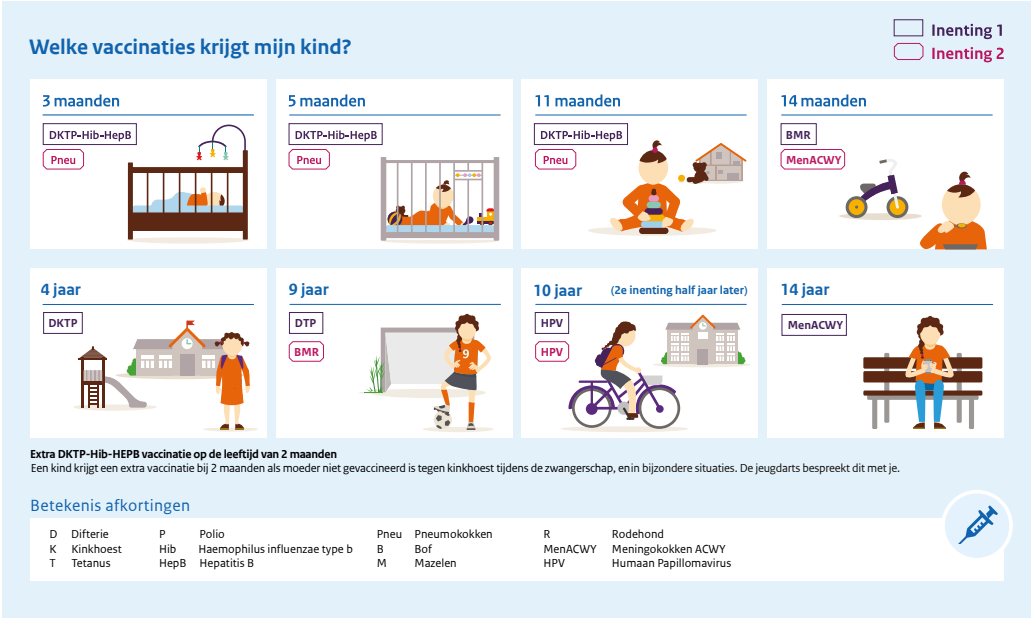
After primary series vaccinations, individuals with a history of SARS-CoV-2 infection had higher IgG levels compared to those who had not previously been infected. The presence of IgG shortly after vaccination also decreased with older age, but three months after the first vaccinations, all participants were still seropositive for SARS-CoV-2-specific IgG.

Vaccination has been found to elicit a robust T cell response in all age groups and for all vaccines, although this response begins to vary in people over 75 years of age. Furthermore, T cell responses against the Spike protein of the different variants of concern after vaccination with Comirnaty® and Spikevax®, were found to be similar, suggesting a high level of cross-reactivity.

Continuous monitoring of safety of COVID-19 vaccines used in the Netherlands, found that most side effects last a few days at most. In rare cases, severe adverse effects can occur.

Uitgebreide samenvatting

Huidige vaccinatieschema



Figuur 1 Nederlandse vaccinatieschema in 2022, inclusief universele HPV vaccinatie in het jaar waarin kinderen 10 jaar oud worden.
Bron: *https://rijksvaccinatieprogramma.nl/document/vaccinatieschema-rijksvaccinatieprogramma*

Vaccinatiegraad

De vaccinatiegraad van bijna alle RVP-vaccinaties, zoals bepaald en gerapporteerd in 2022, was iets lager (1-2 procentpunt) dan een jaar eerder. Dit kwam voor een deel doordat sommige vaccinaties vanwege de coronapandemie later zijn gegeven dan normaal. In Nederland lijken de gevolgen van de coronapandemie op de deelname aan RVP-vaccinaties mee te vallen. Als de daling doorzet, zijn onderzoek naar de oorzaak en maatregelen nodig.

Het grote aandeel anonieme vaccinaties (zo'n 12 procent) door de invoering van een geïnformeerde toestemming voor gegevensuitwisseling met het RIVM baart zorgen (in werking getreden in januari 2022). Deze vaccinaties kunnen niet worden meegeteld in de vaccinatiegraad. Het RIVM kan daarom vanaf 2022 niet meer met zekerheid bepalen of de vaccinatiegraad verandert. Dit belemmert niet alleen de monitoring van deelname aan het RVP, maar ook van vaccineffectiviteit en bijwerkingen. Ook limiteert dit de mogelijkheid om, gebaseerd op vaccinatiegraad-data, te adviseren over politieke keuzes en maatregelen.

Acceptatie van vaccinaties

Een studie onder zwangere vrouwen liet zien dat voorspellende factoren voor acceptatie van de maternale kinkhoestvaccinatie, vergelijkbaar zijn voor het tweede en derde trimester. De voorspellende factoren die positief geassocieerd waren met acceptatie waren vaccinatie intentie, attitude, vernomen veiligheid, risicoperceptie van de ernst op en ontvankelijkheid van bijwerkingen, en morele verantwoordelijkheid. Een andere studie onder zwangere vrouwen liet zien dat vaccinatie-intentie voor de maternale griepvaccinatie toeneemt met de duur van de zwangerschap. Ongeveer de helft van de vrouwen wist niet van de verhoogde risico's die het krijgen van de griep tijdens de zwangerschap met zich meeneemt.

Twee studies over vaccinatie-intentie voor HPV-vaccinatie, lieten zien dat jongens zich voornamelijk wilden laten vaccineren om anderen te beschermen, terwijl meisjes voornamelijk zichzelf wilden beschermen. De meeste redenen die ouders gaven om hun kinderen niet te laten vaccineren, hadden te maken met de leeftijd van vaccineren. Deze vinden zij te jong. De kans om geïnfecteerd te raken met HPV en de effectiviteit van het vaccin werden beide onderschat, terwijl het risico om HPV-geassocieerde kanker te ontwikkelen werd overschat.

HPV-vaccinatie een jaar eerder aanbieden dan in het huidige RVP-schema, en het te combineren met de DTP- en BMR-vaccinaties die dan worden aangeboden, blijkt niet te resulteren in een hogere vaccinatiegraad. Vaccins aanbieden tijdens gezondheidsonderzoeken lijkt wél een positieve invloed te hebben op de vaccinatiegraad.

Bij ouderen bleek vaccinatie-intentie tegen pneumokokkenziekte samen te hangen met percepties van hun eigen gezondheid en risico's van de ziekte, en algemene voorkeuren rondom vaccineren. Uitgenodigd worden voor vaccinatie, verhoogt het ervaren belang en leidt tot her-evaluatie van de risico's van de ziekte, vooral wanneer de uitnodiging wordt vergezeld door een officieel advies vanuit het RIVM.

Een studie naar de acceptatie van COVID-19-vaccinaties laat zien dat het belangrijk is om te anticiperen op publieke perceptie van en reactie op zorgen over de veiligheid van een vaccin. Een andere studie naar de effecten van drie verschillende informatieve video's over COVID-19-vaccins, liet zien dat de video's geen invloed hadden op vaccinatie-intentie of -vertrouwen, het maken van een geïnformeerde keuze, of het herkennen en delen van mis- of desinformatie.

Ziektelast

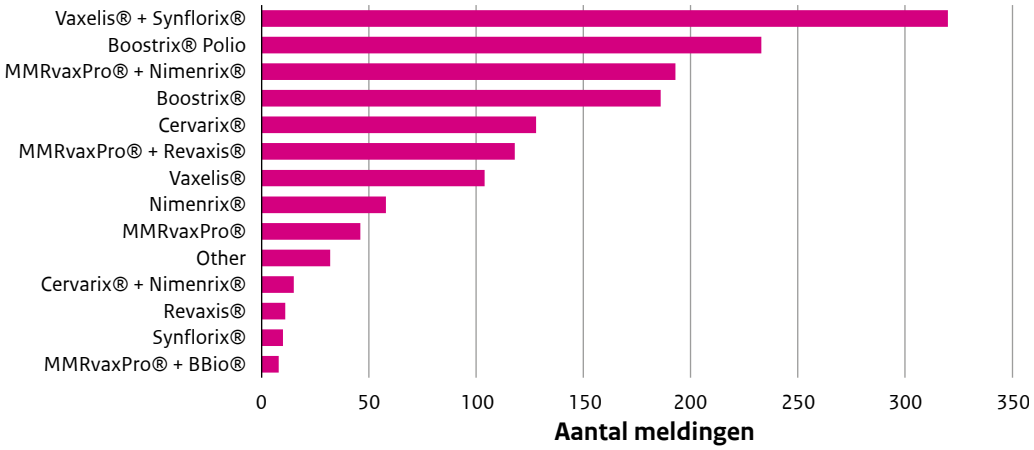
De geschatte totale ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, was in 2021 het hoogst voor HPV (17.200 disability adjusted life years (DALYs); 78% voor vrouwen), invasieve pneumokokkenziekte (5.200 DALYs), rotavirusinfectie (920 DALYs) en invasieve ziekte veroorzaakt door *Haemophilus influenzae* (890 DALYs). Voor de meeste ziekten die door vaccinatie te voorkomen zijn was de totale geschatte ziektelast in 2021 (en 2020) aanzienlijk lager dan de geschatte ziektelast in 2019. Dit is waarschijnlijk toe te schrijven aan de implementatie van verschillende COVID-19-maatregelen zoals afstand houden en handen wassen. Recent is ook aanvullende

vaccinatie van ouderen tegen pneumokokkenziekte en adolescenten tegen meningokokkenziekte ingevoerd. De ziektelast van invasieve *H. influenzae* type b was hoger in 2021 en 2020 dan in 2019.

De ziektelast van COVID-19 wordt geschat op ten minste 219.000 DALYs voor 2021 (exclusief langetermijngevolgen van de ziekte). Voor COVID-19 was de ziektelast in 2021 hoger dan in 2020.

Bijwerkingen

In 2021 ontving Lareb 1.462 meldingen van 4.636 bijwerkingen na een vaccinatie met RVP-vaccinaties (exclusief COVID-19 vaccinaties). Dit aantal is gelijk aan het aantal ontvangen meldingen in 2020 (1.475). Per melding werden gemiddeld tussen de 3 en 4 bijwerkingen gemeld, hetgeen ook gelijk is aan eerdere jaren. Er werden geen nieuwe signalen of verontrustende bijwerkingen gevonden bij kinderen, adolescenten, of zwangere vrouwen.



Figuur 2 Aantal meldingen van mogelijke bijwerkingen per vaccin(s) in 2021.
Bron: Lareb.

Huidig RVP

Zie voor ontwikkelingen rondom griep en tuberculose de rapporten hierover uitgegeven door het Centrum Infectieziektebestrijding (CIb), de Gezondheidsraad, en het KNCV Tuberculosefonds. (Zie Hoofdstuk 1: Introduction voor de referenties.)

Difterie

In 2021 en 2022 tot en met april zijn er geen gevallen van difterie gemeld in Nederland. In dezelfde periode heeft het RIVM 11 (9 in 2021 en 2 in 2022) *C. diphtheriae*- of *C. ulcerans*-stammen voor exotoxineproductie-onderzoek ontvangen. Geen van deze stammen testte positief, wat in lijn is met het feit dat er geen gevallen zijn gemeld.

Internationaal heeft de COVID-19-pandemie de kwaliteit en tijdigheid van zowel de epidemiologische- als de laboratoriumsurveillance van difterie in de Amerikaanse Regio verminderd. Dit heeft bijgedragen aan het optreden van difterie-uitbraken. Vier landen in de regio meldden in 2021 tot en met week 42 in totaal 38 bevestigde gevallen van difterie, waaronder 16 dodelijke gevallen. Alle gevallen waarvan vaccinatiegegevens beschikbaar waren, hadden een onvolledige vaccinatiestatus.

Haemophilus influenzae (Hi) -ziekte

De incidentie van invasieve ziekte door *Haemophilus influenzae* type b (Hib) is nog steeds laag, maar sinds 2020 toegenomen vergeleken met 2019. In 2021 werd een vergelijkbare incidentie gevonden als in 2020: 0,39 per 100.000 inwoners in beide jaren. De toegenomen incidentie in 2020-2021 werd gezien in alle leeftijdsgroepen. In de eerste vier maanden van 2022 waren al 21 gevallen gemeld, vergeleken met 13 in 2020 en 18 in 2021. De incidentie onder kinderen jonger dan 5 jaar neemt sinds 2012 toe, en nam ook in 2021 weer toe. Van de 79 Hib gevallen met een bekende uitkomst (vanaf januari 2021 tot en met mei 2022), zijn er 3 verleden, waarvan een jonger dan 5 jaar (vaccinfalen).

De toename lijkt niet te komen door een afname in vaccineffectiviteit (VE) tegen ziekte; de VE-schatting is nog steeds hoger dan 90%, zelfs tegen een recent verschenen sub-clade. Ook is er in 2020-2021 weinig antibiotica resistentie/afgenomen gevoeligheid gezien. En ook al is er in 2020 een verandering geweest in het vaccinatieschema, van 3+1 naar 2+1, geen van de gevallen tot en met april 2022 die waren gevaccineerd volgens het 2+1 schema, hadden voorkomen kunnen worden als ze gevaccineerd waren volgens het 3+1 schema.

Invasieve ziekte door niet-typeerbare *Haemophilus influenzae* (NTHi) of andere niet-b serotypen, is nog steeds lager dan voor de COVID-19 pandemie, behalve voor serotype f. In de eerste vier maanden van 2022 zijn 18 Hif gevallen gerapporteerd, allemaal in oudere volwassenen. In het algemeen is dit serotype zeldzaam (<20 per jaar vóór COVID-19). Genetische data laten zien dat de Hif gevallen niet aan elkaar waren gerelateerd.

Hepatitis B

De incidentie van acute hepatitis B-meldingen (n=72) daalde in 2021 met 24% tot 0,4 per 100.000 inwoners. Seksueel contact was de meest gemelde risicofactor voor een acute HBV-infectie. In 2021 bleef genotype A het dominante genotype onder acute HBV-gevallen met 60% van de 45 getypeerde gevallen.

Het aantal nieuw gediagnosticeerde chronische HBV-infecties in 2021 (n=743) was vergelijkbaar met 2020 (n=722), en was 4,2 per 100.000 inwoners. De daling in meldingen van chronische hepatitis B in 2020 en 2021 vergeleken met de periode 2014-2019 (ongeveer 1.000 tot 1.100 gevallen per jaar) is waarschijnlijk gerelateerd aan de COVID-19 pandemie.

Humaan Papillomavirus (HPV)

De incidentie van baarmoederhalskanker is in 2021 gestegen naar 10.41 per 100,000 vrouwen (n=947) ten opzichte van 8.68 per 100,000 vrouwen (n=802) in 2020. Het aantal overlijdens veroorzaakt door baarmoederhalskanker is stabiel gebleven (n=213, vergeleken met 230 in 2020). De incidentie en mortaliteit van andere HPV-gerelateerde kankers was tevens stabiel. In een prospectieve cohortstudie (HAVANA) werd een hoge vaccineffectiviteit (VE) gevonden tegen aanhoudende vaginale infecties met vaccintypen HPV types 16/18 tot in ieder geval 11 jaar na vaccinatie met een 3-dosis schema van het bivalente vaccin. Ook werd een hoge VE gevonden tegen nieuwe vaginale infecties met HPV types 16/18 tot 5 jaar na vaccinatie met een 2-dosis schema van het bivalente vaccin (HAVANA2). Daarnaast werd in beide onderzoeken kruisbescherming gevonden tegen vaginale infecties met HPV31/33/45. De virale lading van een nieuwe vaginale HPV infectie met HPV type 16, 18 of 31 was lager voor vrouwen die 3 doses van het bivalente vaccin hadden ontvangen dan voor ongevaccineerde vrouwen. De virale lading van een nieuwe vaginale HPV infectie was niet hoger of lager wanneer de vrouw was gevaccineerd met een 2-dosis schema in vergelijking met ongevaccineerde vrouwen. Dit is mogelijk het gevolg van het kleine aantal vrouwen met een HPV-infectie in deze groep omdat zij mogelijk minder blootgesteld zijn aan HPV door hun lagere leeftijd. Voor aanhoudende vaginale HPV-infecties werd geen verschil in virale lading gevonden tussen gevaccineerde (2 of 3 doses) of ongevaccineerde vrouwen. Met data van een herhaald dwarsdoorsnedeonderzoek (PASSYON) zijn risico factoren onderzocht voor type-specifieke concordantie van genitale en anale HPV-infectie in vrouwen. Een genitale chlamydia infectie was de enige factor die was geassocieerd met een anogenitale concordante HPV-infectie. Sinds februari 2022 worden jongens en meisjes in plaats van allen meisjes uitgenodigd om een HPV vaccinatie te halen. Tegelijkertijd is een inhaalcampagne begonnen waarin jongens en ongevaccineerde of deels gevaccineerde meisjes tot en met 18 jaar worden uitgenodigd voor HPV vaccinatie.

Mazelen

In 2021 en in de eerste zes maanden van 2022 werden geen gevallen van mazelen gemeld. Dit heeft waarschijnlijk te maken met de COVID-19-maatregelen.

Meningokokkenziekte

Sinds de introductie van MenACWY-vaccinatie, de bijbehorende inhaalcampagne, en de COVID-19 pandemie, is de incidentie van invasieve meningokokkenziekten (IMZ) verder afgenomen, van 1,2 per 100.000 in 2018, naar 0,21 per 100.000 in 2021.

In 2021 en de eerste vier maanden van 2022 zijn er slechts vier IMZ-W gevallen geweest. In deze periode is geen vaccinfalen geweest. Vanaf januari 2020 tot en met maart 2022 zijn geen IMZ-C gevallen geweest, maar in april 2022 zijn er twee (niet-gerelateerde) IMZ-C gevallen gerapporteerd. Een van deze was gevaccineerd met het MenC vaccin via het RVP. In 2021-2022 was er één IMZ-Y geval. Van dit geval is geen informatie bekend over de vaccinatiestatus. De incidentie van IMZ-B is verder afgenomen, van ongeveer 0,45 per 100.000 tussen 2011 en 2019, naar 0,15 per 100.000 in 2021. In 2021-2022 zijn twee overlijdens gerapporteerd door IMZ-B (5%).

De voorspelde dekking van de stammen door het gelicenseerde 4CMenB vaccin, was in 2019-2021 77-79% voor kinderen jonger dan 5 jaar, 75-92% voor kinderen tussen de 5 en 14 jaar, en 87-91% voor 15-24 jaar oude personen. Voor MenB-fHbp was de dekking van de stammen 69% voor personen tussen de 10 en 17 jaar, en 85% voor personen tussen de 18 en 25 jaar (de gelicenseerde leeftijdsgroepen). Wanneer gecorrigeerd wordt voor onzekerheid op dezelfde manier als waarop dit gebeurd voor 4CMenB, was de dekking respectievelijk 85% en 92%.

Bof

In 2021 is er één geval van bof gemeld, en in de eerste 6 maanden van 2022 zijn twee gevallen gemeld. Deze lage aantallen gevallen komen waarschijnlijk door de COVID-19-maatregelen.

Kinkhoest

De daling van het aantal kinkhoestmeldingen die werd waargenomen na de invoering van de COVID-19-maatregelen in maart 2020, heeft zich in 2021 doorgezet. In 2021 bedroeg het totale aantal meldingen en de incidentie respectievelijk 74 en 0,4 per 100.000. In de eerste vier maanden van 2022 is nog geen toename van het aantal kinkhoestmeldingen gezien. Naast een afname van de circulatie van *B. pertussis* als gevolg van de COVID-19 maatregelen, kunnen andere redenen, bijvoorbeeld veranderd zorg zoekend gedrag bij klachten die passen bij een kinkhoestinfectie, een deel van de daling van het aantal meldingen hebben veroorzaakt.

Net als vorig jaar is het nog erg moeilijk om een mogelijk effect van de maternale kinkhoest-vaccinatie, die in december 2019 aan het RVP is toegevoegd, te onderscheiden van het effect van de COVID-19-maatregelen op de kinkhoestincidentie bij zuigelingen van 0 tot 5 maanden oud. Uitgaande van een geschatte maternale vaccinatiegraad van 70%, wordt de vaccineffectiviteit van de maternale kinkhoestvaccinatie momenteel geschat op 74% (95% BI: -32 tot 96%). Deze schatting is echter gebaseerd op slechts acht gevallen in 0 tot 3 maanden oude babies in de periode april 2020 – mei 2022.

Resultaten van het PIMPI-onderzoek hebben laten zien dat bij zuigelingen van 2 maanden oud, wiens moeder de maternale kinkhoestvaccinatie ontving tussen de 20-24 weken zwangerschap, de geometrisch gemiddelde concentraties van IgG-antilichamen vergelijkbaar waren tussen a terme geborenen en late prematuren (d.w.z. 32-34 weken zwangerschap) voor alle antigenen in de vaccinatie. Echter, wat betreft filamenteus hemagglutinine, pertactine en tetanustoxoïde, werden significant lagere concentraties gevonden bij vroege prematuren.

Onderzoek heeft laten zien dat antilichamen in sera van (ex)pertussispatiënten, *B. pertussis* kunnen opsoniseren en de productie van reactieve zuurstofsoorten door menselijke neutrofielen kunnen induceren, hetgeen essentieel is voor het doden van deze bacterie.

Pneumokokkenziekte

De incidentie van invasieve pneumokokkenziekte (IPD) is gestegen van 5,0/100.000 in 2020/2021 tot 8,9/100.000 in 2021/2022, waarschijnlijk als gevolg van de geleidelijke openstelling van de samenleving en versoepeling van de COVID-19-maatregelen. De stijging was te zien in alle leeftijdsgroepen. De incidentie is nog steeds lager dan de gemiddelde pre-COVID-19 incidentie van 15,0 per 100.000 per jaar. De incidentie bij kinderen <5 jaar is gestegen en is het hoogst in meer dan tien jaar (8,8/100.000). Dit was voornamelijk het gevolg van een toename van (PCV13-10) serotypen 19A en 3; serotype 19A is nu het meest voorkomende serotype bij kinderen <5 jaar.

Eén vaccinfalen (19F) deed zich voor bij een kind zonder bekende onderliggende medische risicocondities, die gevaccineerd was met PCV7.

De PCV13-serotypen die niet zijn opgenomen in PCV10 (serotypen 3, 6A en 19A), dekten samen met het PCV13-geassocieerde serotype 6C (kruisbescherming van serotype 6A in PCV13/15/20) 37% van alle gevallen in 2021/2022 . Dit was lager dan 2020/2021 (39%) maar hoger dan 2019/2020 (31%). Bij mensen ≥65 jaar werd 77% van de IPD veroorzaakt door een serotype dat was opgenomen in het 23-valente pneumokokkenpolysacharidevaccin (PPV23). De nieuw gelicentieerde PCV15 en PCV20 dekten respectievelijk 46% en 75% (kruisreagerend serotype 6C inbegrepen).

Sinds het najaar van 2020 wordt PPV23 aangeboden aan personen geboren in 1941-1947 en sinds het najaar van 2021 aan personen geboren in 1948-1952. De geschatte impact van PPV23 op vaccintype-IPD in deze leeftijdsgroepen was 31% (95% BI 1,0-50,1).

Polio

In 2021 en 2022 tot en met 20 april, zijn geen gevallen van poliomyelitis gemeld in Nederland.

In 2021 werd een landelijke dekking van de enterovirus surveillance (EV) behaald, en werd geen poliovirus gevonden in de getypeerde monsters. In 2021 zijn er vijf poliovirusdetecties gemeld vanuit de omgevingssurveillance op het Utrecht Science Park (Sabin 1 (n=2), Sabin 3 (n=2), en wildtype poliovirus 1 (n=1)). Geen van de onderzochte werknemers vertoonde tekenen van recente blootstelling aan het poliovirus. Geen van deze incidenten hebben geleidt tot herintroductie van het poliovirus in de Nederlandse populatie. Voor juni 2022 is er geen poliovirus gedetecteerd op deze plek.

Tussen februari en juni 2022 is er poliovirus gedetecteerd in rioolwater in Londen (Engeland), hetgeen heeft geresulteerd in het advies om alle kinderen tussen de 1 en 9 jaar in alle Londense buurten, een poliovirus-booster aan te bieden. In juli 2022 is er in de staat New York (Amerika) een poliogeval (VDVP2) bevestigd in een ongevaccineerd persoon. Vervolgens is er ook poliovirus gevonden in rioolwater in de staat New York. De stammen die in Londen en de staat New York zijn gevonden, waren verwant aan elkaar en aan stammen die gevonden zijn in rioolwater in Jerusalem (Israel).

In november 2021 en maart 2022 werden door respectievelijk Malawi en Mozambique een geval van wildtype 1 poliovirus gemeld. Deze gevallen zijn genetisch verwant aan een stam uit Pakistan (gedetecteerd in 2020). Het totale aantal gemelde wildtype 1 poliovirusgevallen in Afghanistan en Pakistan was in 2021 en 2022 tot en met 24 mei, fors lager dan in 2020 (9 versus 140). Het wereldwijd aantal gemelde gevallen van vaccin-afgeleid poliovirus type 2, is in 2021 afgenomen in vergelijking met 2020 (675 versus 1079). Tweederde van de gevallen in 2021 werden gemeld door Nigeria.

Rodehond

In 2021 en in de eerste zes maanden van 2022 werden geen gevallen van rodehond gemeld. Dit heeft waarschijnlijk te maken met de COVID-19-maatregelen.

Tetanus

In 2021 en 2022 tot en met april zijn geen gevallen van tetanus gemeld in Nederland.

Van de twaalf landen die de maternale- en neonatale tetanuseliminatiestatus nog niet behaald hebben, scoort Guinea momenteel het hoogst op de vijf prestatie-indicatoren van de status. De landen die het laagst scoren zijn Jemen, Zuid-Soedan en Somalië.

Het vaccinatieprogramma in Caribisch Nederland

In het algemeen is de vaccinatiegraad in Caribisch Nederland hoog. In 2021 zijn er geen RVP-ziekten gerapporteerd in Caribisch Nederland.

Recentelijke en toekomstige veranderingen aan de vaccinatieschema's in de Nederlandse overzeese gebieden, zijn de maternale kinkhoestvaccinatie, vaccinatie tegen varicella zoster en MenACWY voor alle kinderen, en HPV-vaccinatie voor jongens.

Potentiële RVP-kandidaten

Hepatitis A

Er werden in 2021 77 hepatitis A gevallen gerapporteerd, wat gelijk is aan 0,4 gevallen per 100.000 inwoners. Het aantal meldingen is vergelijkbaar met 2015 en 2016, en hoger dan de 55 gevallen in 2020. In voorgaande jaren werden de meeste infecties in de leeftijdsgroep 20-49 jaar gezien. In 2021 is er een verschuiving naar de leeftijdsgroepen 10-19 jaar (36%) en 50 jaar en ouder (34%) te zien. Achttien patiënten (21%) hadden de infectie in het buitenland opgelopen. Dit is vergelijkbaar met 2020 (18%), maar lager dan in de voorgaande jaren (2012-2019; gemiddeld 40%). Reizen en mens-op-mens contact zijn belangrijke transmissieroutes voor hepatitis A. Sinds half maart 2020 gelden er allerlei maatregelen om de coronaviruspandemie onder controle te krijgen. Deze maatregelen lijken ook in 2021 effect te hebben gehad op de incidentie van hepatitis A.

Respiratoir syncytieel virus (RSV)-infectie

Terwijl in de winter van 2020/2021 nauwelijks RS-virus gevonden werd is sinds begin juni 2021 sprake van een RS-virus epidemie in Nederland. Het aantal laboratorium meldingen en opnames is na de piek in juli weer gedaald, maar bleef hoger dan gebruikelijk in het najaar. De sterke stijging van RS-virus die we normaal zien in de winter met een piek rond de jaarwisseling is dit jaar uitgebleven. Van week 52 2021 tot week 10 2022 daalde het aantal meldingen gestaag, maar na week 10 stijgt het aantal meldingen weer en blijft tot het einde van de rapportage periode (week 20/2022) hoog. In 96 van 1289 patiënten (7,4%) die de huisarts bezochten met een acute respiratoire infectie (ARI) werd RSV gevonden in de neuswatten en keelwatten die bij deze patiënten was afgenomen tijdens de rapportage periode. Dit percentage was het hoogst bij jonge kinderen 0-1 jaar (36%), gevolgd door de leeftijdsgroep 2-4 jaar (15%) en >65 jaar (7%). Het percentage was het laagst in de leeftijdsgroep 5-64 jaar (range 1 – 5%). Terwijl in 2021 RSV-A het dominante type was, was dit in 2022 RSV-B.

Rotavirusinfectie

Rotavirus-circulatie had in 2021 een opmerkelijk seizoens-patroon, met een laag aantal rotavirus-detecties tijdens het gebruikelijke rotavirus-siezoen in de eerste helft van het jaar. Dit kwam waarschijnlijk door de COVID-19 maatregelen. In oktober 2021 was er echter een toename in rotavirus-detecties, hetgeen een vroege start van het seizoen van 2022 aantoonde.

G9P8 was het vaakst voorkomende genotype in 2021, al was er aan het eind van het jaar een verschuiving te zien naar G3P8.

In september 2022 heeft het ministerie van VWS het advies van de Gezondheidsraad overgenomen om rotavirus-vaccinatie via het RVP aan te bieden aan alle jonge baby's.

Varicella zoster virus (VZV)-infectie (waterpokken en gordelroos)

De epidemiologie van gordelroos (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) in Nederland in 2020 was vergelijkbaar met voorgaande jaren; huisartsen rapporteerden ongeveer 92.000 gordelroosepisodes (530 episodes per 100.000 inwoners). Voor waterpokken was de incidentie van huisartsenbezoeken en ziekenhuisopnames in 2020 echter aanzienlijk lager; huisartsen rapporteerden ongeveer 23.000 waterpokkenepisodes (130 episodes per 100.000 inwoners). De incidentie was ongeveer de helft minder dan in voorgaande jaren. Dit heeft waarschijnlijk te maken met de COVID-19-maatregelen die ook de overdracht van VZV hebben verminderd.

COVID-19

Sinds de start van de COVID-19 pandemie tot en met week 26 van 2022, heeft Nederland zes COVID-19 periodes gehad. Ook al hebben de COVID-19-maatregelen en het vaccinatie-programma de spreiding en incidentie van COVID-19 geremd en de ziekenhuisopnames en overlijdens door SARS-CoV-2 infecties verlaagd, toch blijft het belangrijk om de maatregelen na te leven en de vaccinatiegraad hoog te houden. Tijdens de pandemie zijn verschillende varianten dominant geweest: Alfa vanaf februari tot juni 2021, Delta van juli tot december 2021, en verschillende Omikron sub-varianten vanaf januari tot en met juni 2022.

Het COVID-19-vaccinatieprogramma is in Nederland gestart op 6 januari 2021, en bevat momenteel de mRNA vaccins Comirnaty® (BioNTech/Pfizer) en Spikevax® (Moderna), het vector vaccin Jcovden® (Janssen), en sinds recentelijk (week 11, 2022) het eiwitvaccin Nuvaxovid® (Novavax). Sinds november 2021, wordt Vaxzevria® (AstraZeneca) niet meer gebruikt in Nederland.

De vaccinatiegraad is in het algemeen hoger in de oudere leeftijdsgroepen, en geografisch gezien in het oosten en zuid oosten van Nederland, en het laagst in grotere steden en in de Bible Belt. Vaccineffectiviteit (VE) tegen ziekenhuis- en intensive care opname is hoog, maar is lager voor ouderen en bepaalde medische risico groepen, en lager voor Omikron vergeleken met Delta. De VE tegen transmissie in geval van infectie was middelmatig, en ook al was deze VE lager voor de Delta variant dan voor de Alfa variant, het was gelijk tussen de Delta en Omikron varianten. VE neemt af over tijd, maar wordt hersteld door booster vaccinaties en/of blootstelling aan SARS-CoV-2. Voor alle SARS-CoV-2 varianten, behalve de Alfa variant, is gezien dat ze aan immuniteit door vaccinatie kunnen ontsnappen. De Omikron variant kan ook ontsnappen aan immuniteit door eerdere infectie.

Data van de PICO studie tot en met november 2021, laat zien dat seroprevalentie in de gehele Nederlandse populatie van 12 jaar en ouder, hoger was dan 90%. Tijdens de pandemie zijn jongvolwassenen het vaakst geïnfecteerd geraakt, ouderen het minst vaak. De hoeveelheid infecties in kinderen is met name toegenomen tijdens de periodes waarin de Alfa en Delta varianten dominant waren.

Na de primaire vaccinatie-serie hadden personen die een eerdere SARS-CoV-2 infectie hadden gehad, een hoger IgG niveau dan personen die niet eerder waren geïnfecteerd. Vlak na vaccinatie was de aanwezigheid van IgG ook lager naarmate leeftijd toenam. Drie maanden na de primaire serie, waren alle deelnemers nog seropositief voor SARS-CoV-2 IgG antistoffen.

Vaccinatie blijkt een sterke T-cel reactie op te wekken in alle leeftijdsgroepen en voor alle vaccins. Wel al varieert deze reactie in personen ouder dan 75. Ook zijn T-cel reacties tegen het Spike eiwit na vaccinatie met Comirnaty® en Spikevax®, gelijk gebleken, hetgeen een hoge mate van kruis-reactiviteit suggereert.

Voortdurende monitoring van de veiligheid van de COVID-19-vaccins die in Nederland worden gebruikt, heeft laten zien dat de meeste bijwerkingen verdwijnen binnen een paar dagen. In zeldzame gevallen kunnen ernstige bijwerkingen optreden.

1
Introduction

1.1 NIP vaccination schedule

Vaccination of a large part of the population of the Netherlands against diphtheria, tetanus and pertussis (DTP) was introduced in 1952. The National Immunisation Programme (NIP) started in 1957, offering DTP and inactivated polio vaccination (IPV) to all children born from 1945 onwards in a programmatic approach. Nowadays, in addition to DTP-IPV, vaccinations against measles, mumps, rubella (MMR), *Haemophilus influenzae* serotype b (Hib), meningococcal disease, invasive pneumococcal disease, hepatitis B virus (HBV) and human papillomavirus (HPV) are included in the programme (Figure 1.1). In the Netherlands, NIP vaccines are offered to the target population free of charge and on a voluntary basis.

The schedule presented in Figure 1.1 is the typical schedule offered to all children in 2022. This marks the first year that HPV vaccination is also offered to boys, and is offered in the year girls and boys turn 10. Before 2022, HPV vaccination was offered to girls only, in the year they turned 12. Also, in this typical schedule, DTaP-IPV-Hib-HBV vaccinations are offered at 3, 5, and 11 months, but children receive an additional DTaP-IPV-Hib-HBV vaccination at 2 months of age if their mother did not receive a maternal Tdap vaccination at a sufficiently early moment during her pregnancy, or if the child had a low birth weight or was born prematurely (before 37 weeks gestation). Additionally, new-borns to HBsAg positive mothers are given an HBV vaccination and HBV immunoglobulin, preferably within two hours after birth, or at least no later than 48 hours after birth. These infants also receive an additional DTaP-IPV-Hib-HBV dose at two months of age.

If necessary, asylum seeker children receive additional NIP vaccinations to provide them with long-term immunity against NIP target diseases. The youth healthcare physician assesses their vaccination status and offers a personalised vaccination schedule, including an HBV vaccination series. Furthermore, all asylum seeker infants are offered an additional MMRo dose at 9 months of age.
Lastly, while Ukrainians who settle in the Netherlands after fleeing the war in Ukraine are not registered as refugees, all Ukrainian children of 6 to 12 months of age are offered the additional MMRo vaccine. This is due to a pre-COVID-19 measles outbreak in Ukraine.

1.1.1 Recent changes in the vaccination schedule

In 2022, HPV vaccination was added to the boys' vaccination schedule, and the age at which children are offered HPV vaccination was lowered to the calendar year in which they turn 10. Simultaneously, a catch-up campaign was launched to offer HPV vaccination to all children and adolescents aged 10-18 in 2022 and 2023.

1.1.2 Number of vaccinated children and pregnant women

In 2021, the vaccination schedule consisted of 12 (boys) or 14 (girls) vaccine doses per child. Of these doses, 7 were offered between the ages of 0 and 11 months.
In 2021, 1,703,102 children and 115,886 pregnant women were immunised under the Dutch NIP. The children received 2,219,341 vaccine doses, whereas the pregnant women received a total of 115,886 vaccine doses: one Tdap vaccine each.

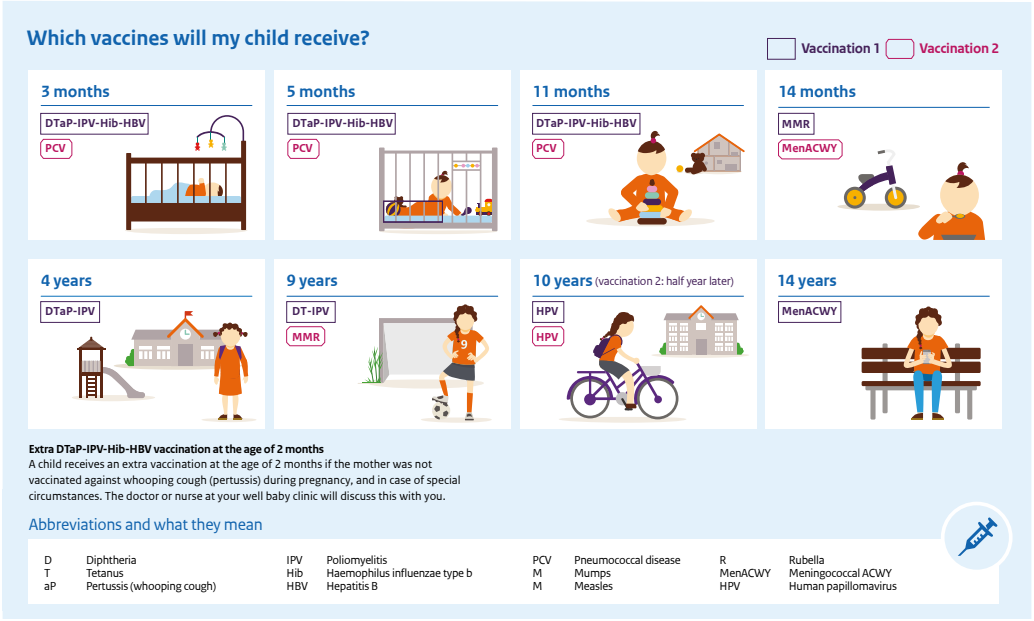


Figure 1.1 The NIP vaccination schedule in 2022, including universal HPV vaccination in the year children turn 10 years old.
Source: *https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-english*

1.2 New recommendations and decisions

1.2.1 New recommendations from the Health Council of the Netherlands

The Ministry of Health, Welfare and Sport (HWS) requested a new advice on rotavirus vaccination after cancelling the original implementation of rotavirus vaccination of risk groups only. On June 30th, 2021, the Health Council issued their new advice on rotavirus vaccination, recommending universal rotavirus vaccination to be offered through the NIP. The Health Council indicated that the price of the available rotavirus vaccines should come down if vaccination was to be cost-effective [1].

On September 20th, 2021, the Health Council (HC) issued a new advice on the indications for influenza vaccination. They recommended to expand the number of risk groups eligible for vaccination, for example by including all pregnant women. Vaccinating them will protect both the women during and after pregnancy, as well as their new-borns in the first six months of their lives. Additionally, the HC advised to expand the influenza vaccination programme by adding people with morbid obesity (BMI>40), people younger than 60 who suffer from dementia (those over 60 are already defined as a risk group due to their age), and people with a cochlear implant [2].

1.2.2 New decisions of the Ministry of Health, Welfare and Sport

In response to the Health Council's advice on rotavirus vaccination on June 30th, 2021, the then State Secretary of HWS decided to leave the decision to adopt this advice or not, to his successor [3]. On May 23rd, 2022, the new State Secretary decided that vaccination against rotavirus would not be added to the Dutch NIP on the short term due to a lack of available funds [4]. However, on September 20th, 2022, the State Secretary amended this decision because financial coverage was found, adding universal rotavirus vaccination to the Dutch NIP from 2024 onwards [5].

In September 2021, the then State Secretary of HWS decided that in 2021, the influenza vaccine would be available free of charge to the newly defined risk groups, including all pregnant women, as per the Health Council's advice [3]. Due to the short time frame until the start of the flu season, these new groups could not be actively invited for vaccination in 2021. Instead, they could directly contact their GP to make an appointment.
On May 23rd, 2022, the new State Secretary of HWS announced that the new risk groups would remain eligible for free influenza vaccination. Because pregnant women are not registered as such at their GP, they will be offered the influenza vaccine through a cooperation between their gynaecologist (to inform them) and the Youth Healthcare in their municipality (to administer the vaccine). However, as it was not feasible to implement this route before the 2022-2023 influenza season, women who are pregnant in 2022 can still contact their GP for their maternal influenza vaccine [4].

Regarding herpes zoster vaccination for adults aged 60 and over, the State Secretary published an update on May 19th, 2022, indicating his wish to offer this vaccination if it can be done cost-effectively [6].

1.3 Vaccinations of risk groups

Influenza vaccination is offered through the National Influenza Prevention Programme (NPG) to individuals aged 60 years and over and to those with an increased risk of morbidity and mortality following influenza. Vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries. For developments regarding influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the Health Council, and the KNCV Tuberculosis Foundation [7-10].

In addition to the inclusion of vaccination against HBV in the NIP, the Netherlands has an additional vaccination programme in place that targets groups particularly at risk of HBV due to sexual behaviour, namely men who have sex with men (MSM) and sex workers [11].

Information on vaccinations for travellers and for employees at risk of work-related infections can be found on the website *www.rivm.nl/vaccinaties*.

1.4 Vaccination outside of public vaccination programmes

A number of registered vaccines in the Netherlands are available to the public outside of vaccination programmes. Vaccinations registered for infants are those against gastroenteritis caused by rotavirus infection, VZV, and meningococcal B disease (MenB). For both older children and adults, vaccination against influenza, MenACWY, and pertussis is available. For adults specifically, vaccination against herpes zoster, pneumococcal disease, HBV, and hepatitis A (HAV) are available. An overview of these vaccinations can be found at *https://www.rivm.nl/vaccinaties-op-maat*. MSM can choose to receive an HAV vaccine simultaneously with their HBV vaccine. They will then get a discount on the HAV component.

Professional guidelines for herpes zoster vaccination, pertussis vaccination for adults, HPV vaccination outside the NIP, MenACWY vaccination, MenB vaccination, rotavirus vaccination, VZV vaccination, pneumococcal vaccination for the elderly, HBV vaccination and HAV vaccination are available at *https://lci.rivm.nl/richtlijnen/*. This website also provides access to guidelines for vaccination of medical risk groups, such as patients with asplenia.

1.5 Literature

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* RIVM publication.

2
Vaccination coverage

E.A. van Lier

2.1 Key points

- The vaccination coverage of almost all NIP vaccinations as determined and reported in 2022, was slightly lower (1-2 percentage points) than a year earlier. This was partly because in 2020 some vaccinations were given later than usual due to the COVID-19 pandemic.
- In the Netherlands, the consequences of the COVID-19 pandemic for participation in the NIP appear to be limited. If the decline continues, research into the cause and measures are needed.
- The large share of anonymous vaccinations (about 12 percent) caused by the introduction of an informed consent for data exchange with the RIVM in January 2022, is a concern. These vaccinations cannot be included in the vaccination coverage. Therefore, from 2022 onwards, RIVM can no longer determine whether the vaccination coverage changes. This not only hampers the monitoring of participation in the NIP, but also of vaccine effectiveness and adverse events. Furthermore, this also limits the ability to advise on political decisions and measures, based on vaccination coverage data.

2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescents in 2006-2022 [1].

	Newborns*								Toddlers*				Schoolchildren*			Adolescent girls*		Adolescents*	
Reporting year	*Cohort*	DTaP -IPV	Hib	HBV [a]	PCV **	MMR	MenC/ ACWY	Full ***	*Cohort*	DTaP -IPV[b]	DTaP -IPV[c]	DTaP -IPV[d]	*Cohort*	DT -IPV	MMR ****	*Cohort*	HPV	*Cohort*	Men ACWY
2006	*2003*	94.3	95.4	15.2	-	95.4	94.8		*2000*	92.5	1.4	93.9	*1995*	93.0	92.9				
2007	*2004*	94.0	95.0	17.1	-	95.9	95.6		*2001*	92.1	1.6	93.7	*1996*	92.5	92.5				
2008	*2005*	94.5	95.1	17.9	-	96.0	95.9		*2002*	91.5	1.6	93.1	*1997*	92.6	92.5				
2009	*2006*	95.2	95.9	18.6	94.4	96.2	96.0		*2003*	91.9	2.0	93.9	*1998*	93.5	93.0				
2010	*2007*	95.0	95.6	19.3	94.4	96.2	96.1		*2004*	91.7	2.6	94.3	*1999*	93.4	93.1				
2011	*2008*	95.4	96.0	19.4	94.8	95.9	95.9		*2005*	92.0	2.6	94.7	*2000*	92.2	92.1				
2012	*2009*	95.4	96.0	19.5	94.8	95.9	95.9		*2006*	92.3	2.1	94.4	*2001*	93.0	92.6	*1997*	56.0		
2013	*2010*	95.5	96.1	19.7	95.1	96.1	96.0		*2007*	92.3	2.4	94.7	*2002*	93.1	92.9	*1998*	58.1		
2014	*2011*	95.4	95.9	51.4	95.0	96.0	95.8		*2008*	92.0	2.4	94.4	*2003*	92.7	92.4	*1999*	58.9		
2015	*2012*	94.8	95.4	94.5	94.4	95.5	95.3		*2009*	91.9	2.2	94.1	*2004*	92.7	92.7	*2000*	61.0		
2016	*2013*	94.2	94.9	93.8	93.8	94.8	94.6		*2010*	91.5	2.1	93.7	*2005*	92.0	92.0	*2001*	61.0		
2017	*2014*	93.5	94.2	93.1	93.6	93.8	93.5	91.2	*2011*	91.1	2.1	93.2	*2006*	90.8	90.9	*2002*	53.4		
2018	*2015*	92.6	93.4	92.2	92.8	92.9	92.6	90.2	*2012*	90.4	2.3	92.7	*2007*	90.0	90.1	*2003*	45.5		
2019	*2016*	92.4	93.1	92.0	92.6	92.9	92.6	90.2	*2013*	90.3	2.2	92.5	*2008*	89.5	89.5	*2004*	45.5		
2020	*2017*	92.6	93.5	92.3	93.0	93.6	93.2	90.8	*2014*	89.9	2.4	92.2	*2009*	89.7	89.7	*2005*	53.0		
2021	*2018*	93.1	93.8	93.0	93.3	93.6	93.3	91.3 (91.9)	*2015*	89.4	2.6	92.0	*2010*	88.9 (91.9)	89.0 (91.9)	*2006*	63.1 (68.0)		
2022	**2019**	**92.2** (92.7)	**92.9** (93.3)	**92.2** (92.7)	**92.5** (92.6)	**92.3** (92.7)	**92.0** (92.8)	**90.1** (90.6)	***2016***	**88.5** (89.0)	**2.3**	**90.8** (91.2)	***2011***	**86.3** (89.7)	**86.4** (89.7)	***2007***	**47.6** (66.4)	***2006***	**84.3** (85.3)

* Vaccination coverage is assessed at the ages of 2 (newborns), 5 (toddlers), 10 (schoolchildren), 14 years (adolescent girls), and 15 years (adolescents). In grey: vaccination coverage including vaccinations given later (reporting year 2021: situation on 02-03-2021, reporting year 2022: situation on 03-03-2022).

** Only for newborns born on or after April 1st, 2006.

*** Key figure for full participation of newborns: who received all NIP vaccinations at 2 years of age.

**** Two MMR vaccinations (in the past 'at least one MMR vaccination' was reported).

[a] Percentage for the total cohort. Universal hepatitis B vaccination was introduced in 2011; only risk groups were vaccinated previously.

[b] Revaccinated toddlers.

[c] Toddlers that reached basic immunity at 2–5 years of age were not eligible for revaccination at toddler age.

[d] Sufficiently protected toddlers (sum of [b] and [c]).

Source: Præventis

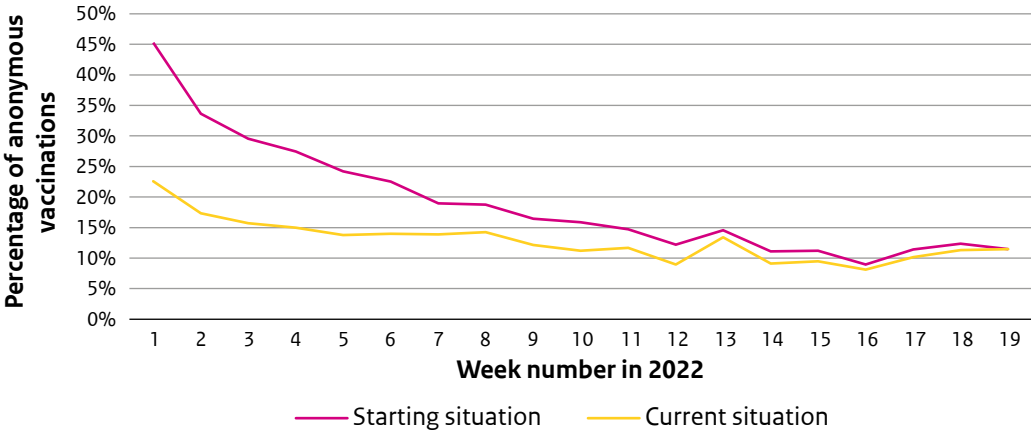

Figure 2.1 Development of the percentage of anonymous vaccinations by week (situation on 12-5-2022) [1].

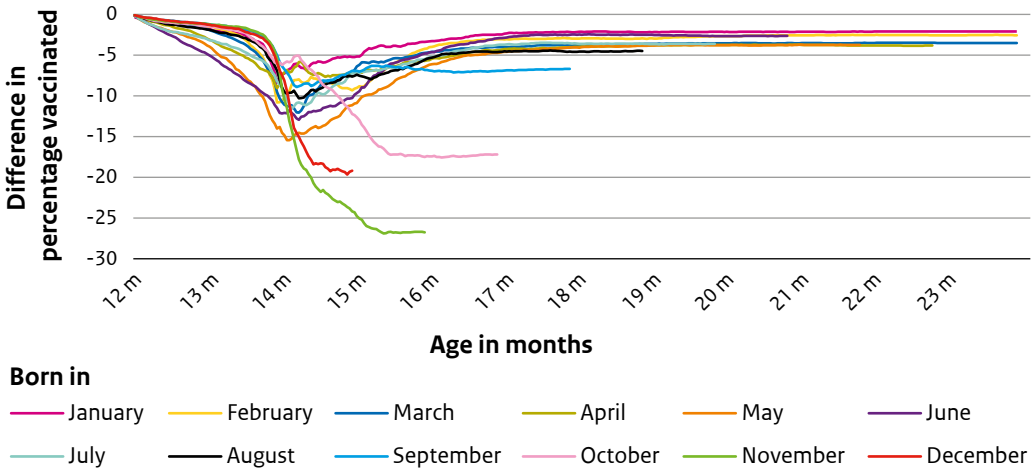

Figure 2.2 Difference in preliminary participation (based on registration with informed consent) in the first measles/mumps/rubella vaccination (MMR1) for children born in January-December 2020 versus children born in January-December 2018 (from 1-1-2022 RIVM receives part of the vaccinations anonymously due to the introduction of informed consent. These anonymous vaccinations are not included) [1].

Note: Children are scheduled to be vaccinated at the age of 14 months. Children born in January 2020 are scheduled to be vaccinated from March 2021. Children born in February 2020 from April 2021, and so on. The duration of follow-up ranged from 455 days (14.9 months) for children born in December 2020 to 730 days (2 years) for children born in January 2020. For example, a difference of -19 for children born in December (endpoint red line) means that in Præventis the percentage vaccinated for children born in December 2020 at the age of 455 days (14.9 months) was 19 percentage points lower than for children born in December 2018 (52.5% versus 71.7%).

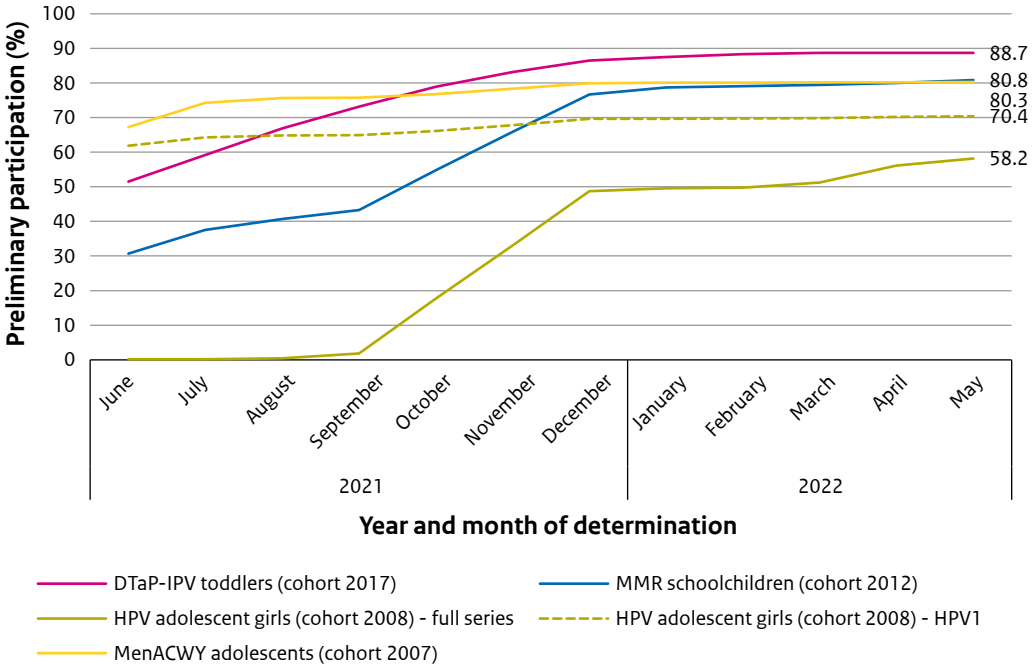

Figure 2.3 Development of preliminary participation in vaccination over time for children eligible for vaccination in 2021 [1].

2.3 National developments

The vaccination coverage of almost all NIP vaccinations as determined and reported in 2022 was slightly lower than a year earlier. This was partly because in 2020 some vaccinations were given later than usual due to the COVID-19 pandemic. NIP group vaccinations were postponed in the spring of 2020. Also, some appointments for a vaccination had to be rescheduled, for example because people had to self-isolate. If the vaccinations that were given a little later are included (i.e., vaccination coverage without age limit covering up to and including March 3rd, 2022), the vaccination coverage was higher. However, for most vaccinations this was still slightly lower than in 2021 (Table 2.2.1). For newborns up to two years old, the difference is still about 1 percentage point. For older children this is 1-2 percentage points.

Approximately 66% of pregnant women with a child born in 2021 took part in the 22-week vaccination that protects babies against whooping cough from birth. This is slightly lower than last year, when a participation of 70% was reported. However, there are administrative issues in three GGD regions (Amsterdam, Rotterdam-Rijnmond, and Limburg-Noord), as a result of which not all maternal pertussis vaccinations have yet been registered in Præventis (situation March 3rd, 2022). Excluding the data from these regions, the participation is 72%. This is slightly higher than last year (71%), if those regions are also excluded.

In the Netherlands, the consequences of the coronavirus epidemic for participation in NIP vaccinations appear to be limited. Youth healthcare services employees went to great lengths to contact as many families and vaccinate as many children as possible. Should the decline continue, as preliminary figures for younger children seem to suggest (see section 2.3.2), research into the cause will be necessary, and measures will need to be taken.

Due to privacy legislation, the registration of vaccinations has changed. Since January 1st, 2022, a digital record must be kept of whether parents (and/or the child) have given permission to youth healthcare services to pass on vaccination data *with* personal data to RIVM. RIVM needs these personal data to be able to include vaccinations in the vaccination coverage. If these data are incomplete, RIVM cannot determine whether the vaccination coverage has changed. Therefore, the large share of anonymous vaccinations (about 12 percent since January 2022) is a concern (see section 2.3.1).

2.3.1 Informed consent

From January 1st, 2022, NIP vaccinations are sent to RIVM anonymously if no informed consent of the parent(s) and/or juvenile for the exchange of vaccination data *with* personal data was registered. Among other things, the year of birth and place of residence of the vaccinated person are unknown in these cases, as well as the involved dose. These anonymous vaccinations can therefore not be included in the calculation of vaccination coverage for completed series per birth cohort and municipality.

Up to and including May 12th, 2022, 12% of all NIP vaccinations were submitted anonymously (Figure 2.1). The percentage decreased from 45% in the first week of January to about 11% from week 14. The percentage of anonymous vaccinations also decreased retrospectively. If informed consent is registered at a later date, then previously administered vaccinations are still passed on to RIVM with personal data. For example, the percentage of anonymous vaccinations for week 1 is now 23%, while this was 45% immediately after week 1 (data up to and including Thursday). The spread between different youth health care organisations in the total percentage of anonymous vaccinations is considerable, ranging from 32% to 1%. This indicates that most parents and/or juveniles do give informed consent, but this is not always processed correctly in the DD JGZ (digital file of the youth health care organisations).

The reporting year 2022 (Table 2.2.1) largely concerns vaccinations administered up to and including 2021. Because the birth cohorts of reporting year 2022 had already reached the age limit before January 1st, 2022, the introduction of informed consent has limited consequences for the calculation of their vaccination coverage. Informed consent has a greater effect on the calculation of vaccination coverage without age limit and the provisional participation figures (section 2.3.2). This is because vaccinations administered in 2022 are only included if informed consent has been registered (this excludes anonymous vaccinations that have been received since January 1st, 2022).
From 2023, the informed consent for data exchange will have consequences for the annual vaccination coverage report. It is then only possible to report on a minimum vaccination coverage based on the non-anonymous vaccinations in Præventis of people who have

given permission (which has also been registered) for the exchange of vaccination data *with* personal data between the youth healthcare services and RIVM. This will lead to significant underestimation of the actual vaccination coverage. Therefore, RIVM can no longer determine whether the vaccination coverage changes. This not only hampers the monitoring of participation in the NIP, but also of vaccine effectiveness and adverse events. Furthermore, this also limits the ability to advise on political decisions and measures based on vaccination coverage data.

2.3.2 Impact of the COVID-19 pandemic

This section presents the preliminary participation figures of newborns born in 2020, toddlers born in 2017, schoolchildren born in 2012 and adolescents born in 2007-2008. Therefore, it concerns other children than in Table 2.2.1. Vaccinations for these groups largely took place in 2021, during the second year of the COVID-19 pandemic.

2.3.2.1 Participation infant vaccination

In Figure 2.2 the provisional participation per month of birth (based on registration with informed consent) in the first MMR vaccination for children born in 2020 is compared with the participation of children born in 2018. This figure shows not only that there was some delay in the participation in the first MMR vaccination, just like for children born in 2019, but also that at a later point, the vaccination is caught up with to a large extent. However, the participation for children born in the period January-June 2020 still lags about 2-4 percentage points behind that for children born in 2018, while for children born in 2019 this was about 1-2 percentage points. Therefore, the effect of the COVID-19 pandemic on the participation of infants born in 2020 in the NIP appears to be slightly larger than for infants born in 2019.

However, due to the introduction of informed consent, the development in participation for children born in 2020 is more difficult to interpret, because in 2022 approximately 12% of the administered MMR vaccinations were received anonymously (situation on 12 May 2022). The effect of this is becoming increasingly apparent for children born after September 2020 (Figure 2.2). Based on the non-anonymously registered vaccinations, participation is almost 20 percentage points lower than before. The anonymous vaccinations cannot be linked to a year of birth and a dose (first or second MMR vaccination). Consequently, these vaccinations cannot be included in the calculation. For children born from 2020, we can therefore no longer determine whether there actually is a lower participation than before, or whether the decrease based on the non-anonymously registered vaccinations is fully explained by the introduction of informed consent.

2.3.2.2 Participation vaccination other age groups

The provisional participation (based on registration with informed consent) in a number of vaccinations in other age groups is also monitored on a monthly basis (Figure 2.3). Here too, participation lags slightly behind when compared to last year. Signals from the field indicate that young people prioritised their COVID-19 vaccination in the autumn of 2021, and postponed their HPV and MenACWY vaccinations to the spring of 2022. Therefore, participation is expected to increase. However, insight in this catch up will also be impacted

by the introduction of informed consent on January 1st, 2022. The final vaccination coverage, based on only the non-anonymously registered vaccinations in Præventis, will be an underestimation of the actual vaccination coverage.

2.4 International developments

Last year, WHO European Region already reported a 1% decrease in routine immunisation coverage in 2020, with larger decreases in some countries [2]. It was hoped that 2021 would be a year of recovery and catching up. However, in 2021, a similar decrease compared to 2019 was seen. While overall the European region prevented a further backslide in 2021, the WHO concluded that disparities in immunisation performance among countries are evident [3]. Globally, the immunisation coverage for three doses of the vaccine against diphtheria, tetanus and pertussis (DTP3) even fell by 5 percentage points between 2019 and 2021, to 81 percent, the lowest level since 2008. The decline was due to various factors, including an increased number of children living in conflict areas and fragile settings where access to immunisation is often challenging, the rise of misinformation and disinformation, and COVID-19 related issues such as service and supply chain disruptions, diversion of resources to response efforts, and containment measures that limited the availability of and access to immunisation services and access to them [4]. To prevent outbreaks of measles and other vaccine-preventable diseases in the future, national immunisation programmes now face the triple challenge of increasing routine immunisation coverage and ensuring unvaccinated children catch up on all their missed doses, while continuing to provide COVID-19 vaccinations [3].

2.5 Literature

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* RIVM publication.

3
Acceptance of vaccination

A.J.M. Pluijmaekers, C. Oostdijk, M. Immink, I. Schreuder, M. Carpay, N.A.T. van der Maas, S. Teelen, M. de Vries, C. Veerman

3.1 Key points

- Predictors for acceptance of maternal pertussis vaccination (MPV) were found to remain the same between the second and third trimester. Vaccination intent for maternal influenza vaccination (MIV) increases with duration of pregnancy.
- Pregnant women want to receive the MIV to protect their unborn child; about half were unaware of the increased risks of influenza during pregnancy. Healthcare providers promote the MPV more than the MIV.
- Boys and young men seem more intent to be vaccinated against HPV than girls and young women, but more research is needed. For young adults, having a non-Western migration background decreases vaccination intent, while increased stability in life improves intent.
- For boys, the most important reason to be vaccinated is the belief that HPV vaccination is important to also protect others, while girls primarily want to protect themselves. Parents' reasons to not have their children vaccinated most often relate to the perceived young age of vaccination. The chance of getting infected with HPV and the effectiveness of the vaccine are underestimated, while the risk of developing HPV-associated cancer is overestimated.
- Pneumococcal vaccination intent in the elderly is framed by perceptions of own health and general vaccine-related preferences. Receiving an invitation for vaccination, combined with an official advice from RIVM, confers importance and leads to re-evaluation of the risks of the disease, thus improving intent to be vaccinated.
- A study into the acceptance of COVID-19 vaccinations shows the importance of anticipating public perception and response after a vaccine safety scare. Informational videos about COVID-19 vaccines did not influence intent, confidence, informed decision making, or the recognition and sharing of content presenting misinformation or disinformation.
- Offering HPV vaccination one year earlier and in combination with the then planned DT-IPV and MMR vaccinations, does not seem to result in higher vaccine uptake. Offering vaccinations during well-child appointments, however, does appear to positively impact vaccine uptake.

3.2 Monitoring acceptance of the NIP

In this chapter, we define vaccine acceptance as the timely acceptance of all recommended vaccines according to the National Immunisation Programme (NIP) schedule. Although most parents believe in the importance of childhood vaccination, there are significant differences in vaccine acceptance within and between Western countries, making it important to monitor acceptance continuously.
This chapter covers relevant research regarding vaccine acceptance, improving vaccine communication campaigns, and the decision-making processes driving vaccine acceptance or refusal.

3.3 RIVM studies into vaccine acceptance

3.3.1 Pregnancy (pre-birth)

3.3.1.1 Sociopsychological factors associated with acceptance of 2nd trimester Tdap vaccination among pregnant women

Pregnant women (n=1,120) filled in a questionnaire on determinants that underlie acceptance of a second trimester tetanus, diphtheria and acellular pertussis (Tdap) vaccination, before they were offered the vaccine. Preliminary results show that predictors highly associated with acceptance were vaccination intent, attitude, perceived safety, risk perception of the severity of side effects, risk perception of the susceptibility to side effects, and moral responsibility. The model correctly predicted 100% of the vaccine acceptors (model sensitivity), and 44% of the vaccine rejectors (model specificity). Repeating these analyses among 32 vaccine rejectors and 75 acceptors, reflecting the Dutch maternal Tdap vaccination coverage of 70%, yielded comparable results (99% sensitivity, specificity increased to 69%).

Factors associated with second trimester Tdap vaccination acceptance are therefore comparable with third trimester vaccination acceptance, as previously studied.

3.3.1.2 Maternal influenza vaccination

In April and May 2022, an online survey was distributed to 2,155 women, of whom 1,892 were pregnant during the survey (197 (10%) first trimester, 1,098 (58%) second trimester, 597 (32%) third trimester), and 263 had delivered within the past two years (from now on referred to as recent mothers).

Both pregnant women and women with a child under two years of age, rated vaccination against infectious diseases positively. Indeed, of the 263 recent mothers, 94% participates in the NIP.
Of the pregnant women in this study, 38% received the routinely offered maternal pertussis vaccination (MPV), while 47% intended to get this vaccination later in pregnancy. Pregnant women in the first trimester were more often in doubt about getting the MPV compared to women in the second or third trimester (23%, compared to 8% and 1% respectively).
Of the pregnant women, 79% (1,495) had been vaccinated against COVID-19, of which 38% (568) during pregnancy, which was especially the case for women in the third trimester (73%, 415 women).

One in seven participants (302, 14% of total) said to have received an invitation from their GP for influenza vaccination at least once before because they were part of a risk group. However, more than half (52%, 157) had not responded to this invitation, mainly because they felt no need to get the vaccination (44%) or because their employer had also offered the vaccination (19%). Additionally, 7% worried the influenza vaccine would make them ill by causing influenza or by eliciting an allergic response.
88% of all participating women recognised that influenza is a (very) serious infection for new-born babies (87% of pregnant women, 90% of recent mothers). A lower percentage of women perceived catching influenza during pregnancy as serious: 52% of pregnant women

thought it would be (very) serious (compared to 59% of recent mothers), while 26% thought it would not be serious (at all).
Respondents indicated that the main reason for getting the influenza vaccine during pregnancy would be to protect the baby against infection (71%), followed by preventing serious illness for the new born baby (54%). Reasons for not getting the influenza vaccination were feeling healthy (36%), not belonging to a risk group (36%), and either not feeling vulnerable to or feeling resistant against influenza (32%).

Intent to vaccinate increased with pregnancy duration: 63% of pregnant women in the third trimester would get the influenza vaccine during pregnancy, compared to 55% of women in the first trimester (60% of all pregnant women). 22% indicated they would not get vaccinated. Both income and educational background influenced intent to vaccinate. 46% of all responding women from low educational backgrounds (147) would get vaccinated during pregnancy, compared to 67% of women who had a high level of education (1,188). Of women living below the line of modal income (€ 36.500, 333 women), 55% would get vaccinated, compared to 67% of the women with an above modal income (over € 43.500, 898 women). Age and migration background did not greatly influence intent to vaccinate against influenza during pregnancy.

Participating women indicated they trust information most when it comes from their midwife (83%), followed by RIVM (67%). While 29% of pregnant women in the first trimester indicated they lacked (any) trust in governmental information, this improved with pregnancy duration (21% for second trimester, 19% for third trimester). A similar trend was seen for trust in information from RIVM, which had not been specified in the survey as being part of the government.

3.3.2 Childhood and adolescence

3.3.2.1 HPV vaccination intent and perception among parents to 9-15-year-olds, and adolescents aged 13-18

A quantitative study among parents to 9-15-year-olds (1,186), indicated that 65% intended to let their child(ren) be vaccinated against HPV. While about 45% of adolescent boys aged 13 to 18 (562) intended to get vaccinated, only 33% of adolescent girls in the study (425) intended to be vaccinated. This difference is likely due to selection bias; only unvaccinated adolescents were invited for the survey, and while boys had not previously been invited for HPV vaccination, girls had, yet had not made use of the opportunity to be vaccinated. While for some this may have been due to planning-related issues, many were not vaccinated because they did not want to be, indicating low intent to get vaccinated.

Both parents and adolescents put a lot of trust in the NIP, leading to an automatic positive response to the HPV vaccination. For both groups, their direct social environment heavily influenced their intent to vaccinate. Adolescent vaccination intent is also influenced by the opinions held by parents and friends. As the social environment increases in size, its influence on vaccination intent decreases.

Regarding HPV and HPV vaccination, parents underestimated the risk of being infected, and cited the age of vaccination as the most common reason for resisting vaccination of their child; vaccination is offered to children in the calendar year in which they turn 10, which is (intentionally) well before the child becomes sexually active. Parents who worried about side effects were also less willing to let their child be vaccinated.
Lastly, boys indicated that they believe HPV vaccination is important to also protect others. Girls on the other hand, choose to be vaccinated against HPV primarily to protect themselves.

3.3.3 Adults

3.3.3.1 HPV vaccination intent in women and men aged 18 to 26

In November 2021 and March 2022, two online surveys were distributed to young adult women and men, aged 18 to 26 years. Only unvaccinated respondents were included: 309 women and 300 men in November, and 305 women and 305 men in March.

Unvaccinated men intended to be vaccinated more often than still unvaccinated women (63-65% and 51-52% respectively). As stated above, this likely resulted from the fact that the women had been invited for HPV vaccination before, but had declined. Respondents with a non-Western migration background (10% of respondents in November) less often intended to be vaccinated against HPV: 56% of men (46) and 43% of women (111), compared to 63% and 51% respectively overall in November. Of the respondents without a non-Western migration background, 64% of men (163) and 55% of women (110) intended to be vaccinated.
The March survey indicated that intent to vaccinate increased with increasing stability of romantic relationships. Of the single respondents (189), 46% intended to be vaccinated, followed by 54% of respondents who were 'somewhat in a relationship' (107), 57% of respondents in long-term relationships without children (160), and 60% of respondents in long-term relationships with children (48). Lastly, the March survey showed that employed respondents (340) were slightly more likely to get the vaccine than respondents who were still in school (224), respectively 52% and 47%.

The survey from March 2022 also looked at the perception of the risks related to not being vaccinated against HPV. Regardless of their vaccination intent, respondents underestimated the chance of getting infected with HPV and the effectiveness of the vaccine, while they overestimated the risk of developing HPV-associated cancer.

3.3.4 Elderly

3.3.4.1 Factors influencing intent to vaccinate against pneumococcal disease in adults 60 and over

A qualitative study was performed among people aged 60 and over. For many respondents their decision-making or intent was framed by perceptions of their own health and their general preferences concerning vaccinations. This might, in part, be due to people expressing unfamiliarity with (the specifics of) pneumococcal disease.
Receiving an invitation to get vaccinated appeared to influence people's reasoning.

Respondents explained that being invited to get vaccinated must mean it is important, and that the invitation either made them or would make them reassess potential and previously unknown risks of the disease.

The subsequent quantitative study looked at which factors potentially influence intent to be vaccinated against pneumococcal disease. All 943 respondents were aged 60 and over, and had not (yet) received an invitation to be vaccinated.
Influential factors in shaping vaccination intent were thinking of getting vaccinated as self-evident, a higher perceived chance of getting pneumococcal disease, the perceived importance of protecting oneself, and one's own perceived health. The perceived severity of side-effects of the vaccination influenced intent to not get vaccinated.
On a policy level, the importance conveyed by receiving an invitation to be vaccinated, combined with an official advice by RIVM, positively influenced people's intent to do so. Variables focussed on the influence of people around them (e.g. family or friends), the influence of conversations with health professionals, or the perceived importance of protecting others in society, all proved insignificant in shaping intent.

3.3.5 COVID-19

3.3.5.1 The influence of suspending use of Vaxzevria

From March 14th to March 18th, 2021, COVID-19 vaccinations with the Vaxzevria® vaccine (AstraZeneca) were temporarily suspended in the Netherlands after reports of a rare but severe adverse event. RIVM investigated the impact of this (first) suspension on the Dutch public's COVID-19 vaccination intentions, COVID-19 vaccination perceptions, and trust in the government's COVID-19 vaccination campaign. Two surveys were conducted (n=2,628); one shortly before the (first) suspension of Vaxzevria®, and one shortly after vaccinating with Vaxzevria® resumed.
The results suggest that the suspension did not have an immediate effect on intent to vaccinate against COVID-19, nor on attitudes and feelings towards COVID-19 vaccination in general. However, trust in the vaccination campaign declined slightly after the suspension. In addition, respondents were less likely to report intent to vaccinate with Vaxzevria®, and reported less positive attitudes, less positive feelings, and more negative feelings towards Vaxzevria® than to COVID-19 vaccines in general. These results stress the importance of anticipating public perception and response following a vaccine safety scare, as well as the importance of informing people about the possibility of very rare severe adverse events prior to the introduction of novel vaccines.

3.3.5.2 The effect of different kinds of informational videos

By means of a repeated survey experiment, RIVM tested three short informational videos about COVID-19 vaccines:

- Confidence video: focused on building trust in vaccination and debunking possible misconceptions. This video contained brief information about the possible advantages and disadvantages of vaccination.

- Informed decision video: focused on supporting informed decision-making about vaccination. In this video, the possible advantages and disadvantages of vaccination were discussed in more detail than in the confidence video, and the viewers were guided less in their vaccination choice.
- Misinformation video: focused on recognising and preventing the sharing of misinformation and disinformation about COVID-19 vaccines. No information was given about possible advantages and disadvantages of vaccination against COVID-19.

The respondents (2,539, aged 18 to 34) either watched one of the videos, or the misinformation video and either the confidence or informed decision video, or no video (control), and completed two surveys: right before watching the video(s) and one week after watching the video(s).

Between the measurements or conditions, no differences were found in vaccination intent, confidence in vaccination, or how well informed the respondents felt (informed decision). There was no change in recognising and sharing misinformation or disinformation either. At the time of the experiment, a lot of information about COVID-19 vaccines was distributed, potentially hampering the effect of the videos. In addition, only 26% (489) of the (at that time) unvaccinated respondents (1,887) were unsure about their vaccination choice. The remaining 74% (1,398) indicated they had already made their choice, and may therefore not have changed their mind during the experiment. Of the three videos, the informed decision video was rated as the most informative, interesting, and educational.

3.4 Strategies and interventions to increase vaccine uptake

3.4.1 HPV/DT-IPV vaccination at nine years of age during mass-vaccination efforts

Since 2022, all ten-year-olds in the Netherlands are invited for HPV vaccination. To make vaccinations more easily accessible, nine-year-olds in Amsterdam were offered to replace the DT-IPV and MMR vaccinations typically offered at that age, with two separate vaccination moments in which these two vaccines are combined with the HPV vaccinations. During the first vaccination moment the DT-IPV and first HPV vaccination were offered, and six months later the MMR and second HPV vaccination.
75% of all nine-year-olds chose the combination with the HPV vaccinations. With 74%, this was similar to neighbourhoods with low vaccination coverage.
The disappointing turnout, the fact that one in four nine-year-olds did not choose to combine the DT-IPV, MMR, and HPV vaccines, and potential upcoming changes in the vaccination schedule, make it meaningless to continue to offer this combination of vaccines.

3.4.2 Pilot: vaccinating during well-child appointments

Earlier discussions with parents and children 9-10 years of age, indicated a need for more efficient well-child consultations, closer to home. By including vaccinations in the periodic well-child appointments, parents and children need to attend fewer consultation moments. Additionally, Youth Healthcare professionals can bring up vaccinations more naturally during these visits. To this end, a pilot has started in two Amsterdam boroughs, in which children can be vaccinated during these periodic well-child examinations. The offered vaccinations are the

HPV vaccinations, HPV and DT-IPV vaccinations, or the DT-IPV and BMR vaccinations. Before the appointment, parents were informed over the phone about the possibility to have their child vaccinated. From March 17th until June 28th, 2022, 159 pupils from 6 primary schools in the boroughs Northeast and Old North were invited. These schools were chosen because of the relatively low vaccination coverage and the diverse population in their respective boroughs. Thus, it would be possible to judge the applicability of this intervention for the city as a whole.

Out of the children that had already made it to the appointment, 67% (54) have received one or two vaccinations during their well-child appointment, translating to 45% of the total number of invited children (including no-shows and upcoming appointments). General vaccination uptake for the same period in the two boroughs (Northeast and Old North), was 39.8% and 46% respectively.

Seeing as the schools were chosen for their position in an area with low vaccination coverage, these results may indicate that combining vaccinations with the periodic well-child appointments is more effective for this group than the standard approach of offering these vaccinations as mass-vaccinations. Because of the small number of initial participants, this pilot will be continued.

3.5 International literature and studies

3.5.1 Maternal vaccination

A New Zealand study found that mothers and midwives alike, strongly believed that the decision to take maternal vaccinations (MVs) was fully up to the woman [1]. While healthcare professionals (HCPs) were important for creating awareness of MVs, they were careful not to influence the women, but rather encouraged them to look for additional information and truly decide for themselves. Women indeed based their decisions on their own beliefs, knowledge, and perceived risk, although they did take recommendations and information from their HCPs into account. Information that was delivered without discussing risks and benefits turned out to be the least convincing, while messages that appeared ambivalent were found to sometimes discourage vaccine uptake [ibid.].

In line with previous research, the maternal pertussis vaccination (MPV) got more focus from HCPs and was regarded as more important by the women than the maternal influenza vaccination (MIV) [ibid.]. This because the MPV was known to protect the baby, while women believed the MIV would benefit them rather than their child and trusted on their good health to carry them through a possible infection. Indeed, they were unaware of the higher risk of hospitalisation after being infected with influenza during pregnancy, with few HCPs communicating this risk to the women [ibid.].

A study in the USA, measuring intent to vaccinate after women read an informational text about MVs, also found that women were more likely to opt for the MPV than (also) for the MIV [2]. The informational text was found useful and had a positive effect; after reading the

text, the women who were not yet vaccinated indicated a greater likelihood of getting the MIV or the MPV respectively. Influence on women who previously said they did not plan to be vaccinated was limited. A more personalised discussion and repeated messaging would more likely benefit their vaccination intent. Overall, intent to vaccinate increased towards the end of pregnancy, and was higher for women who were more highly educated, and/or white, and/or had previously received flu vaccinations [ibid.].

3.5.2 HPV

3.5.2.1 Adolescents and young adults

Studies continue to indicate that knowledge and awareness of HPV and HPV vaccination typically remain low or incomplete among adolescents and young adults [3-7]. Furthermore, when knowledge is not missing but rather is incorrect, it decreases vaccine confidence, a determining factor for vaccine hesitancy. Adolescents and young adults indeed report anxiety and fear as a result from stories promoted by vaccine-critical adults, especially about supposed side effects [3-6].

This again highlights the importance of improving dissemination of information from trusted sources, such as HCPs, about HPV vaccination in trusted places, such as schools [3-6]. Educational efforts should also include learning how to identify trustworthy sources. For instance, a 2022 French study found that adolescent girls also view trustworthy, official information with suspicion, because they know not to trust everything they read about HPV vaccination [5]. More time for conversations with HCPs brings the added benefit of improved relationships and trust between children and young adults and their doctors [5].

While the role of sexual transmission appears to be well-known [3, 6], it is best not included in intervention materials, because it suggests a connection between the importance of HPV vaccination and currently being sexually active [3]. Indeed, for young adults sexual activity, or the lack thereof, is a factor in their decision-making processes about HPV vaccination [ibid.]. Instead of including it in intervention materials, the sexual transmissibility of HPV is best included in communication about sexual health in general, while young adults who are not (yet) sexually active are best targeted at a personal level [ibid.].

On the connection between vaccine hesitancy and vaccine uptake, a Swiss study found that HPV vaccine uptake in men aged 15-26 was lower than in women, despite vaccine hesitancy in these men being 10 percentage points lower than in women [7]. This may be because the recommendation to vaccinate Swiss boys against HPV stems from 2015, and only as a supplemental vaccination, while girls have been offered routine HPV vaccination since 2007. As a result, men appear to face additional barriers compared to women: they know less about HPV vaccination, are less aware about it, and have less access to it. These factors are likely exacerbated by reduced awareness in HCPs of the importance of HPV vaccination for men, keeping them from discussing the vaccine with their male patients and recommending it to them [ibid.]. Men also show less healthcare-seeking behaviour than women, and therefore less often find themselves in situations in which they can be offered the vaccine [ibid.].

3.5.2.2 *The dynamic between children, adolescents, and young adults, and their HCPs and parents*

While deciding about HPV vaccination, adolescents and young adults typically include the opinions of their HCPs, parents, and peers, or they even completely defer the decision to their parents [3-5]. Still, despite relying on the opinions of their parents, peers, and HCPs, children and adolescents also prefer to receive more information and/or to be included in the decision [4-6]. The actual degree of involvement of adolescents and young adults in HPV vaccination was found to depend on dynamics involving their HCPs and parents, specifically their mothers [3-5]. Adolescent girls in a French study were often excluded by their HCP in conversations about HPV vaccination, despite wanting to be involved. The girls' mothers did not speak out against this lack of engaging their daughters [4].

Additionally, some adolescents (feel like they) would have to go against their parents' wishes when choosing to be vaccinated, putting them in an undesirable position [4]. Furthermore, by being excluded from the decision, adolescents are unable to influence their parents' opinions with their positive views and the wish to protect themselves, while their parents are free to influence the adolescents' beliefs with their negative opinions, and in fact do so. Parents thus instil their own health beliefs in their children, thereby determining their children's future health behaviours and beliefs, which develop during adolescence in particular [4, 5]. This further emphasises the importance of informational efforts taking place in trusted places away from home [5].

3.5.2.3 *Parents*

In a 2021 study, French mothers described the HPV vaccine as 'controversial' [5]. While mothers said to have great trust in healthcare providers, sometimes even deferring the decision to vaccinate to them, their trust in the government, health authorities and scientific experts was more nuanced. This was likely a result of previous mismanaged health-related events in France. However, regardless of their trust in HCPs, mothers emphasised that the decision to vaccinate should be made freely. As a consequence, HCPs who judged the mothers or pressured them into making a specific decision lost the mothers' trust [ibid.].

An American study among Latina mothers, found they typically lacked correct knowledge about HPV transmission and HPV-associated cancer risks for men, and consequently underestimated the importance of HPV vaccination for boys [8]. This is in line with other research on the topic. Therefore, a continued effort must made to educate parents about the importance of HPV vaccination for boys.

3.5.3 Pneumococcal vaccination for the elderly

An Israeli study found that pneumococcal vaccine uptake in the elderly was higher for the younger age bracket (65-70) than for older one (71-74), even though both groups were offered the vaccine in the same program [9]. Besides age, uptake was positively associated with a number of preventative healthcare-seeking behaviours, specifically related to cancer screening. Contrastingly, a negative association was found with the preventative behaviour of influenza vaccination [ibid.].

While seeking preventative healthcare leads to increased exposure to primary health care staff, a generally increased level of exposure to primary health care staff was found to negatively associate with pneumococcal vaccine uptake [ibid.].

3.6 Literature

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4
Burden of disease

E.A. van Lier, S. McDonald, P. de Boer, E. Benincà, A. Steens, I. Veldhuijzen, D.L. van Meijeren, J. van de Kassteele, H.E. de Melker

4.1 Key points

- The estimated total burden of diseases caused by (partially) vaccine-preventable diseases for the year 2021 was highest for HPV (17,200 disability adjusted life years (DALYs); 78% among women), invasive pneumococcal disease (5,200 DALYs), rotavirus infection (920 DALYs), and invasive *Haemophilus influenzae* disease (890 DALYs).
- For most vaccine-preventable diseases, the estimated burden in 2021 (and 2020) was considerably lower compared to the estimated burden in 2019, probably due to the implementation of various COVID-19 response measures, e.g. social distancing and hand hygiene. Additional vaccination against pneumococcal disease (elderly, start in 2020) and meningococcal ACWY disease (adolescents, start in 2018; newborns, meningococcal ACWY instead of meningococcal C vaccine since 2018) was also implemented. The burden of invasive *H. influenzae* disease type b was higher in 2021 and 2020. The reason behind this increase is under investigation, but no indications for a lower vaccine effectiveness against disease were found.
- The burden of COVID-19 is estimated to be 219,000 DALYs for 2021, where 98% of the burden is due to premature death because of COVID-19. This is an underestimation of the actual burden, since long-term consequences of the disease have not been taken into account. In 2021, COVID-19 control measures were in place, and vaccination against COVID-19 started in January 2021. For COVID-19, the burden in 2021 was higher than in 2020.

4.2 Tables and figures

Table 4.1 Estimated annual burden of disease in DALYs in 2017–2021, and DALYs per 100 infections in 2021 in the Netherlands (with 95% uncertainty intervals) [1-3].

	DALYs (95% uncertainty interval)					DALYs/100 infections
Disease	2017	2018	2019	2020	2021	in 2021
Diphtheria	4 (3-4)	3 (3-4)	0 (0-0)	3 (3-4)	0 (0-0)	n/a
Hepatitis A virus infection	200 (120-340)	100 (62-170)	90 (55-150)	28 (17-45)	42 (26-69)	11 (8-15)
Hepatitis B virus infection (acute)	150 (140-160)	130 (120-140)	120 (110-120)	100 (98-110)	170 (150-180)	40 (37-43)
Human papillomavirus infection[a]						
- *Females*	11,100 (10,500-11,800)	12,200 (11,500-12,900)	12,700 (12,000-13,400)	11,700 (11,100-12,500)	13,400 (12,700-14,200)	n/a
- *Males*	3,800 (3,200-4,500)	4,000 (3,300-4,700)	3,900 (3,300-4,700)	3,700 (3,100-4,400)	3,800 (3,200-4,500)	n/a
Invasive *H. influenzae* disease	980 (930-1,000)	1000 (960-1,100)	970 (920-1,000)	1,000 (970-1,100)	890[b] (840-950)	480 (450-510)
Invasive meningococcal disease	1,100 (980-1,300)	1,100 (960-1,300)	890 (740-1,100)	400 (300-510)	280[c] (190-380)	730 (640-810)
Invasive pneumococcal disease	9,800 (9,200-10,400)	10,800 (10,100-11,400)	9,500 (8,900-10,000)	6,200 (5,800-6,600)	5,200[d] (4,900-5,500)	380 (360-400)
Measles	3 (2-3)	5 (4-5)	16 (15-18)	0.4 (0.3-0.5)	0 (0-0)	n/a
Mumps	0.4 (0.3-0.4)	0.6 (0.5-0.6)	1 (1-1)	0.5 (0.5-0.5)	0.01 (0.01-0.01)	0.4 (0.4-0.4)
Pertussis	2,000 (1,900-2,200)	2,000 (1,900-2,100)	2,600 (2,500-2,800)	390 (370-420)	32 (30-35)	1 (0.9-1)
Poliomyelitis	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	n/a
Rabies	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	n/a
Rotavirus infection	1,100 (440-2,200)	1,200 (470-2,400)	1,100 (440-2,300)	390 (160-790)	920 (360-1,900)	0.5 (0.3-1)
Rubella	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	n/a
Tetanus	0.6 (0.5-0.8)	1 (1-1)	0 (0-0)	11 (9-12)	0 (0-0)	n/a

DALY = disability adjusted life year.

n/a = not applicable; no cases occurring in 2021 or unknown number of infections (HPV).

For HPV, the burden in 2017-2019 is somewhat lower than previously reported due to a resolved error regarding the integration of life expectancy in the DALY calculation.

[a] To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. The most recent year of available data on the incidence of anogenital warts and high-grade cervical lesions was 2016 and 2020, respectively. Therefore, the incidence rate of anogenital warts for 2016 was carried forward to 2017–2021 and the incidence of high-grade cervical lesions for 2020 was carried forward to 2021; in addition the incidence for 2017–2019 was updated.

[b] Proportion of disease burden due to disease caused by vaccine-preventable type b in 2021: 50%.

[c] Proportion of disease burden due to disease caused by vaccine-preventable type C in 2021: 0%; proportion caused by type B in 2021: 91%; proportion caused by type W in 2021: 6%.

[d] Proportion of disease burden due to disease caused by vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2021: 1%.

Sources: Osiris, NRLBM, sentinel laboratory surveillance, national cancer registry, PALGA, NIVEL-LINH.

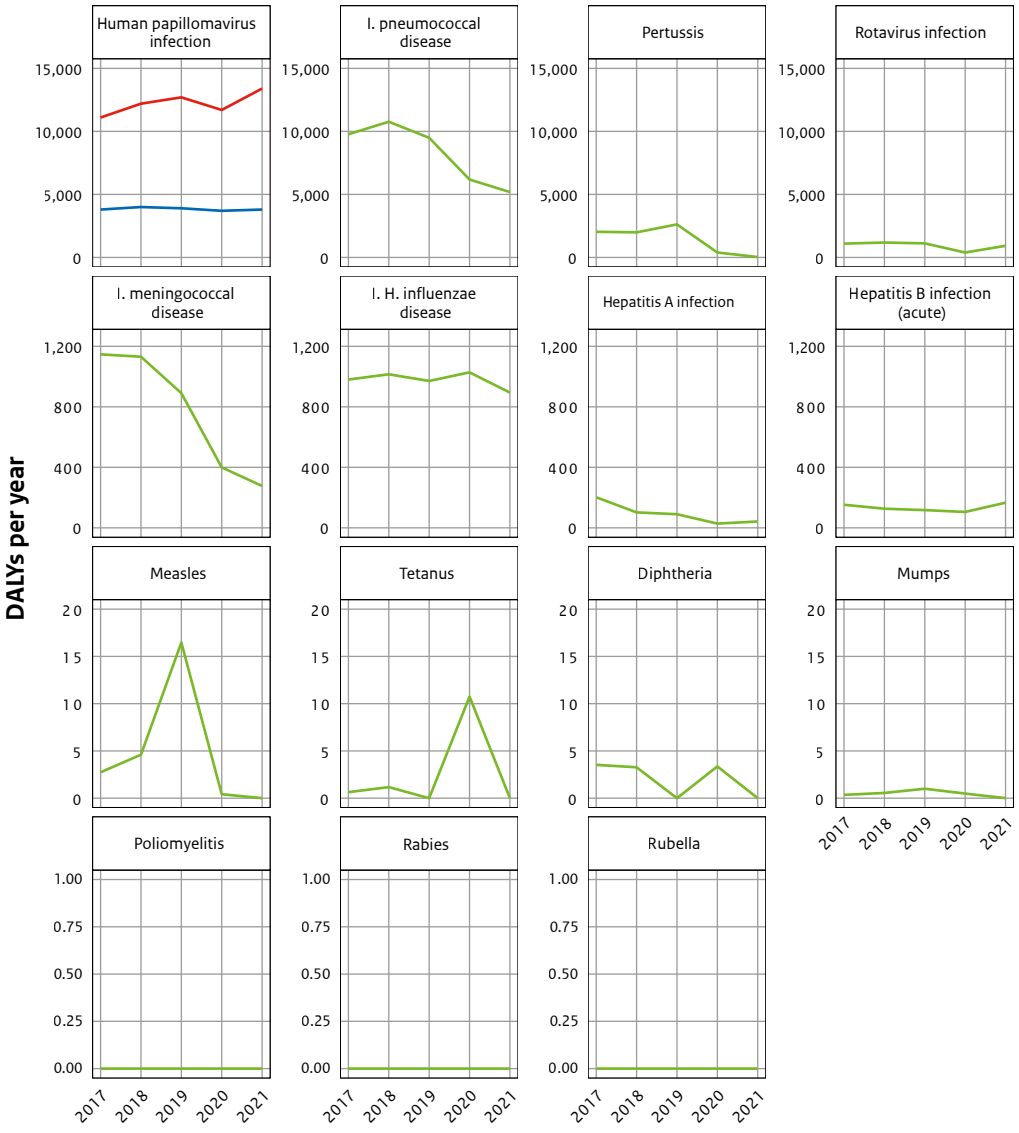

Figure 4.1 Estimated annual disease burden in DALYs in the Netherlands in 2017–2021 [1-3].

Notes:

1. DALY= disability adjusted life year; for HPV, the burden in 2017-2019 is somewhat lower than previously reported due to a resolved error regarding the integration of life expectancy in the DALY calculation.
2. Vaccination against rabies, hepatitis A and rotavirus infection is not included in the NIP.
3. For the three invasive diseases, a vaccine was only available against certain serotypes: *Haemophilus influenzae* serotype b (Hib), meningococcal serotypes A, C, W, and Y, and PCV10 pneumococcal serotypes for children and PPV23 serotypes for older adults. For HPV infection, a vaccine was only available against two types: HPV 16 and 18.
4. For HPV, the burden is based on the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV. The red line shows the burden for females, the blue line shows the burden for males.
5. Note that the y-axes are not the same for all diseases.

Sources: Osiris, NRLBM, sentinel laboratory surveillance, national cancer registry, PALGA, NIVEL-LINH.

4.3 Burden of NIP-diseases

In this section, we present an update of the disease burden of vaccine-preventable diseases in the period 2017–2021, expressed in disability adjusted life years (DALYs). We present the same estimates as published in the 'State of infectious diseases in the Netherlands, 2021', in which more detailed information on the parameters used can be found [1]. Estimates for hepatitis A infection and rotavirus infection were derived from the report 'Disease burden of food-related pathogens in the Netherlands, 2021' [3], and estimates for COVID-19 from the report 'Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2021/2022' [4]. Estimates for human papillomavirus (HPV) infection were derived from a separate analysis [2] and updated for more recent years using the Global Burden of Disease (GBD) 2010 life expectancy. For HPV, the burden in 2017-2019 is somewhat lower than previously reported due to a resolved error regarding the integration of life expectancy in the DALY calculation. Note that the calculation method used for HPV is not fully comparable to that used for other diseases: instead of using the number of incident infections (which is unknown), the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV was used. All DALY estimates were rounded up or down: to three significant digits for numbers ≥10,000, to two significant digits for numbers between 10 and 10,000, and to one significant digit for numbers <10.

Table 4.1 shows the estimated DALYs per year in the period 2017–2021 and the DALYs per 100 infections in 2021 (a measure of the disease burden at individual patient level) in the Netherlands, with 95% uncertainty intervals. For diphtheria, measles, poliomyelitis, rabies, rubella, and tetanus, the estimated disease burden in 2021 was zero because no cases were reported. For mumps, hepatitis A, pertussis, and meningococcal disease, the disease burden in 2021 was estimated to be relatively low, while the highest burden was estimated for HPV infection, followed by invasive pneumococcal disease, rotavirus infection and invasive *Haemophilus influenzae* disease.

The incidence of pertussis and rotavirus infection is known to surge every few years (Figure 4.1). For most vaccine-preventable diseases, the estimated burden in 2021 (and 2020) was considerably lower compared to the estimated burden in 2019. This is probably an effect of the implementation of COVID-19 control measures, such as social distancing and hand hygiene (see also [5] and [6]). In addition, the Netherlands started vaccinating the elderly against pneumococcal disease in the autumn of 2020. Furthermore, meningococcal ACWY vaccination for adolescents started in 2018 and is included in the NIP from 2020 onwards, whereas newborns are vaccinated with meningococcal ACWY instead of meningococcal C vaccine since 2018.
For the second year since the introduction of vaccination in 2002, no cases of invasive meningococcal C disease were reported in 2021, and therefore the burden was zero DALYs. The proportion of the burden of invasive meningococcal disease due to serogroup W decreased further: from 42% in 2018 to 29% in 2019, 14% in 2020, and 6% in 2021. In 2021, the burden of the PCV10-preventable pneumococcal serotypes was only 1% of the total burden due to invasive pneumococcal disease. The proportion of the burden due to the vaccine-preventable

H. influenzae disease serotype b (Hib) in the total burden of invasive *H. influenzae* disease increased from 28% in 2018/2019 to 47% in 2020, and 50% in 2021, due to an increase of Hib and a decrease of non-typeable invasive *H. influenzae* disease. The latter development is probably due to the COVID-19 control measures. The absolute number of DALYs due to Hib also increased in 2020 and 2021 (2018: 289 DALYs, 2019: 272 DALYs, 2020: 484 DALYs, 2021: 445 DALYs). Possible reasons for the increase in Hib are under investigation, but it is unlikely that it is caused by a decreased vaccine effectiveness against invasive disease, as this was estimated to be stable over time and above 90% [7].

It must be noted that the total disease burden for pneumococcal disease, meningococcal disease, and *H. influenzae* disease, is higher than presented here as the analyses were limited to invasive disease. Furthermore, the disease burden of these diseases, as well as of HPV infection, is not fully preventable through vaccination because not all serotypes are covered by the vaccine. The disease burden related to hepatitis B virus infection has also been underestimated. The analyses only reflect the (future) burden of new cases of hepatitis B virus infection in the period 2017–2021, because the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

4.4 Burden of COVID-19

To estimate the disease burden of COVID-19, the total number of registered positive SARS-CoV-2 tests (adjusted for underascertainment), admissions to hospitals and ICUs, and deaths due to COVID-19 served as direct input for the calculations. DALYs were calculated using the GBD-2010 life expectancy values.

The disease burden of COVID-19 in 2021 is estimated to be 219,000 DALYs (95% uncertainty interval 215,000-223,000), where 98% of the burden is due to premature death because of COVID-19. In 2020 the burden, when computed using the GBD-2010 life expectancy values, was estimated to be 207,000 DALYs (95% uncertainty interval 204,000-210,000). In 2021 (and 2020) COVID-19 control measures were in place, and vaccination against COVID-19 started in early January 2021.
The burden estimate of COVID-19 represents an underestimation of the actual burden since long-term consequences of the disease have not been taken into account. Furthermore, there is insufficient data about the epidemiology and long-term impact of COVID-19 at this time to properly estimate the disease burden in DALY/100 cases [4].

4.5 Literature

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* RIVM publication.

5
Adverse events

J.M. Kemmeren

5.1 Key points

- In 2021, Lareb received 1,462 notifications, representing a total of 4,636 adverse events following immunisation (AEFI) for NIP vaccinations. This is similar to the number of reports received in 2020 (n=1,475) [1]. The number of reported AEFIs per report was 3 to 4, which is the same as in earlier years.
- No new signals of disturbing adverse events were found in children, adolescents, or pregnant women.

5.2 Tables

Table 5.1 Number of reports per age category and suspected vaccine(s).

Vaccines	Total 2019	Total 2020	0-2m	3-4m	5-6m	7-8m	9-10m	11-12m	13-14m	15-16m	17-23m	2-5yrs	6-9yrs	10-14yrs	15-19yrs	Pregnant women	Other/Unknown
Vaxelis® + Synflorix®	358	**320**	3	137	76	4	3	79	15	2	1						
Vaxelis®	133	**104**	29	26	9	2	1	14	3	3	1	10	5	1			
Synflorix®	12	**10**		1	3		1	3	1	1							
MMRVaxPro® + Nimenrix®	172	**193**	1						108	74	6	2	2				
MMRVaxPro®	65	**46**	1						22	9	3	2	4	1	3		1
Nimenrix®	60	**58**							4	3	1	2		46	2		
Boostrix Polio®	268	**233**		1				2			1	223	1			5	
MMRVaxPro® + Revaxis®	124	**118**											117	1			
MMRVaxPro® + DTP Bbio	0	**8**											8				
Revaxis®	12	**11**											11				
Cervarix®	52	**128**												92	36		
Boostrix®	189	**186**														186	
Combination of vaccines not in NIP	15	**35**		1						2			4	20	2	6	
Vaccinated within old schedule	15	**12**	1	1	2				2	1	1	1	2	1			
Other	0	**0**															
Total 2021		**1462**	**35**	**167**	**90**	**6**	**5**	**98**	**155**	**94**	**14**	**240**	**153**	**163**	**44**	**197**	**1**
Total 2020	1475		58	165	94	7	5	143	145	86	22	292	144	87	26	198	3
Total 2019	2009		181	192	46			128	236			316	128	75	497	9	201
Total 2018	1519		187	169				170	263			326	110	65	62		167
Total 2017	1383		216	167				154	200			387	106	77			76
Total 2016	1483		174	155				126	171			572	84	146			55
Total 2015	1494		173	156				142	208			422	88	257			48
Total 2014	982		148	138				101	139			274	108	59			15
Total 2013	1212		217	193				118	133			335	92	82			42
Total 2012	1387		250	264				103	138			423	52	104			53
Total 2011	1103		212	240				105	129			280	51	51			35

Table 5.2 Reported severe adverse events per vaccination moment.

Adverse events	0-2m	3-4m	5-6m	7-8m	9-10m	11-12m	13-14m	15-16m	17-23m	2-5yrs	6-9yrs	10-14yrs	15-19yrs	Unknown	Pregnancy	Total
Rash, eczema	**1**	**10**	**14**	**0**	**0**	**10**	**54**	**32**	**4**	**22**	**19**	**7**	**2**	**0**	**2**	**177**
Respiratory symptoms	**1**	**13**	**2**	**0**	**0**	**2**	**5**	**1**	**1**	**5**	**1**	**3**	**2**	**0**	**5**	**39**
Apnoea, dyspnoea, irregular breathing	0	8	1	0	0	1	3	1	0	2	1	3	1	0	5	**26**
Breath-holding spells	0	2	0	0	0	0	1	0	1	0	0	0	0	0	0	**2**
Other	1	3	1	0	0	1	1	0	0	3	0	0	1	0	0	**11**
Neurologic symptoms	**9**	**27**	**15**	**0**	**1**	**11**	**14**	**11**	**2**	**16**	**23**	**35**	**4**	**0**	**14**	**188**
Ataxia, spasms, tics	0	0	0	0	0	0	1	0	0	0	0	2	0	0	0	**3**
Autism spectrum disorder	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	**1**
Delirium febrile	0	0	0	0	0	1	0	0	0	1	4	1	0	0	0	**7**
Febrile convulsion, seizures, tonic convulsion, epilepsy	2	8	3	0	0	7	8	6	1	4	1	2	2	0	0	**43**
Facial paresis/Bell's palsy	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	**1**
Hypotonic-hyporesponsive episode	1	6	3	0	0	0	0	0	0	0	0	0	0	0	0	**10**
Migraine	0	0	0	0	0	0	0	0	0	0	1	3	0	0	0	**4**
Status epilepticus	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Other	6	13	9	0	1	3	5	4	1	10	16	27	2	0	14	**118**
Extensive swelling of vaccinated limb	**0**	**2**	**2**	**0**	**0**	**2**	**0**	**0**	**0**	**9**	**2**	**2**	**0**	**0**	**0**	**19**
Body temperature ≥40.5 - ≤42°C	**0**	**3**	**3**	**0**	**0**	**3**	**5**	**4**	**1**	**5**	**2**	**0**	**0**	**0**	**0**	**26**
Persistent crying	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Skin discolouration	**1**	**18**	**5**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**29**
Abscess	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**
Injection site abscess	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	**2**
Injection site abscess sterile	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Immune mediated disorders	**0**	**0**	**0**	**0**	**0**	**1**	**2**	**0**	**1**	**0**	**2**	**0**	**1**	**0**	**0**	**7**
Acute haemorrhagic oedema of infancy	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	**1**
Autoimmune disorder	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	**1**
Autoimmune thyroiditis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	**1**
Immune thrombocytopenia	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	**1**
Systemic lupus erythematosus	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	**1**
Type 1 diabetes mellitus	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	**2**
Dehydration	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
Death*	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Sudden Infant Death Syndrome (SIDS)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
Adverse events with fatal outcome	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**

Table 5.2 (continued)

Adverse events	0-2m	3-4m	5-6m	7-8m	9-10m	11-12m	13-14m	15-16m	17-23m	2-5yrs	6-9yrs	10-14yrs	15-19yrs	Unknown	Pregnancy	Total
Encephalitis/meningitis	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Postural orthostatic tachycardia (POTS)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Vaccine failure	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Chronic fatigue	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Kawasaki's disease	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**
Juvenile idiopathic arthritis	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**
Complex regional pain syndrome (CRPS)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Adverse events concerning pregnancy															**29**	**29**
Foetal death*															2	**2**
Foetal growth restriction															1	**1**
Foetal heart rate abnormal															2	**2**
Foetal hypokinesia															3	**3**
Haemorrhage in pregnancy															1	**1**
Normal newborn															6	**6**
Premature baby															2	**2**
Premature labour															1	**1**
Premature rupture of membranes															1	1
Premature separation of placenta															1	1
Preterm premature rupture of membranes															2	2
Stillbirth															2	2
Uterine contractions during pregnancy															5	**5**

* For a full description of the causes of death, see Lareb's annual report [1].

5.3 Spontaneous Reporting System

5.3.1 Reports

The enhanced passive surveillance system, as managed by the National Centre for Pharmacovigilance Lareb, receives AEFI reports for all vaccines covered by the NIP. This chapter gives an overview of the reports received by Lareb after paediatric or maternal pertussis vaccination. Reports of adverse events after COVID-19 vaccination are described in chapter 9.09.
In 2021, Lareb received 1,462 reports with a total of 4,636 AEFIs (Table 5.1) [1]. The number of reports is almost similar to the number of reports received in 2018 (n=1,519) and in 2020 (n=1,475). In 2019, Lareb received a higher number of reports (n=2,009) due to the catch-up campaign of MenACWY vaccination in adolescents. Most reported AEFIs were injection site reactions (n=995), fever (n=526), vomiting (n=193), headache (n=174) and crying (n=165). For most vaccines, the number of reports is mostly within the range of the last years (Table 5.1).

As a result of the introduction of maternal pertussis vaccination in December 2019, newborns do not receive their first vaccination until the age of 3 months. This explained the decrease in reports in infants aged 2 months in 2020, and this line continued in 2021. No remarkable findings were noted for the other vaccines given in the first and second year of life.
The decrease in the number of reports after administration of DTaP-IPV at the age of 4 years, which started in 2017, continued in 2021 (n=240), whereas an increasing trend is seen after the vaccination at 9 years of age. For HPV vaccination, Lareb received more reports of adverse events in 2021 compared to the four years before. This increase may be explained by the fact that group vaccinations were postponed due to the COVID-19 pandemic, and therefore largely took place in 2021 instead of in 2020.
A report to Lareb may include more than one adverse event. The number of reported AEFIs per report in 2021 was 3 to 4, which is similar to earlier years.

Table 5.2 summarises severe adverse events per vaccination moment, as reported to Lareb. These events are included because of their severity and their known or perceived relation with vaccination. In general, the spectrum of reported AEFIs is mostly in line with previous years. Remarkable is the low number of reports concerning extensive limb swelling among 4-year-olds (n=9).
No reports of postural orthostatic tachycardia syndrome (POTS) and chronic fatigue syndrome (CFS) after HPV vaccination were received.

In 2021, Lareb received 11 reports of serious adverse events following maternal pertussis vaccination. In ten of these reports, there were complaints related to the pregnancy. In the 11th report, complaints in the mother were described without further effects on the pregnancy and the unborn child. Given the low number of reports and the large variations in latency time, a possible association with vaccination is unlikely and further research was not considered necessary. Overall, no new signals of disturbing adverse events were found.

5.3.2 Signals/overviews

Lareb did not publish signals and overviews in 2021.

5.4 International Developments

5.4.1 Vaccines targeting diseases included in the current NIP

5.4.1.1 Meningococcal ACWY vaccine

MenACWY-TT vaccine was well tolerated in children [2], even in coadministration with other paediatric vaccines [3] or when given as a booster dose [4]. No safety concerns were identified in adolescents either [5]. Additionally, a review confirmed the safety of MenACWY-TT vaccines as both an initial vaccine for prevention as well as a booster dose [6], and their suitability for inclusion in National Immunization Programmes globally [7].

Information gathered during clinical trials of MenACWY-CRM confirms that this vaccine is well tolerated and has an acceptable safety profile [8]. Two phase 2 studies demonstrated the safety of a new investigational MenACWY-CRM liquid vaccine [9, 10].

In China, no safety issues were found for MenACWY vaccination after administration to children [11].

A pentavalent vaccine that also includes serogroup X (NmCV-5) is under development. Tapia *et al.* [12] reported the results of a phase 2 study in which participants were assigned to receive nonadjuvanted NmCV-5, alum-adjuvanted NmCV-5 or MenACWY-DT [12]. No safety concerns were identified with two doses of NmCV-5, and adjuvanted NmCV-5 provided no discernible benefit over non-adjuvanted NmCV-5.

5.4.1.2 MMR/MMRV

The MMR, MMRV and measles-containing vaccines are generally well tolerated [13-19], also in children with autism spectrum disorders [20], hematopoietic cell transplant recipients [21] and paediatric liver transplant recipients [22], or when co-administered with an inactivated enterovirus 71 and live-attenuated Japanese encephalitis vaccine [23]. Another study showed that MMR vaccination is not associated with atopic diseases [24]. Several reviews confirmed this conclusion [25-28].

5.4.1.3 Pneumococcal vaccine

No safety concerns were found for PCV13 in infants or older children [29-33], in healthy adults [33] and in immunocompromised patients [34, 35]. PCV13 co-administered with recombinant zoster vaccine [36] or sequentially administrated with PPV23 [37], also had an acceptable safety profile. In addition, Zou [38] showed that PPV23 can be safely administered to HIV-1 infected individuals.

A novel PCV15 vaccine administered alone [39-41], or sequentially with PPV23 [39, 42], was well tolerated, even in patients with HIV [43]. PCV15 concomitantly administered with quadrivalent inactivated influenza vaccine [44] was also generally well tolerated.

Several phase 2 and 3 studies demonstrated the safety of a PCV20 vaccine in children [45] as well as in adults [46-48], so in a review Janssens *et al.* [49] concluded that the available evidence on the safety of PCV20 is promising.

A phase 4 trial demonstrated that the safety in infants and toddlers of PCV13 formulated in a multidose vial was comparable with PCV13 formulated in a single prefilled syringe [50].

5.4.1.4 *DTaP-IPV-HBV-Hib*

Several studies showed the safety of infant tetravalent, pentavalent, and hexavalent vaccines [19, 51-59]. DTaP is also generally well tolerated [19]. However, the combined DTaP-IPV-HBV-Hib vaccine showed a higher incidence of fever, but then combination vaccines are known to lead to higher incidences or reporting rates of AEFIs than vaccines with fewer antigens [60-62]. A disproportion of febrile seizures notifications following immunisation with a pentavalent vaccine was noticed in El Salvador, suggesting the existence of a safety signal [63]. This disproportion could be due to the change in provider. A significant decrease in AEFI reports was observed in Chile in the year in which a wP-containing vaccine was replaced by an aP-containing vaccine [64].

A study analysing time trends in sudden unexpected infant death showed an inverse relation with immunization coverage (DTP/Hib or DTP), although this decline has slowed down since 1996 [65]. No new safety signals were found for inactivated poliomyelitis vaccine produced from Sabin Stains (sIPVs) administered concomitantly with DTaP [66].

Several study results provided reassuring evidence of the safety of maternal pertussis vaccination, with no increased risk of adverse pregnancy and birth outcomes [15, 67-70]. However, results from a systematic review and a meta-analysis demonstrated an increased risk of chorioamnionitis among women who received the pertussis vaccine during pregnancy [71]. However, the primary basis of these findings were retrospective cohort studies, which weakens the credibility of the results.

5.4.1.5 *HPV vaccines*

5.4.1.5.1 *2vHPV, 4vHPV and 9vHPV vaccines*

Several studies demonstrated the safety of HPV vaccines [72-76]. It was also reported that HPV vaccination does not increase the risk of morbidity in any manner that manifests as absence from school to due to illness [77]. Another study indicated that girls experiencing suspected AE following HPV vaccination were more vulnerable prior to vaccination [78]. Ahsanuddin [79] concluded that the likelihood of facial palsy following HPV vaccination as reported in VAERS is low. On the other hand, one study suggested the presence of a potential safety signal of premature ovarian failure associated with HPV vaccination [80], although these results only represent statistical associations between HPV vaccine and events related to premature ovarian failure because they were detected in spontaneous reporting data and were therefore prone to notoriety bias.

A systemic review and meta-analyses did not find an increase in background rates of Guillain-Barré syndrome after HPV vaccine administration [81]. Another study concluded that HPV vaccination would prevent substantially more cancer cases than it would hypothetically induce instances of Guillain-Barré syndrome [82].

The safety of 2vHPV and 4vHPV was shown when administered concomitantly or sequentially with a dengue vaccine in healthy, dengue seropositive children [83, 84]. No safety issues were found for 4vHPV in men (heterosexual and MSM) [85]. Two other studies confirmed the safety of 4vHPV and 9vHPV [86, 87] even in a vulnerable population [86]. Several other studies also did not reveal new or unexpected safety issues for 9vHPV [15, 88-92], not even in HIV infected persons and solid organ transplant recipients [93]. Afrin [94] posed a hypothesis that Gardasil

may cause pre-existing (but not yet clinically recognised) mast cell activation syndrome to a clinically significant degree, with the emergence of POTS and other issues. They conclude that the recognition and management of mast cell activation syndrome prior to vaccination in general may be a strategy worth investigating in order to reduce adverse events following HPV vaccination. A review of the safety of various HPV vaccines showed that the 2vHPV vaccine resulted in more systemic adverse events than the other vaccines and a placebo, although no significant differences in serious adverse events were observed [95].
One case report described a previously healthy boy who developed acute hemorrhagic leukoencephalitis three weeks after receiving 9vHPV vaccination [96]. The authors mentioned that HPV vaccine may trigger demyelinating CNS (central nervous system) disease in genetically susceptible individuals. Further research is needed to elucidate what these specific genetic factors are.

5.4.1.5.2 *New HPV vaccines*

In a clinical trial, a novel Escherichia coli-produced HPV-16/18 bivalent vaccine showed an acceptable safety profile [97].

5.5 Other potential future target diseases

5.5.1 Meningococcal B

Results from a post-marketing surveillance program in Italy confirmed the good safety profile of the universal mass vaccination with 4CMenB in children [98]. However, in the UK a self-controlled case series analysis showed an increased risk of febrile seizures, although it was not possible to attribute the finding to one specific vaccination as the majority of 4CMenB was given with other vaccinations [99]. In addition, a product review of Bexero showed a safety profile similar to other childhood vaccine when administered alone [100].
In adolescents and young adults no new safety signals were determined for 4CMenB [101] or MenB-FHbp [102-105] and unspecified meningococcal B vaccines [15].
The Brazilian Oswaldo Cruz Foundation has been working on the development of a vaccine with detergent-treated outer membrane vesicles and detoxified endotoxin from *Neisseria meningitidis* serogroup B prevalent strains. A phase 1 study in 26 adults, showed that these experimental vaccines were well tolerated [106]. Two phase 2 studies showed that the safety and tolerability profile of an investigational MenABCWY vaccine was acceptable in adolescents and young adults [107, 108].

5.5.2 Varicella

Several studies showed the safety of live attenuated varicella vaccines [109-112], even in paediatric patients with heart transplants [113] and in paediatric liver transplant recipients [22]. Ahsanuddin [79] concluded that the likelihood of facial palsy following varicella vaccination as reported in VAERS is low.
Varicella vaccine meningitis is an uncommon delayed adverse event of vaccination. It has been diagnosed earlier in 12 children, of whom 3 were immunocompromised. Ramachandran [114] reported two additional cases of vaccine meningitis in twice-immunised immunocompetent children. After a review of all 14 cases, they concluded that there is no common explanation

for this adverse event, but ingestion of an oral corticosteroid burst 3-4 weeks before onset of vaccine meningitis, may be a risk factor in some cases.
Preclinical data suggest that the live-attenuated varicella vaccine candidate (v7D) is a promising candidate as a safer vaccine, with reduced risk of vaccine-related complications [115].

5.5.3 Herpes Zoster

No safety concerns were identified for adjuvanted recombinant zoster vaccine (RZV) in adults [15, 116-119], even when co-administered with PCV13 [36] or in several immunocompromised populations [120-123]. A review of spontaneously reported post-marketing data did not raise safety concerns regarding the occurrence of vesicular and bullous cutaneous eruptions following vaccination with RZV [124], and a retrospective cohort study showed that administration of RZV was not associated with the risk of Inflammatory Bowel Disease [125]. Guillain-Barre syndrome may occur after vaccination. Findings of a case series cohort study indicate a slightly increased risk of Guillain-Barré syndrome during the 42 days following RZV vaccination [126]. However, in a data-mining study, no cluster of Guillain-Barré syndrome was detected after RZV vaccination, although the authors noted that this may be due to an insufficient sample size [119]. A base case analysis highlighted the projected health benefits of RZV vaccination, compared to the relatively low potential risk of developing Guillain-Barré syndrome following RZV vaccination [127].
A randomised controlled trial found that the live attenuated herpes zoster vaccine was safe in participants who were also taking tumour necrosis factor inhibitors for a broad range of inflammatory disorders [128].

5.5.4 Hepatitis A

Several studies showed a good safety profile for inactivated hepatitis A vaccine [129], the biological E inactivated hepatitis A vaccine [130], and the inactivated hepatitis A vaccine combined with an inactivated enterovirus 71 vaccine [131]. A phase 4 study demonstrated the safety of both live attenuated and inactivated hepatitis A vaccines for HBs-Ag-positive participants [132]. A literature review concluded that hepatitis A vaccination is safe for post-transplantation patients, and AEFIs have typically been rated as mild or moderate [133].

5.5.5 Hepatitis B

Hepatitis B vaccination has shown to be safe and well-tolerated in infants of HBsAg-positive mothers, children undergoing intensive induction chemotherapy, children with haematological malignancies, liver-transplanted children, people living with HIV or diabetes mellitus and in patients receiving methadone maintenance therapy [134-140]. A literature review concluded that hepatitis B vaccination is safe for post-transplantation patients, and AEFIs have typically been rated as mild or moderate [133]. Intradermal hepatitis B vaccination in inflammatory bowel disease patients [141] or in patients living with HIV [142] also showed a good safety profile. A hepatitis B vaccine produced in Bangladesh, showed to be non-inferior to the well-known licensed Engerix-B vaccine [143].
The safety of a tri-antigenic hepatitis B vaccine was shown in healthy adults [144-146]. A good safety profile was also found for a hepatitis B vaccine containing CpG adjuvant in patients receiving haemodialysis [147]. Furthermore, pregnancy outcomes appear to be similar to those

in women who received HepB-CpG or HepB-alum prior to pregnancy [148]. In a phase 2 trial, the safety of the de novo designed liposome-based nanoparticle lipopeptide vaccine εPA-44, was comparable to that of a placebo [149]. Also, a newly formulated recombinant hepatitis B vaccine was shown to be equally safe as the registered control vaccine [150].

5.5.6 Rotavirus

A retrospective cohort study showed that inadvertent administration of the rotavirus vaccine in infants of women with inflammatory bowel disease did not result in more AEFIs [151]. In addition, data from a cohort study suggest that rotavirus vaccination is not associated with development of inflammatory bowel disease [152]. A large cohort study did not provide evidence that rotavirus vaccination prevents coeliac disease and type 1 diabetes, nor it is associated with increased risk, delivering further evidence of rotavirus vaccine safety [153].
A review concluded that administration of rotavirus vaccine is also safe for age-eligible preterm children and unvaccinated children in the same neonatal ward [154].
Several studies did not identify serious adverse effects for Rotarix and Rotateq [15, 155-163]. Rotarix was also well-tolerated in vulnerable medical risk infants, although co-administered with routine vaccines it was associated with a higher risk of (mostly gastrointestinal) AEs [164]. Two studies confirmed the known increased risk of intussusception post-vaccination with Rotarix, mostly within 7 days post dose 1 [165, 166]. A case report described an immunocompromised infant who suffered from persistent rotavirus symptomatic diarrhoea after receiving the rotavirus vaccine, and was found to be infected with the vaccine strain [167]. This publication attempts to contribute to the discussion of those diseases that need to be incorporated into a screening program, since an early diagnosis permits clinicians to withhold live attenuated immunisation.
A good safety profile was also demonstrated for several new rotavirus vaccines like Rotavac and Rotasiil [155, 158, 168], and a second generation Rotavin-M1 vaccine [169].
New vaccines, such as a liquid porcine circovirus-free rotavirus vaccine [170], a trivalent live human-lamb reassortant rotavirus vaccine [171, 172], and a non-replicating rotavirus vaccine developed using virus-like particle technology, were shown to be well-tolerated.

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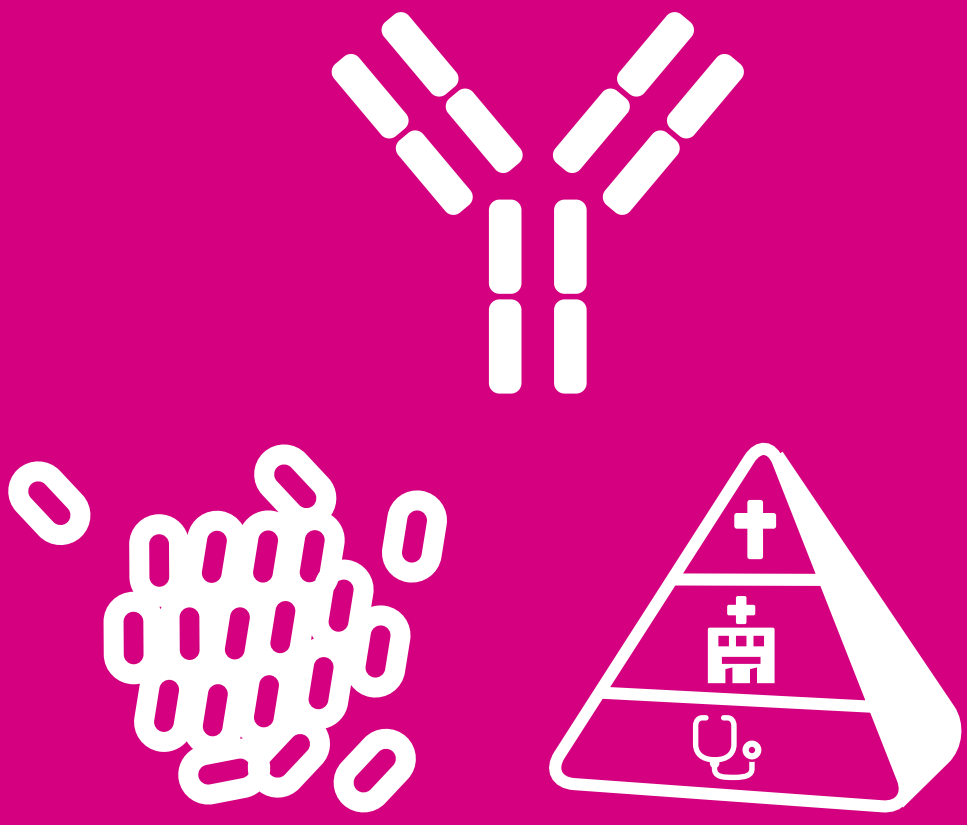
* RIVM publication.

6
Current National Immunisation Programme



6.1 Diphtheria

D.L. van Meijeren, M.J.C. van den Beld, D.W. Notermans, H.E. de Melker

6.1.1 Key points

- In the Netherlands, no diphtheria cases were reported in 2021 and in 2022 up to and including April.
- In 2021 and in 2022 up to and including April, the RIVM received 9 and 2 *C. diphtheriae* or *C. ulcerans* strains for confirmation testing, respectively. None of these strains tested positive for exotoxin production.
- Four countries in the Region of the Americas reported a total of 38 confirmed diphtheria cases, among which 16 fatal cases in 2021, up to and including week 42.

6.1.2 Tables and figures

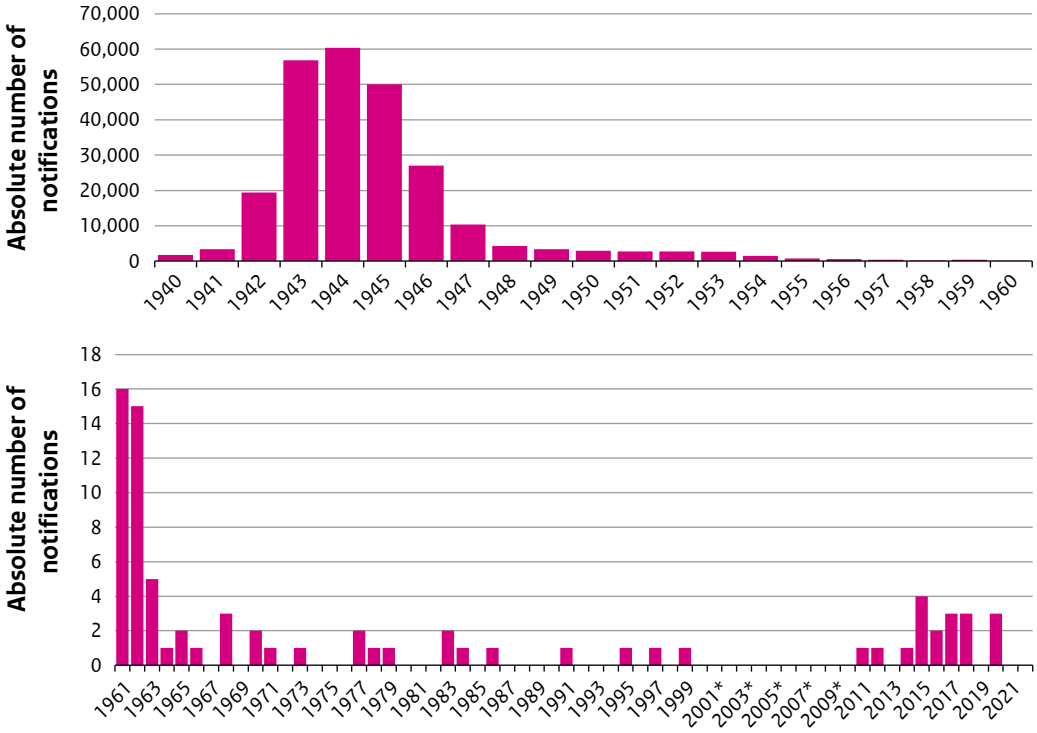


Figure 6.1.1 Yearly number of diphtheria notifications for 1940-1960 (above) and 1961-2022* (below). Until 2009, only infections with *C. diphtheriae* were notifiable. From 2009 onwards, infections with *C. ulcerans* are notifiable, too.

* Notifications up to and including April are included.

Table 6.1.1 Laboratory results of confirmation testing for *C. diphtheriae* and *C. ulcerans* at RIVM for 2016-2022*. Date of arrival at the laboratory is used for year of classification.

	Corynebacterium diphtheriae				*Corynebacterium ulcerans*			
	PCR		Elek		PCR		Elek	
	Negative	Positive	Positive	Non-conclusive	Negative	Positive	Positive	Non-conclusive
2016	12	1	1	n/a	2	1	1	n/a
2017	9	1	1	n/a	0	2	2	n/a
2018	9	0	n/a	n/a	2	3	3	n/a
2019	7	0	n/a	n/a	7	0	n/a	n/a
2020	3	1	1	n/a	5	1	0	1
2021	7	0	n/a	n/a	2	0	n/a	n/a
2022*	1	0	n/a	n/a	1	0	n/a	n/a

* Strains that were sent to the RIVM up to and including April 2022, are included.

6.1.3 Epidemiology

No diphtheria cases were reported in 2021 or in 2022 up to and including April (Figure 6.1.1).

6.1.4 Pathogen

In 2021, RIVM received seven *C. diphtheriae* and two *C. ulcerans* strains isolated from wounds or ulcera. In 2022, for the period up to and including April, the RIVM received one *C. diphtheriae* strain from a throat swab and one *C. ulcerans* strain from unknown material. Out of the nine strains in 2021 and two strains in 2022, no positive test results regarding exotoxin production were found. See Table 6.1.1 for details on laboratory results for the respective strains. In 2021, Elek tests of previous years were performed again. Therefore, the results in the table may deviate from the results published in previous years.

6.1.5 International developments

The COVID-19 pandemic has reduced the quality and timeliness of both the epidemiologic and laboratory surveillance of diphtheria in the Region of the Americas, which contributed to the occurrence of outbreaks [1]. Up to and including week 42 of 2021, four countries in the region reported a total of 38 confirmed diphtheria cases, among which 16 fatal cases. It concerned Colombia (1 case, 1 death), Brazil (1 case), the Dominican Republic (18 cases, 12 deaths) and Haiti (18 cases, 3 deaths). The majority of cases and deaths were 1-14 years of age. The cases for which vaccination data was reported, all had an incomplete vaccination history [2].

A decline from 94% to 84% in the vaccination coverage for the third dose of diphtheria, tetanus, and pertussis (DTP3) vaccine was observed in the Region of the Americas between 2010 and 2020. This decline is attributed to several reasons, such as natural disasters, increasing urbanisation, political reasons, and growing inequities in access to healthcare.

Moreover, the COVID-19 pandemic has accelerated the decline even further [1]. Because vaccination coverage declined in most countries of the region, the occurrence of cases in any country in the region is considered to pose a risk to the other countries [2, 3].

6.1.6 Literature

1. Pan American Health Organization (PAHO). XXVI Meeting of PAHO's Technical Advisory Group (TAG) on Vaccine-Preventable Diseases - Vaccines bring us closer. Washington D.C. USA: PAHO/WHO; 2021 14-16 July 2021.
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6.1.7 RIVM publications

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6.2 *Haemophilus influenzae* disease

A. Steens, L.J. Visser, N. Plantinga, W. Freudenburg-de Graaf, R. Mariman, H.E. de Melker, N.M. van Sorge

6.2.1 Key points

- The Hib incidence had increased in 2020; in 2021 this increase was still present, with an incidence of 0.39 per 100,000 inhabitants. The increased incidence in 2020-2021 was seen in all age groups. In the first 4 months of 2022, 21 cases occurred already, compared to 13 in 2020 and 18 in 2021.
- The incidence among children <5 years old has been increasing since 2012 and continued to increase in 2021. The increase seems not due to a decrease in vaccine effectiveness (VE) against disease; this VE estimate is still above 90%.
- An increase in an emerging subclade has been observed since 2012, but the VE against disease by this subclade is similar to the VE against disease by other clades.
- Little antibiotic resistance/decreased susceptibility was observed in 2020-2021, and it is unlikely that antimicrobial resistance plays a (important) role in the observed increase.
- There has been a schedule change from 3+1 to 2+1 in 2020. In the period 2020 up to and including April 2022, none of the cases that were vaccinated with the 2+1 schedule could have been prevented if vaccinated with the former 3+1 schedule according to the age at disease onset.
- Out of 79 Hib cases with known outcomes from 2021-May 2022, 3 died (one <5 years old, two 65+; the child had been sufficiently vaccinated).
- Invasive disease caused by non-typeable *Haemophilus influenzae* (NTHi) or other non-b serotypes has still been lower than before the COVID-19 pandemic, except for serotype f disease. In the first 4 months of 2022, 18 Hif cases were reported, all among older adults. Generally, this serotype is uncommon (<20 yearly pre-COVID). Genetic data showed that the Hif cases were unrelated to each other.

6.2.2 Tables and figures

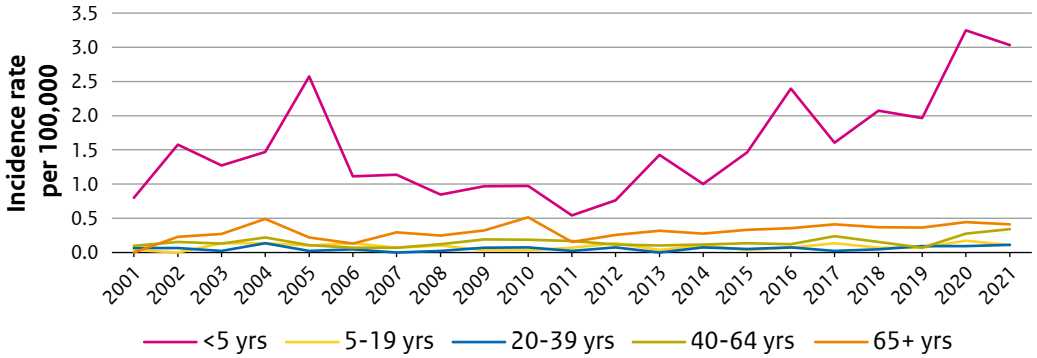

Figure 6.2.1 Age-specific incidence rate of *Haemophilus influenzae* type b (Hib) invasive disease, 2001-2021.

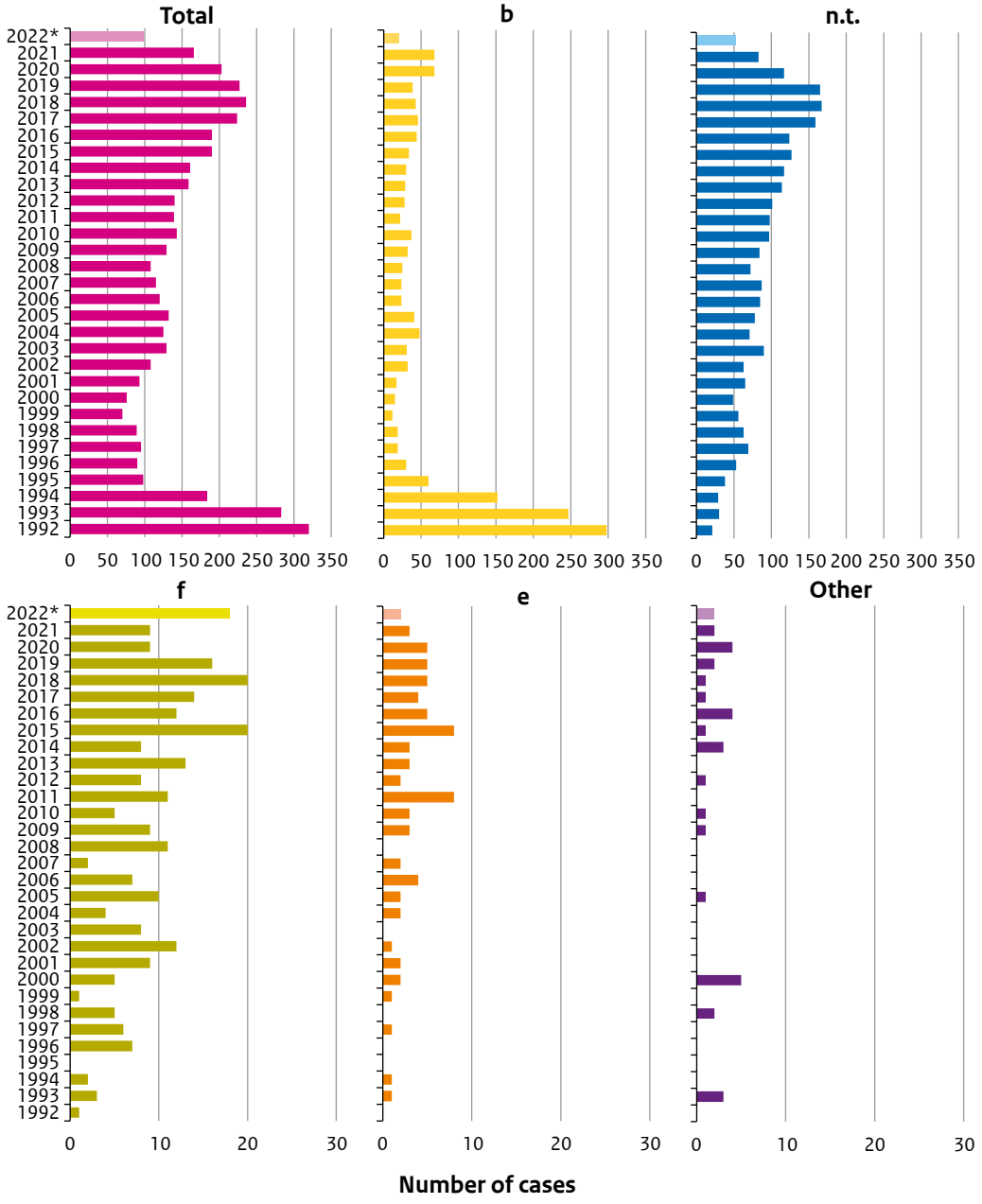

Figure 6.2.2 Number of *Haemophilus influenzae* invasive disease cases per serotype, 1992-2022*.

* Up to and including April.

Note: the 'Other' category includes serotype a and serotype d.

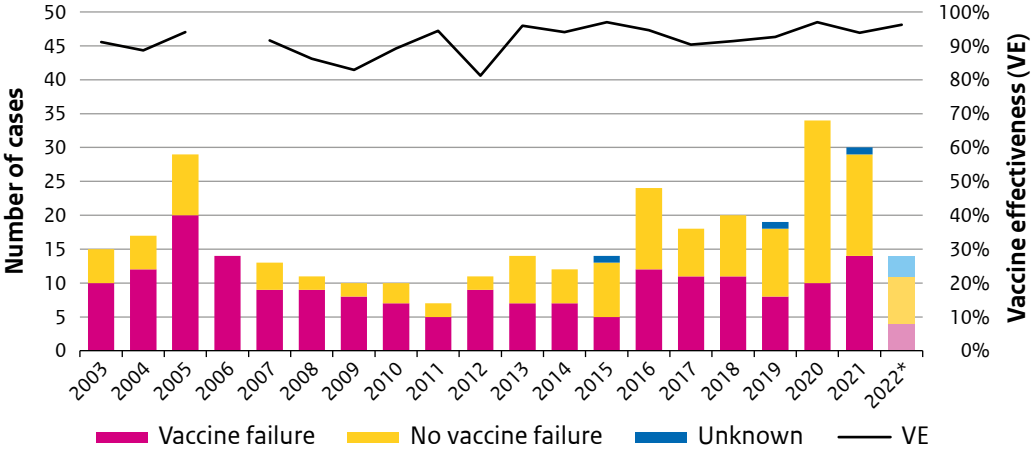

Figure 6.2.3 Number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after 1 April 1993) by vaccination status and estimated vaccine effectiveness, 2003-2022*.

* Up to and including April.

Note: in 2006, VE could not be estimated because 100% of the cases were vaccinated.

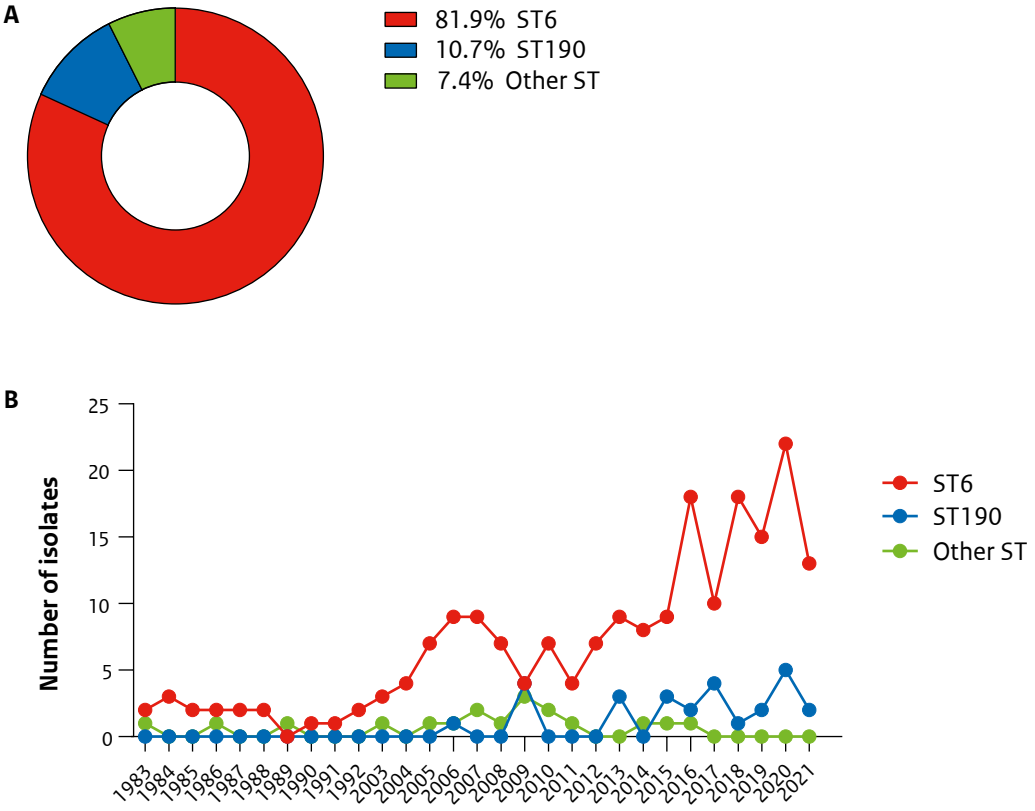

Figure 6.2.4 Classical multi locus sequence type (MLST) distribution of invasive Hib isolates for children aged <5 years (n=242). (A) Distribution of sequence types (ST) in the Netherlands. (B) The number of isolates with the different STs per year. Note that the data presented to the left of the vertical line, describe the years prior to vaccine introduction, and on the right for the period 2003-mid 2021. Data of 2021 is incomplete; only the first 6 months of the year were included.

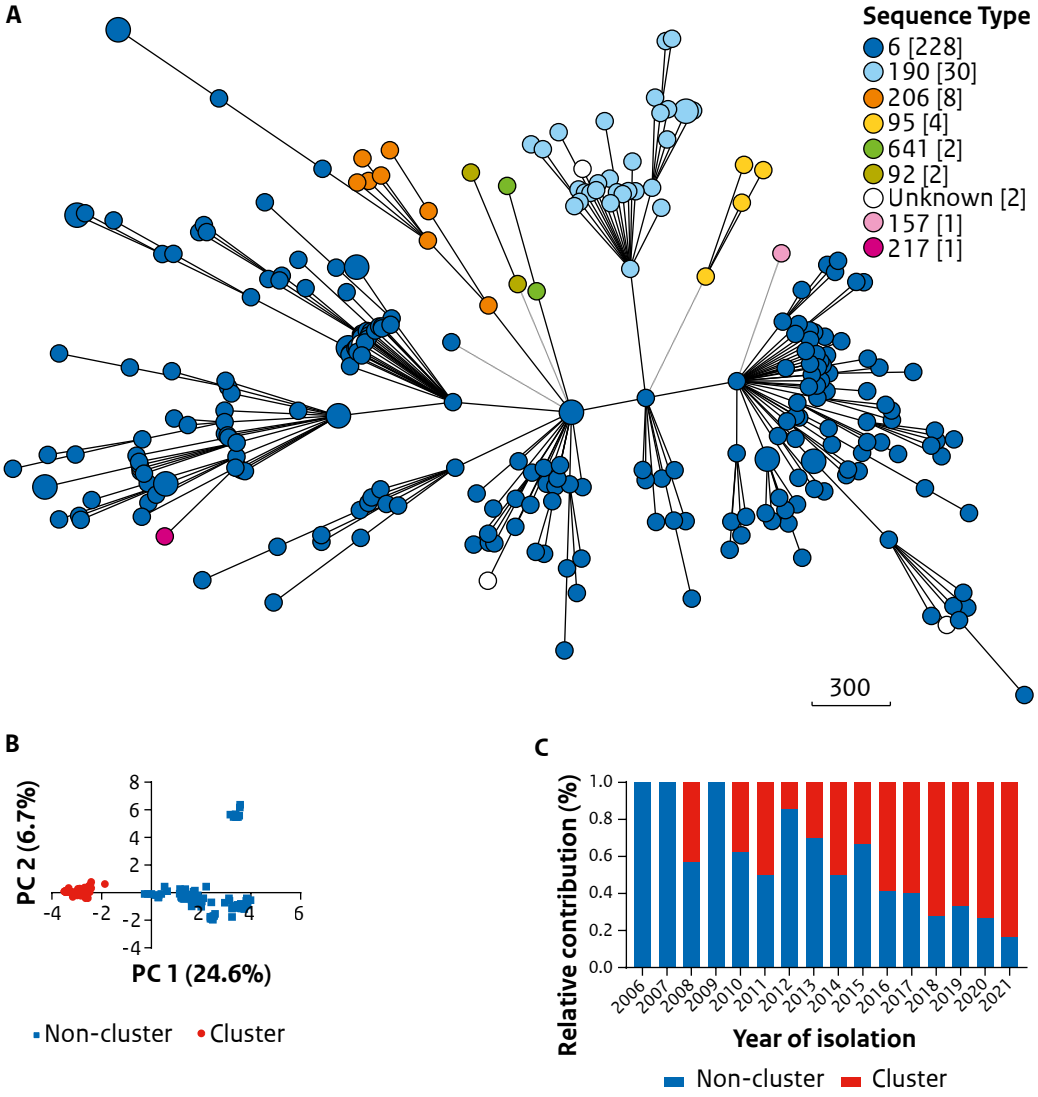

Figure 6.2.5 Genetic relationship between 270 invasive and 11 carriage Hib isolates. (A) Whole genome MLST (wgMLST) based on 1599 core genes visualised using minimum spanning tree (MST) in GrapeTree. Each node of the minimum spanning tree based on wgMLST represents a single Hib isolate. The length of the lines between isolates represents the number of different genes, node colours represent sequence type (ST). The number between brackets in the figure legend represents the number of isolates for each ST. (B) Unsupervised principal component analysis (PCA) on the wgMLST data of ST6 isolates showing clusters along components 1 and 2. (C) Relative contribution (percentage) of red and black cluster to the total number of ST6 isolates analysed that year.

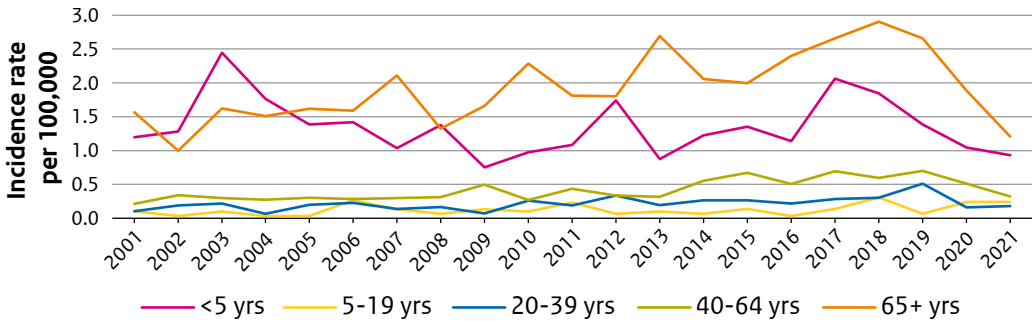

Figure 6.2.6 Age-specific incidence of non-typeable *Haemophilus influenzae* disease, 2001-2021.

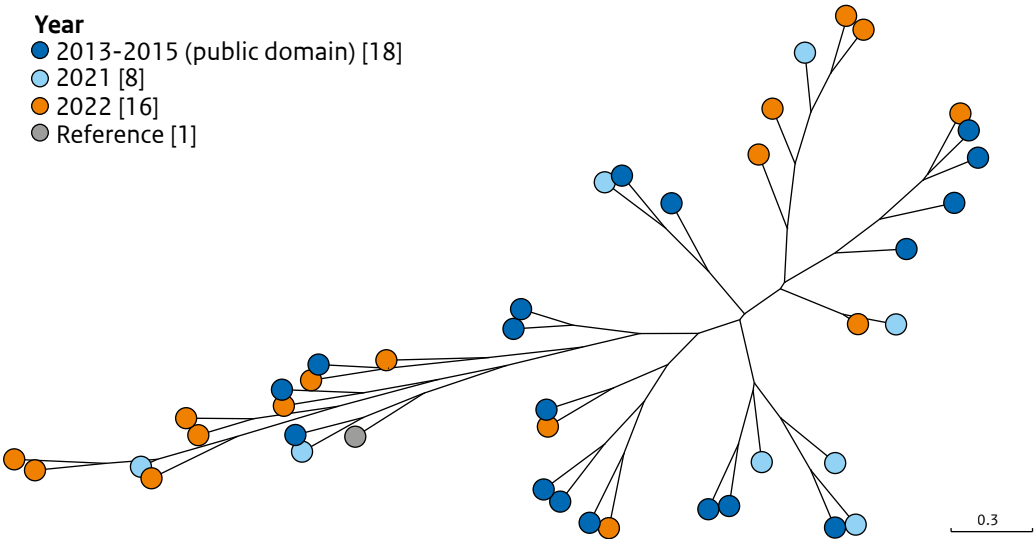

Figure 6.2.7 Genetic relationship between 42 invasive *Haemophilus influenzae* serotype f isolates based on SNP analysis using Snippy. (A) Maximum-likelihood tree (MLT) based on SNP analysis was calculated using IQTree (GTR+G4 model) and is visualised in GrapeTree. Each node of the MLT represents a single Hif isolate. The length of the lines between isolates represents the number of SNPs. The dark blue (2013-2015) and light blue (2021) nodes represent stable years. The orange nodes reflect isolates from the peak year 2022.

Table 6.2.1 Distribution of antimicrobial susceptibility, susceptibility with increased exposure and resistance of invasive Hib isolates registered in ISIS-AR of 2020-2021 according to the EUCAST clinical breakpoints and/or expert rules. Note that many results are missing (numbers indicated in the table) as not all laboratories report their susceptibility results to ISIS-AR and for some antimicrobials, laboratories may only test on indication. The indicated percentage is determined for the isolates with available result on the antimicrobial susceptibility tests.

	Susceptible	Area of technical uncertainty	Susceptible at increased exposure	Resistant	Missing
Beta-lactam antibiotics[1]					
Ampicillin	64 (97%)			2 (3%)	32
Augmentin (IV)	73 (100%)			0	25
Cefuroxim (IV)	63 (94%)	4 (6%)[2]		0	31
Cefotaxime	63 (100%)			0	35
Ceftriaxone	70 (100%)			0	28
3rd generation cephalosporins (cefotaxime, ceftriaxone)	77 (100%)			0	21
Other antimicrobials					
Ciprofloxacin	55 (100%)				43
Ofloxacin	10 (100%)				88
Fluoroquinolones (ciprofloxacin and/or ofloxacin)	59 (100%)				39
Cotrimoxazol	51 (78%)		1 (2%)	13 (20%)	33
Doxycycline[3]	60 (95%)			3 (5%)	35

[1] For all beta-lactam antimicrobials, the result is set to negative if a negative result on the penicillin screening test was observed. The screening test was performed for 56 isolates, of which 54 had a negative result.
[2] Area of technical uncertainty (ATU) is relevant only if the benzylpenicillin 1 unit disk screen is positive (inhibition zone). For 75% of the isolates, no penicillin screening-test had been performed. 25% of isolates was penicillin resistant.
[3] Derived from testing result for tetracycline according to the expert rules.

6.2.3 *Haemophilus influenzae* serotype b (Hib)

Invasive Hib disease can present itself as epiglottitis, meningitis, sepsis, pneumonia, and septic arthritis. To confirm an infection with Hib, the isolate needs to be serotyped. In the Netherlands, all *Haemophilus influenzae* (Hi) isolates from invasive infections are submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) for serotyping. Only Hib is vaccine preventable and notifiable. For non-b Hi infections, there is only limited case information available.

6.2.3.1 Hib epidemiology

6.2.3.1.1 Incidence

Hib vaccination was introduced in the Netherlands in April 1993. After an initial decrease following vaccination, the number of Hib cases fluctuated around 30 cases per year with a maximum of 48 cases in 2004 (range in 1996-2019: 12-48, Figure 6.2.2). In 2020, 68 Hib cases were observed, which translates to an incidence of 0.39 per 100,000 inhabitants. In 2021, again 68 Hib cases were observed. The cases are not clustered but observed scattered throughout the country. These numbers are striking as the country experienced various lockdown periods from March 2020 and in 2021 due to the control measures for the COVID-19 pandemic.
The control measures coincided with a decrease in the incidence of most other respiratory infectious diseases, including disease caused by other Hi types [1]. Most control measures have been lifted since mid-March 2022. In the first 4months of 2022, 21 Hib cases already occurred, compared to 13 in 2020 and 18 in 2021.
The increased incidence in 2020-2021 was seen in all age groups (Figure 6.2.1). The relative increase was largest in those aged 40-64 years (incidence rate ratio (IRR) 2020-2021 versus 2016-2019: 2.1) and smallest among those aged 65 years and older (IRR 1.1). Among children below the age of 5, the IRR was 1.6. In the first four months of 2022, already fourteen cases occurred below the age of 5 years; in 2020-2021 six cases occurred in the same period. The increase among young children has been developing since 2012 (Figure 6.2.2). As described in section 6.2.3.1.2 and in [2], the increase seems not to be due to a decrease in vaccine effectiveness (VE) against disease. The VE estimate against invasive disease is still above 90% (see below). Except for France, where an increase is observed among <5-year-olds, no other (European) country has reported an increase in the Hib incidence (personal communication EMGM, 25 November 2021).
Disease outcome is known for 63 (93%) invasive Hib cases in 2021 and 16 (76%) cases in 2022. Of these, three patients died in 2021 (one aged <5 years, two aged 65+ so not eligible for vaccination; the child was sufficiently vaccinated) and one in 2022 (adult; not eligible for vaccination). In the pre-pandemic period, this was 0 or 1 yearly although outcome data was not available for some cases (69% available data in 2016-2019).

6.2.3.1.2 Vaccine history and vaccine effectiveness

In 2021 and 2022 (up to and including April), 30 and 14 Hib cases, respectively, were reported among cohorts eligible for vaccination (born from 1 April 1993 onwards; Figure 6.2.3). Out of the 39 cases with a known number of vaccine doses, 20 (51%) were unvaccinated, one case was insufficiently vaccinated and 18 (46%) were sufficiently vaccinated (i.e., received at least 2 vaccinations with at least 2 weeks between the second vaccination and date of diagnosis; 14 in 2021 and 4 in 2022). The absolute number of sufficiently vaccinated cases was slightly higher than in previous years (eight to twelve annually in the previous five years) but the proportion that was sufficiently-vaccinated was similar to before. The estimated VE of Hib vaccination using the 'screening method' (see Appendix 1) was 94% (95% CI: 87-97) in 2021 (Figure 6.2.3). The overall VE for 2003-2022 (up to and including April) was 93% (95% CI: 91-94).

Most vaccinated cases in 2021-22 (n=14/18) were younger than 5 years and seven (39%) had an underlying medical condition, of whom at least two with a known immune disorder. No premature cases were notified. Of the seventeen unvaccinated cases in 2021-22 with available information about the opinion about vaccination, four reported to be Reformed orthodox, one to be a follower of anthroposophy, and eight to be generally critical to vaccination. The unvaccinated children were between 0 and 4 years of age.
In 2019, the used product in the NIP has changed from a tetanus toxoid conjugated vaccine (Infanrix hexa; DT3aP-HBV/Hib) to a vaccine using the *Neisseria meningitidis* outer membrane protein complex with the Hib antigen (Vaxelis; DT5aP-HBV/Hib). The recommendation was that children finished their schedule with the same product as received earlier. Still, it is known that 6.5% of the children born in 2018 had received two different vaccines (most often, started with Infanrix hexa, finishing with Vaxelis; personal communication Nienke Voerman, Department for Vaccine Supply and Prevention Programmes, RIVM). Although numbers per birth cohort are small, we determined whether there were indications that a combined schedule would lead to a lower effectiveness. We therefore asked the respective municipal health services to report the product name in addition to the regular vaccination history that is notified through Osiris for the cases born in 2018. Out of the fifteen included cases, eight had received Infanrix hexa only, six had received only Vaxelis, and one case had received the primary series with Infanrix hexa and the booster with Vaxelis (6.7%). On the basis of these data, we concluded that a combined schedule was not a clear explanation for the vaccine failures.
In January 2020, the standard vaccination schedule for Hib was changed from a 3+1 schedule at 2, 3, 4 months to a 2+1 schedule at 3 and 5 months. Since then, seven cases occurred in infants aged <5.5 months (used as cut-off for being protected through vaccination in the 2+1 schedule). All these cases were younger than 3.5 months and therefore younger than the cut-off for protection with the 3+1 schedule. This means that in the period 2020 up to and including April 2022, no cases occurred that could have been prevented through vaccination with the former schedule.

6.2.3.2 Genetic relationship of Hib isolates

We updated the genotypic characterisation of clinical Hib isolates which was presented in the 2021 report of the NIP [3]. The aim was to identify genetic changes that may explain the changes in Hib epidemiology. Invasive Hib isolates (n=270) were obtained from the collection of the Netherlands Reference Laboratory of Bacterial Meningitis (NRLBM) as well as eleven isolates from carriage surveillance studies in children in 2009 and 2018-2019. The invasive isolates consisted of 20 randomly selected isolates from children in the pre-vaccine era (1983-1992), 222 isolates from children in the vaccine era (2003-2021) and 23 isolates from older individuals (2021). All isolates were subjected to whole-genome-sequencing (WGS) and analysed using various approaches.
Multi locus sequence typing (MLST) revealed that Sequence Type (ST)6 and ST190 (both clonal complex (CC)-6) are dominant within the invasive Hib population in the Netherlands; 82% of the isolates belonging to ST6 (Figure 6.2.4A). The distribution of STs remained stable over the past decades (Figure 6.2.4B), and there was no geographical clustering. A higher resolution analysis of the WGS data using whole-genome MLST (wgMLST) showed substantial genetic

variation within the Dutch ST6 Hib population as visualised in the minimum spanning tree (Figure 6.2.5A), with an average distance of twenty genes between two neighbouring isolates. In-depth analysis of the dominant ST6 isolates using Principal Component Analysis (PCA) on the binary transformed cgMLST data revealed three distinct clusters of isolates (Figure 6.2.5B). One cluster has been gradually increasing and currently comprises over 75% of invasive Hib ST6 isolates (red cluster in Figure 6.2.5C). This cluster was first observed in 2008 but has increased since 2012. As the relative and absolute increase coincides with the increase seen in children <5 years old, this may suggest that the increase is (partly) caused by the expansion of a more successful subclade within ST6. We did not observe clustering of age, invasiveness, or capsule duplication (a known Hib virulence factor) with this emerging subclade. Furthermore, the vaccine effectiveness of this emerging subclade is not affected (VE≥93%), suggesting this clone is not a vaccine escape variant. Genome-wide association studies to elucidate genetic drivers of the subclade are currently ongoing.

6.2.3.3 Antibiotic susceptibility

We determined whether the following hypothesis could play a role in the increase in Hib incidence: the presence of a substantial/increased proportion of antimicrobial non-susceptibility may lead to more treatment failure of less severe Hib infections which would then more often develop into invasive infections. As a pilot, we therefore determined the proportion of Hib isolates that were non-susceptible for different antimicrobials in 2020-November 2021. All available isolates of invasive Hib infections in that period were selected (n=124). Data from the NRLBM was probability-matched with data from ISIS-AR [4]. ISIS-AR is the infectious disease surveillance information system for antibiotic resistance. The majority of Dutch medical microbial laboratories voluntarily sends pseudonymised data of the cultured isolates that are tested for antimicrobial susceptibility to ISIS-AR. Overall, 98 isolates (79%) could be matched and included in the analysis. Isolates were categorised based on results of the disk diffusion method or on minimal inhibiting concentrations (MICs) as susceptible (S), susceptible at increased exposure (I) or resistant (R) according to the EUCAST clinical breakpoints [5] and/or expert rules [6]. In cases where the isolate was tested susceptible to (benzyl)penicillin, susceptibility was assumed to all beta-lactam antibiotics according to expert rule 1. Information on the beta-lactam test was not available.
Overall, resistance to beta-lactam antibiotics was rare (see Table 6.2.1), with only 2 isolates resistant to (benzyl)penicillin and therefore to ampicillin and amoxicillin. Those two isolates were both sensitive to augmentin and to ceftriaxone or cefotaxime (whichever tested).
More resistance was found for cotrimoxazole (n=13, 20%) and doxycycline (n=3, 5%). Amoxicillin, augmentin and doxycycline, but not cotrimoxazole, are routinely used for treatment of (mild) pneumonia; doxycycline is not used in children <6 years old. Cotrimoxazole and doxycycline are otherwise not used in (empirical) treatment of invasive infections; third-generation cephalosporin (ceftriaxone or cefotaxime) or, in case of known susceptibility, amoxicillin is used [7]. These results do, therefore, not point towards substantial antimicrobial resistance as explanation for the increase in invasive Hib disease in 2020-2021, and no further analysis over a longer time period is performed.
In addition to the phenotypical results, a genotypical analysis on antimicrobial resistance was performed using ResFinder on the isolates of 2020-2021 that had WGS results available.

Of these 66 isolates, 50 were also present in the ISIS-AR database. A beta-lactamase gene (bla-TEM1B) was found only in the two isolates that were reported (benzyl)penicillin resistant in the phenotypic analysis. This finding is consistent with the phenotypic susceptibility to augmentin of these two isolates. ResFinder is a bio-informatic tool that was not developed specifically for resistance detection in *Haemophilus influenzae*, and species-specific mechanisms for resistance cannot be detected using this tool.

6.2.3.4 Summary of Hib changes and possible explanations

An increase in the Hib incidence has been observed since 2012 in the group aged <5 years and since 2020 among all age groups. Possible explanations are I: an increased number of susceptible individuals, II: increased exposure or III: increased disease after exposure. Based on the epidemiology of other Hi serotypes, we do not expect a change in notification behaviour and surveillance.

I, concerning an increased number of susceptible individuals: The vaccine coverage in the population has been stable and high. However, the number of susceptible individuals may have increased over time due to low Hib transmission since vaccine introduction in the NIP (1993) and thereby reduced opportunities to boost (natural or vaccine-induced) immunity during carriage episodes. In last years' NIP report [3] it was shown from the PIENTER-3 study, which was performed in 2016/17, that the geometric mean concentration (GMC) of Hib-specific antibodies is low among those born before 1993. It was also shown that the GMCs of those aged 2-6 years were slightly lower compared to those aged 6-20 years. Note that these younger age groups were offered the hexavalent vaccine, while the 6-20 age groups were offered a pentavalent vaccine in the NIP. Lower GMCs may affect the susceptibility for colonisation and disease.

II, concerning increased exposure: although there have likely been behavioural changes because of the control measures against COVID-19, these are thought to have led to decreased transmission instead of increased exposure at societal level. Exposure within families could have increased due to more shared time at home during the lockdown. Changes in colonisation and transmission due to pathogen changes or a decreased VE against colonisation would also lead to increased exposure. Colonisation is, however, difficult to measure in countries with Hib vaccination in the NIP. Our pilot among Hi carriage isolates from the OKIDOKI-5 study (2018) [8] did not find Hib colonisation in children and <1% (3/330) colonisation among parents. Whether the identified ST6 subclade is a better transmitter/coloniser is yet unknown. It is known that higher titres are needed to prevent carriage than to prevent disease [9], but we do not have data to determine whether the decreased titres in PIENTER-3 as mentioned above may be related to increased colonisation or transmission in that age group.

III, concerning increased disease after exposure: there is an increase in the absolute number of vaccine failures, but the proportion of vaccinated cases is stable; the VE against invasive disease including against the ST6 subclade has been stable and sufficiently high (>90%). The increased incidence may, however, be the result of pathogen changes resulting in increased invasiveness. The lack of colonisation data unfortunately precludes a determination

of the invasive capacity of the different strains. Increased numbers of severe infections due to failure of antibiotic treatment of respiratory infections seem unlikely. Further genetic analysis into the identified subclade among ST6 is currently ongoing.

6.2.4 *Haemophilus influenzae* disease caused by non-b serotypes

6.2.4.1 Non-typeable Hi (NTHi) disease

In 2021, 83 cases of invasive NTHi disease were reported, resulting in an incidence of 0.47 per 100,000 (Figure 6.2.6). This number was lower compared to 2020, the first COVID-19 year (n=117), and ~50% lower compared to the pre-COVID-19 period (165 in 2019 and 167 in 2018; Figure 6.2.1). The decrease is likely a result of the COVID-19 control measures. The monthly numbers of NTHi cases have been low for the entire period of April 2020-October 2021, but in November-December 2021, monthly numbers reached pre-COVID-19 levels again. In the first four months of 2022, 53 cases of NTHi disease have occurred; the monthly numbers of cases are back at pre-COVID-19 levels.

As observed previously, the incidence has been highest among persons aged 65 and over (1.2 per 100,000; n=41) and children aged under five years (0.93 per 100,000; n=8) (Figure 6.2.6).

6.2.4.2 Disease caused by other Hi serotypes

In the first four months of 2022, 18 Hi cases with serotype f (Hif) were reported among older adults; one of them had a reported COVID-19 coinfection. This serotype is generally uncommon with nine cases in 2020 and 2021 and fewer than twenty cases per year pre-COVID (Figure 6.2.2). To possibly explain this sudden rise in invasive Hif disease, WGS was applied to isolates from 2021 up to and including March 2022 (n=24). Additionally, WGS data from eighteen Dutch invasive isolates from 2013-2015 that are available in the public domain were also included in the analysis to give context to the invasive Hif cases from 2022. As shown in Figure 6.2.7, we found substantial genetic variation between the strains from 2022 (40-60 SNPs) indicating that there was no common source of these cases. Whether the increase is related to the recent lockdown periods because of the COVID-19 pandemic, and thereby decreased exposure and immunity, is unknown. We are not aware of other countries reporting a similar increase in Hif disease.

For other Hi serotypes, few cases have been observed in 2021 and during the first four months of 2022. Three cases with Hi serotype e (Hie) invasive disease were observed in 2021 and two in 2022. Two Hi serotype a (Hia) cases were observed in 2021 and in 2022. No Hi serotype d disease has been found since 2017.

6.2.5 (Inter)national developments

6.2.5.1 Hib

In France, an increase in Hib incidence was observed among children aged <5 years. France introduced Hib vaccination in 1992, using a 3+1 schedule, but changed in 2013 to a 2+1 schedule (vaccinations at 2 and 4 months of age), with a coverage of 95% (in 2017). Surveillance data for 2017-2019 were analysed and combined with seroprevalence data [10]. The number of Hib cases increased during the study period to 25 cases in 2019, with a total of 56 isolates.

MLST data showed that 98% of all the Hib isolates belonged to CC-6. 66% of the cases were aged <5 years (n=37). Nine cases were completely vaccinated with a Hib-containing vaccine. Furthermore, fifteen cases had received one or two doses; thirteen were unvaccinated. All 24 cases that had at least been vaccinated once, had received the 2+1 schedule. Their anti-PRP IgG levels, i.e., antibodies against the main virulence factor of Hib, were all <1 µg/ml. For comparison, the authors determined the seroprevalence of anti-PRP IgG in residual sera from children born before 2013 (n=130) and from children born from 2013 onwards (n=102); sera were categorised according to the age of the child. Although the median anti-PRP IgG levels were slightly lower in the 2+1 group compared to the 3+1 group, this difference was only statistically significant for those aged 2 years, at which the median anti-PRP concentrations were 2.9 and 0.58 for the 3 + 1 and 2 + 1 groups, respectively. The proportion of children reaching the putative threshold for short-term protection (≥0.15 µg/ml) and long-term protection (≥1 µg/ml) was higher for the 3+1 than the 2+1 group, but the difference was not statistically significant. For both groups at all investigated ages, the levels were above 80%. The authors concluded that the 2 + 1 schedule seemed to be associated with lower levels of anti PRP IgG and levels may not be high enough to ensure long-term protection.

Several reviews have recently been published, which describe the different Hib-containing vaccines and their impact on the global incidence of Hib [11-13]. One showed that >90% of the countries have implemented Hib vaccination in their NIP [11]. Most countries use a vaccine where PRP is conjugated to tetanus toxoid (like Infanrix, which the Netherlands used before 2019), but *Neisseria meningitidis* outer membrane protein complex vaccines are also used, as currently included in the Netherlands (Vaxelis). It was shown that the immune responses differ between the vaccines and used schedules, but all scenarios induce high impact on the control of invasive Hib infections. The effect of Hib vaccination on carriage is inconsistent; while one review indicates the direct effect against Hib carriage and the accompanied indirect protection [12], the other concludes that Hib carriage seems to be less frequent, but data is still needed to fully evaluate the impact of vaccination [11]. The generally increased incidence (except for the COVID19 years) in non-b *Haemophilus influenzae* disease, as we have observed in the Netherlands, has also been seen in other countries [11]. Whether these changes are induced by the use of Hib vaccination or are the result of natural, temporal variations, is unknown.

A recent systematic review and meta-analysis determined the global burden of Hib meningitis [14]. Based on 33 studies, the pooled case-fatality rate was 11% (95%CI 7-17), but this differed per region. The lowest case-fatality rate was found in Europe (4%, 95%CI 2-10). Before the COVID-19 pandemic it was estimated that 7645 Hib meningitis cases and 857 deaths would occur globally in 2020.

6.2.5.2 *NTHi*

Currently, no vaccine is available against invasive NTHi disease. In a proof-of-concept, phase 2b randomised controlled trial, a candidate vaccine containing surface proteins from NTHi and *Moraxella catarrhalis* (Mcat) was tested in patients with COPD aged 40-80 years [15]. In the analysis, 279 patients were included in the NTHi–Mcat vaccine group and 292 in the placebo group. The primary analysis included 340 exacerbations (in 102,123 days) in the NTHi–Mcat

vaccine group and 333 (in 104,443 days) in the placebo group. The vaccine efficacy was estimated at 2.3% (87%CI: –18.3-11.6). Local adverse events were more common in the vaccine group than the placebo group, but general adverse events occurred at similar frequency in the two groups. Altogether, although no safety concerns were identified, the candidate vaccine did not reduce the frequency of moderate or severe exacerbations.

6.2.6 Literature

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* RIVM publication.

6.3 Hepatitis B

I.K. Veldhuijzen, K.S.M. Benschop, F. van Heiningen, A. Meiberg, J. Cremer, A.J. King, E. Op de Coul, H.E. de Melker

6.3.1 Key points

- Of the total number of 827 reported hepatitis B cases in 2021, 9% had an acute infection (n=72) and 90% a chronic infection (n=743) (type of infection unknown for 1%).
- The incidence of acute hepatitis B notifications in 2021 (n=72) decreased by 24% compared to 2020 and was 0.4 per 100,000 population.
- The number of newly diagnosed chronic HBV infections (n=743) was comparable to 2020 and amounted to 4.2 per 100,000 population.
- Among both men and women, sexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2021, genotype A continued to be the dominant genotype among acute HBV cases with 60% of 45 genotyped cases, followed by genotype F (31%). The molecular subcluster of genotype F1b identified in 2019 continued to grow, with sexual transmission as the common risk factor.

6.3.2 Tables and figures

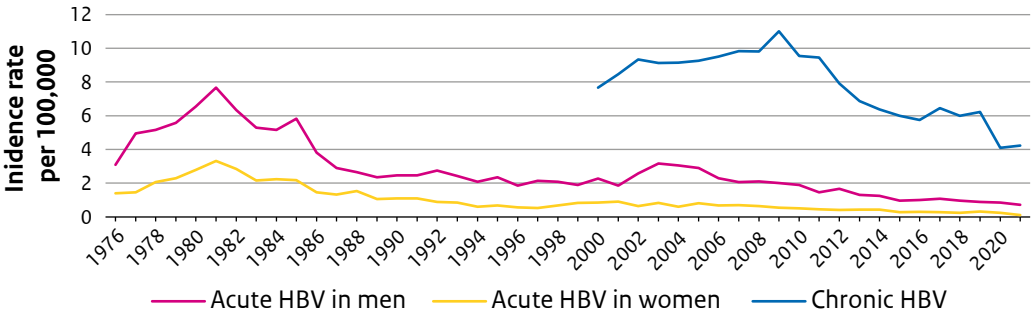

Figure 6.3.1 Incidence of acute HBV infections in men and women by year in the Netherlands 1976-2021, and chronic HBV infections 2000-2021.
Source: Osiris

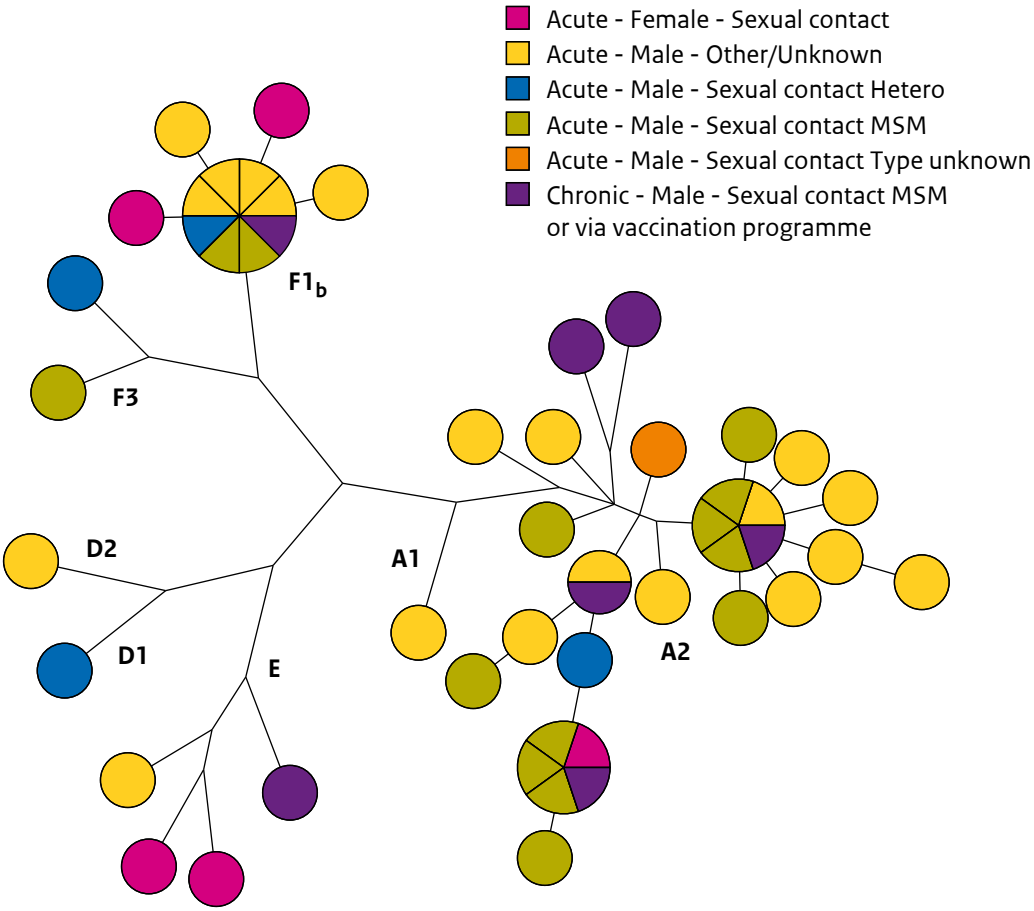

Figure 6.3.2 Optimised maximum parsimony tree based on the full length-sequence of HBV cases in the Netherlands in 2021 by reported transmission route (n=51); Letter=genotype.

Figure 6.3.3 Genotype distribution of acute HBV cases in the Netherlands from 2004 to 2021.

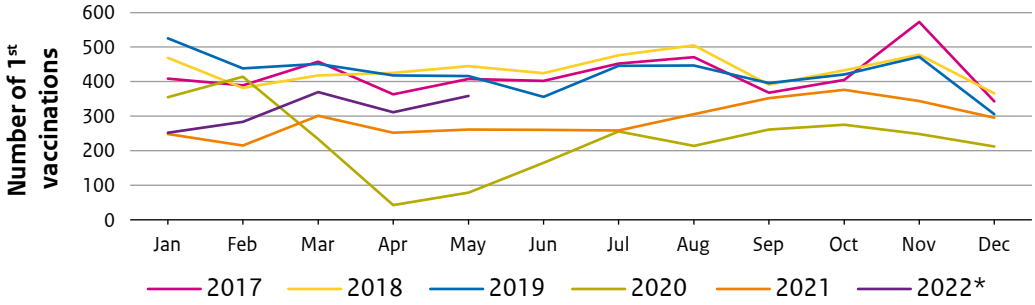

Figure 6.3.4 Number of first vaccinations per month from 2016 up to and including May 2022 in the programme for behavioural risk groups.

6.3.3 Epidemiology

In 2021, 827 cases of hepatitis B virus (HBV) infection were notified. Of these, 743 (89%) were chronic infections and 72 (9%) acute infections (11 cases with unknown status).

6.3.3.1 Acute HBV epidemiology

The number of notified acute HBV infections was 72 in 2021, a decrease of 24% compared to 2020 when 96 cases were notified. Up to and including May 2022, 29 cases of acute HBV were reported. The incidence of acute HBV notifications in 2021 was 0.4 per 100,000 population, 0.7/100,000 among men and 0.1/100,000 among women. The HBV incidence over time is shown in Figure 6.3.1. The mean age of patients with acute HBV infection was 44.5 years and was higher in men (45.9) than in women (35.9). Four cases (5.5%) of acute hepatitis B were reported among 0-19-year-olds; the youngest patient was 14 years old. Vaccination status was unknown for one of these adolescents, two were unvaccinated, and one was vaccinated.

Twenty-five (35%) patients with acute hepatitis B were admitted to the hospital in 2021, of which one in the 0-19 age group. One patient died.

In 2021, most cases of acute HBV infection (49%) were acquired through sexual contact. For 40% of the reports of acute HBV infection, the most likely route of transmission remained unknown despite source tracing. While the proportion with unknown transmission route was higher for men than women in previous years, in 2021 it was similar. Among men (62 cases), sexual contacts between MSM accounted for 26% of acute infections, and heterosexual transmission for 18%. Among women (ten cases), sexual contact accounted for 50% of cases. The majority of patients with acute hepatitis B were born in the Netherlands (86%).

6.3.3.2 Chronic HBV epidemiology

The number of chronic HBV notifications was around 1,000-1,100 per year from 2014 to 2019 (incidence 5.8-6.4 per 100,000) but declined in 2020 to 722 cases and 743 cases in 2021 (incidence 4.2 per 100,000) (Figure 6.3.1). Since chronic hepatitis B is largely asymptomatic, the number of new diagnoses is highly influenced by testing practices. The number of people tested for HBV infection annually is unknown, but the lower number in 2020 and 2021 is probably related to the COVID-19 pandemic (see 1.5.1.1).

In 2021, 91% of the chronic HBV patients where the country of birth was known were born abroad. The number of newly diagnosed chronic HBV infections in people born abroad is about 60 times higher than that of people born in the Netherlands (27 compared to 0.4 per 100,000 population). The number of notifications per country of birth fluctuates over time. In 2021, the most frequently reported countries of birth were Turkey (n=69, 9%), China (n=62, 8%), Syria (n=44, 6%), and Poland (n=37, 5%). Between 24 to 29 cases each were born in Ghana, Bulgaria, Vietnam, Morocco, and Romania. A large proportion of cases (43%) acquired chronic HBV infection through vertical transmission. In 41% of the reports of chronic HBV infection, the most likely route of transmission was unknown. Sexual contact was the source of infection for 7%, and for the remaining 9%, transmission may have occurred via other routes such as nosocomial transmission, needle stick injuries, or via injecting drug use (IDU).

In 2021, no chronic HBV infections were reported in children born in the Netherlands after 2003, since when serological evaluation of children from mothers with chronic HBV infection is recommended.

6.3.4 Pathogen

Samples for genotyping are collected from all acute HBV infections, from chronic infections in MSM and in people detected through the vaccination programme for behavioural risk groups. In 2021, 47 samples of the 72 acute HBV cases (65%) and 9 of the 16 chronic HBV cases from risk groups (56%) were available for molecular typing. PCR amplification and sequencing gave results for 51 samples of HBV infections for the full-length genome. An optimised maximum parsimony tree of these sequences by the most likely transmission route is shown in Figure 6.3.2. In 2021, four different genotypes were found (Genotype A, D, E and F). The largest cluster of cases continues to be among genotype A cases, the most common genotype for acute HBV in the Netherlands. Of acute cases with genotype information, 60% were genotype A. Genotype F was the second most detected genotype among acute cases, (n=14, 31%). Genotype A was also most common among chronic cases in risk groups (5/7; 71%).

Since 2004, the molecular surveillance of HBV gives an impression of which genotypes occur in the Netherlands. The distribution of genotypes found in acute HBV cases from 2004 until 2021, is shown in Figure 6.3.3. Overall, around two-thirds of all typed samples from acute HBV cases are typed as genotype A (range 58-74%), followed by genotype D with 17% (range 4-27%). In addition, genotypes B, C, E and F are found in 3-6% of the samples. Genotype G and H are sporadically found (range 0-2 samples/patients (0-3%)). In 2019, a remarkable increase of genotype F was observed. The proportion of genotype F was 0-8% in the period 2004 to 2018, and 18% in 2019. Only 4 genotype F cases were detected in 2020, but in 2021, the increase continued, with genotype F detected in 14 of the 45 acute HBV cases (31%) with genotype information. All genotype F viruses from 2021 were identical to the cluster identified since 2018, indicating the subcluster continued to grow with sexual transmission as the common risk factor. Genotype F is endemic in regions such as Central and South America. Nevertheless, the Netherlands is stated as the most likely country of infection in the majority of cases.

6.3.5 (Inter)national developments

6.3.5.1 HBV vaccination programme for risk groups during the COVID-19 pandemic

The number of first vaccinations given as part of the HBV vaccination programme for high behavioural risk groups (started in 2002) has been relatively constant over the years up to 2019. Figure 6.3.4 shows the monthly numbers of first vaccinations from 2016 up to July 2022. In February and March 2020, the number of first vaccinations among sex workers and MSM decreased sharply from around 400 to 50. In the three following months the number increased again and varied between 200 and 300 vaccinations per month until July 2021. In the second half of 2021, a further increase was seen, and the number of vaccinations was between 300 and 400 in March, April, and May 2022 The decrease in vaccinations in 2020 and 2021 is probably related to the COVID-19 pandemic.

6.4 Human papillomavirus (HPV)

J.G.M. Brouwer, M. Middeldorp, J.M.A. Kusters, K. van Eer, A.J. King, H.E. de Melker

6.4.1 Key points

- Since February 2022, HPV vaccination is offered to boys and girls in the year they turn 10. At the same time, a catch-up campaign started in which boys and previously unvaccinated or partly vaccinated girls up to and including the age of 18 are also invited for HPV vaccination.
- The vaccine effectiveness (VE) of the bivalent vaccine against persistent vaccine-targeted HPV types (HPV types 16 and 18) remained high (VE 96.5%, 95% CI: 88.7, 98.9) up to eleven years after vaccination with a three-dose regimen.
- The vaccine effectiveness against incident vaccine-targeted HPV types (HPV types 16 and 18) remained high (VE 92.1%, 95% CI: 73.9, 97.6) up to seven years after receival of two doses of the bivalent vaccine.
- Median viral loads of clearing genital infections with vaccine-targeted HPV types (HPV types 16 and 18) and cross-protective HPV type 31 was lower in women vaccinated three times compared with unvaccinated women.

6.4.2 Tables and figures

Table 6.4.1 Vaccine effectiveness against incident and persistent HPV infections (12 months) in young women in the HAVANA study up to eleven years post vaccination.

	Adjusted* VE (95% CI)	
	Incident infections	Persistent infections
Vaccine types (16/18)	78.2% (68.5-84.8)	96.5% (88.7-98.9)
Cross-protective types (31/33/45)	50.0% (33.3-62.5)	62.0% (38.4-77.3)
hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59)	9.7% (-0.9-19.3)	15.9% (-0.1-29.3)
hrHPV types 9-valent vaccine (16/18/31/33/45/52/58)	31.2% (19.5-41.1)	43.3% (27.4-55.7)

* VE adjusted for age, urbanisation degree, smoking status, sexual intercourse, and contraception use.
CI, confidence interval; VE, vaccine effectiveness.

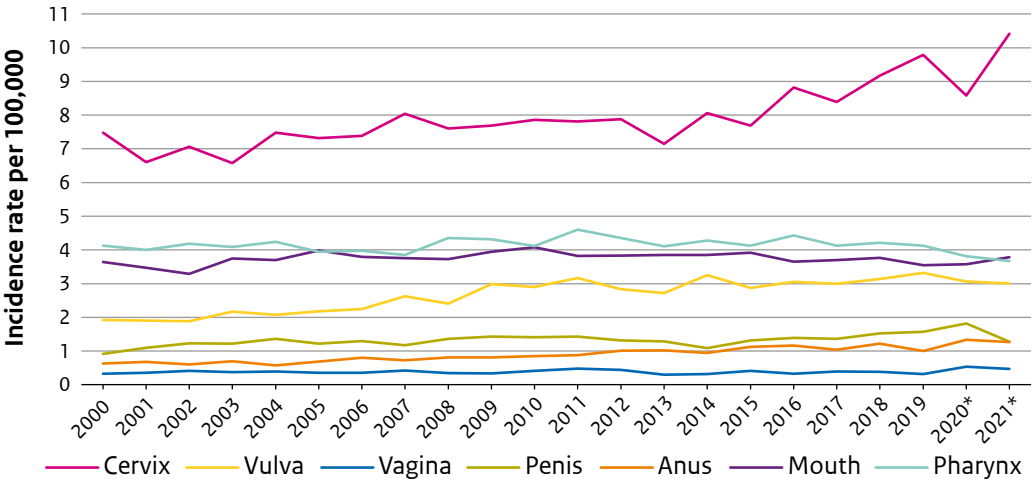

Figure 6.4.1 Incidence rates[α] (per 100,000, standardized by European standardized rates) of cervical, vulvar, vaginal, penile, anal, mouth/oral and pharyngeal cancer in the Netherlands, 2000-2021.

* Preliminary incidence rates.

α Incidence rates were obtained from the Netherlands Cancer Registry, IKNL (iknl.nl/nkr-cijfers, accessed 6 May 2021).

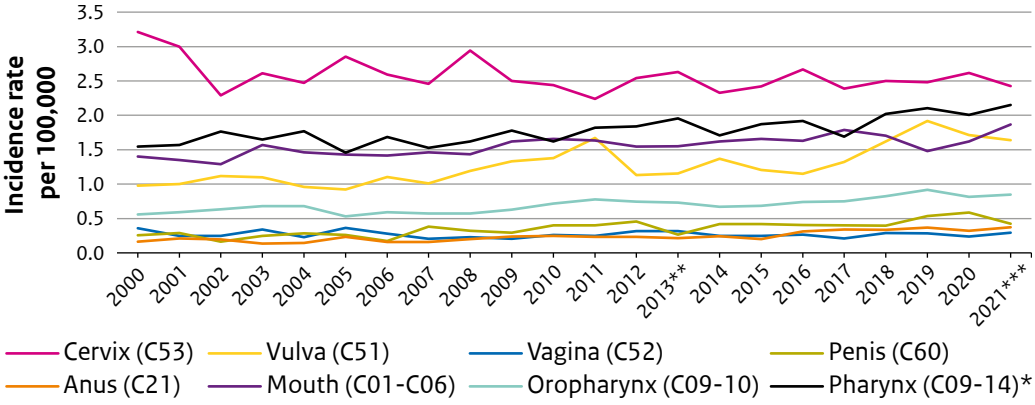

Figure 6.4.2 Incidence rates per 100,000 of deaths related to cervical, anogenital, mouth, oropharyngeal and pharyngeal cancers in the Netherlands, 2000-2021.

* Number of deaths due to pharynx cancer includes the number of oropharynx cancer deaths.

** In 2013, CBS started using international software for automatically coding the causes of death. This makes the numbers more reproducible and internationally comparable. Due to this change, there have been some significant shifts in the causes of death.

*** Preliminary incidence rates.

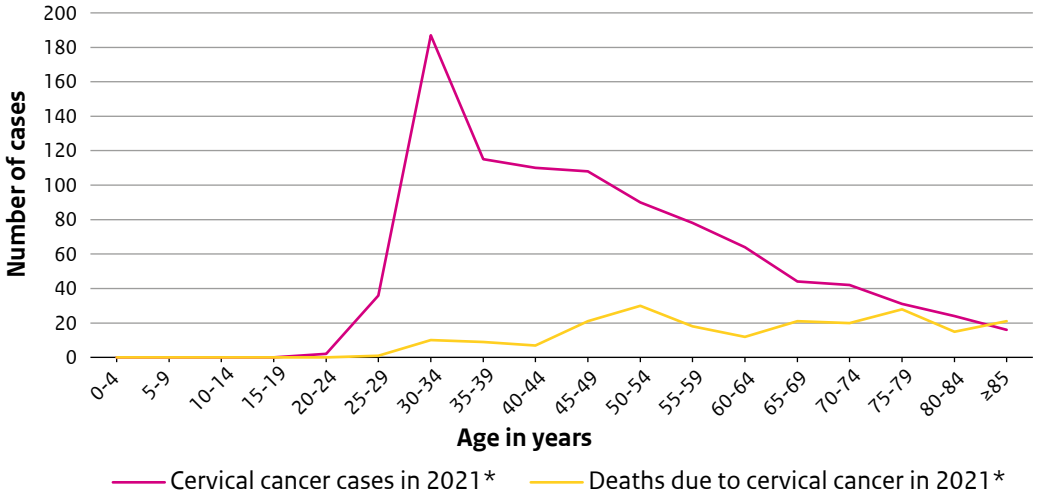

Figure 6.4.3 Absolute number of newly diagnosed cervical cancer cases and absolute number of deaths due to cervical cancer in 2021*.
* Preliminary data.

6.4.3 Epidemiology

Human papillomaviruses (HPV) are DNA containing viruses that can infect cutaneous and mucosal epithelia of the human body. Over 170 different HPV types have been identified [1]. HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 are classified as high risk (hrHPV) due to their oncogenic properties [2]. Even though the majority of the (genital) HPV infections are asymptomatic and cleared or suppressed within two years after exposure [3-6], a persistent infection with a hrHPV can lead to the development of (pre)cancerous lesions at anogenital and oropharyngeal areas. The most common cancer caused by a persistent HPV infection is cervical cancer for which a HPV infection is a necessary cause [7]. Besides cervical cancer, persistent HPV infections are also associated with vulvar, penile, anal, mouth/oral and oropharyngeal cancers [7].

The incidence rate of HPV-related cancers in the Netherlands in 2021 ranged between 0.47 per 100,000 individuals for vaginal cancer to 10.41 per 100,000 individuals for cervical cancer (preliminary data, Figure 6.4.1). The preliminary incidence rate for cervical cancer was higher in 2021 compared with the preliminary incidence rate of 2020. Mortality rates of cervical cancer reached 2.42 per 100,000 women in 2021 and 0.30 per 100,000 women for vaginal cancer (preliminary data, Figure 6.4.2). In absolute numbers, preliminary data in the Netherlands show that 2,321 women and 1,472 men were diagnosed with HPV-related cancers in 2021 [8] while 665 women and 522 men died of HPV-related cancers (CBS). The age-specific number of cervical cancer diagnoses and deaths caused by cervical cancer in the Netherlands is shown in Figure 6.4.3.

The non-oncogenic low-risk HPV types 6 and 11 can cause genital warts (GWs). In 2021, 808 sexual health clinic visitors in the Netherlands were diagnosed with GWs [9] of which 34% were women, 42% were heterosexual men, 20% were men who have sex with men that fall within the regulation 'Additional Sexual Healthcare' (MSM-ASG), and 4% were MSM that consulted the clinic as part of the national PrEP pilot programme.
At general practices, the number of GW episodes was 46,500 in 2020, with 2.2 and 3.1 episodes per 1,000 population in women and men respectively. The absolute number of diagnosed GWs and GW episodes was lower compared with 2019. The COVID-19 pandemic may have affected the GW diagnoses and episodes since consultations at sexual health centres were downscaled, access to GPs may have been limited and behavioural changes during the pandemic may have altered the risk of acquiring sexually transmitted diseases.

6.4.4 Current/ongoing research

6.4.4.1 HPV among vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study (HAVANA) among vaccinated and unvaccinated 14- to 16-year-old girls eligible for the catch-up campaign, which was initiated in 2009, is still ongoing. The primary aim of this study is to monitor the effect of the bivalent HPV vaccine on HPV type-specific presence amongst three-times vaccinated and unvaccinated young women. Vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Vaccine effectiveness (VE) against incident and persistent infections is determined every year. Up to eleven years post-vaccination, the bivalent vaccine showed a high VE against both incident and 12-month persisting vaccine-type infections (HPV16/18) (78% and 97%, respectively) (Table 6.4.1). Moreover, the VE against cross-protective HPV types 31/33/45 was 50% (95% CI: 33.3, 62.5) for incident infections and 62% (95% CI: 36.4, 77.3) against 12-month persisting infections.
VE estimates up to eleven years post-vaccination against incident and persistent infections are shown in Table 6.4.1.Type-specific VEs up to eleven years post-vaccination against 12-month persistent infection were 95.2% (95% CI: 84.7, 98.5) for HPV16, 100% (model did not converge due to absence of infections among vaccinated) for HPV18, 75.7% (95% CI: 51.0, 88.0) for HPV31, -26.6% (95% CI: -175.4, 41.8) for HPV33, and 59.9% (95% CI: -33.3, 87.9) for HPV45. VE estimates between 69.0% and 85.3% against incident infections were found for HPV types 16, 18 and 45.

6.4.4.2 HAVANA2

In 2016, a second prospective cohort study (HAVANA2) was initiated among vaccinated and unvaccinated girls who were eligible for the two-dose HPV vaccination schedule in 2014 (birth cohort 2001). Follow-up of this cohort is performed annually, where the girls are asked to fill out a questionnaire and hand in a vaginal self-swab. Vaccine effectiveness against incident infections could be estimated until seven years after vaccination. This resulted in a VE of 92.1% (95% CI: 73.9, 97.6) against incident vaccine type (HPV types 16/18) infections and 49.7% (95% CI: 11.9, 71.3) against incident cross-protective HPV types 31/33/45 infections. This indicates that the two-dose schedule provides high protection in a population-setting against both vaccine and cross-protective HPV types up to seven years post-vaccination. Due to low numbers of 12-month persistent infections, VE estimates against persistent infections could not be calculated.

6.4.4.3 Trends in HPV prevalence among sexual health clinic visitors (PASSYON)

PASSYON is a repeated cross-sectional study on HPV prevalence among girls and boys aged 16-24 years who visit sexual health clinics (SHCs). This study started in 2009, before the introduction of HPV vaccination for girls in the NIP and has been repeated every two years since. In 2021, the seventh round of PASSYON was conducted, which was the last round before the introduction of HPV vaccination for boys in the NIP. Preliminary results regarding HPV prevalence are available with data from 2009-2019. These data show that genital HPV type 16 and 18 prevalence is decreasing for women, which is in line with previous observations. A slight decrease is also observed for heterosexual men. For MSM, no decrease or increase is observed for those genotypes. No clear differences are observed for the pooled prevalence estimates 'any high-risk HPV' or 'any HPV' for women, heterosexual men or MSM. These results are preliminary and the analyses for type-specific trends are expected in 2023.

6.4.4.4 Concurrent anogenital HPV detection among young women and MSM who visit sexual health clinics

Concordant human papillomavirus (HPV) infection between genital and anal sites is known to be common among women and may be common among men who have sex with men (MSM). The exact risk factors are not known for type-specific anogenital concurrent infection, but potential risk factors include receptive anal intercourse and autoinoculation. Therefore, we analysed the prevalence of concurrent anogenital HPV detection, measured the type-specific concordance of genital and anal HPV detection for women and MSM independently [10]. If at least moderate concordance was found for one genotype per populations group (i.e., women or MSM), an additional risk factor analysis was done for that group, or for both groups, where participants with only genital HPV detection were compared to participants with type-specific concurrent infection. For these analyses, data from the PASSYON study were used from 2009 to 2019. In total, 1,492 women and 614 men were analysed. Among women, type-specific anogenital concordance was common; 607 women (40.7%) had at least one type-specific concordant detection. Out of the 25 tested genotypes, 20 genotypes showed at least moderate concordance (Cohen's kappa value between 0.40 and 0.60). Among MSM type-specific anogenital concordance was not common; 64 men (10.4%) had at least one concordant detection. None of the tested genotypes showed at least moderate concordance for MSM. Since only women showed type-specific concordance, risk factors were only determined for women. The only significantly associated risk factor for concordance among women was genital chlamydia infection. Receptive anal intercourse was not related to concurrent anogenital HPV. As no other observed sexual or demographic factor was associated, autoinoculation seems a likely explanation for concordant HPV infection between genital and anal sites for women.

6.4.4.5 The effect of two-dose and three-dose vaccination on type-specific HPV viral load

Since the introduction of HPV vaccination, multiple studies have shown a significant decrease in the prevalence of HPV types 16 and 18 and cross-protective effects against several non-vaccine hrHPV types (HPV31/33/35/45) in women with two-dose or three-dose vaccination compared to unvaccinated women [11-17]. The effectiveness of three-dose vaccination was high against persistent genital infections (identical HPV type present at least two rounds during follow-up) but slightly lower against clearing genital infections (HPV type present in one round and not detected again in at least two consecutive rounds during follow-up).

HPV infection persistency and consequentially risk of cancer development is associated with higher viral loads [18-20]. Vaccinated women may therefore carry lower type-specific HPV viral loads compared to unvaccinated women.
HPV was detected in 52.3% (n=458) of women vaccinated with three doses and in 50.0% (n=380) of unvaccinated women. Furthermore, median viral loads of clearing genital infections with vaccine types HPV16 (0.00023 and 2.21 copies/cell, respectively) and HPV18 (1e-5 and 1.40 copies/cell, respectively) and cross-protective type HPV31 (1e-5 and 0.00062 copies/cell, respectively) were significantly reduced in women vaccinated with three doses compared to unvaccinated women (p=0.002, p=0.00016 and p=0.00067, respectively). No significant decrease was observed in the viral load of clearing genital infections with the other HPV types against which cross-protection was established. The median viral loads of persistent genital infections were similar in three-dose vaccinated women and unvaccinated women for the majority of the HPV types. However, a trend was visible where the median HPV16 viral load in persistent infections was reduced in vaccinated women compared to unvaccinated women (0.0037 and 0.32 copies/cell, respectively, p=0.066).
Women eligible for two-dose vaccination had few genital HPV infections, which made subsequent viral load analyses difficult. HPV was detected in 18.9% (n=249) of women vaccinated with two doses and 21.6% (n=243) of unvaccinated women. Viral load analyses of clearing and persistent HPV infections showed no significant differences between two-dose vaccinated women and unvaccinated women, probably due to a low number of HPV infections. No clearing and persistent genital infections with HPV16 and 18 were present in vaccinated women. Persistent HPV31 and 58 genital infections and clearing genital HPV35 infections were also absent in vaccinated women. In addition, genital HPV35 and 45 infections were completely absent in vaccinated and unvaccinated women.
Our data suggests that three-dose vaccination hampers HPV infection persistence by reducing HPV viral load at the beginning of the infection, thereby reducing the risk of developing cancer. This effect might not yet be seen in women with two-dose vaccination, since these women are younger and might have been less exposed to HPV. In addition, herd-immunity effects may have a greater impact in the women with a two-dose vaccination due to an increasing vaccine uptake over the years coupled with a declining trend in HPV prevalence [21].

6.4.5 International developments

6.4.5.1 Impact of HPV vaccination

Real-world data on the impact of HPV vaccination is becoming increasingly available. In Italy, the effect of the bivalent HPV vaccine on hospitalisations associated with HPV-related diseases was determined. Data on patients hospitalised between 2006 and 2019 was used. The cohort was divided into two groups: a cohort born before 1996 (not eligible for vaccination) and a cohort born after 1997 (eligible for vaccination – the first cohort that was offered vaccination starting from 2008). Women from cohorts born after 1997 registered lower hospitalisation rates with an average reduction of 61% and 67% between the ages of 17 and 21 years for genital warts (GW) and cervical intraepithelial neoplasia (CIN) respectively [22]. Also, in Portugal, the prevalence of GWs among 8636 female patients aged ≤19 and 20–24 years has decreased by 86.8% and 77.4% respectively, between 2008 (the last year before implementation quadrivalent vaccine) and 2017 [23].

In Denmark, real-world effectiveness of HPV vaccination against high-grade vulvovaginal lesions was determined. Using nationwide registries, individual-level information on bivalent HPV vaccination and first diagnoses of vulvar and vaginal high-grade squamous intraepithelial lesions or worse (HSIL+) were retrieved. The cohort consisted of 514,537 women. At baseline, 50.6% were vaccinated (<16 years), 31.8% were vaccinated during follow-up (17-26 years), and 17.6% remained unvaccinated. The cumulative incidence was less than 0.6‰ for vulvar HSIL+ and less than 0.2‰ for vaginal HSIL+. Adjusted analyses showed reduced hazard rates for both vulvar (hazard ratio (HR) = 0.22, 95% CI: 0.13, 0.38) and vaginal HSIL+ (HR = 0.16, 95% CI: 0.04, 0.55) for women vaccinated at the age of 16 years or younger compared with unvaccinated women. The reduction was less pronounced for women vaccinated at the age of 17-26 years. The results indicate that HPV vaccination before the age of 17 years reduces the risk of vulvar and vaginal HSIL+ [24].

In order to gain insight into the effect of HPV vaccination with the bivalent vaccine on cervical cancer and cervical carcinoma in situ (grade 3 CIN) in England, data from a population-based cancer registry were used. The risk of cervical cancer in vaccinated cohorts was compared with earlier cohorts that were not eligible for HPV vaccination. Using data from 13,7 million-years of follow-up of women aged 20 years to younger than 30 years, the estimated relative reduction in cervical cancer rates by age at vaccine offer were 34% (95% CI: 25, 41) for age 16–18 years, 62% (95% CI: 52, 71) for age 14–16 years, and 87% (95% CI: 72, 94) for age 12–13 years, compared with the unvaccinated cohort. For CIN3, the risk reductions were 39% (95% CI: 36, 41) for age 16–18 years, 75% (95% CI: 72, 77) for age 14–16 years, and 97% (95% CI: 96, 98) for age 12–13 years. This shows that the bivalent vaccine provided a substantial reduction in cervical cancer and incidence of CIN3 in young women, especially in those who were offered the vaccine at the age of 12–13 years. Almost all cervical cancer was eliminated in women born since September 1995 [25].

6.4.5.2 Vaccination in boys and/or men

According to the World Health Organisation (WHO), vaccinating adolescent girls is the most effective long-term intervention for reducing the risk of cervical cancer [26]. Nevertheless, more and more (high income) countries are implementing HPV vaccination for boys in addition to girls. In 2019, almost one third of the countries with an HPV vaccination programme had a gender-neutral vaccination (GNV) programme [27]. In the Netherlands, GNV is offered to children in the year they turn 10 since February 2022 with a simultaneous catch-up campaign up to and including the age of 18 years for boys and previously unvaccinated or partly vaccinated girls. More evidence regarding the HPV vaccine effectiveness against HPV-related outcomes in men is emerging.

In Australia, the trends in genital wart diagnoses among heterosexual men who attended sexual health clinics before and after the introduction of GNV was examined in a serial cross-sectional study [28]. School-based GNV at the age of 12-13 years was implemented in February 2013, with a two-year catch-up programme through to age 15 years. Up to and including 2018, invited boys received three doses of the quadrivalent vaccine. From 2019 onwards, two doses of the nonavalent vaccine were provided. A total of 10,848 (9.0%) of the 121,038 included heterosexual men were diagnosed with genital warts. A 13% (95% CI: 11, 15)

mean annual reduction in genital warts prevalence was observed in the GNV period. Among men aged 15-20 years who were eligible for the GNV programme, the diagnosis of genital warts decreased by 97% 11 years after introduction of the female-only programme with a mean annual reduction of 16% (95% CI: 2, 18) in the GNV period. It was concluded that GNV has led to substantial and ongoing reduction in genital warts among heterosexual men.

After a median of 9.5 years of follow-up after vaccination with the quadrivalent vaccine at the age of 16-26 years within an RCT, the incidence of genital warts related to HPV types 6 or 11 was 0.0 (95% CI: 0.0, 8.7) per 10,000 person years vs. 137.3 (95% CI: 83.9, 212.1) per 10,000 person years for men who received a placebo [29]. For external genital lesions related to HPV types 6, 11, 16 or 18 the incidences were 0.0 (95% CI: 0.0, 7.7) and 140.4 (95% CI: 89.0-210.7) per 10,000 person years for quadrivalent vaccinated men vs. men who received a placebo respectively. For MSM, the incidence per 10,000 person years for anal intraepithelial neoplasia or anal cancer related to the vaccine-targeted HPV types was 20.5 (95% CI: 0.5, 114.4) in quadrivalent vaccinated MSM vs. 906.2 (95% CI: 553.5, 1399.5) for MSM who received a placebo. All men were seronegative at study inclusion and PCR-negative from study inclusion through month 7 (i.e., receival of the third dose) for the HPV types being analysed. It was concluded that the results support quadrivalent HPV vaccination in men, including catch-up vaccination.

In the United States, the Vaccine Impact in Men (VIM) study was conducted to estimate HPV vaccine effectiveness in young adult men who have sex with men (MSM) and transgender women seeking STD/HIV services [30]. The ability of HPV vaccines to prevent penile HPV was estimated with samples from participants in this cross-sectional study in Seattle. A total of 687 gay, bisexual, and other MSM, and transgender women aged 18-26 years provided self-reported HPV vaccination history and self-collected a penile swab. Participants could have received either the quadrivalent or nonavalent vaccine, but the participants were not asked to recall which vaccine was received. The prevalence of HPV types 6, 11, 16 and/or 18 was similar in vaccinated (12.1%) versus unvaccinated participants or those with unknown vaccination history (15.6%) (adjusted prevalence ratio: 0.69, 95% CI: 0.47, 1.01). However, the vaccine effectiveness against penile HPV type 6, 11, 16 and/or 18 infections was 85% (95% CI: 38, 96) if the first vaccine was provided at ≤18 years of age. It was concluded that HPV vaccination is effective in preventing penile HPV infections in young MSM when administered at age ≤18 years.

6.4.5.3 Reduced doses

A two-dose schedule is currently most commonly implemented globally in NIPs targeting 9- to 14-year-olds. A one-dose schedule has been under consideration for several years. HPV vaccination in a one-dose regimen or a two-dose regime for those aged ≥15 years has not been registered by the European Medicine Agency. Nevertheless, the interest in such schedules increased due to, among others, a previously limited HPV vaccine supply and the COVID-19 pandemic which hampered provision for many vaccines. Additionally, in the last few years, evidence has been accumulating about HPV vaccine efficacy, effectiveness, and immunogenicity of a one-dose schedule.

As reported in one of June's WHO's weekly epidemiology records of 2022, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) Working Group Human Papillomavirus Immunization updated a previously published systematic review on the immunogenicity and efficacy of a single dose of HPV vaccine [31, 32]. After the update, 55 studies were included of which 3 were randomized controlled trials (RCTs), 4 were post-hoc analyses of RCTs, 3 were case-control studies and 45 were observational cohort studies. While there is no known antibody correlate of protection, a one-dose schedule resulted in lower geometric mean concentrations for HPV types 16 and 18 compared with a two- or three-dose schedule. However, they remained stable, and seropositivity rates for HPV type 16 and 18 were similarly high after one dose vs. two or three doses. A one-dose schedule resulted in little to no difference in persistent HPV type 16/18 infections, compared with a two- or three-dose schedule. However, the effect estimates comparing one, two, and three doses came mostly from observational studies, which may have a serious risk of bias due to confounding. Vaccine efficacy against HPV type 16/18 infections of a one-dose schedule is estimated up to 10 years for the quadrivalent vaccine and up to 11 years for the bivalent vaccine.

Based on all evidence combined, the WHO SAGE recently recommended an update for the dosing schedule to reach the global goal of eliminating cervical cancer as a public health problem [26] as follows [31]:
- One or two-dose schedule for the primary target of children aged 9-14 years;
- One or two-dose schedule for adolescents aged 15-20 years;
- Two doses with a 6-month interval for adults aged ≥21 years.

In February 2022, the Joint Committee on Vaccination and Immunisation recommended a move to a one-dose schedule for the routine adolescent HPV immunisation programme in the United Kingdom [33]. A move from a three- to a two-dose schedule for individuals aged ≥15 years was advised previously and implemented from 1 April 2022 onwards [33].

6.4.5.4 Cost-effectiveness
Linertová *et al.* conducted a systematic review to the cost-effectiveness of extending the HPV vaccination to boys [34]. A total of nine economic evaluations were included that compared a GNV programme with a girls-only vaccination programme for children vaccinated between ages 9 to 13. Either the bivalent, quadrivalent, or nonavalent vaccine could be evaluated, and studies could be industry or non-industry funded. Four studies concluded in favour of GNV while four found it cost-effective only in alternative scenarios. The most influential parameters are discount rate for health effects (equal to costs vs lower than costs), vaccine price (listed vs. publicly negotiated), and included health problems (inclusion of oropharyngeal and penile cancers). Sponsorship was not decisive for the final result, but there were differences between industry-funded and independent studies in some cost categories. It was concluded that the evidence of the cost-effectiveness of GNV is scarce and ambiguous. The authors concluded that before the adoption of such a strategy, countries should carry out context-specific cost-effectiveness analyses, but the decision should also take into account other criteria, such as gender-related equality.

The health and economic implications of adopting a one-dose nonavalent HPV vaccination regimen in a high-income country setting was investigated in a study funded by Merck & Co., Inc [35]. Dynamic transmission modelling was used to investigate the impact of switching from a two-dose nonavalent HPV vaccination programme (vaccine coverage of 89%, status quo) to a one-dose programme on health and economic outcomes. The model focused on HPV data in the United Kingdom setting. All major HPV disease-related endpoints (i.e., cervical, vaginal, and vulvar cancers and pre-cancers, anal, penile, oropharyngeal cancers, genital warts, and recurrent respiratory papillomatosis) were included. For vaccination, a piecewise constant vaccination rate was included with the assumption of a 'leaky' vaccine where all uninfected vaccinees have partial protection that may wane at a constant rate over time. The duration of protection against the vaccine-targeted HPV types was assumed to be lifelong for complete series if the vaccine was administered in a two-dose regimen at the age of 13 years. A dose cost of £45.21 was used. The probability of a one-dose regimen with a median duration of protection of 20 years being cost-effective were 7.8% and 1.7% for the willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per quality-adjusted life year (QALY) respectively. The probability of being cost-effective increased with a higher median duration of protection (up to 34.9% with a median protection duration of 50 years for a WTP threshold of £20,000 per QALY). Sensitivity analyses showed that the probability that a one-dose regimen was cost-effective with a WTP of £20,000 per QALY was 2.4% with a 40% vaccine coverage and 9.6% with a 95% vaccine coverage. It was concluded that adoption of a one-dose nonavalent HPV vaccination regimen had a low probability of being cost-effective compared to a two-dose regimen.

Simons *et al.* assessed the cost-effectiveness of a catch-up HPV-vaccination programme for boys and men in the Netherlands in a study funded by GlaxoSmithKline Biologicals SA [36]. The developed model reflected a lifetime multi-stage static Markov approach, comparing vaccination of boys or men with the situation in which only girls are vaccinated. Three different scenarios were assessed: 1) boys aged 12-14 years are vaccinated, 2) boys aged 12-16 years are vaccinated, and 3) boys aged 12-26 years are vaccinated. A vaccine coverage of 30% with a vaccine price of €50.- per dose was considered. No herd immunity in the female population was assumed. Hence only male HPV-related cancers due to HPV types 16 and 18 were considered. The incremental cost-effectiveness ratio (ICER) of vaccinating boys aged 12-14 years was €18,197. Vaccinating boys aged 12-16 years resulted in an average ICER of €22,109 while vaccinating up to the age of 26 years resulted in an average ICER of €32,256. The authors concluded that a catch-up vaccination programme for men until the age of 26 years is considered nearly cost-effective based on a willing to pay threshold of €20,000.

6.4.6 Literature

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6.5 Measles

I.K. Veldhuijzen, R. Bodewes, W.L.M. Ruijs, R. van Binnendijk, N.Y. Rots, C.A.C.M. van Els, H.E. de Melker

6.5.1 Key points

- In 2021 and in the first six months of 2022, no measles cases were reported.

6.5.2 Tables and figures

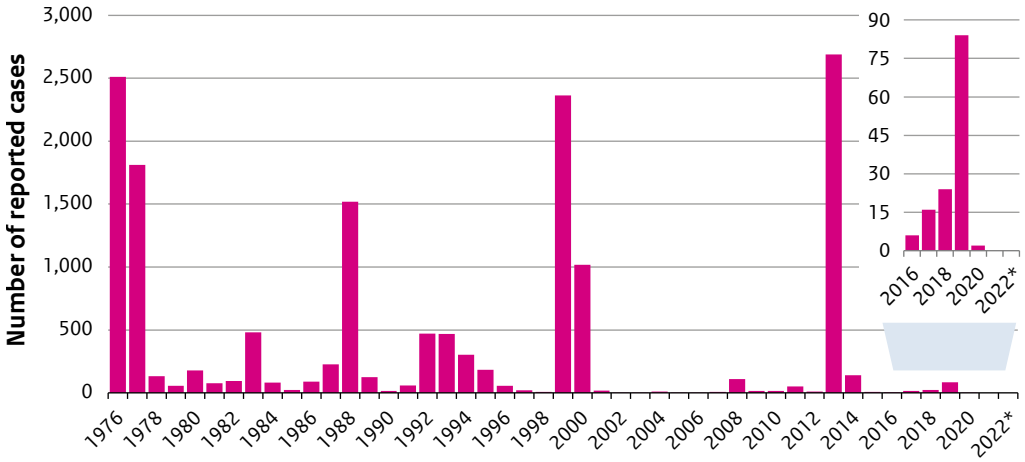

Figure 6.5.1 Annual reported measles cases since 1976.

6.5.3 Epidemiology

Since 1976, when vaccination was introduced, the Netherlands has experienced large outbreaks (Figure 6.5.1). These occurred in 1977, 1988, 1999 and 2013. In 2013, more than 2,500 cases were reported. Since 2014 fewer than 100 cases have been reported per year. After the outbreak of 2013/2014, the number of reported measles cases was below 10 in 2015 and 2016, around 20 in 2017 and 2018, and relatively high with 84 in 2019. In 2020, only two cases were reported, with dates of onset in January and February. Since then, most likely as a result of the implementation of COVID-19 control measures, up to and including June 2022, no measles cases were reported (Figure 6.5.1).

6.5.4 Research

A measles seroprevalence study was conducted in 2016-2018 among 246 Dutch family members travelling to Eastern European or non-European countries. Of the participants, 30% were children (12-18 years old), and 97% reported to be vaccinated according to the NIP. Seroprevalence of protective antibodies measured with an enzyme-linked immunoassay (ELISA) was 72% for children, and 87% for adults. For the birth cohort (1965–1975) considered at risk for measles, the seroprevalence was 89%. The measles antibody concentrations were lower in children compared to adults who more often had higher titres due to natural infections. The authors suggest waning of vaccine-induced immunity is a probable explanation for the lower seroprevalence in children and propose to give more attention to compliance with the NIP in travelling children [1].

6.5.5 International developments

In 2021, only 60 measles cases were reported in EU/EEA countries, compared to 2043 in 2020 and over 13.000 in 2019. In the first six months of 2022, 69 cases were reported [2]. The decrease in cases in 2020 and 2021 is probably related to the implementation of COVID-19 control measures.

6.5.6 Literature

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6.6 Meningococcal disease

A. Steens, B.C.L. van der Putten, W. Freudenburg-de Graaf, H.E. de Melker, N.M. van Sorge

6.6.1 Key points

- Since the introduction of MenACWY vaccination, its accompanied catch-up vaccination campaign, and the COVID pandemic, the incidence of invasive meningococcal disease (IMD) has decreased further from 1.2 per 100,000 in 2018 to 0.21 per 100,000 in 2021.
- In 2021 and the first four months of 2022, only four IMD-W cases have occurred. No vaccine failure occurred in this period.
- In 2020-March 2022, no IMD-C cases occurred, but in April 2022, two (unrelated) IMD-C cases were notified. One of them had been vaccinated with MenC through the national immunisation programme.
- In 2021-2022, one IMD-Y case occurred. No information on vaccine status was available for this case.
- The incidence of IMD-B has decreased further from around 0.45 per 100,000 between 2011 and 2019 to 0.15 per 100,000 in 2021. Two deaths were reported among IMD-B cases in 2021-22 (5%).
- The predicted strain coverage by the licenced MenB vaccine during 2019-2021 was, for 4CMenB, 77-79% among those <5 years old, 75-92% for those aged 5-14 years and 87-91% for 15-24-year-olds, and, when calculated in the same way for MenB-fHbp, 85% for those aged 10-17 years and 92% for the 18-25-year-olds (the licensed age groups).

6.6.2 Tables and figures

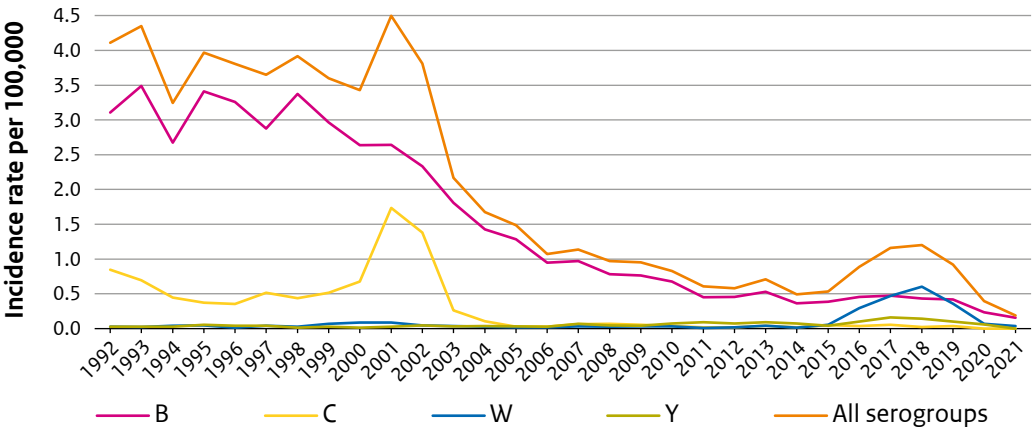

Figure 6.6.1 Incidence of meningococcal disease by serogroup, 1992-2021.

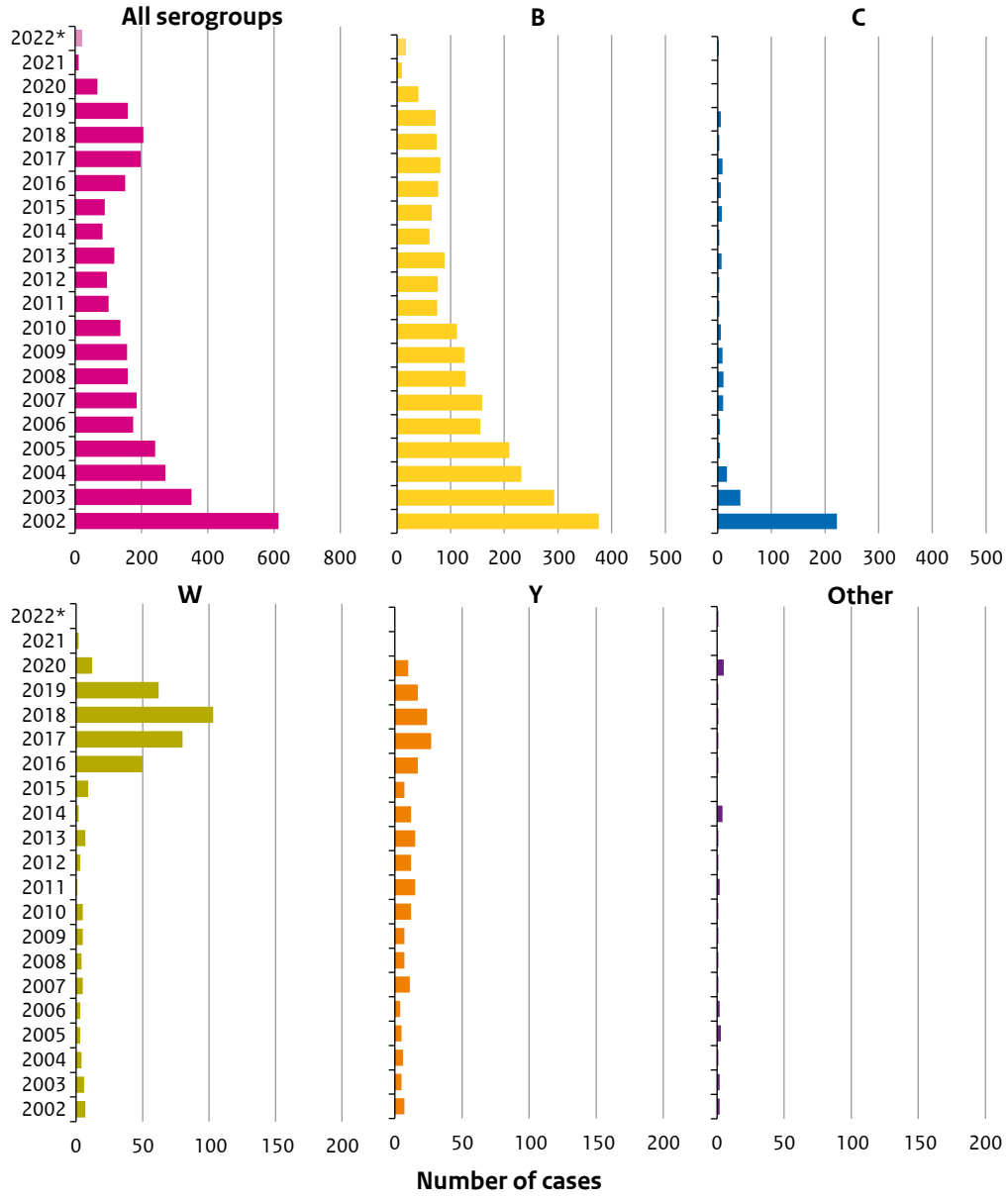

Figure 6.6.2 Number of cases of meningococcal disease by serogroup, 2002-2022*. Note the different scales in the graphs.

* Up to and including April.

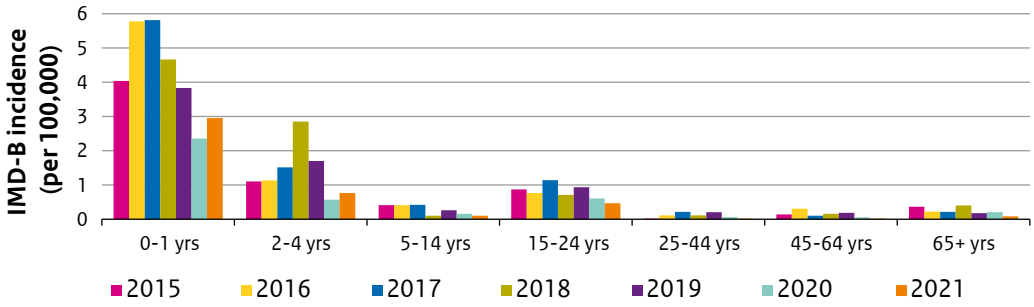

Figure 6.6.3 Age-specific incidence of meningococcal serogroup B disease by year, 2015-2021.

6.6.3 Epidemiology

6.6.3.1 Meningococcal disease

The incidence of invasive meningococcal disease (IMD) declined from 4.5 per 100,000 in 2001 to 0.49 per 100,000 in 2014 (n=83), after which it again rose to 1.2 per 100,000 in 2018 (n=206). In May 2018, vaccination against serogroups A, C, W and Y (MenACWY) was introduced in the infant national immunisation programme (NIP) and in 2020, for 14-year-olds. Also, adolescents born between January 1st 2001 and December 31st 2005 (14- to 18-year-olds) were offered MenACWY vaccination in response to increased IMD-W incidence. Next, in 2020 and 2021, transmission very likely decreased as a result of the control measures in response to the COVID-19 pandemic. Together, this resulted in a decreased IMD incidence of 0.21 per 100,000 in 2021 (n=37; see Figure 6.6.1). In the first four months of 2022, twenty IMD cases occurred, which is much less than in the pre-COVID-19 years 2015-2019 (median 70 within the first four months of the year).

6.6.3.2 Meningococcal disease caused by serogroup W

After an increase in IMD-W from 2015 onwards, the IMD-W incidence peaked at 0.60 per 100,000 in 2018 (n=103; Figure 6.6.1). Since then, the incidence of IMD-W has decreased as a result of the vaccination campaign. In 2021 and in the first four months of 2022, only four IMD-W cases have occurred (incidence 0.03 per 100,000 population in 2021). All occurred in 2021 and the cases had not been eligible for MenACWY vaccination (minimal age of the IMD-W cases was 27 years). Among individuals who were vaccinated during the MenACWY catch-up campaign or through the NIP, only one vaccine failure has occurred; this IMD-W case was two years old without known underlying medical condition and occurred in 2019.

6.6.3.3 Meningococcal disease caused by serogroup B

Meningococcal serogroup B has been the main serogroup that has caused IMD in the Netherlands for many years. The incidence of IMD-B has been declining steadily since the late nineties and stabilised around 0.45 per 100,000 between 2011 and 2019 (see Figure 6.6.1). Subsequently, the incidence has decreased to 0.23 per 100,000 in 2020 and 0.15 in 2021 (n=40 in 2020, n=31 in 2021; Figure 6.6.2), likely as a result of the COVID-19 control measures; the

number of IMD-B cases in April 2022 returned to pre-COVID levels. Overall, serogroup B caused 86% of all IMD cases in 2021. In 2022, up to and including April, 16 IMD-B cases have occurred, which represent 84% of the IMD cases in 2022. The incidence of IMD-B is highest among infants (Figure 6.6.3: 3 per 100,000 in the <2-year-olds and 0.8 per 100,000 in 2-4-year-olds in 2021), followed by adolescents (0.5 per 100,000 in 15-24-year-olds in 2021).
Since 2015, 21 out of the 448 (5%) IMD-B cases with information on survival died. There were two deaths reported among IMD-B cases in 2021-22 (5%), one of which was aged <5 years; for two additional IMD-B cases, survival status was unknown. Case fatality was similar to the last five years: in that period, 1-2 children under 5 years of age died of IMD-B annually.

6.6.3.4 Disease caused by other meningococcal serotypes

Since the introduction of the conjugated meningococcal serogroup C (MenC) vaccine at 14 months of age in 2002 with a catch-up for 1- to 18-year-olds, the number IMD-C disease cases decreased significantly from 277 in 2001 to an average of 6 cases per year in 2005-2019 (see Figure 6.6.1). In 2020-March 2022, no IMD-C cases occurred, but in April 2022, two IMD-C cases were notified. One case was between 5-10 years old, and one was over 50 years old. The child had been sufficiently vaccinated against MenC through the NIP and thus was a vaccine failure. The IMD-C cases had different finetypes and are therefore unrelated.
Meningococcal serogroup Y is included in the MenACWY vaccine that has been used since 2018. Before that, the incidence of IMD-Y increased in the years 2015-2017 to an incidence of 0.16 per 100,000 (n=27). Since vaccine implementation, the incidence has decreased to <0.01 per 100,000 (n=1) in 2021. No cases have occurred in the first four months of 2022. Note that, besides MenACWY vaccination, the COVID-19 control measures will also have played a role in this decrease.
One case of IMD-Z occurred in the period 2021-April 2022. The last time IMD-Z was observed in the Netherlands was in 2012.

6.6.4 Pathogen

Within serogroups, the finetype is routinely determined based on the sequence variation of two variable regions of PorA (VR1, VR2) and one region of the FetA protein (VR1). Among IMD-B cases in 2021, several different finetypes were observed. Serotype P1.22,14:F5-1, which increased in 2016-2019, occurred in 3 out of 26 strains (12%) with available information in 2021. The most common finetype among IMD-W cases in 2015-2020, P1.5,2:F1–1, was still present in 2021; two out of the four IMD-W cases had been infected with this finetype.
The predicted strain vaccine coverage, i.e., the proportion of IMD(-B) strains that match the MenB vaccine antigens, has been determined recently for isolates of 2019-2021 [1].
This theoretical coverage was determined for both the multivalent 4CMenB and the bivalent MenB-fHbp vaccines. In short, the strain coverage for 4CMenB for IMD-B was 77-79% among those younger than 5 years, 75-92% for those aged 5-14 years and 87-91% for 15-24-year-olds. For MenB-fHbp, the strain coverage was 69% for those aged 10-17 years and 85% for the 18-25-year-olds (the licensed age groups). If half of the isolates with uncertain results were added to the covered strains, as is standard practice when estimating coverage of 4CMenB, the coverage was estimated at 85% and 92%, respectively.

6.6.5 Current/ongoing research at RIVM

RIVM, together with the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) determined the pathogen- and type-specific changes during the first year of the COVID-19 pandemic, although no causal effects can be conclusively determined because of the used design [2]. Overall, IMD decreased by 78% compared to the 5-year pre-pandemic period. Since MenACWY vaccination was implemented, the decrease in IMD-B most likely reflects the changes occurring as a result of by the COVID-19 control measures; the IMD-B incidence decreased by 61%. IMD-W and IMD-Y decreased by >90%. The decrease in IMD was larger among those aged 65 years and over (86% decrease) compared to children under 5 years of age (58% decrease).

The burden of IMD in the Netherlands has been determined for the period July 2011-May 2020 [3]. Retrospective chart review was performed for all cases with isolates submitted from one of the nine sentinel laboratories, which cover about 25% of the Dutch population. Overall, this included 278 IMD cases, of which 55% was IMD-B, 27% was IMD-W, 13% was IMD-Y, and 5% was IMD-C. Overall, 7% of the IMD cases died, and the case fatality rate (CFR) was highest among IMD-Y (14%) and IMD-W (13%) and lowest for IMD-B cases (2%). The disease course, based on hospitalisation duration and ICU admission, was more severe for patients with sepsis and for patients of older age but was not serogroup-dependent. Of all IMD cases, 52% had sequelae at discharge, and 28% still had sequelae after at least one year post-discharge. Although numbers per age group were small, the proportion with sequelae seemed lowest for children under 5 years of age (41%), but the proportion with sequelae at ≥1-year post-discharge seemed highest in that age group (38%); most of these sequelae were categorised as being mild. For sequelae at discharge, an association was observed with meningitis and sepsis. The burden of IMD, defined as disability adjusted life years (DALYs) was highest during the peak years in IMD-W incidence (in 2017-2018 this was 328 DALYs/year). For IMD-B, the burden was quite stable over time, ranging between 100 and 200 DALYs per year.

6.6.6 (Inter)national developments

6.6.6.1 Carriage

Meningococcal carriage among teenagers has been determined in 2018 among students in the area of Utrecht, the Netherlands [4]. At that time, just before the MenACWY vaccine introduction, 25% (74/299) of the students carried meningococci, of which 8% carried MenACWY vaccine-type genogroup meningococci and 9% carried serogroup B. Coming fall, another carriage study with a similar design and population will be carried out, which can give insight in the effect of the MenACWY vaccination on carriage. A similar study, but with a focus on meningococcal B carriage among participants who completed high school (aged 17-25) the previous year, was performed in in South Australia [5]. That study confirmed the absence of a preventive effect of MenB vaccination on carriage; meningococcal B carriage remained at around 5% despite an increase in vaccine coverage from 43% to 76-78%. These results are also summarised in the RIVM report for the Health council [1].

6.6.6.2 *Invasive meningococcal disease*

A paper summarising information from the 4th Global Meningococcal Initiative summit meeting was recently published [6]. Besides a decrease in IMD incidences during COVID-19 years (see also below), the paper discussed the temporary decrease in vaccine coverage against IMD in several countries, likely related to the COVID-19 pandemic and accompanied control measures. A referred study that investigated the effect of the pandemic on NIPs found that 95% of the included countries (18/19) had disruptions during the first COVID-19 year. Furthermore, the paper discussed possible effects of overuse of antibiotics during the pandemic in an attempt to prevent bacterial coinfections. Particularly in the Asia-Pacific region, there is already substantial antimicrobial resistance; e.g., in China, only 25% of meningococcal isolates are susceptible to ciprofloxacin. Resistance to ciprofloxacin or beta-lactams are mainly linked to modifications of gyrA or penA alleles, respectively. Alterations in the penA gene, associated with non-susceptibility in penicillin, were also found in Dutch meningococcal isolates: 7/54 isolates from 2020 (13%) [7, 8]. In phenotypical tests, 22% of meningococcal isolates were moderately-susceptible to penicillin and one isolate (IMD-B) was penicillin-resistant [7, 8]. The 11 moderately-susceptible isolates belonged to serogroup B, serogroup Y and serogroup W. Note that there was a weak correlation between the penA gene and phenotypical tests (eTest).

The COVID-19 control measures have had effects on the IMD incidence, as also presented above. For the Netherlands, we estimated an overall decrease of IMD incidence of 78% during the first year, but, when only focusing on IMD-B, for which no vaccination is implemented, the decrease was 61% [2]. Similar changes were observed in other countries [9-11]. In the UK, IMD was 75% lower during lock down compared to the pre-COVID-19 period, but the decrease may partly still be the result of recent implemented vaccination (adolescent MenACWY and infant MenB vaccination in 2015) [9]. In France, changes in clonal complexes (CC) causing IMD were determined; fewer hyperinvasive meningococcal genotypes were found since COVID-19 emerged (main decrease in CC11, but CC32 increased) [10]. Furthermore, they showed a rebound effect after the COVID-19 control measures were lifted in the second half of 2021. A similar increase after lifting the control measures, was also observed in the UK. After lifting the control measures in July 2021, a sharp increase in IMD(-B) was observed among adolescents/young adults in September-November 2021 [12]. Together, these data show that it remains important to be on the alert, especially when social interaction is increased again.

Long-term mortality after having suffered from IMD was investigated in France using the national insurance database with data for the period 2012-2017 [13]. Mortality data for cases and matched controls were determined for the acute phase and post-discharge, with a median follow-up time of 2.8 and 3.0 years (range 0-6), respectively. Controls were randomly selected from the database, independent from any hospitalisation, but were matched on age, sex, and geographic location. The median age of the included population was 21 years (IQR 4-52). As expected, mortality was higher in the acute phase of disease in cases compared to random controls. Overall, 13% of the cases and 3% of controls died during the study period. Two-thirds of the cases died during hospitalisation for IMD. Cases that had survived the acute phase of IMD still had an increased risk of dying than controls (hazard rate [HR] 1.8, 95% CI 1.5-2.2).

6.6.6.2.1 IMD-B disease

A report with updated information on IMD-B epidemiology and MenB vaccination was prepared for the Health Council of the Netherlands [1]. It describes the decrease in IMD-B over several years, and specifically during the COVID-19 pandemic. Furthermore, it summarises the recent publications on the effectiveness of the available vaccines (4CMenB in infants and adolescents, and MenB-fHbp in adolescents) with at least 70% prevention of IMD but no effect on carriage. Updated information on the most recent strain coverage is presented, i.e., more than 75% of the IMD-B cases were infected by a strain that is covered by the MenB vaccines (see also section 6.6.4).

Additional data on the effectiveness of the MenB vaccines have been published after finalising the report. Surveillance data of the MenB vaccination programme in South Australia (children 0-3 years, adolescents 15-16 years and young adults 17-20 years since 2018/2019) was used to estimate the effectiveness against IMD-B as well as against gonorrhoea (cross-protection) [14]. Vaccine coverage was 79% in infants (3 doses), and 69% in adolescents (2 doses). Two years after vaccine introduction, the incidence of IMD-B was significantly reduced in those aged 3-11 months (IRR 0.40, 95% CI 0.23-0.69) but not in 1-, 2- or 4-year-olds (all 95% CIs included 1). In adolescents aged 15-18 years, the impact on the incidence was borderline significant two years after implementation (IRR 0·27 (0·06-1·16). No significant impact was observed after the first year in those aged 19-21 years. Note that the COVID-19 pandemic may have affected the impact estimations of the second year. The VE of two doses in children was estimated at 95% (95% CI 40-100); in adolescents, the VE was 100%. The VE of two doses against gonorrhoea in adolescents and young adults was 33% (95% CI 8-51).

A comparison was made of the national policies to prevent IMD-B in all countries (n = 58) where one or both MenB vaccines are authorized for use [15]. MenB vaccination was either used in age-based risk groups (mainly infants; 15 countries), for individuals with medical underlying illnesses (e.g., asplenia; 21 countries) or those with increased risk for exposure (e.g., laboratory staff; 13 countries).

A description of an outbreak of IMD-B in a Belgian nursery school was published and has led to the addition to the Wallonian regional guidelines of offer MenB vaccination to close contacts of the people infected with MenB [16]. During a 9-month period, three IMD-B cases occurred; two in spring-summer 2018 and one in late 2018. After the first two cases, chemoprophylaxis was provided to close contacts of the cases. Still, the third case occurred in the same school, caused by the same finetype, which was antimicrobial susceptible. 4CMenB was provided after the third case occurred, and in the year following vaccination, no additional cases had occurred.

6.6.6.3 Meningococcal vaccination

The paper of the Global Meningococcal Initiative summit meeting [6] discussed the two pentavalent MenABCWY vaccines that are being developed: one combining MenB-FHbp with MenACWY-TT and another combining 4CMenB with a quadrivalent MenACWY-CRM197, as well as the pentavalent MenACWXY that is developed for Africa. The MenABCWY vaccines have been tested in phase II. It was shown for the 'MenB-FHbp-MenABCWY' vaccine that a higher proportion of participants had a ≥ 4-fold increase in hSBA titre against serogroups A, C, W and Y one month after doses 1 and 2 compared to a single dose of the MenACWY-CRM197, and a similar pattern was also reported for serogroup B.

In two phase 2b clinical trials, the immunogenicity and safety of the '4CMenB-MenABCWY' vaccination as well as antibody persistence and response to a booster dose two years after the last vaccination, were assessed among adolescents (10-18 years) [17]. Approximately 1,000 individuals were included in the trial. It was found that MenABCWY vaccination was immunogenic against MenB test strains, with the following point estimates: fHbp: 86-89%, NadA: 97-99%, NHBA: 66-70% and PorA: 63% or 72-73%, depending on the used schedule. The safety-profile was similar to 4CMenB.
[18]Sex-specific differences in immune responses have been observed before. Similar differences have been investigated in a Dutch study among 10-, 12- and 15-year-olds who had been primed with MenC vaccination between 14 months and 6 years of age and who received a booster with MenC or MenACWY [19]. The study included 342 girls and 327 boys from two clinical trials. At one month post-MenACWY, no consistent sex-specific differences were observed. However, one year after the MenACWY booster, girls had higher titers than boys (GMT-ratio range: 1.31 (1.02-1.70) for MenA IgG to 1.54 (1.10-2.16) for MenW IgG). For MenC, at all timepoints, girls had higher titres than boys (GMC- and GMT-ratios: 1.16/1.17 at one month, 1.16/1.22 at one year, and 1.12/1.15 three years post-vaccination). Note, however, that the percentage of participants who were protected according to an SBA titre ≥8 presented no statistical differences between sexes.
The impact of the MenACWY vaccination in the UK in 2015 to control an IMD-W cc-11 outbreak was assessed four years after the campaign. The vaccine uptake had been 37-41% in 18-year-olds and 71-86% in teenagers [20]. Compared to what was expected on the basis of pre-vaccination trends, significant reductions were observed among 14–18-year-olds for IMD-W (IRR 0·35, 95% CI 0·17–0·76) and IMD-Y (0·21, 95% CI 0·07–0·59). Indirect protection prevented about ten times as many IMD-W cases (n=205–1193, depending on the scenario) as direct protection (n=25). The overall VE against IMD-CWY was estimated at 94% (95% 80-99).
After the MenACWY vaccination campaigns in the Netherlands in 2018, a questionnaire study was performed to determine the tolerability of the vaccination [21]. Out of 5,000 invitees, 139 returned the questionnaire. More than half of the participants (56%) reported a local reaction in the week post-vaccination; pain (50%) and reduced use of the injected arm (21.3%) were most often reported. No increase in systemic events were reported.
In the US, an evaluation was performed of the breakthrough cases among those vaccinated with MenACWY at 11-12 years and a booster at 16 years, as well as among individuals with underlying medical conditions that are recommended meningococcal vaccination (2+1 schedule). They used the National Notifiable Diseases Surveillance System (NNDSS) and additional data from the State health department from 2014 through 2018 [22]. Out of the 822 IMD cases in that period, 34 (7% of those with known vaccine status) had received at least 1 dose MenACWY. In 2018, the vaccine coverage for adolescents was 87% for at least one dose and 51% for two doses. Out of 30 breakthrough cases with information on the number of doses, 23 had been sufficiently vaccinated. When comparing with unvaccinated cases, those with breakthrough infections seemed to suffer more from immunosuppression (direct comparison not possible). Otherwise, several had incomplete vaccination or had a relative long time since vaccination indicating that waning may have occurred.

6.6.6.4 Communication during vaccination campaigns

During the Dutch MenACWY vaccination catch-up campaign directed at teenagers in 2018-2019, a study was performed aiming to appraise the ability of the healthcare professionals to meet the information needs [23]. The study was directed at information needs of teenagers and their parents at the start of the vaccination campaign. Online surveys among 1,603 teenagers (53% response) and 1,784 parents (57% response) were performed. Furthermore, expectations of healthcare professionals (478 GPs (13% response), and 42 youth health care professionals (2% response on a newsletter)) were determined about what information teenagers and parents needed. Information regarding IMD prevention, vaccine effectiveness and vaccine protection duration were important in the three groups. Although healthcare professionals' expectations of the information needs were quite accurate, some important discrepancies were found. E.g., the need for information on IMD was overestimated by health care professionals, while the importance of information on vaccination was underestimated. The largest underestimation was found on information on vaccine research; only 14% of healthcare professionals thought this was important, while 45% of teenagers found this important.

Another study undertaken in response to the MenACWY vaccination campaign, looked into the dynamics of public perceptions of and responses to the outbreak and the menACWY vaccination and into the media coverage about the outbreak [24]. To study these aspects, three repeated surveys were performed between 2017 and 2019 among parents of teenagers invited for vaccination, other parents, and individuals with no children under the age of 18 years. The surveys included questions on IMD risk perception, attitudes towards the menACWY vaccination, trust in involved institutions, and willingness to vaccinate with the menACWY vaccine. 1,110 individuals participated in the first round (68%), of whom 784 participated in the second, and 558 in the third round. Over time, the perceived IMD severity, the attitude towards the menACWY vaccination, and the willingness to vaccinate increased, as well as the trust in involved institutions (slight increase). There was substantial and increasing newspaper coverage during the study period, providing elaborate information about the increase in disease and the severity of the disease as well as of the importance of MenACWY vaccination. The absence of doubt in the news about vaccine safety possibly affected the (positive) societal response to this outbreak and the MenACWY vaccine.

6.6.7 Literature

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* RIVM publication.

6.6.8 Other RIVM publications

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6.7 Mumps

I.K. Veldhuijzen, R. Bodewes, P. Kaaijk, N.Y. Rots, C.A.C.M. van Els, W.L.M. Ruijs, H.E. de Melker

6.7.1 Key points

- In 2021, only one, and in the first 6 months of 2022, two cases of mumps were reported.

6.7.2 Tables and figures

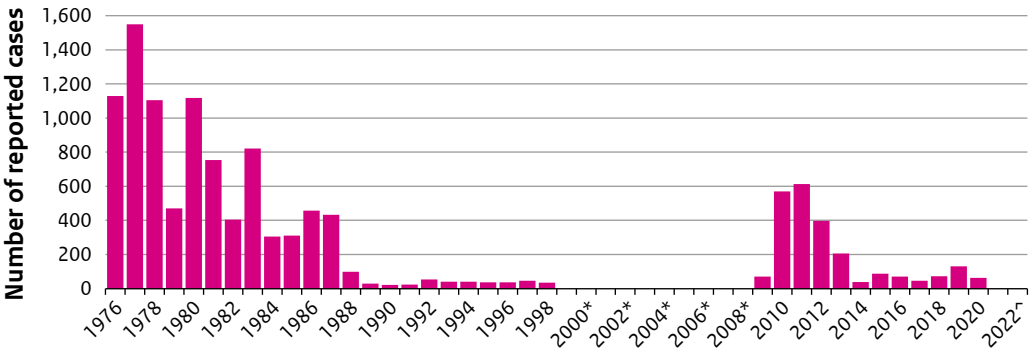

Figure 6.7.1 Number of notified mumps cases in the period 1976-2022.
* In the period 1999-2008 mumps was not notifiable.
^ Cases up to and including June.
Source: Osiris

6.7.3 Epidemiology

Following the introduction of mumps vaccination in the NIP in 1987, there was a large decline in the incidence of mumps in the Netherlands. From late 2009 until 2012, a countrywide epidemic with over 1,500 reported cases occurred that especially affected (vaccinated) student populations (Figure 6.7.1). After 2012, the number of reported mumps cases among students declined. In 2019, the number of cases was relatively high with 131, and the increase continued in the first quarter of 2020. However, the control measures in response to the COVID-19 pandemic resulted in a sharp decline of reported cases after 1 April 2020. In 2021, only one case was reported with clinically compatible symptoms but laboratory confirmation on a serological IgM response only. In the first six months of 2022, two cases were notified with disease onset in April and May. Only the last case was confirmed by PCR. This case was likely infected by a household contact who developed symptoms after returning from Pakistan but was not tested.

6.7.4 Pathogen

In the past decade, most mumps cases in the Netherlands were caused by infection with genotype G mumps viruses. In 2021, no material for PCR testing was available for the only reported case. In the first half of 2022, material for genotyping was available for one of the two reported cases. Sequence analysis of the SH gene of the detected virus indicated that it was a mumps genotype G virus. In recent years, this exact sequence has not been detected in The Netherlands, nor was an exact match found with mumps viruses detected in other countries.

6.7.5 Research

RIVM performs multi-disciplinary research to gain insight into the cause of, and to create possible solutions for, the occurrence of mumps outbreaks among young, vaccinated adults.

6.7.5.1 Immunity to mumps virus

6.7.5.1.1 Clinical MMR-3 study

Previously, we reported that an extra (third dose) of the MMR vaccine (MMR-3) is expected to be an effective and safe intervention for controlling a mumps outbreak among young adults based on an immunogenicity and safety study that we had performed [1]. Now we report that mumps-specific IgG and virus neutralising antibody levels at three years after vaccination are still elevated compared to pre-vaccination antibody levels [2].

6.7.5.1.2 T cell immunity

Apart from waning of vaccine-induced antibody responses, suboptimal induction of T-cell responses may reduce immune protection against mumps. In a recent study, we further explored the T cell response induced after mumps virus infection and revealed a stable mumps-specific T-cell repertoire over time that characterises the long-term cellular memory response induced after natural infection [3]. Furthermore, we identified novel mumps virus epitopes that induced high frequencies of activated T cells in mumps patients, but only marginal T cell responses against these novel mumps virus epitopes could be detected in recently vaccinated individuals [4]. This provides insights that improve understanding of the discrepancies between natural infection and vaccination-induced protective T cell immunity. Furthermore, antigenic differences between mumps virus vaccine and outbreak strains were investigated that may contribute to lower vaccine effectiveness due to a diminished T cell recognition of the outbreak virus. Amino acid differences were found in 78% (31/40) of T cell antigenic determinants of the vaccine strain when compared with a total of 462 genomes of circulating mumps viruses available on GenBank. These amino acid differences within T cell antigenic determinants may potentially lead to reduced T cell immunity against circulating mumps viruses [5].

Nevertheless, it is good to consider that the mumps vaccine has proven to be highly efficacious resulting in a 99% decline in disease incidence compared to the pre-vaccine era [6]. However, a third dose of the MMR vaccine may help to prevent and/or control mumps outbreaks by improving immunity to mumps virus [1, 7, 8].

6.7.6 Literature

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* RIVM publication.

6.8 Pertussis

D.L. van Meijeren, M.M. Immink, R. Mariman, P. Versteegen, A. Buisman, E. Pinelli Ortiz, C.A.C.M van Els, H.E. de Melker

6.8.1 Key points

- The decreasing trend in the number of notifications that was observed after the introduction of the COVID-19 measures in March 2020 has continued in 2021. In 2021, the overall number of pertussis notifications and the incidence rate (IR) were 74 and 0.4 per 100,000 respectively. It should be noted that in 2021, the incidence was affected by a pseudo-outbreak in infants diagnosed with *Bordetella parapertussis*. In the first four months of 2022, no increase in the number of pertussis notifications was observed yet.
- Besides a reduction of circulation of *B. pertussis* due to the COVID-19 measures, other reasons, for example changed care-seeking behaviour for complaints that are consistent with a pertussis infection, might have caused part of the decrease in the number of notifications.
- Between April 2020 and May 2022, only eight *B. pertussis* cases in 0- to 3-month-olds were reported. Using an estimated maternal vaccination coverage of 70% [2], VE was estimated at 74% (95% CI: -32 to 96%).
- Among others, preliminary results from the PIMPI study showed that in 2-month-olds whose mother received the maternal Tdap vaccination between 20-24 weeks of gestational age (GA), geometric mean concentrations (GMCs) of IgG antibodies were comparable between terms and late preterms for all antigens in Tdap vaccination. However, regarding filamentous hemagglutinin (FHA), pertactin (Prn) and tetanus toxoid (TT), significantly lower concentrations were found in early preterms [4].
- Research showed that antibodies in sera from (ex)pertussis patients can opsonise *B. pertussis* and induce reactive oxygen species production by human neutrophils, which is essential for killing this bacterium [5].

6.8.2 Tables and figures

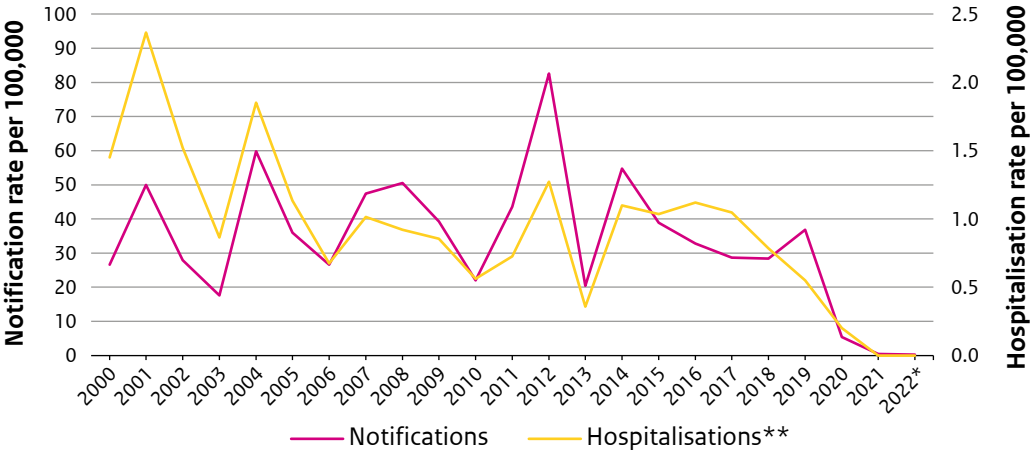

Figure 6.8.1 Pertussis notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 2000-2022*.

* For 2022, notifications are depicted for the period up to and including April 26th, extrapolated to numbers for a whole year.

** No hospitalisation data from 2021 onwards are available yet.

Source: Osiris and Statistics Netherlands

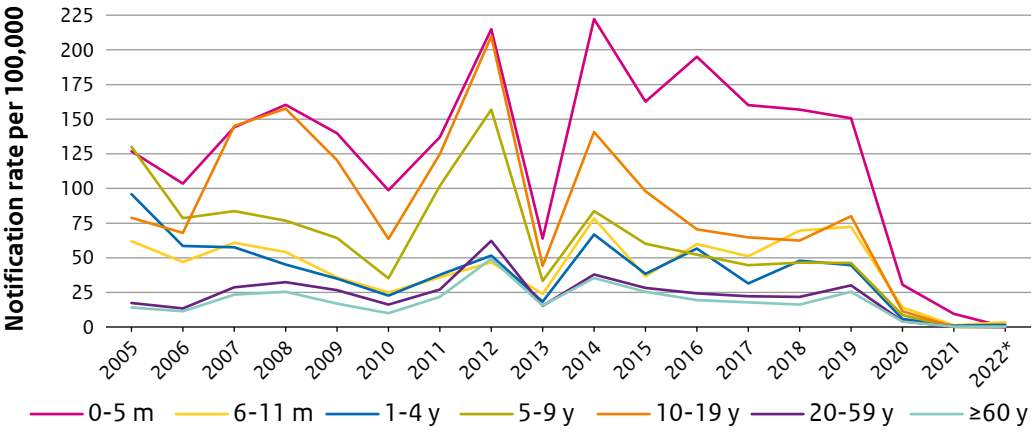

Figure 6.8.2 Pertussis notifications per 100,000 per age category for 2005-2022*.

* For 2022, notifications are depicted for the period up to and including April 26th, extrapolated to numbers for a whole year.

Source: Osiris

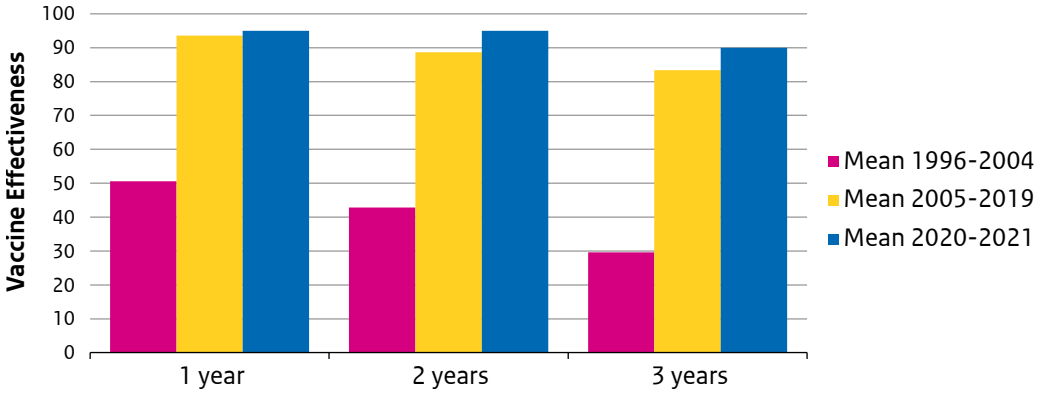

Figure 6.8.3 Vaccine effectiveness of primary pertussis vaccination, calculated with the screening method*, estimated for 1-, 2- and 3-year-olds during use of the whole-cell pertussis vaccine (mean 1996-2004) and during use of the acellular pertussis vaccine (mean 2005-2019, and 2020-2021 separately).

* A population coverage of 94% was used for 2017, and 93% for 2018-2021. For all other years, a population coverage of 96% was used.

Source: Osiris, National vaccination coverage report [1]

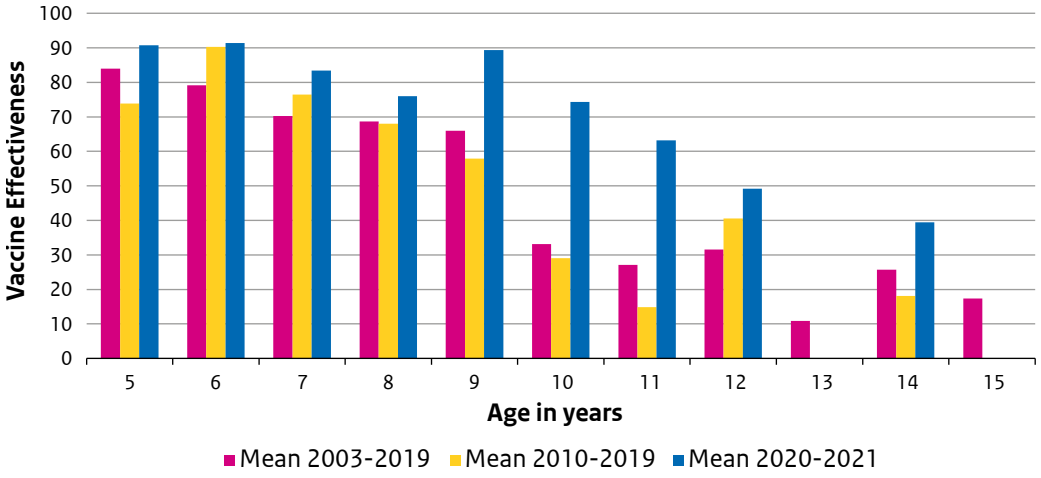

Figure 6.8.4 Vaccine effectiveness of the pre-school booster, calculated with the screening method*, estimated for 5- to 15-year-olds for the whole-cell pertussis priming cohorts (mean 2003-2019, birth years 1998-2004) and the acellular pertussis priming cohorts (mean 2010-2019 and 2020-2021 separately, birth years 2005 and younger).

* For all separate birth cohorts, the registered population coverage of the booster vaccination was used, as retrieved from the National vaccination coverage report.

Source: Osiris, National vaccination coverage report [1]

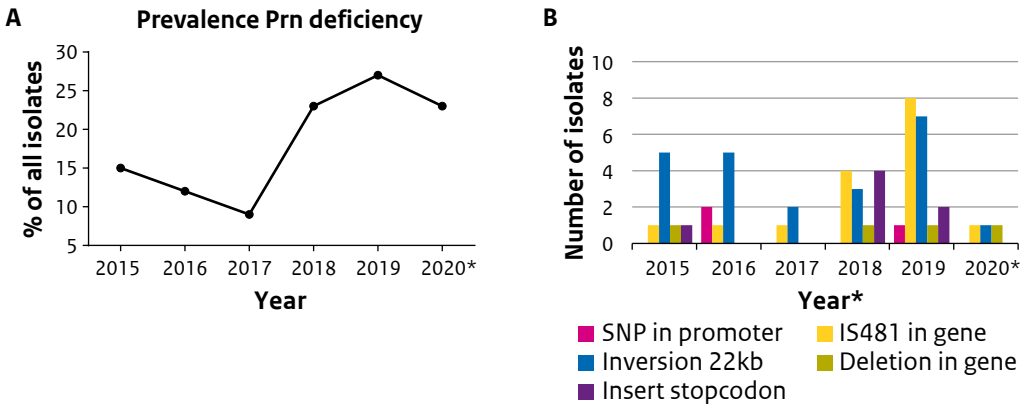

Figure 6.8.5 Prevalence (A) and molecular mechanism (B) of loss of pertactin (Prn) production in clinical isolates collected between 2015 and 2020**.

* Data from 2020 was based on a limited number of isolates.

** No isolates were available for 2021 and 2022.

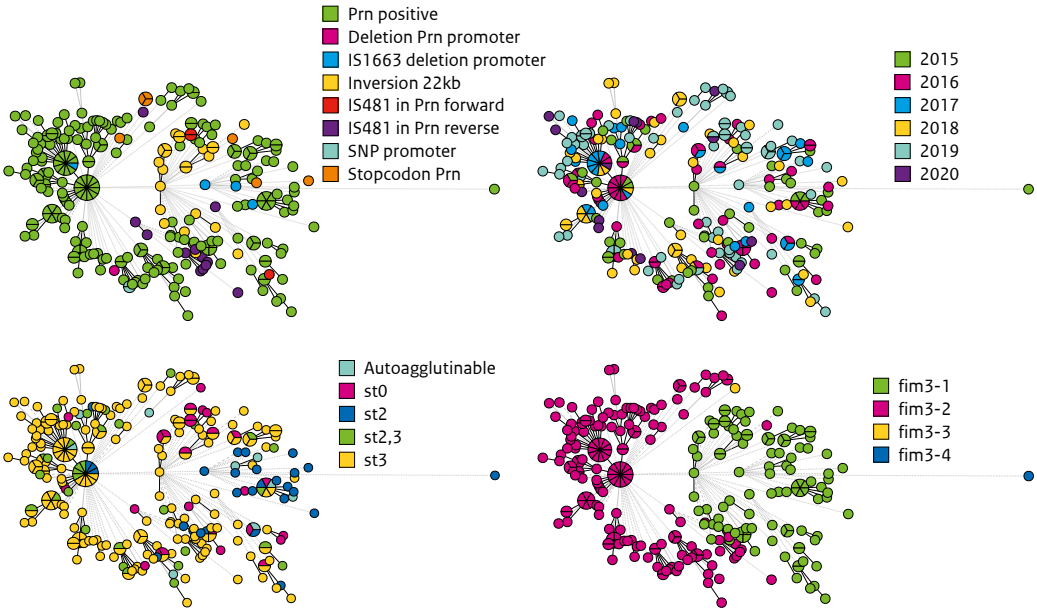

Figure 6.8.6 Genetic relationship between 271 clinical isolates obtained between 2015-2020, based on wgMLST, with clustering based on the genetic relationships between Prn strains by molecular mechanism (A), year (B) and serotype (C), and Fim3 subtype (D). In 2021 and 2022, up to and including May, no isolates were sequenced.

Table 6.8.1 Geometric mean concentrations with 95% confidence intervals in early and late preterms, term-born infants, and term-born infants whose mothers were vaccinated between 30-33w GA. Preliminary results from the PIMPI-study.

	Maternal Tdap vaccination between $20^{0/7}$-$24^{0/7}$w GA			Maternal Tdap vaccination between $30^{0/7}$-$33^{0/7}$w GA (historical comparator)
	Delivery between $25^{2/7}$-$31^{6/7}$w GA	Delivery between $32^{0/7}$-$34^{6/7}$w GA	Delivery between $37^{0/7}$-$42^{0/7}$w GA	Delivery between $37^{0/7}$-$42^{0/7}$w GA
Mother at delivery	*n=38*	*n=35*	*n=138*	*n=55*
Anti-PTx	75.24 (48.90-115.79)	47.64 (29.85-76.03)	32.88 (26.01-41.57)	61.83 (46.79-81.70)
Anti-FHA	241.03 (165.97-350.03)	200.19 (141.14-283.93)	161.10 (135.52-191.52)	163.39 (132.48-204.59)
Anti-Prn	194.15 (112.92-333.84)	213.21 (110.94-409.74)	176.52 (129.93-239.81)	285.97 (182.42-448.30)
Anti-DT	0.77 (0.57-1.03)	0.49 (0.36-0.68)	0.30 (0.24-0.37)	0.35 (0.26-0.47)
Anti-TT	6.84 (5.07-9.22)	4.47 (3.42-5.85)	3.32 (2.88-3.83)	3.53 (2.99-4.16)
Infant cord blood	*n=45*	*n=41*	*n=146*	*n=54*
Anti-PTx	56.24 (39.98-79.12)	49.30 (32.50-74.78)	58.65 (46.38-74.16)	125.05 (94.03-166.31)
Anti-FHA	169.30 (124.01-231.14)	224.10 (162.81-308.45)	295.19 (249.05-349.87)	330.93 (261.18-419.32)
Anti-Prn	106.36 (62.35-181.43)	200.15 (112.26-356.85)	295.45 (216.70-402.82)	500.46 (322.48-776.66)
Anti-DT	0.58 (0.42-0.80)	0.47 (0.35-0.64)	0.48 (0.39-0.59)	0.64 (0.48-0.86)
Anti-TT	5.48 (4.18-7.19)	4.84 (3.49-6.72)	5.95 (5.15-6.88)	7.39 (6.19-8.82)
Infant at 2m of age	*n=37*	*n=36*	*n=66*	*n=55*
Anti-PTx	8.63 (5.52-13.48)	14.58 (9.25-22.99)	14.70 (10.58-20.44)	27.32 (20.13-37.08)
Anti-FHA	34.36 (23.28-50.69)	69.97 (49.40-99.11)	83.07 (63.25-109.11)	83.68 (67.36-103.94)
Anti-Prn	21.56 (10.88-42.73)	71.49 (40.49-126.24)	59.76 (38.42-92.97)	110.31 (71.58-169.98)
Anti-DT	0.09 (0.06-0.14)	0.13 (0.09-0.18)	0.12 (0.087-0.16)	0.13 (0.10-0.17)
Anti-TT	1.02 (0.75-1.39)	1.40 (1.00-1.96)	1.53 (1.24-1.89)	1.67 (1.42-1.97)

GA: gestational age, GMC: Generalised mean concentration, PTx: pertussis toxin, FHA: filamentous hemagglutinin, Prn: pertactin, DT: diphtheria toxoid, TT: tetanus toxoid. Concentrations were presented in international units per millilitre. Women vaccinated between 200/7-240/7w GA were included in the current study, as opposed to women vaccinated between 300/7-330/7w GA, who were included in the historical comparator study.

6.8.3 Epidemiology

6.8.3.1 Disease

The decreasing trend in the number of notifications that was observed after the introduction of the COVID-19 measures in March 2020 has continued in 2021. In 2021, the overall number of pertussis notifications and the incidence rate (IR) were 74 and 0.4 per 100,000 respectively, which are unprecedentedly low numbers compared with the past 25 years. In 2020 the overall number of notifications was 943 and the IR 5.4 per 100,000 (Figure 6.8.1), of which most notifications were made between January-March. In the first four months of 2022, no increase in the number of pertussis notifications was observed yet. Besides a reduction of circulation of *B. pertussis* due to the COVID-19 measures, other reasons, for example changed care-seeking behaviour for complaints that are consistent with a pertussis infection, might also have caused part of the decrease in the number of notifications.

Compared with 2020, the IR continued decreasing in all age categories in 2021. The IR was lowest in children aged 5-9 years (0.1 per 100,000) and remained highest in 0- to 5-month-old infants (9.5 per 100,000) (Figure 6.8.2). However, for all notified infants, *B. parapertussis* was the reported pathogen. Analyses during 2021 revealed that batches of contaminated nasopharyngeal swabs were associated with a pseudo-outbreak of *B. parapertussis*, resulting in incorrect diagnoses and public health notifications [3]. Therefore, it is unlikely that they were truly infected with *B. parapertussis*. Hence, the IR among 0- to 5-month-old infants is in reality probably lower than 9.5 per 100,000.

Since the maternal pertussis vaccination (Tdap, MPV) was introduced in the NIP only 3 months before the COVID-19 measures were introduced, it is as of yet very difficult to distinguish a potential effect of the vaccination from the effect of the COVID-19 measures on the pertussis incidence among 0- to 5-month-old infants.

In 2021, no deaths due to a pertussis infection were reported, compared to one or two deaths each year since 2014. No hospitalisation data for 2021 are available yet.

6.8.3.2 Vaccine effectiveness (VE)

Maternal Tdap vaccination was introduced into the NIP in December 2019, and is recommended at 22 weeks pregnancy. Infants whose mothers had received the maternal Tdap vaccination, no longer received their first pertussis-containing vaccine at two months of age, but rather at three months of age; the first infants whose mother had received the maternal Tdap vaccination, were eligible for their first pertussis-containing vaccine from April 2020 onwards. Between April 2020 up to and including May 2022, eight *B. pertussis* cases in 0- to 3-month-olds were reported, of which three infants had received maternal Tdap vaccination. Using an estimated maternal vaccination coverage of 70% [2] VE was estimated at 74% (95% CI: -32 to 96%) with the screening method. It should be noted that the VE estimates of the years 2020-2021 are based on a relatively low number of notifications. These VE estimates might therefore not be accurate.

Figure 6.8.3 shows the VE estimates of the infant series during use of the whole-cell pertussis vaccine (mean 1996-2004) and use of the acellular pertussis vaccine (mean 2005-2019, and 2020-2021 separately). Since the switch from whole-cell pertussis (wP) vaccine to an infant combination vaccine with an acellular pertussis (aP) component in 2005, the VE estimate has been consistently high up to the booster vaccination given at 4 years of age. It should be noted that the VE estimates of the years 2020-2021 are based on a relatively low number of notifications compared with the period 1996-2019, and that most of these notifications were made in the first three months of 2020. A separate estimate for 2021 could therefore not be made.

Following the booster dose at the age of 4, the VE estimate shows a decrease after ~5 years, i.e., when children reach the age of 10 (Figure 6.8.4). This is in agreement with the notification rates in these age groups as 10-to-19-year-olds have a higher IR compared to 5-to-9-year-olds. It should again be noted that the VE estimates of the years 2020-2021 are based on a relatively low number of notifications compared with the period 2003-2019, and that most of these notifications were made in the first three months of 2020. A separate estimate for 2021 could therefore not be made.

The VE estimates discussed above, are made by use of the screening method. This is a rather crude method to easily calculate VE that can be used to monitor VE over time. Appendix 1 provides an overview of the methods that can be used to estimate VE.

6.8.4 Pathogen

In the Netherlands, the NIP makes use of an acellular pertussis (aP) vaccine consisting of five pertussis antigens, i.e., fimbriae 2 and 3 (Fim2 and Fim3), pertussis toxin (PTx), filamentous hemagglutinin (FHA) and pertactin (Prn). The re-emergence of pertussis has been attributed to several factors, including bacterial strain adaptation due to vaccine pressure [6]. Hence, careful monitoring of bacterial expression of vaccine targets, in particular Prn, is essential. Therefore, Dutch medical microbiology laboratories are asked to submit their *B. pertussis*-suspected samples to RIVM. Confirmed *B. pertussis* strains are whole genome sequenced (WGS), and an antigen expression validation assay is performed for the pertussis antigens PTx, Prn, and FHA. In 2021 and 2022, for the period up to and including May, no strains were received for strain surveillance, which is in line with the low number of pertussis notifications in this period. We expect an increase in the number of isolates due to the easing of COVID-19 control measures in the second half of 2022. Results of the strain surveillance for the years 2015-2020 can be found in Figure 6.8.5 and Figure 6.8.6.

Between 2010 and 2015, an emergence of *B. pertussis* isolates deficient in the vaccine component Prn was observed with a prevalence of 10-15% in 2015-2017. However, in 2018, a sharp increase was observed, with Prn deficiency in 24% (11/46) of clinical isolates. This alarming increase continued in 2019, with Prn deficiency in 27% of all isolates (19/71). In 2020, 21% (3/14) of all collected isolates were found to be Prn-deficient (Figure 6.8.5A). Sequence analysis from 2015-2020 showed that an inversion of ~22 Kb in the promotor region was the most frequently observed cause of Prn deficiency (n=23), followed by an insertion of the IS481 element in the

prn gene (n=16), and insertion of a stop codon (n=7) as shown in Figure 6.8.5B. In 2021 and in 2022 for the period up to and including May, no data are available.

In 2018, one clinical strain was isolated that lacks production of the acellular vaccine immunogen FHA.

Core-genome whole genome multi locus sequence typing (cgMLST) using an in-house scheme consisting of 3,180 genes based on *B. pertussis* isolate B1917, was used to infer genetic relationships between the isolates. Figure 6.8.6 shows the genetic relationship between all 271 *B. pertussis* strains isolated between 2015 and 2020. No clustering of isolates based on year (Figure 6.8.6B) or serotype (Figure 6.8.6C) was observed. However, close genetic relationships between Prn strains caused by 22kb inversion (Figure 6.8.6A) and distinct clusters identified based on Fim3 subtype can be observed (Figure 6.8.6D). This is of interest because of an observed shift from Fim3-1 to Fim3-2 strains, which comprised 65% of all *B. pertussis* strains in 2016 and 2017, and 76% of all isolates in 2018.

6.8.5 Immunology

6.8.5.1 Maternal pertussis vaccination

In the PIMPI-study, pregnant women (n=221) received a Tdap vaccination between $20^{0/7}$ and $24^{0/7}$w gestational age (GA). At delivery, a maternal blood sample was drawn and infant blood was drawn from the umbilical cord. Additionally, 60 term (≥37w GA) and 66 preterm (<35w GA) mother-infants-pairs donated an infant blood sample at 2 months of age, before primary infant vaccinations. Results showed that as GA at delivery increased, and the time window between vaccination and blood sampling extended, geometric mean concentrations (GMCs) of IgG antibodies decreased in mothers in case of pertussis toxin (PTx), tetanus toxoid (TT) and diphtheria toxoid (DT) (Table 6.8.1). Nevertheless, increased GA, which permits time for antibody transfer, resulted in comparable (PTx, TT, and DT) or higher (FHA and Prn) GMCs in term-born cord sera compared to early preterms (i.e., <320/7w GA), see Table 8.8.1. Ultimately, GMCs at 2 months of age were comparable between terms and late preterms (i.e., $32^{0/7}$-$34^{6/7}$w GA) for all antigens (for PTx 14.70 IU/mL, 95% CI 10.58-20.44 vs 14.58 IU/mL, 95% CI 9.25-22.99, respectively, early preterms 56.24 IU/mL, 95% CI 39.58-79.12), but significantly higher than in early preterms for FHA, Prn and TT. In addition, data from term mother-infant-pairs were compared to a historical control group in which mothers were vaccinated between 30-33w GA. Results showed that cord sera and sera at 2 months provided higher GMCs in the historical control group for PTx and Prn. In conclusion, this study showed that preterm infants depend on maternal antibodies that may be optimally induced by early timing of maternal Tdap vaccination throughout gestation. While term infants may benefit more from maternal Tdap vaccination later throughout gestation, the vulnerability of preterm infants should be taken into account during the evaluation of the maternal Tdap vaccination and the concomitant reduced and postponed infant vaccination schedule [4].

6.8.5.2 *Humoral immunity*

Booster vaccinations for pertussis are advised in many countries during childhood and/or adulthood. In a phase IV longitudinal, interventional study, long-term immunity following an extra pertussis booster vaccination was assessed in children and in adults. Children (9 years of age) were primed in infancy with either the Dutch whole cell pertussis (wP) vaccine (n=49), or an acellular pertussis (aP) vaccine (n=59), and all children received a preschool aP booster. Adults (25-29 years, n=86) were wP primed in infancy and did not receive a preschool booster. All were followed-up for approximately six years. After the additional booster, antibody responses to pertussis were more heterogeneous but generally higher in adults than in children, and additional modelling showed that antibody concentrations remained higher for at least a decade. Serologic parameters indicative of recent pertussis infection were more often found in aP primed children than in wP primed individuals. This suggests that aP booster vaccination in aP primed children offers less long-term protection against pertussis infection and consequently against transmission. Differences in antibody kinetics between wP primed children and wP primed adults with ultimately higher antibody concentrations in the young adults, are probably caused by exposure to *B. pertussis* during life [7].

6.8.5.3 *Innate and adaptive immunity to B. pertussis*

Despite vaccination, *B. pertussis* remains capable of circulating and infecting individuals of all ages. This is due to a combination of waning or suboptimal immunity and emergence of *B. pertussis* strains that can escape or modulate pre-existing immunity. Evidence is accumulating that the initial priming of the specific cellular immunity to *B. pertussis*, steered by innate cells, determines the duration of acquired protective immunity. The underlying cellular mechanisms, explaining why both natural infection and the previous wP vaccine induce a far more effective and durable immune response than the current aP vaccine, are being studied with international partners (see section 6.8.6). Pertussis is seen in all age groups, causing a considerable burden at older age. In a clinical cohort (Immfact study) of pertussis cases of various ages, we currently study various specific mechanisms throughout life. Recently we found that functional hallmarks of *B. pertussis*-specific T cells, which are important regulators of immune protection, are affected in older adults [8]. Together with the general weakening of the immune system with age (immunosenescence), loss of *B. pertussis*-specific T cell responsiveness might underly susceptibility to elderly.

Research aiming to unravel innate immune responses to *B. pertussis* shows the importance of innate cell-to-cell communication in combating this bacterium. In addition, the interaction between the innate and adaptive branches of the immune system were investigated. An in vitro model was published that allows measuring reactive oxygen species (ROS) production by human neutrophils (essential for killing this bacterium) upon encountering opsonised *B. pertussis*. The study also shows that antibodies in sera from convalescent (ex)pertussis patients, even three years after acute disease, are functional as they can opsonise *B. pertussis* and induce ROS production by human neutrophils. Since to date there are no well-established correlates of protection (CoP) for pertussis, it is here proposed to further explore ROS production by human neutrophils in response to opsonised *B. pertussis* as a CoP [5].

6.8.6 International developments

The Periscope consortium, consisting of pertussis experts from four national institutes including RIVM, sixteen European universities, and two vaccine companies, are working on an extensive Innovative Medicines Initiative (IMI)-2 project (2016-2021; extension 2021-2022). The main objective of this project is to unravel the difference in protective properties between the aP vaccines, the wP vaccines, and natural infection, and to characterise new biomarkers for protective immunity to *B. pertussis*. The role of RIVM is to develop and apply immunological assays for the measurement of antibodies, T cells, and B cells, and to conduct natural infection and clinical vaccine studies. We identified the frequencies of antigen specific memory B cells before aP booster vaccination, studied the induction of memory B cells one month post-vaccination and monitored the waning of these cells one year post-vaccination. We showed that memory B cell frequencies are highly elevated after aP boosting and that frequencies were still elevated after one year. Furthermore, variations between UK, Finland, and the Netherlands were small, indicating that responses to aP are similar regardless of the pertussis epidemiology in different populations. Our results also show that memory B cell frequencies are reduced in the older adults probably due to immunosenescence. Circulating memory B cells seem most pronounced during adolescence, which is probably a consequence of both vaccinations and natural boosting in this age group [9].

6.8.7 Literature

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* RIVM publication.

6.8.8 Other RIVM publications

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6.9 Pneumococcal disease

A. Afrian, A. Steens, W. Miellet, A. Niessen, K. van Ewijk, R. Mariman, W. Freudenburg-de Graaf, N.M. van Sorge, H.E. de Melker

6.9.1 Key points

- The incidence of invasive pneumococcal disease (IPD) increased from 5.0/100,000 in 2020/2021 to 8.9/100,000 this year, probably as a result of the gradual opening up of society and relaxing of the COVID-19 measures. An increase was seen across all age groups. However, the incidence is still lower than the pre-COVID-19 average of 15.0 per 100,000 per year.
- In 2021/2022, the incidence in children <5 years has increased to the highest level in more than a decade (8.8/100,000). The increase was mainly due to an increase in (PCV13-10) serotypes 19A and serotype 3; serotype 19A is now the most common serotype in children <5 years.
- In the epidemiological year 2021/2022, one vaccine failure (19F) occurred in a child without known underlying medical risk conditions who had received PCV7. The vaccine effectiveness of at least two doses of PCV10 was estimated at 91% (95% CI: 71-97%) compared with no vaccination.
- The PCV13 serotypes that are not included in PCV10 (serotypes 3, 6A and 19A), together with the PCV13-associated serotype 6C (cross-protection of serotype 6A in PCV13/15/20) covered 37% of all cases in 2021/2022. This was lower than 2020/2021 (39%) but higher than 2019/2020 (31%). This percentage was only slightly lower for children <5 years (32%).
- For people ≥65 years, 77% of IPD was caused by a serotype included in the 23-valent pneumococcal polysaccharide vaccine (PPV23). The newly licensed, PCV15 and PCV20 covered 46% and 75%, respectively (note, cross-reacting serotype 6C is included).
- Since autumn 2020, PPV23 is offered to individuals born in 1941-1947 and since autumn 2021 to those born in 1948-1952. The estimated impact of PPV23 on vaccine-type IPD in these age groups was 31% (95%CI 1.0–50.1).

6.9.2 Tables and figures

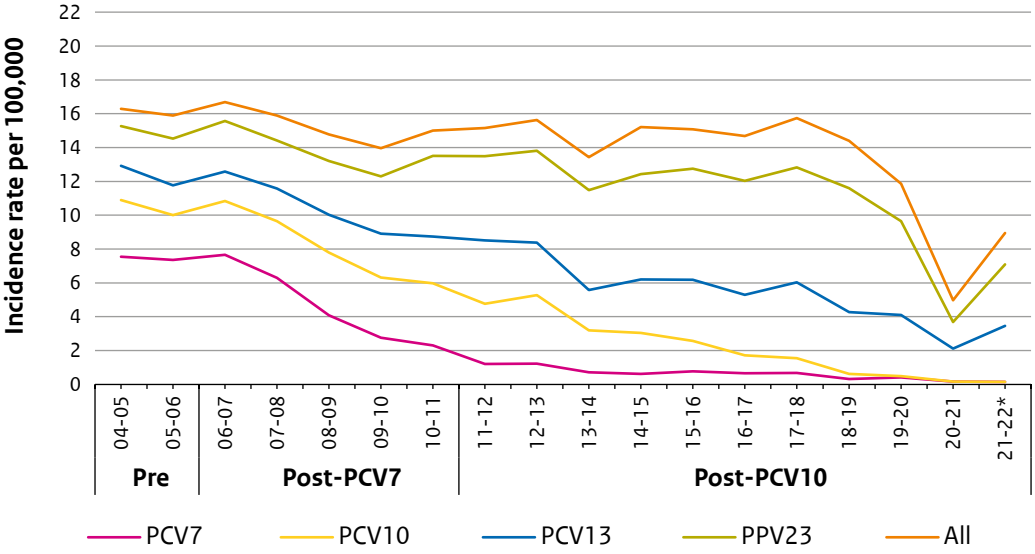

Figure 6.9.1 Incidence of invasive pneumococcal disease (IPD) in all ages by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes, PPV23 serotypes), as well as all serotypes IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005). PCV7 was introduced in the childhood immunisation programme in June 2006 and PCV10 in May 2011. PPV23 was introduced in autumn 2020 for those born in 1941-1947, and in autumn 2021 for those born in 1948-1952. Sentinel surveillance data has been used and are extrapolated to the Dutch population. Only IPD presented with positive blood or liquor samples were included.

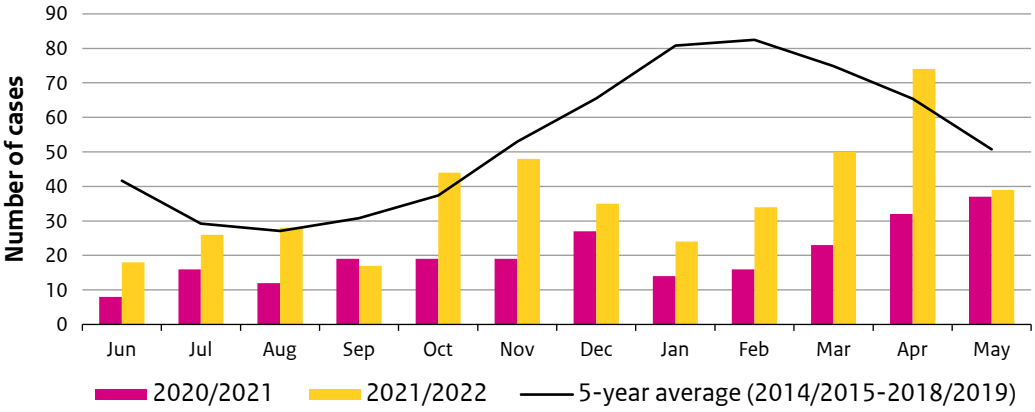

Figure 6.9.2 Number of cases of invasive pneumococcal disease (IPD) from June 2020 up to and including May 2021 (light blue) and June 2021 up to and including May 2022 (dark blue) reported by nine sentinel labs (covering ~28% of the Dutch population) by month compared to the pre-COVID 5-year moving average (2014/2015-2018/2019). Only IPD presented with positive blood or liquor samples were included.

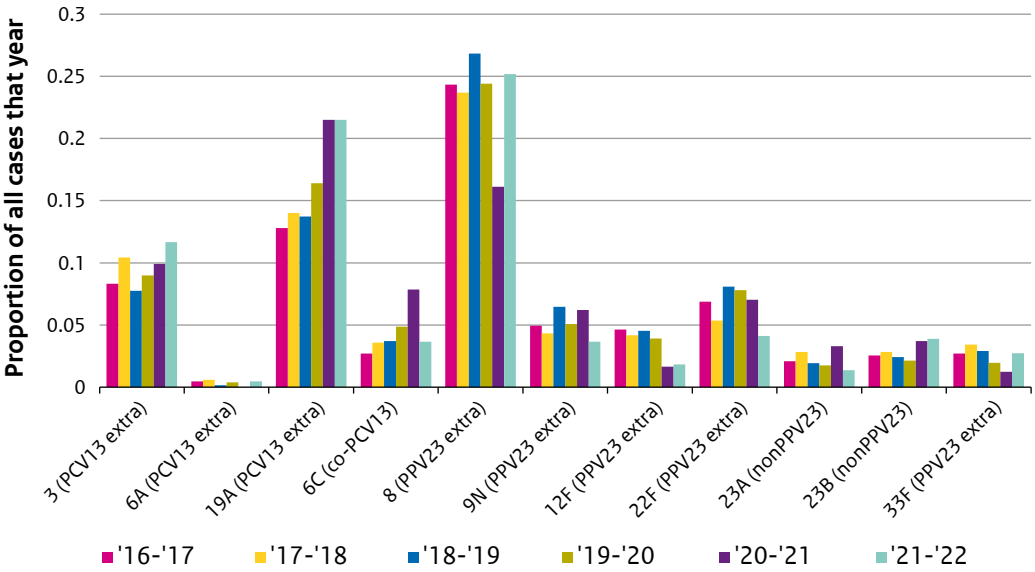

Figure 6.9.3 The proportion of cases in all age groups per serotype of interest in the period 2011-2022. The serotypes have been selected on the basis of their coverage by PCV13 but not PCV10 (PCV13 extra; serotypes 3, 6A and 19A) or related to a serotype within PCV13/15/20 (6C cross-protection from 6A), because they have been described internationally as a serotype of concern (serotypes 8, 9N, 12F) and/or on the basis of their incidence (22F, 23B, 33F). Sentinel surveillance data have been used of IPD presented with positive blood or liquor samples. The epidemiological year ranges from June to May.

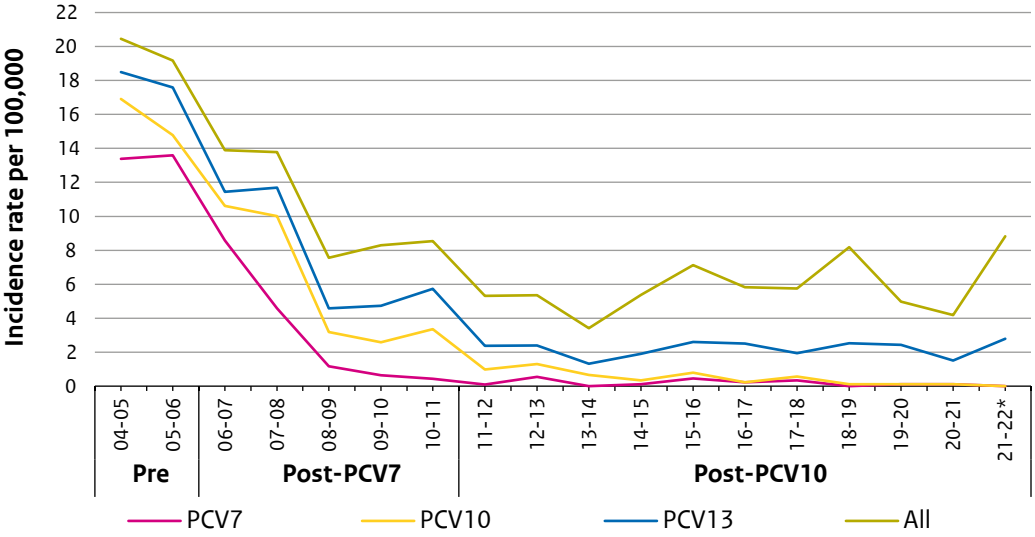

Figure 6.9.4 Incidence of IPD in children <5 years of age by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes), as well as all serotypes IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005).
PCV7 was introduced in June 2006 and PCV10 in May 2011. From 2004-2005 to 2007-2008, sentinel surveillance data has been used and extrapolated to the Dutch population. From 2008-2009 onwards, data of national surveillance has been used of IPD presented with positive blood or liquor samples.

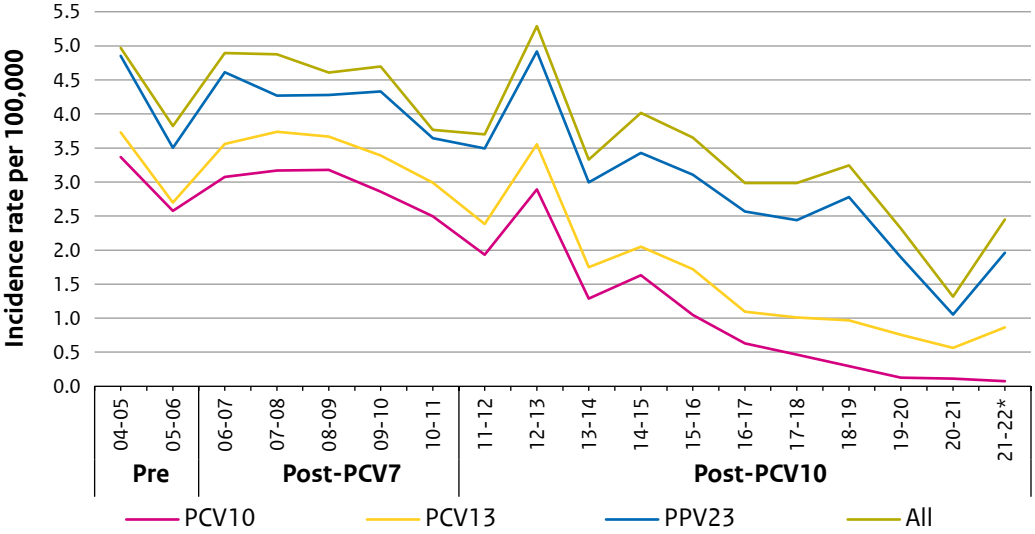

Figure 6.9.5 Incidence of IPD in persons 5-49 years of age by vaccine serotype (PCV1 serotypes, PCV13 serotypes, PPV23 serotypes), as well as all serotypes IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005).
Sentinel surveillance data has been used of IPD presented with positive blood or liquor samples and is extrapolated to the Dutch population.

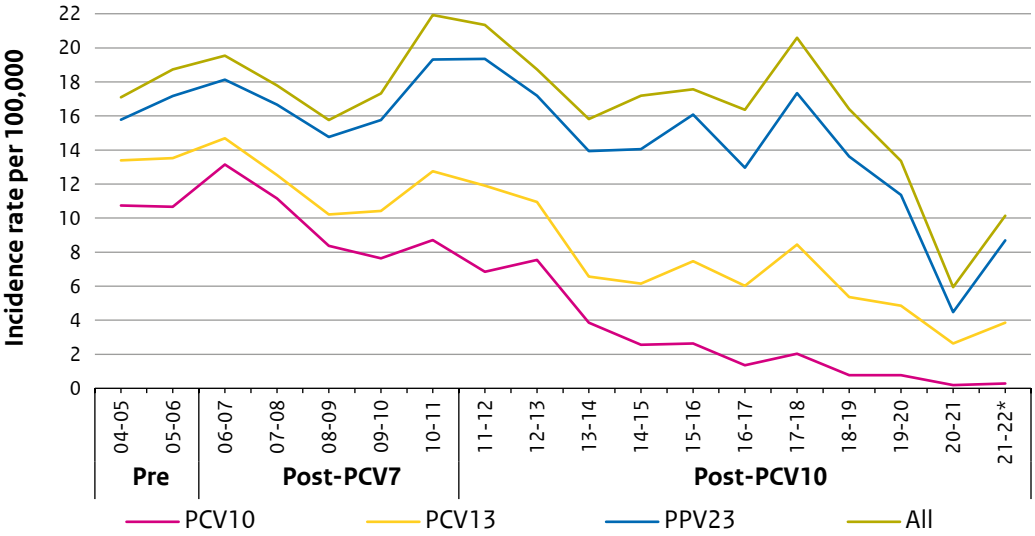

Figure 6.9.6 Incidence of IPD in persons 50-64 years of age by vaccine serotype (PCV10 serotypes, PCV13 serotypes, PPV23 serotypes), as well as all serotypes IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005).
Sentinel surveillance data has been used of IPD presented with positive blood or liquor samples and is extrapolated to the Dutch population.

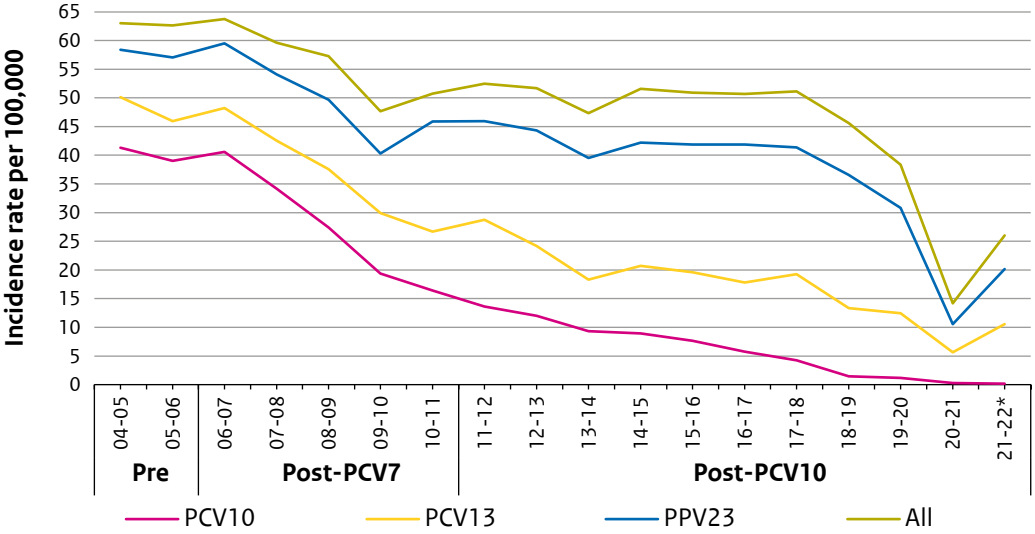

Figure 6.9.7 Incidence of IPD in persons aged 65 years or over, by vaccine serotype (PCV10 serotypes, PCV13 serotypes, PPV23 serotypes), as well as all serotypes IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005).
PPV23 was introduced in autumn 2020 for those born in 1941-1947, and in autumn 2021 for those born in 1948-1952. Sentinel surveillance data has been used of IPD presented with positive blood or liquor samples and is extrapolated to the Dutch population.

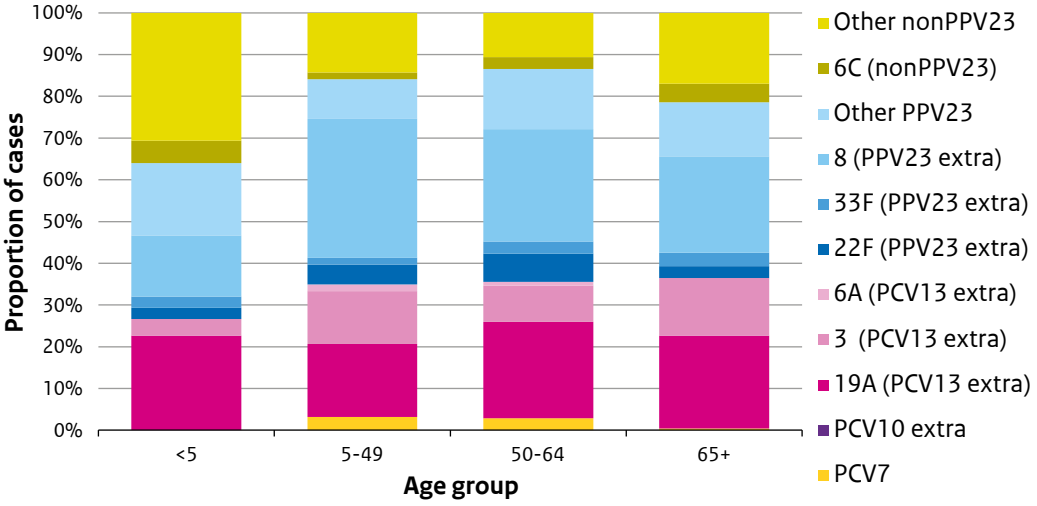

Figure 6.9.8 Distribution of IPD-causing serotypes in epidemiological year 2021/2022. Note that no serotypes that are covered by PCV10 but not PCV7 (PCV10-extra) were observed in this time period.
For children <5 years, data of the national surveillance system has been used. For other age groups, sentinel surveillance data has been used. Only IPD presented with positive blood or liquor samples are included.

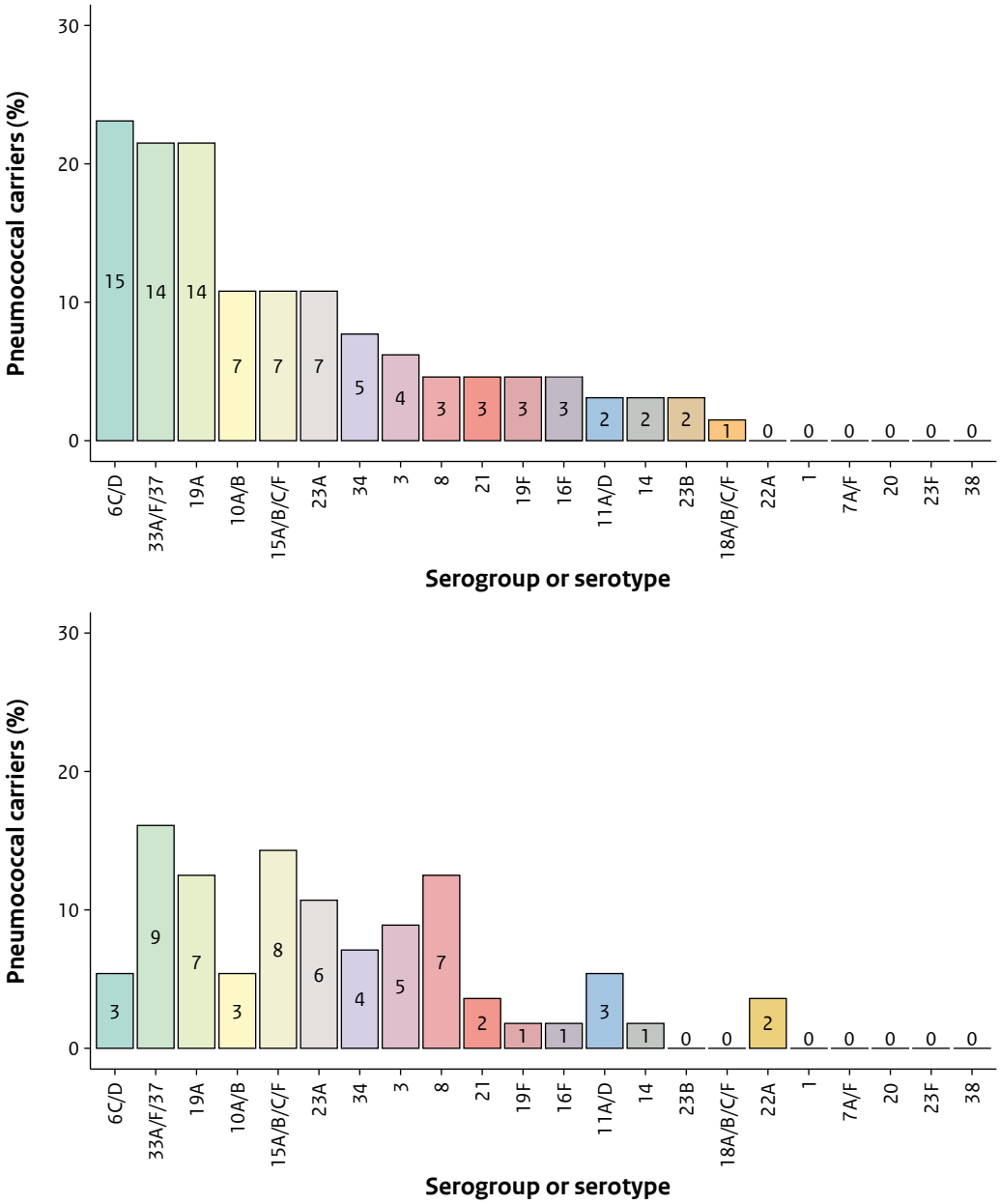

Figure 6.9.9 Bar charts of serogroup-specific or serotype-specific proportions among pooled positive samples (n=1116) of pneumococcal carriers (n=121) found in the SARS-CoV-2 household study SARSLIVA (Oct 2020-Jan 2021), in A: children and B: adults. Pneumococcal serogroups or serotypes are ordered by their rank-frequency. The number shown in the bars indicate the number of positive individuals.

Table 6.9.1 Children eligible for vaccination (born since June 2006) with vaccine-type invasive pneumococcal disease (IPD) who received at least two vaccinations before the diagnosis based on nationwide surveillance data up to and including May 2022.

Year of diagnosis	Age in months	Serotype	Vaccine received	Number of vaccinations	Underlying disease
2008	3	6B	PCV7	2	?
2008	7	6B	PCV7	3	?
2009	29	19F	PCV7	4	?
2009	6	19F	PCV7	3	None
2010	12	6B	PCV7	4	?
2011	59	19F	PCV7	4	Nephrotic syndrome
2012	63	18C	PCV7	4	None
2012	45	19F	PCV7	4	Leukaemia
2012	54	9V	PCV7	4	?
2013	73	19F	PCV7	4	?
2014	68	19F	PCV7	4	CSF leakage, history of meningitis
2014	18	7F	PCV10	4	None
2014	41	23F	PCV10	4	Beta thalassemia with chronic blood transfusions
2015	13	7F	PCV10	3	None
2015	34	19F	PCV10	4	None
2015	50	23F	PCV10	4	?
2016	45	1	PCV10	4	None
2016	25	23F	PCV10	3	None
2017	115	14	PCV7	4	?
2018	31	1	PCV10	3	?
2019	3	14	PCV10	2	None
2021	89	19F	PCV10	3	Immunological underlying illness
2021	24	14	PCV10	3	None

Table 6.9.2 Serotypes included in the different pneumococcal vaccines (current and those in development). In bold, the vaccines routinely used in the vaccination programmes in the Netherlands.

	Vaccine						
Serotype	**PCV7#**	**PCV10**	**PCV13**	**PCV15[2]**	**PCV20[2]**	**PCV21[3]**	**PPV23**
4	X	X	X	X	X		X
6B	X	X	X	X	X		X
9V	X	X	X	X	X		X
14	X	X	X	X	X		X
18C	X	X	X	X	X		X
19F	X	X	X	X	X		X
23F	X	X	X	X	X		X
1		X	X	X	X		X
5		X	X	X	X		X
7F		X	X	X	X	X	X
3			X	X	X	X	X
6A[1]			X	X	X	X	
19A			X	X	X	X	X
6C[1]			(X)	(X)	(X)	(X)	
22F				X	X	X	X
33F				X	X	X	X
8					X	X	X
10A					X	X	X
11A					X	X	X
12F					X	X	X
15B					X	(X)[1]	X
2				X			X
9N				X		X	X
17F						X	X
20[2]						X	X
15A						X	
15C[1]						X[1]	
16F						X	
23A						X	
23B						X	
24F						X	
31				X	X	X	
35B				X	X	X	

Note that PCV7 is no longer in use.

[1] Note that PCV21 defines 6A/C and 15B/C as one serotype each. PCV13, PCV15 and PCV20 protect against 6C through cross-protection of the 6A antigen.

[2] PCV15 and PCV20 have been licenced for adults in Europe since 2022. PCV15 had recentlybeen licensed for children in the US.

[3] PCV21 is currently tested in phase-3 clinical trials.

6.9.3 Epidemiology

Invasive pneumococcal disease (IPD) is notifiable for children born in 2006 or after and for individuals aged 60 years and older [1]. Isolates of persons with IPD in these age groups, are submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) for serotyping, and are linked to notification data. Additionally, nine sentinel laboratories covering about 25% of the population up to 2020, and around 28% of the population since 2020, submit all IPD isolates to the NRLBM. Because of an ongoing evaluation of the surveillance of cases aged 60 years and over, here, we still focus on the sentinel data for that age group, too. For the <5-year-olds, national data is used. In this report, IPD presented by positive blood or liquor samples are included in the analysis of trends over time.

6.9.3.1 Overall

While the overall IPD incidence has been quite stable since 2004/2005, with an average incidence of 15.0 per 100,000 per year (range: 13.4 to 16.7 per 100,000 per year), the incidence in epidemiological year 2020/2021 (June to May) decreased to 5.0 per 100,000, probably as a result of the COVID-19 control measures. The incidence increased again in 2021/2022 to 8.9 per 100,000 (Figure 6.9.1). This re-emergence of IPD in 2021/2022 coincides with the gradual opening up of society and relaxing of the COVID-19 measures (e.g., removal of social distancing and requirement to wear face masks). Still, in the epidemiological year 2021/2022, the number of cases per month was below the pre-COVID 5-year moving average for most months (Figure 6.9.2); in April 2022, the number of cases per month, was above the pre-COVID 5-year moving average and coincided with a large influenza peak after the full opening of the society [2].

The distribution of IPD-causing serotypes has been changing since PCV7 introduction and has continued to change after the switch to PCV10 in May 2011 (Figure 6.9.3). Serotypes that are of specific interest and have increased over the last years (in incidence, or in proportion) are PCV13-serotypes 19A and 3, PCV13-associated serotype 6C (cross-protection of serotype 6A in PCV13/15/20 (2)), PPV23 serotypes 8, 22F and 9N and non-PPV23 serotype 23B. Overall, the most common serotypes in 2021/22 were serotype 8 (25% of all cases), serotype 19A (22%) and serotype 3 (12%). Altogether, PCV10 covered 2% of IPD cases, PCV13+6C 37%, PCV15+6C 46%, PCV20+6C 77% and PCV23 80% of the cases in 2021/2022 (Table 6.9.1).

6.9.3.2 Children <5 years of age (Figure 6.9.4)

In the epidemiological year 2021/2022, 76 IPD cases with a positive blood or liquor sample were reported in children <5 years of age, resulting in an incidence of 8.8 per 100,000 per year. In addition to these 76 cases, there were 5 IPD cases <5 years for which pneumococci were isolated from other normally-sterile places. After the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2006 and the switch to PCV10 in 2011, the incidence decreased substantially and stabilised around 2015/2016 at an incidence 16% lower than the incidence before PCV10 introduction (Figure 6.9.4). Although the incidence in the first COVID-19 year (2020-2021) was lower than previous years, probably related to the control measures, the incidence among children <5 years in 2021-2022 was the highest in more than a decade. This increase was mainly due to an increase in IPD caused by serotypes covered by PCV13 but not

by PCV10 (2.3/100.000 in 2021/2022 versus 1.0/100.000 in 2020/2021; especially 19A and 3). No cases caused by PCV10 serotypes were observed. Out of the 76 cases (26%) aged <5 years in 2021/2022, 20 were caused by PCV13 serotypes that are not in PCV10 (see Table 6.9.2); 17 of these were caused by serotype 19A, the most common serotype seen in 2021/2022 in this age group (Figure 6.9.8). An increase in serotype 19A disease has been reported by more (PCV10) countries after easing the COVID-19 control measures [3]. Another common serotype in this age group was serotype 8 (11 cases, Figure 6.9.8). This serotype is not included in the currently available childhood vaccines but is included in PCV20. Overall, 32% of cases <5 years in 2021/2022 were caused by a PCV13 or PCV13/15/20-associated serotype (6C), 37% by a PCV15 serotype and 68% by a PCV20 serotype. PCV15 and PCV20 are expected to be licensed for use in children within one or two years.

6.9.3.3 Persons aged 5-49 years (Figure 6.9.5)

In the epidemiological year 2021/2022, 65 IPD cases were reported by the nine sentinel laboratories (covering about 28% of the Dutch population) in persons aged 5-49 years, resulting in an incidence of 2.4 per 100,000 per year. The incidence in this age group has decreased slightly over time since the introduction of PCV7. After an even sharper decrease in the incidence in 2019/2020 and 2020/2021 as a result of the COVID-19 control measures, in 2021/2022 the incidence increased again to pre-COVID levels (Figure 6.9.5). This increase coincided with the lifting of the control measures. The IPD incidence due to serotypes included in PCV10 in 2021/2022 was similar to 2020/2021 at 0.1 per 100,000, which is substantially lower compared to the incidence before the introduction of childhood vaccination in 2006 (3.0 per 100,000).
The incidence caused by serotypes not included in PCV10, has been rising from 1.8 to 2.2 per 100,000 per year in 2019/2020; this non-PCV10 incidence was 2.4 per 100,000 in 2021/2022. In 2021/2022, the most common serotypes were serotype 8 (covered by PPV23; 21 cases), serotype 3 (PCV13 serotype; 8 cases) and serotype 19A (PCV13 serotype; 11 cases) causing 63% of all cases in this age group (Figure 6.9.8).

6.9.3.4 Persons aged 50-64 years (Figure 6.9.6)

In the epidemiological year 2021/2022, the 9 sentinel laboratories reported 105 IPD cases in persons aged 50-64 years, resulting in an incidence of 10.1 per 100,000 per year. This was lower than reported in 2019/2020 (pre-COVID-19; 13.4 per 100,000), but higher than in 2020/2021 (first COVID-19 year; 5.9 per 100,000). Before the COVID-19 pandemic, the incidence in this age group fluctuated around 18 per 100,000 annually, with a decrease after PCV7 introduction and a further decrease after the switch to PCV10. Since epidemiological year 2018-2019, IPD caused by PCV10 serotypes has become very rare in this age group; in 2021/2022, the incidence of IPD for these serotypes was 0.3 per 100,000.
Since the switch to PCV10 in 2011, IPD incidence caused by serotypes not included in PCV10 has been increasing from 14.5 to 15.6 per 100,00 in 2018/2019 (Figure 6.9.6). Incidence was only 5.7 per 100,00 in 2020/2021, but increased to 9.9 per 100,000 in 2021/2022. In 2021/2022, the most common serotypes were 8 (PPV23 serotype; 28 cases) and 19A (PCV13 serotype; 24 cases) causing 50% of all cases in this age group (Figure 6.9.8).

6.9.3.5 Persons aged 65 years or over (Figure 6.9.7)

Since April 2021, IPD in individuals aged 60 years and over is notifiable and isolates are submitted to the NRLBM. The notification requirement was implemented because of the introduction of PPV23 vaccination for 60-year-olds, starting in autumn 2020 for people born in 1941-1947, and in autumn 2021 for people born in 1948-1952. Overall, the sentinel labs sent 252 isolates of IPD patients aged 65 years and over to the NRLBM during the epidemiological year 2021/2022, representing an incidence of 26.0 per 100,000. The incidence decreased after PCV7 introduction and remained stable since the switch to PCV10 at around 20 per 100,000 cases per year and up to the COVID-19 pandemic. The incidence has decreased in the last two years, presumably as a result of the COVID-19 control measures and because of corresponding absence of influenza leading to fewer numbers of secondary bacterial infections (see section 6.9.5.4), as well as the introduction of PPV23 vaccination for elderly age groups (see paragraph 6.9.4.2). IPD caused by PCV10 serotypes was very rare in 2021/2022 (incidence 0.2 per 100,000), but non-PCV10 IPD increased to 25.8 per 100,000 in 2021/2022, compared to 13.9 per 100,000 in 2020/2021. Note that the (non-PCV10 and all-type) IPD incidence was still only about half compared to recent pre-COVID years (Figure 6.9.7). Of all IPD in this age group, 77% was caused by a serotype included in PPV23, PCV15+6C covered 46% and PCV20+6C covered 75%. In 2021/2022, the most common serotypes were 8 (PPV23 serotype; 57 cases), 19A (PCV13 serotype; 55 cases), and 3 (PCV13 serotype; 34 cases), together causing 59% of all cases in this age group (Figure 6.9.8).

Of all notifications in Osiris of cases aged 65 years and over since January 2022 (n=392; the time since the question was asked for all cases), information on comorbidity was available for 344 cases (88%), of which 69% had a reported comorbidity. Of the cases who were reported to be vaccinated, 82% was reported to have at least one comorbidity. For unvaccinated cases, this was 68%. No conclusion can be drawn regarding the effectiveness of vaccination in case of comorbidity, as prevalence data on comorbidity for the population under surveillance is needed for such an analysis.

6.9.3.6 Vaccine failure

Since the introduction of PCV7, 48 cases of vaccine-type IPD have been reported among vaccine-eligible children born after 1 April 2006 and aged 2 months and over in the nationwide surveillance. Note that since 2020, children aged 3 months and over are eligible for the standard schedule of the national immunisation programme (NIP). Of the children born after April 2006 and aged 2 months, 24 children (50%) were vaccinated with at least 2 doses (with the second dose given at least 2 weeks before diagnosis), and therefore were considered vaccine failures (Table 6.9.1). Since the change of the standard schedule, no vaccine failure has occurred among that eligible group. Overall, serotype 19F was the most common serotype among vaccine failure cases (n=9, 38%), a serotype that has been described in relation to vaccine failure in other settings, too [3]. There was one vaccine failure case in 2021/2022 (serotype = 19F).

6.9.3.7 Vaccine effectiveness (VE) against IPD

The VE of PCV10 was calculated using the indirect cohort (or Broome) method, in which the odds of vaccination in cases infected with a vaccine serotype (VT cases) is compared to the odds of vaccination in cases infected with a non-PCV10 serotype (non-VT cases). As the standard schedule for vaccination has changed in 2020, now starting at three months of age, we included here all reported IPD cases for the period from June 2011 up to and including May 2022, who had a known serotype and vaccination status and were aged 3 months or over (instead of two months of age in previous reports). Cases were assumed to be correctly vaccinated if vaccination according to age occurred at least 20 days before arrival of the isolate in the reference laboratory (i.e., 14 days pre-disease onset, taking into account the median time between sampling and the arrival of the isolate).

Out of the 18 (39%) vaccine type IPD cases, 7 were vaccinated with at least 2 doses, as were 346 out of the 375 (92%) non-VT IPD cases. This resulted in a VE of 91% (95% CI: 71-97%) for at least two doses of PCV10 compared with no vaccination.

6.9.3.8 IPD mortality among children <5 years

From 2014 up to and including May 2022, 459 IPD cases among children younger than 5 years were reported nationally. For 330 cases (72%), the mortality status was known. Out of the 330 cases, 23 (7%) died. These 23 cases all had non-VT IPD (serotypes 8 (n=6), 10A (n=3), 15C (n=3), 12F (n=2), 3 (n=2), 6C (n=2), 19A, 22F, 23A, 24F, 31). Twenty-one fatal cases were <2 years of age and seven of them had known comorbidities.

6.9.4 Current/ongoing research at RIVM

6.9.4.1 Evaluation of IPD surveillance among individuals aged 60 years and older

With the implementation of the PPV23 vaccination programme for adults, the existing surveillance system for IPD was expanded as of April 2021. As was already the case for children born in 2006 and after, the diagnostic laboratories submit IPD isolates to the NRLBM for serotyping and results are shared with, among others RIVM. The regional public health services (GGD) notify RIVM about the cases through the OSIRIS notification system with epidemiological data. RIVM links the two datasets for surveillance analyses. We evaluated this enhanced surveillance system ten months after implementation on (1) the completeness of the isolates sent from the diagnostic laboratories to the NRLBM, (2) the completeness of cases notified in ORISIS compared to cases reported by the NRLBM, and (3) the completeness of epidemiological data of cases in OSIRIS.

1) To assess the completeness of isolates received by the NRLBM, we compared the number of isolates that were received in July-December 2021 with the number of isolates in the Infectious disease Surveillance Information System for Antibiotic Resistance (ISIS-AR; only for shared laboratories, n=37 laboratories). ISIS-AR receives pseudonymised susceptibility test results of all isolates tested in the participating laboratories [4]. Overall, there were 20 isolates in ISIS-AR that were not sent in to the NRLBM and 370 isolates for which information was available in both databases; approximately 95% of IPD isolates are submitted to the NRLBM. Out of the 37 shared laboratories, 26 (70%) had (at least) a similar number of isolates sent in to the NRLBM as to ISIS-AR, indicating that they submitted all IPD isolates to the NRLBM.

2) Between April 2021 and February 2022, there were 713 cases of IPD in adults in the NRLBM database, and 619 in the OSIRIS database. Of the 713 in NRLBM, 567 (80%) could be matched to OSIRIS. Reporting to Osiris was more complete for cases that were infected with a PPV23 serotype (447/547; 82%) compared to cases infected with a non-PPV23 (120/166; 72%).
A similar pattern was seen for those who have already been targeted for vaccination (154/188; 82%) compared to those not yet eligible for vaccination (413/525; 78%).
3) The completeness of data was determined for indicators needed for matching the databases and for vaccine effectiveness calculations, i.e., year of birth, sex, NRLBM number, serotype, date of symptom onset, postal code (4 digits), diagnosis date and comorbidity. Completeness of year of birth, sex, diagnosis date, and postal code, was 98-100% for the cases notified in OSIRIS (N=613). Vaccination status was reported in 89% of cases, and serotype in 81%. The NRLBM number was reported correctly only in 57% and was unknown in 40%. Again, when stratifying by eligibility for vaccination, serotype was more often reported in those eligible (140/162; 85%) than those not eligible (363/457; 79%). The same was the case for NRLBM number; 122/162 (77%) versus 226/457 (50%), respectively. Together, these results suggest that cases with PPV23 serotypes or in people who are eligible for vaccination, could more often be matched compared to those who are not, and that the indicators are more often completed in these individuals as well. Non-differential reporting will lead to biased results in vaccine effectiveness and impact studies. The results will be shared with the public health society to strengthen surveillance.

6.9.4.2 Impact of PPV23

An estimation of the impact of the adult pneumococcal vaccination programme was performed on surveillance data from October 2020 up to and including April 2022. An odds ratio (OR) was calculated for having PPV23-serotype IPD in those people invited for vaccination based on the year of birth compared to those aged 60+ who were not invited as they were too young or too old. This OR was compared with the OR found in the corresponding age group during the four respiratory seasons previous to the introduction of the vaccination programme (2016/2017–2019/2020). Since the start of the vaccination programme in 2020, the percentage of IPD cases with a PPV23 serotype among those invited for vaccination was 70%, while this was 76% in those not invited. These percentages resulted in an OR of 0.75 (95% CI: 0.56-1.0). The OR for having PPV23-IPD during the same period within the seasons before the start of the vaccination programme (n=4101) was 1.07 (95% CI: 0.88-1.29) for people aged 70-79 years. Combining these estimates resulted in an estimated impact of 31% (95%CI 1.0 – 50.1). Note that this impact is lower than estimated after the first half year [5], likely due to random variation (the sample size of the first estimation was small) and possibly due to some waning immunity of the first vaccinated cohort (not yet determined).

6.9.4.3 Disease and carriage during COVID-19

The RIVM, together with the NRLBM, determined the pathogen- and type-specific changes during the first [6] and second year of the COVID-19 pandemic [7]. Overall IPD was 67% lower during the first COVID-19 year compared to the 5-year pre-COVID period, and 35% lower during the second COVID-19 year. The decrease was lower for children ≤5 years of age; during the first year, the decrease was 53%, while during the second year, IPD increased by 16%.

The latter was mainly due to an increase in serotype 19A. Generally, the decrease differed per serotype; in both years, serotypes 8 and 12F (PPV23 serotypes) and serotype 15A (non-vaccine type) decreased more than other serotypes while serotypes 19A and 6C showed a smaller decrease. Serotypes 1 and 7F (PCV10 types) were not observed since the start of the COVID-19 pandemic, but this decrease had already started before the COVID-19 pandemic.

The dynamics of pneumococcal carriage in households with SARS-CoV-2 transmission was studied [8, 9]. Molecular detection of pneumococci was applied to saliva collected during six consecutive weeks in the period October 2020 to January 2021 in eighty households of index-cases infected with SARS-CoV-2. Samples were collected from adults (n=176; age range=18-64 years, median=44 years) and children (n=98; age range 0-17 years, median 11 years) over ten sampling events. Samples that were pneumococci-positive were pooled per pneumococcal carrier for serotype detection with qPCR. In the entire cohort, cumulative pneumococcal carriage and SARS-CoV-2 infection rates were 58% (160/274) and 65% (177/274), respectively. Serotype-specific prevalences were determined in pooled samples of the pneumococcal carriers, including 56 adults (median age 42 years) and 65 children (median age 10 years), (Figure 6.9.9). PCV-10 serotypes accounted for 6% (7/121) of carriers; only PCV-10 serotypes 19F and 14 were observed. The serotype distribution differed between age groups, but serotypes 33A/F/37 and 19A were among the most commonly carried serotypes in both groups. No decline in pneumococcal carriage rates during the study period and no clear evidence for altered serotype distribution among carriers was observed (data not shown). In coming fall (2022), the serotype distribution among children and their parents will be determined in the 6th OKIDOKI study and compared to the pre-pandemic OKIDOKI studies.

6.9.5 (Inter)national developments

6.9.5.1 Impact of childhood vaccination

The RIVM has participated in in two international projects that determine the effects of the introduction of PCVs in the NIP: PSERENADE and SpIDnet. PSERENADE (Pneumococcal Serotype Replacement and Distribution Estimation project) is a global network that includes 41 countries [10]. In their comparison of the IPD incidence, 33 countries were included because of the availability of data. Among children, the incidence of PCV7 and of PCV10/PCV13 serotype IPD declined by 86-99% and 70-94%, respectively during nine years post-vaccine introduction, and the decline was expected to continue. In children, there has been cross-protection of PCV10 against serotype 6A IPD. Serotype 19A disease decreased in PCV13 countries and increased in PCV10 countries. For serotype 3 IPD, no clear trend was observed for PCV13 or PCV10. In children <5 years, NVTs had increased 2-2.8-fold by year five post-vaccine introduction, and this seemed to increase. No difference was observed between PCV10 and PCV13 sites. Overall, in children <5 years, IPD declined by 60-79% by five years after introduction of PCV10/13, and there was no meaningful difference between products. For meningitis, the effect was about 5% less than for all IPD. Indirect protection among adults aged ≥65 years took 2-3 years longer for the full effects than for children <5 years. The serotype distribution stabilised among children within five years and among adults within seven years. Overall, VT-IPD decreased by 75%, but NVTs increased 1.7-2.5-fold. The indirect

effects on VT and NVT disease were heterogenous among the countries with substantial decreases in some sites but no decrease in other sites. When focusing on specific serotypes, serotype 3 remained dominant in both, PCV13 and PCV10 sites, in children and adults. Serotype 19A was the leading serotype in PCV10 countries and was not eliminated in PCV13 countries. The more-valent PCVs PCV15 and PCV20 covered about a similar proportion in PCV10 and PCV13 countries but the specific serotype distributions were not equal.
SpIDnet is an enhanced IPD surveillance project in Europe and includes 13 sites in 10 countries. Recently, the effects of PCV10 and PCV13 were published [11, 12]. SpIDnet showed that during eight years of PCV10 and PCV13 childhood vaccination, the IPD incidence declined first (2011–2014) but increased subsequently (2015–2018) in all age groups. As found in PSERENADE, the overall trends were similar in countries using PCV13 or PCV10, but serotype 19A was common in PCV10 countries. SpIDnet found, however, that the proportions of serotypes that are covered by PCV13, PCV15, and PCV20 were larger in places where PCV10 is used compared to places where PCV13 is used. Serotype 8 has become a major serotype that has increased in many countries [11].
The SpIDnet project also determined the VE for PCV10 and PCV13 in different age groups [12]. The Overall VE of at least one dose PCV13 against vaccine-type disease was 84% (95%CI: 79–88), but this decreased with time since booster vaccination (93% (95%CI 88–96), 84% (95%CI 70–91) and 85% (95%CI 72–92) for < 12, 12–23 or 24 months since vaccination, respectively). The VE of PCV10 against vaccine-type disease was 85% (69-93); no data by time since vaccination was presented. The VE of PCV13 against serotypes 3 and 19A were 65% (44-78) and 83% (74-89), respectively, but the VE of these serotypes declined more rapidly than for other serotypes. The VE of PCV10 against 19A was estimated at 33% (-28 to 65), indicating large uncertainty for any cross-protection of the 19F antigen.

The special role of serotype 19A in the IPD epidemiology has also been shown in New Zealand, another country besides Belgium that switched from PCV13 to PCV10 in the NIP. Analysis of IPD notification data showed a sharp increase in serotype 19A disease in children below the age of two years (from 0.0 before the switch in 2017 to 7.3 cases per 100,000) and in those aged 2-4 years (approximately from 2.4 to 4.8 per 100,000) [13]. The rates of serotype 19A IPD in those aged 5-64 years stayed relatively low in 2017–2020 (approximately 1 per 100,000). In the 65+ age group, the 19A incidence decreased slightly, which was interpreted as a delayed indirect effect of PCV13 vaccination.

A Dutch study determined the impact of the switch from PCV7 to PCV10 on non-invasive pneumococcal disease in primary care across various age groups [14]. The study included records of 397,441 individuals from July 2006 to June 2016. The study focused on pneumonia-bronchitis, otitis media and sinusitis and showed that preventive effects were only present for bronchitis in paediatric and adults age groups and for sinusitis for the age group 20-50 but that no clear changes were observed for otitis media. Among older adults, none of the symptoms decreased in incidence. This study supports, however, that direct and indirect effects of the switch from PCV7 to PCV10 were also found in primary care attended infections.

6.9.5.2 Pneumococcal vaccination and vaccine effectiveness

NIVEL investigated the vaccine coverage of PPV23 vaccination among older adults eligible for vaccination in the first year (those born in 1941-1947) and estimated an uptake of 73% on average [15]. However, the coverage differed considerably between general practitioners (GPs); while at some GPs the uptake was as low as 19% and for some as high as 91%, the uptake determined per GP varied mainly between 65% and 85%.

An Israelian study determined the VE of PCV7 and PCV13 against otitis media [16]. The study was performed in October 2009-July 2013 among 223 cases aged 5–35 months with (mostly complex) otitis media. Controls (n=1,370) were children with rotavirus-negative gastroenteritis, whom were group matched on age, ethnicity, and geographic location. PCV13 was shown to be effective in preventing vaccine-type otitis media (VE 77%, 95%CI 53-92), including otitis media caused by serotype 19A (95% (34%–100%)) and serotype 3 (89% (24%–98%)).

A meta-analysis was performed on the effects of PCV10 and PCV13 in reducing the frequency of community-acquired pneumonia (CAP) hospitalisations in children aged younger than 2 years [17]. Twenty studies were included. Compared to PCV7, both PCV10 and PCV13 were associated with lower CAP hospitalisation rates (OR, 0.78 (95%CI 0.68-0.90) and OR, 0.63 (95%CI: 0.56-0.71), respectively). When PCV10 and PCV13 were compared, PCV13 was associated with a lower hospitalisation rate for CAP (OR, 0.67 (95%CI: 0.48-0.93).

Although PCVs do not directly prevent virus infections, it was shown that PCV13 was effective in preventing (symptomatic) lower respiratory tract infections (LRTI) [18]. The analysis included 13,856 virus-associated LRTI cases and 227,887 matched controls. The VE of PCV13 against virus-associated pneumonia was 25% (95%CI: 18-31%) and was 22% (11-31%) against other (non-pneumonia) virus-associated LRTI. An explanation is that the severity of the LRTI is affected by the presence of pneumococci through the known, synergistic effects.

The use of a combined schedule of PCV13 followed by PPV23 two months after PCV13 has been tested in a Dutch prospective cohort study among adults using immunomodulators [19]. The immunogenicity of the combined schedule was determined in adults using conventional immunomodulators (cIM), biological immunomodulators (bIM), combination therapy, and controls during 12 months. The main outcome was seroprotection, as defined as having an IgG concentration of ≥1.3 µg/mL for at least 17 of the 24 serotypes included in the schedule. The study showed that seroprotection peaked at 44% (combination therapy), 58% (cIM), 57% (bIM), and 82% (controls) at two (for PCV13 serotypes) to four (PPV23 serotypes) months since enrolment, but at 12 months after vaccination, the rates had already decreased to 24%, 48%, 39%, and 63%, respectively. Because of the modest immunogenicity, the authors recommended that the use of additional doses with PCV13/more-valent PCVs should be investigated.

6.9.5.3 *More-valent PCVs*

Recently, PCV15 and PCV20 have been licensed for use in adults in Europe [20, 21]. PCV15 is already licensed for children in the United States [22] and licensing of PCV20 is expected in the coming year; licensing of PCV15 and PCV20 for children in Europe is anticipated in 2023. Furthermore, a 21-valent vaccine, V116, is being developed and phase 3 clinical trials will be initiated in 2022 [23]. PCV21 has a different distribution of covered serotypes compared to PPV23 and the other PCVs with 8 serotypes not covered by currently licensed vaccines (see Table 6.9.2). V116 is designed to have a large serotype-coverage among adults. A vaccination strategy whereby a different PCV is used in adults than in children has been discussed at the 12th International Symposium on Pneumococci and Pneumococcal Diseases to be a more ideal strategy than the current vaccination strategies. Besides the discussed vaccines, more pneumococcal vaccines are being developed, such as protein vaccines and combined pneumococcal-protein and conjugate vaccines. However, because of the challenges in testing and registration, these vaccines will not be on the market in the near future.

6.9.5.4 *Effects of the COVID-19 pandemic*

At the start of the COVID-19 pandemic one was concerned that COVID-19 would be associated with an increased risk for IPD, as is known for influenza. Several studies have now shown that COVID-19 is not associated with IPD [24]. Still, it was shown that PCV13 vaccination but not PPV23 was associated with lower incidence of COVID-19 [25]. This association was not seen in case PCV13 receivers were treated with antibiotics. These results indicate that pneumococcal carriage may contribute to SARS-CoV-2 pathogenesis.

While the COVID-19 control measures coincided with decreases in IPD [6], pneumococcal carriage was shown not to be decreased [26]. The incidence of IPD during the COVID-19 pandemic was temporarily associated with the decreased incidence / full suppression of RS virus, influenza viruses, and human metapneumo virus. The temporal association of disease but not of carriage with the respiratory viruses indicate an important role of influenza and especially RS virus vaccination (when available) in the prevention of childhood IPD in a serotype-independent way [27]. In Dutch adults, it was also shown that carriage was not decreased during the COVID-19 pandemic (see above and [9]).

6.9.5.5 *Other*

As also described in this report, the incidence of serotype 19A has increased in the Dutch population. A collaboration of Radboud University Medical Center, RIVM, NRLBM and others examined single-nucleotide polymorphisms (SNPs) in the capsular locus among Dutch 19A isolates from the period 2004-2016 [28]. They showed large variation in the capsular locus, but these SNPs were predicted not to induce phenotypical changes and seem therefore not associated with the observed increase in 19A.

Diagnosing (serotype) specific pneumococcal community acquired pneumonia (CAP) is known to be challenging. Using an extended spectrum serotype-specific urine antigen detection assay as well as culture and PCR, pneumococcal CAP was determined in a large Canadian study, in which the proportion being attributable to pneumococci was estimated in (mainly) PCV13

times [29]. Among 8,912 CAP cases, 14% was attributed to pneumococci, of which 65% was non-bacteraemic. Non-bacteraemic CAP was relatively more common among adults aged 65 years and over. Note that in Canada, PPV23 is recommended for those aged 65 years and over, and for high-risk groups, PCV13 should be used before receiving PPV23 [30]. Serotypes 22F, 11A and 9N were most frequently found; PCV13 serotype CAP decreased between 2010-2014 but plateaued in 2015-2017 as a result of the persistence of some vaccine-type disease.

6.9.6 Literature

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* RIVM publication.

6.10 Poliomyelitis

D.L. van Meijeren, A.J.M. Pluijmaekers, K.S.M. Benschop, H.E. de Melker, E. Duizer

6.10.1 Key points

- In 2021 and 2022, for the period up to and including June 2022, no cases of poliomyelitis were reported in the Netherlands.
- Nationwide coverage of the clinical enterovirus surveillance (EV) was obtained for the reporting period, and no poliovirus was found in any sample.
- One Sabin-like poliovirus type 3 was isolated in 2021 in the environmental surveillance covering refugee centres. One Sabin-like poliovirus type 3 was detected in 2022 in the environmental surveillance covering the Bible Belt.
- In 2021, five poliovirus detections were reported from the environmental surveillance at Utrecht Science Park (Sabin 1 (n=2), Sabin 3 (n=2) and wild type poliovirus 1 (n=1)). Up to June 2022, no poliovirus was detected at this site.
- The combined number of reported wild poliovirus type 1 cases in Afghanistan and Pakistan was substantially lower in 2021 (n=2) and 2022 up to and including June (n=13), compared with 2020 (n=140).
- Between February and July 2022, poliovirus was detected in sewage in London (UK) and New York State (US). The strains were related to each other as well as to strains found in Jerusalem (Israel) sewage. Additionally, in July 2022, a VDPV2 case in an unvaccinated person was confirmed in New York State.
- A WPV1 case was reported by Malawi in November 2021 and another case by Mozambique in March 2022. These are genetically linked to a strain detected in Pakistan in 2020.
- In 2021, the worldwide number of reported vaccine-derived poliovirus 2 cases, decreased compared with 2020 (675 versus 1,079). Two-thirds of the cases in 2021 occurred in Nigeria. Up to and including June 2022, 158 VDPV2 cases have been reported.

6.10.2 Tables and figures

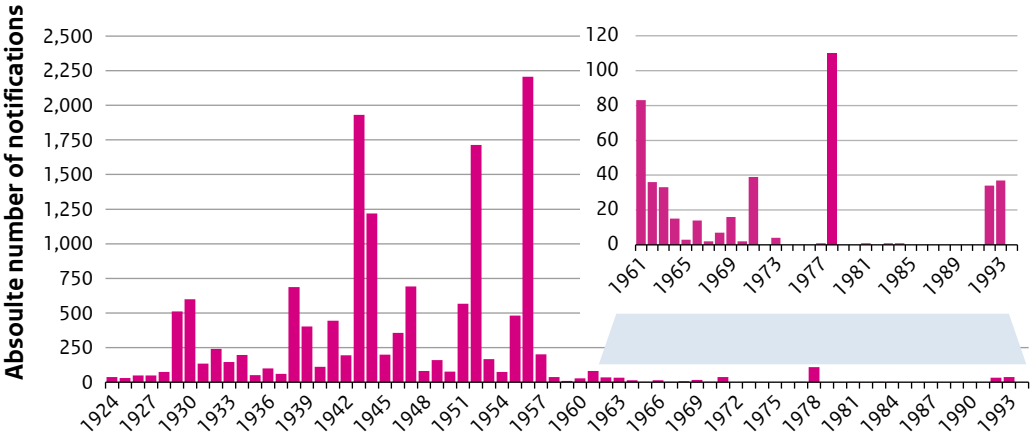

Figure 6.10.1 Notifications of poliomyelitis (AFP cases) in the Netherlands from 1924-1994 and zoomed in on 1960-1994 (right-hand part). From 1994 up to and including June 2022, no notifications of poliomyelitis were made.

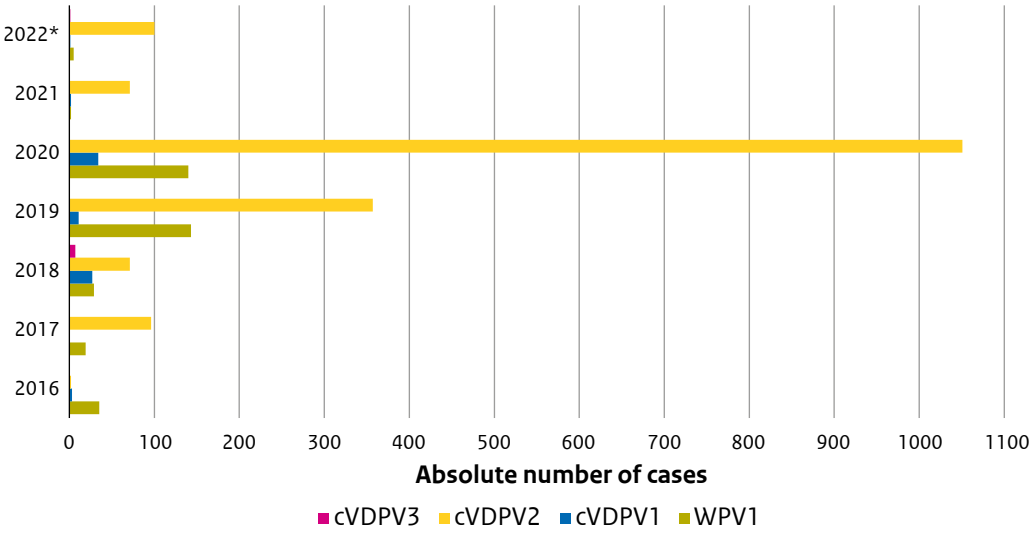

Figure 6.10.2 Total number of global polio cases 2016-2022* as reported to WHO HQ.
* For 2022, data for the period up to and including May 24th are included.

6.10.3 Epidemiology and pathogen

6.10.3.1 Epidemiology

In 2021 and 2022 for the period up to and including June, no cases of poliomyelitis were reported in the Netherlands (Figure 6.10.1).

6.10.3.2 Polio-free status

In 2002, the WHO region Europe was declared wild poliovirus (WPV) free. Until all six WHO regions are declared WPV free, establishing and/or maintaining high vaccination coverage and performing high-sensitive surveillance of polio cases are key. For countries with a strong healthcare system, high levels of sanitation, and a long period of non-endemicity, including the Netherlands, other surveillance strategies, including enterovirus and environmental surveillance, are also approved [1].

6.10.3.3 Enterovirus surveillance

For the year 2021, nationwide coverage of enterovirus (EV) surveillance was obtained as complete data from 32/35 virological diagnostic laboratories were received and the remaining 3 laboratories referred their samples to another laboratory in the nationwide network. In total, 12,585 stool samples were tested for the presence of EV and to exclude poliovirus. Stool sampling yielded 1,032 EV positives, resulting in an average EV positivity rate of 8.2% [2]. According to the Global Polio Laboratory Network, an effective enterovirus surveillance system detects between 5 and 25% of enteroviruses in all stool samples tested annually [1].

Exclusion of poliovirus presence based on EV surveillance can be defined at two levels: the percentage of stool samples for which the presence of poliovirus is excluded and the percentage of EV-positive samples for which the presence of poliovirus is excluded. Poliovirus in EV-positive samples is excluded by the detection of non-polio EVs through sample sequencing. In 95.5% (12,016/12,584) of the total stool samples analysed in 2021, poliovirus was shown to be absent. The percentage of poliovirus excluded in EV-positive stool samples was 48.8% (504/1032). This is in line with the years 2015-2019, when poliovirus was excluded in 40-50% of EV-positive stool samples. In 2020, the percentage was lower (29.7%) due to the fact that less sequencing was performed on the EV-positive samples compared to other years [3]. Whereas it is mandatory to send in stool samples for poliovirus testing when polio is suspected, it is highly recommended but not mandatory to send in EV-positive stool samples in non-AFP cases for sequencing [2]. In 2021, 446 EV-positive stool samples were not sent in for typing and 82 EV-positive stool samples were un-typable. A further reduction of the percentage of EV-positive stool samples for which poliovirus is not excluded may be achieved only if poliovirus exclusion on all EV-positive stool samples is mandatory or if laboratories are offered financial compensation for contributing to the EV surveillance. Nonetheless, no poliovirus was found in any clinical sample in 2021 [2].

6.10.3.4 Environmental surveillance

Environmental surveillance for poliovirus has been in place in the Netherlands since 1997 and has provided, in combination with the system for enterovirus surveillance, clear documentation

for the absence of poliovirus circulation in the country over the years. The data for 2021 underline this statement, as no polioviruses (wild, vaccine, vaccine-derived) were detected during regular sampling at 15 locations in the Bible Belt. In May 2022, a SL3 vaccine virus without mutations in VP1, was isolated from one Bible Belt sample. The enteroviruses detected through environmental surveillance in the Bible Belt were strongly related, and often identical, to the viruses detected in the Netherlands by EV surveillance. Environmental surveillance activities performed in the Netherlands in 2021 have again documented the absence of poliovirus circulation in the country in combination with the system for EV surveillance [4].

In 2021, environmental surveillance at Utrecht Science Park (USP), where RIVM and two vaccine manufacturers are located, led to the detection of poliovirus in five samples. Research showed that the isolated wild type 1 poliovirus (WPV1) in the sample from October 12th, 2021, had one mutation that was also found in the vaccine harvest of that month. None of the manufacturers' employees who were screened had any sign of a recent exposure to poliovirus. Thus, the found samples resulted most likely from a direct release from the facility, and no employees were infected. This incident did not lead to poliovirus introduction into the Dutch population. The other four poliovirus isolations from sewage from the USP were twice a Sabin 1 and twice a Sabin 3 strain. Sabin 1 and 3 strains are part of the oral (live) polio vaccine (bivalent OPV with Sabin 1 and 3 strains) that is widely used internationally, for example in Morocco, Turkey and India [4].

In August 2021, the Taliban quickly took over in Afghanistan and emergency evacuation of thousands of Afghan people was initiated. Those who were evacuated to the Netherlands were accommodated at different locations where environmental surveillance based on sewage sampling was initiated. The primary goal was to exclude poliovirus introduction into the Netherlands, or detect it early on, since Afghanistan is one of the last two countries endemic for WPV1 and was experiencing several outbreaks of circulating vaccine derived poliovirus type 2 (cVDPV2) in 2021. No pathogenic poliovirus was found: from one sample a poliovirus Sabin 3 strain with 0 mutations in the VP1 gene was isolated [4].

6.10.4 Research

The National Polio Laboratory (NPL) of the Netherlands is also a WHO Global Specialized Laboratory (GSL). It participates in several projects run by the WHO Global Polio Laboratory Network (GPLN), including development of sensitive methods for direct poliovirus detection in clinical samples and the feasibility of Next Generation Sequencing methods to detect poliovirus sequences in sewage samples and samples from immunocompromised children.

The NPL participates in the validation of new poliovirus strains (S19 strains), including type 2, that can be used outside of GAPIII containment for the poliovirus neutralisation assay. Environmental surveillance as supplemental surveillance in addition to acute flaccid paralysis (AFP) surveillance, is mandatory for countries that will be using novel oral polio vaccine type 2 (nOPV2) under the current Emergency Use Listing (EUL) [5]. The NPL analysed sewage samples from Tajikistan following an optimised algorithm for the period April 23rd, 2021, up to and including March 25th, 2022. Eight weeks after the last of two vaccination rounds using nOPV2,

the last cVDPV2 was detected in the environmental surveillance in Tajikistan. After the last and third vaccination round with nOPV2, the nOPV2 strains were isolated from the sewage system for another nine weeks. None of the isolated strains showed the characteristic mutations known to correlate to reversion to pathogenicity. Between March 2021 and May 2022, over 350 million doses of nOPV2 were used in 18 countries.

6.10.5 International developments

In 2021-2022, the WHO classified two countries – Afghanistan and Pakistan – as polio-endemic countries [6]. However, a WPV1 case was reported by Malawi in November 2021 and another WPV1 case by Mozambique in March 2022 [7]. These cases are genetically linked to a WPV1 strain detected in Pakistan in 2020 [8-10]. The African WHO region was declared wild-type polio free in 2020 after no WPV cases have been notified in Nigeria since 2016 [11]. Both in Malawi and Mozambique, the last WPV cases were reported in 1992. The current WPV1 cases do not affect the polio free status of the African region, since the virus strain originated from Pakistan [9].

In Afghanistan and Pakistan, a combined total of nine WPV1 cases were notified in 2021 and 2022 for the period up to and including May 24th [7]. This is a substantial decrease compared with 2020, when a total of 140 cases was reported. Moreover, the environmental surveillance detected low levels of WPV1 in both countries in 2021 and 2022 up to and including May 24th [7, 8]. In environmental surveillance, no WPV1 was detected in countries other than Afghanistan or Pakistan in the same period [7, 8]. Both countries also reported a decrease in the number of cVDPV2 cases in 2021. In Afghanistan, the number of cases decreased from 308 in 2020 to 43 in 2021, and in Pakistan, a decrease from 135 to 8 cases respectively was reported [12].

The global number of cVDPV2 cases increased from 366 cases in 2019 to 1,079 in 2020. In 2021, the number of worldwide cVDPV2 cases decreased again to 675 (Figure 6.10.2). However, two-thirds (415) of the cases occurred in Nigeria, while Nigeria reported only 8 cases in 2020 [12]. These outbreaks are a potential risk for international spread [8]. The current cVDPV2 outbreaks are mainly the result of the use of monovalent type 2 oral polio vaccine (mOPV2) in areas with previous cVDPV2 outbreaks but where the required >80% vaccination coverage could not be reached. Due to insufficient implementation of vaccination by injection with trivalent IPV, there is insufficient anti-PV2 immunity at the population level. To prevent the development of new cVDPV2 outbreaks due to massive use of mOPV2 (to fight fire with fire), the WHO has granted EUL for the nOPV2 vaccine. The strain in this novel OPV is a Sabin 2 strain that has been genetically engineered to prevent reversion to virulence. The chance that the use of nOPV2 will lead to new cVDPV2 outbreaks is therefore much smaller than with the use of mOPV2 [13]. The first use in a supplementary immunization activity (SIA) started in Nigeria on March 13th 2021.

In June 2022, the UK Health Security Agency reported the detection of several related VDPV2 strains in the sewage of the London Beckton Sewage Treatment Plant (STP) between February and June 2022 [14]. Multiple detections from different but related strains suggest that local spread of the virus has occurred and that multiple people have been infected. No associated

cases of paralysis had been reported up to and including June 2022. In response to the detection, sewage surveillance has been expanded, health care professionals were alerted to be aware of patients with symptoms of polio, and the UK's Joint Committee on Vaccination and Immunisation (JCVI) advised all children between 1 and 9 years of age living in London boroughs should be offered an IPV booster dose [15].

On July 21st, 2022, the New York State Department of Health (NYSDOH) confirmed a VDPV2 polio case in Rockland County in an unvaccinated person [16]. As of August 12th, 2022, 20 samples collected as part of the New York sewage surveillance (implemented for COVID-19 surveillance) had tested positive for poliovirus and were genetically linked to the virus responsible for both the Rockland case [17] and the strains detected in the London sewage [18]. cVDPV2 strains with a common ancestor as the strains found in New York State and London, were detected in the sewage system of Jerusalem (Israel) [18].

In the Netherlands, the environmental surveillance for poliovirus, as performed in 15 locations in the Bible Belt, is routinely expanded by performing a poliovirus-specific PCR on RNA extracted from the samples from the national sewage surveillance for SARS-CoV-2. This intensified environmental surveillance started in March 2022, in response to the increased influx of refugees from Ukraine, and is being continued to date (August 2022), mostly as a response to the cVDPV2 detection in the London sewage.

To sustain a world free from all polioviruses, the Global Polio Eradication Initiative (GPEI) released a Polio Endgame Strategy 2019-2023 in 2019. This so-called roadmap builds on the proven lessons and tools of the strategic plan 2013-2018, and focuses on eradication, integration, containment, and certification. The GPEI presented the new Polio Eradication Strategic Plan 2022-2026 at a virtual event on June 10th, 2021 [19].

6.10.6 Literature

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* RIVM publication.

6.10.7 Other RIVM publications

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6.11 Rubella

I.K. Veldhuijzen, R. Bodewes, W.L.M. Ruijs, R. van Binnendijk, N.Y. Rots, C.A.C.M. van Els, H.E. de Melker

6.11.1 Key points

- In 2021 and in the first six months of 2022, no rubella cases were reported.

6.11.2 Figures

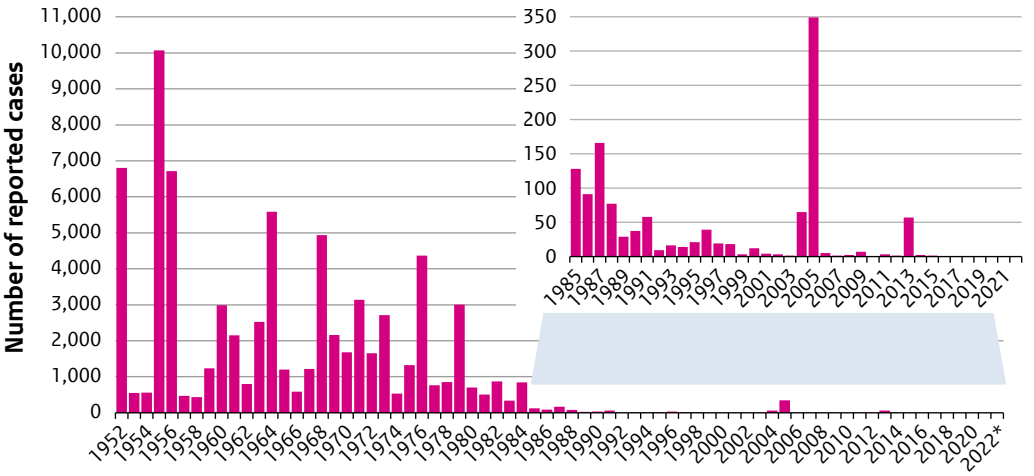

Figure 6.11.1 Reported rubella cases by year, 1952-2022*.
* Cases up to and including June.

6.11.3 Epidemiology

From 1974-1987, rubella vaccination was offered to girls, and since 1987 to all children. The last major outbreak, with around 3,000 reported cases, occurred in 1979. Since 1987, the last outbreak took place in 2004/2005 in the Bible Belt in which almost 400 cases were reported. In 2020 and in the first six months of 2021, no rubella cases were reported. The last case of rubella was reported in 2015 (Figure 6.11.1).

6.11.4 International developments

In 2021, 60 cases of rubella were reported EU/EEA, compared to 143 in 2020 and 383 in 2019. In the period 2019-2021, 74% of cases in the EU/EEA were reported by Poland, of which only 1.4% were confirmed [1]. In the first six months of 2022, 67 cases were reported. The COVID-19 control measures may have contributed to the decrease in 2020 and 2021, although the number of cases has been decreasing since 2013.

6.11.5 Literature

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6.12 Tetanus

D.L. van Meijeren, D.W. Notermans, H.E. de Melker

6.12.1 Key points

- In 2021 and 2022 up to and including April, no tetanus cases were reported in the Netherlands.
- Out of the twelve countries that did not achieve the maternal and neonatal tetanus elimination (MNTE) status yet, Guinea currently scores best on five performance indicators of the status.

6.12.2 Tables and figures

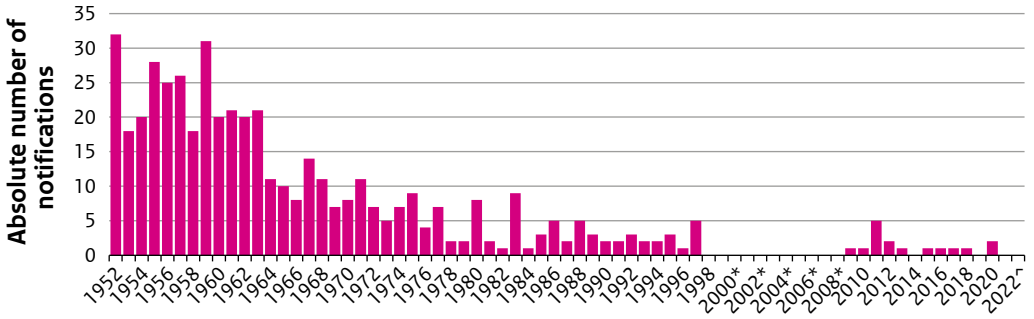

Figure 6.12.1 Reported cases of tetanus in the Netherlands by year, 1952-2022^.
* Between 1999 and 2009, tetanus was not notifiable.
^ For 2022, notifications for the period up to and including April were included.

6.12.3 Pathogen

The diagnosis of tetanus is usually made on clinical recognition; laboratory diagnosis is not often made. *Clostridium tetani* is rarely isolated from suspected patients, and in 2021 and 2022 up to and including April no isolates were received at RIVM for the tetanospasmin gene PCR. Serological diagnosis is not possible, as infection does not lead to a detectable antibody response; the presence of a protective antibody level in a blood sample taken before immunoglobulins are given, will make a tetanus diagnosis unlikely.

6.12.4 Epidemiology

In 2021 and 2022 up to and including April, no tetanus cases were reported in the Netherlands (Figure 6.12.1).

6.12.5 International developments

A review performed by Yusuf *et al.* [1] examined the progress and barriers to reach the Maternal and Neonatal Tetanus Elimination (MNTE) status for the 12 countries that had not reached this status yet by the end of 2020 [2, 3]. These 12 countries are Afghanistan, Angola, Central African Republic, Guinea, Mali, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan, and Yemen. The authors assessed for each country whether it covered at least 80% (the percentage needed for MNTE elimination) of the following indicators: (1) at least two doses of tetanus toxoid-containing vaccine for all pregnant women, (2) protection at birth, (3) skilled personnel birth attendance to promote clean births, (4) antenatal care visits, and (5) health care facilitated delivery. According to the joint reporting form (WHO/UNICEF), only Guinea and Afghanistan achieved a two-dose vaccination coverage of at least 80% for all pregnant women. Based on estimates by the WHO, Guinea, Mali, Pakistan, and Sudan achieved the 80% coverage of protection at birth. Data from the most recent Demographic and Health Surveys or Multiple Indicator Cluster Surveys showed that Guinea, Mali, Pakistan, and Angola achieved the 80% coverage of antenatal care visits. None of the countries reached the 80% coverage of skilled birth attendance and health care facilitated delivery. The countries with the lowest mean coverages for all five indicators are Yemen, South Sudan and Somalia.

6.12.6 Literature

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6.12.7 Other RIVM publications

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7
Immunisation programme in the Dutch overseas territories, including Dutch Caribbean islands

A.J.M. Pluijmaekers, E.A. van Lier, J.F. van Slobbe, P.H. Voskuil, T. Gordon, M.M. Henry, S. Blomont-Frederick

7.1 Key points

- In general, vaccination coverage in the Dutch overseas territories, including the Caribbean Netherlands (Bonaire, St. Eustatius, and Saba), is high.
- Recent and upcoming changes to the vaccination schedules in the Dutch overseas territories include the maternal pertussis vaccination, VZV and MenACWY vaccination for all children, and HPV vaccination for boys.
- In 2021, no diseases covered by the NIP were reported in the Caribbean Netherlands.

7.2 Tables and figures

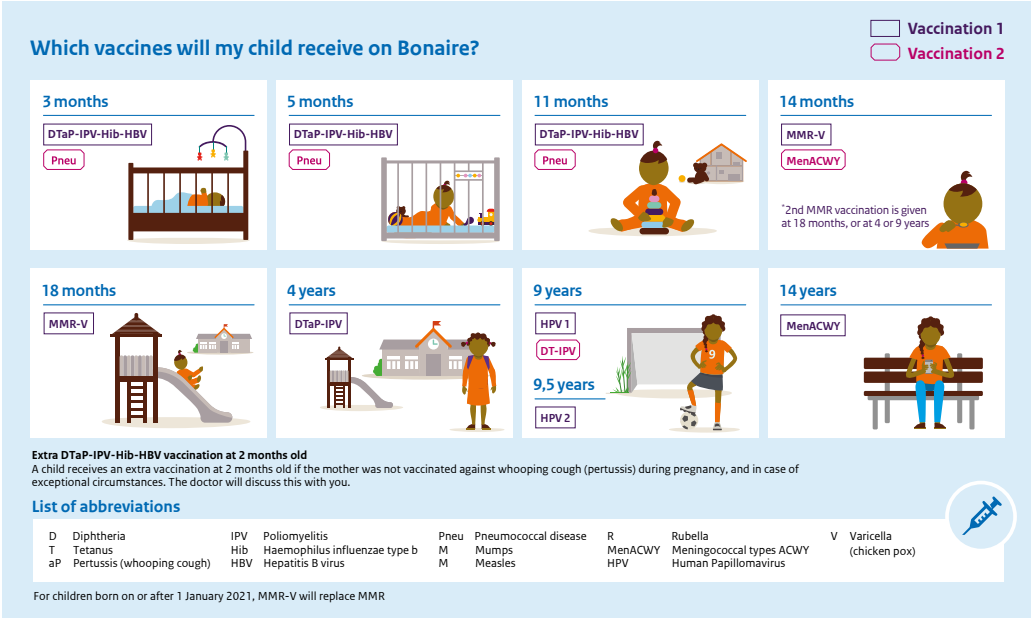

Figure 7.1 Immunisation schedule for Bonaire.
Source: *https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-bonaire-english*

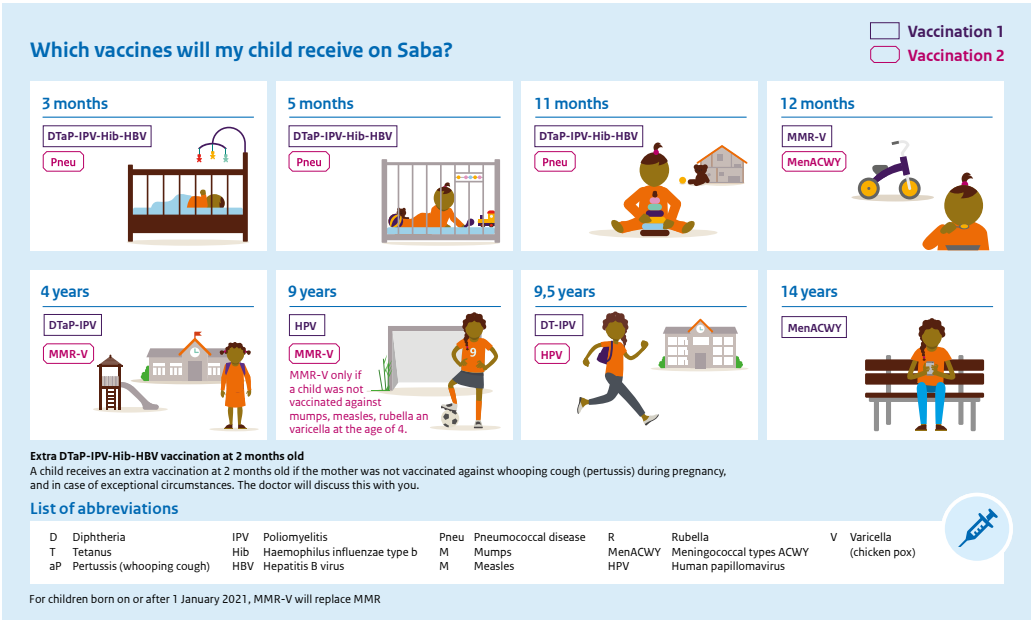

Figure 7.2 Immunisation schedule for Saba.
Source: *https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-saba-english*

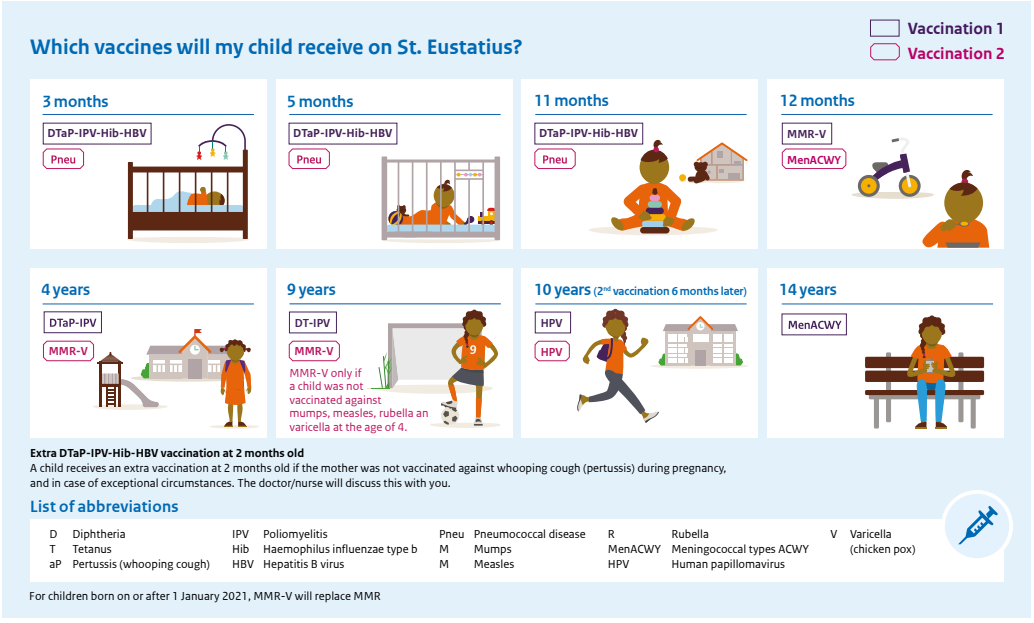

Figure 7.3 Immunisation schedule for St. Eustatius.
Source: *https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-st-eustatius-english*

Table 7.1 Immunisation schedule for Curaçao.

Age	Vaccination 1	Vaccination 2	Vaccination 3
2 months (= 7-9 weeks)	DTaP-Hib-HBV 1	Polio 1 (IPV)	
3.5 months	DTaP-Hib-HBV 2	Polio 2 (bOPV)	Pneu 1 (10-valent)
5 months	DTaP-Hib-HBV 3	Polio 3 (bOPV)	Pneu 2 (10-valent)
> 12 months	MMR 1		Pneu 3 (10-valent)
15 months	DTaP-Hib-HBV 4	Polio 4 (bOPV)	MMR 2
4 years	DT 1 (paediatric)	Polio 5 (bOPV)	
10 years	DT 2 (adult)		

Table 7.2 Immunisation schedule for Aruba.

Age or school year	Vaccination 1	Vaccination 2
1 month	HBV 1	
2 months	DTaP-IPV-Hib 1	Pneu 1
3 months	HBV 2	
4 months	DTaP-IPV-Hib 2	Pneu 2
6 months	DTaP-IPV-Hib 3	
9 months	HBV 3	
12 months	MMR 1	Pneu 3
15 months	DTaP-IPV-Hib 4	
4 years	MMR 2	DTaP-IPV 1
5^{th} year (10/11 years)	DTaP-IPV 2	
6^{th} year (11/12 years)	HPV*	

* Girls only, given twice, second dose after 6-month interval.

Table 7.3 Immunisation schedule for St. Maarten.

Age	Vaccination 1	Vaccination 2
2 months	DTaP-IPV-Hib 1	HPV 1
3 months	DTaP-IPV-Hib 2	HBV 2
4 months	DTaP-IPV-Hib 3	Pneu 1
6 months	HBV 3	Pneu 2
12 months	DTaP-IPV-Hib 4	MMR 1
15 months	Pneu 3	
4 years	DT-IPV	MMR 2
9 years	DT-IPV	HPV 1*
9.5 years	HPV 2*	

* Girls only, given twice, second dose after 6-month interval.

Table 7.4 Vaccination coverage[a,b] in the Caribbean Netherlands.

		Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Newborns (2 years of age)							
Number in cohort 2019		*1,188*	*229*	*1,750*	*15*	*33*	*384*
Dta(P)-IPV-Hib(-HBV)	Number	974	199	1,420	15	26	335
	%	82.0%	86.9%	81.1%	100%	78.8%	87.2%
HBV	Number	1,121	n/a	n/a	n/a	n/a	343
	%	94.4%	n/a	n/a	n/a	n/a	89.3%
Polio	Number	n/a	n/a	1,416	n/a	n/a	n/a
	%	n/a	n/a	80.9%	n/a	n/a	n/a
Pneu	Number	1,066	198	1,536	15	26	297
	%	89.7%	86.5%	87.8%	100%	78.8%	77.3%
MMR1	Number	1,103	186	1,548	15	23	343
	%	92.8%	81.2%	88.5%	100%	69.7%	89.3%
MMR2	Number	n/a	128	1,381	n/a	n/a	n/a
	%	n/a	[g] 55.9%	78.9%	n/a	n/a	n/a
MenACWY	Number	n/a	186	n/a	15	24	n/a
	%	n/a	81.2%	n/a	100%	72.7%	n/a
Toddlers (5 years of age)							
Number in cohort 2016		*1,325*	*	*1,956*	*18*	*28*	*
DTaP-IPV	Number	763	*	995	16	10	*
	%	[d] 57.6%	*	[h] 50.9%	88.9%	[d] 35.7%	*
MMR2	Number	752	n/a	n/a	16	15	*
	%	[d] 56.8%	n/a	n/a	88.9%	[d] 53.6%	*
Schoolchildren (10 years of age)							
Number in cohort 2011		*1,318*	*	*2,148*	*12*	*42*	*
DT-IPV	Number	19	*	1,265	11	33	*
	%	[e] 1.4%	*	58.9%	[c] 91.7%	78.6%	*
MMR2	Number	1,231	*	n/a	11	n/a	*
	%	93.4%	*	n/a	[c] 91.7%	n/a	*
Girls (10 years of age)							
Number in cohort 2011		*761*	*	*n/a*	*<10*	*20*	*
HPV	Number	474	*	n/a	<10	10	*
	%	[f] 62.3%	*	n/a	[c] 85.7%	50.0%	*
Adolescents (15 years of age)							
Number in cohort 2006		*n/a*	*n/a*	*n/a*	*22*	*n/a*	*n/a*
MenACWY	Number	n/a	n/a	n/a	20	n/a	n/a
	%	n/a	n/a	n/a	90.9%	n/a	n/a

* Not reported in time.

[a] The registration systems in Caribbean Netherlands are not linked to the national population register, so children who have emigrated to neighbouring islands or elsewhere may be included in the denominator (the total number of children), but not in the numerator (the number of vaccinated children). The vaccination coverage may therefore be higher in reality than shown here. For Bonaire, the data from birth cohort 2012 is linked ad hoc to the population administration.

[b] Vaccination status at 2 years of age: DTaP-IPV/MMR = basic immunity, Hib/HBV/PCV/MenC = completed; at the age of 5 years: DT(aP)-IPV = revaccinated; at the age of 10 years: DTaP/MMR/HPV = full participation.
[c] Interim vaccination coverage: the vaccination is linked to school year, not birth year; vaccination will be offered in 2022 for part of these children.
[d] Interim vaccination coverage: there are still repeat vaccinations that need to take place.
[e] On Aruba, the DT(aP)-IPV is provided in year 7 of regular education, and at the age of 10 years in special education. At the end of 2021, 52.2% of the school-going cohort 2011 was in year 7 of in special education, of which 73.1% was vaccinated with DT(aP)-IPV. On Aruba, the MMR2 vaccination was moved up to the age of 4 years starting from birth cohort 2008. Due to this, the percentage of vaccinated children in cohort 2011 was much higher than that of the DT(aP)-IPV. Catch-up vaccinations will be offered at schools.
[f] On Aruba, HPV vaccination is given to girls in year 8, regardless of age. These numbers describe schoolyear 2020-2021, instead of cohort 2011, at age 10.
[g] Bonaire has moved its MMR2 vaccination up from 9 years to 18 months.
[h] This is the vaccination coverage for DT. For polio (IPV), it is 923/1,956; 47.2%.

7.3 Immunisation schedules

The immunisation schedules for the Caribbean Netherlands are presented in Figures 7.1, 7.2, and 7.3, and Tables 7.1, 7.2, and 7.3. See below the recent and upcoming changes to immunisation schedules in the Caribbean Netherlands.

7.3.1 Recent and upcoming changes to Bonaire's immunisation schedule

Since October 2021, Bonaire's Youth Healthcare offers pregnant women the maternal pertussis vaccination (MPV, Tdap), at or after 22 weeks gestation. New-borns whose mother received the MPV, are no longer offered a DTaP-IPV-Hib-HepB vaccine at 2 months. Instead, their DTaP-IPV-Hib-HepB basic series immunisation schedule consists of vaccinations at 3, 5, and 11 months. This change in the immunisation schedule is accompanied by a shift of the first dose of the pneumococcal vaccination series from 6-9 weeks to 3 months.

Additionally, from March 1st, 2022, VZV vaccination is being offered to all children aged 14 months (born on or after January 1st, 2021). This addition was made by replacing the previously offered MMR vaccine with the MMR-V vaccine. After the existing supply of MMR vaccine has been depleted, children who are due for a follow-up dose of an MMR-containing vaccine will be offered an MMR-V vaccine, even if they previously received an MMR vaccine.

From June 2022 onwards, the MenACWY vaccine is offered to adolescents aged 14 years (born in 2008), supplemented with a catch-up campaign for all adolescents aged 15 to 18 (born in 2004 to 2007). Lastly, on top of offering HPV vaccination to girls, starting at the end of 2022, the HPV vaccination will also be offered to boys (born in 2013).

7.3.2 Recent and upcoming changes to Saba's immunisation schedule

As of January 1st, 2022, VZV vaccination was added to Saba's NIP schedule by replacing the MMR vaccine offered at 12 months with the MMR-V vaccine for children born on or after January 1st, 2021. After depleting current MMR vaccine stocks, the same switch will be made for children aged 4 years (born on or after December 1st, 2018), who are due for their next MMR-containing vaccine, and 9-year-olds who have previously missed their second MMR-containing vaccine.

Additionally, since April 1st, 2021, boys born on or after January 1st, 2013, are being invited for HPV vaccination alongside girls in the year in which they turn 9. A catch-up campaign was run for boys born from 2004 to 2012.

7.4 Vaccination coverage

In general, vaccination coverage in the Caribbean part of the Netherlands is high (Table 7.4) However, due to differences in target groups and vaccination schedules, data on vaccination coverage are not always easy to compare. The method used for determining vaccination coverage often results in an underestimation for schoolchildren, as vaccinations are usually offered per school year regardless of a child's year of birth. In that case, the age limits of 5 and 10 years are not always met.

7.5 Epidemiology of diseases included in the NIP

Surveillance data in the Dutch Caribbean Islands is available from 2017 onwards for Bonaire and Saba, and since 2021 for St. Maarten. In those five years, there have been two pertussis cases in Bonaire in 2017, and one in 2018. In 2021, no diseases covered by the NIP were reported in the Caribbean Netherlands, although on Saba, Hib cannot be reported accurately.

8
Potential NIP target diseases

8.1 Hepatitis A

I.H.M. Friesema, H. Vennema

8.1.1 Key points

- In 2021, 77 hepatitis A cases were reported, corresponding to 0.4 cases per 100,000 population;
- A shift in age was seen with most cases in the age groups 10-19 years (36%) and 50 years and over (34%);
- The percentage of travel-related cases (21%) was comparable to 2020 (18%), and low compared to the previous years (2012-2019; mean: 40%);
- Although the number of cases was higher in 2021 compared to 2020, it Is still lower than before COVID-19. Travel and person-to-person contact are important hepatitis A transmission routes, which were limited due to the measures taken to control COVID-19.

8.1.2 Tables and figures

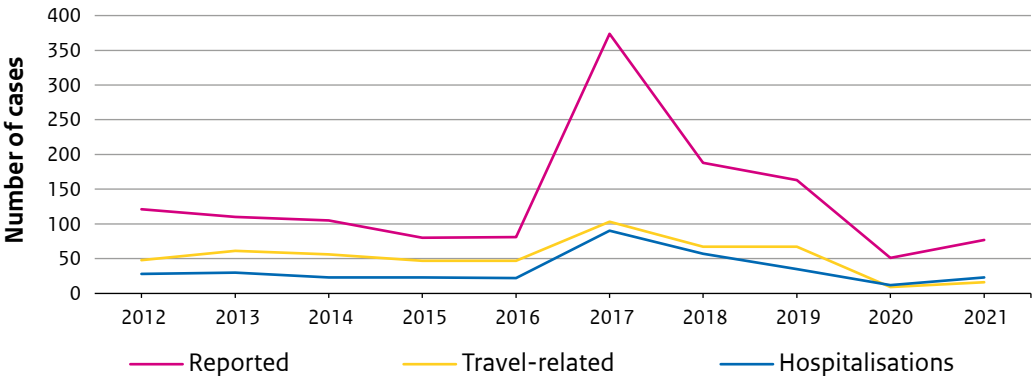

Figure 8.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2012-2021.
Source: Osiris

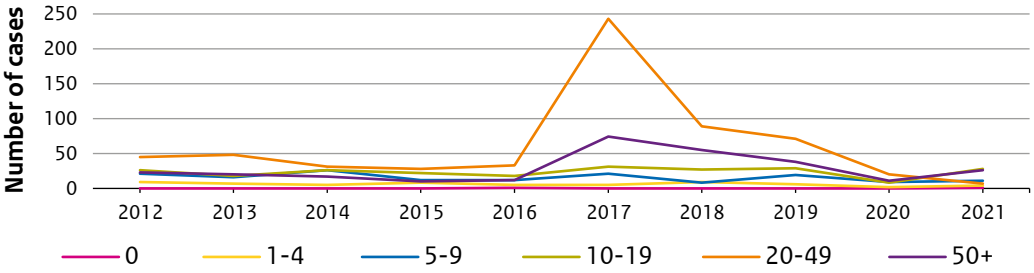

Figure 8.1.2 Age distribution of hepatitis A cases, 2012-2021.
Source: Osiris

8.1.3 Epidemiology

In 2021, 77 hepatitis A cases were reported, corresponding to 0.4 cases per 100,000 population. This is a higher number of cases than in 2020 (n=50 cases), but comparable to 2015 and 2016 (Figure 8.1.1/ Appendix 2). The peak in cases in 2017 was caused by a large, international, hepatitis A outbreak with 243 outbreak-related cases in the Netherlands. Two-thirds of these cases were men who have sex with men (MSM) [1]. The outbreak lagged in 2018, both national as international [2]. No mortality due to hepatitis A was reported in 2021. The age distribution over the years 2012-2021 is given in Figure 8.1.2. Infections were mainly seen in the 20 to 49 years old. Nevertheless, in 2021 a shift is seen with most cases in the age groups 10-19 years (36%) and 50 years and older (34%). In total, 23 patients were hospitalised (30%), which is comparable to the percentages of hospitalisation seen in the previous years (2012-2020: 21-30%; mean: 25%).

In 2021, the percentage of travel-related cases, 21%, was similar to 2020 (18%), and low compared to the previous years (2012-2019; mean: 40%). This is probably the result of the restrictions in travel because of the COVID-19 pandemic. Most travel-related cases had been in Asia (14 out of 18 cases), three had been in Africa, and one within Europe. Countries mentioned most were Afghanistan and Pakistan (both three times), and India and Lebanon (both two times).

Based on the notifications, eight epidemiologically linked clusters with in total 15 cases in 2021 and one in 2022 could be deduced. Four clusters occurred within one household, one occurred within a family not living together (the secondary case occurred in 2022), one cluster had a secondary case within the household and a third case had contact with the secondary case outside the household. The cases of the remaining two clusters got infected abroad.

The low number of cases, especially travel-related cases and cluster-related cases, can be explained by the COVID-19 pandemic. The two main transmission routes for hepatitis A are travel and person-to-person contact. Both were limited due to the measures taken since mid-March 2020 to control COVID-19.

8.1.4 Pathogen

Hepatitis A virus (HAV)-specific IgM-positive samples can be sent to IDS of the RIVM for typing as part of the molecular surveillance of this virus. In 2021, samples of 69 of 77 reported cases (90%) samples were submitted for virus typing. Of these samples, 64 samples (93%) were positive by PCR and available for sequence analysis. Samples from the remaining cases were not submitted for various reasons; sometimes because the Municipal Health Service already identified the source. In these cases, it is still worthwhile to sequence a sample because the same strain may show up somewhere else where no clear source is indicated.

A total of 348 serum and faecal samples of 341 unique persons were tested at the RIVM in 2021. HAV RNA was detected in 67 samples (19%) and 64 of reported cases could be typed, which resulted in 28 unique sequences; a total of 44 cases could be assigned to clusters of 2 or more cases. These concerned 6 molecular clusters varying between two and 15 cases. The two largest clusters (15 and 10 cases) were most likely foodborne outbreaks, but no source was identified. All clusters were contained by contact tracing and vaccination. Transmission occurred within households and a school. Hepatitis A virus was detected a in sewage at a location where refugees from Afghanistan were staying. This was followed up by testing faecal samples of 124 children between 0 and 4 years old. Two positive cases were found and all children up to the age of 15 were vaccinated. One of the positive cases was typed and the sequence was identical to the sequence in the sewage sample.

8.1.5 Research

Progress has been made towards whole genome sequence (WGS) analysis for HAV. The biggest advantage is the increased resolution, which makes it possible to examine transmission chains in outbreaks and which also reveals small differences between old and recent strains from the same origin. An overlapping amplicon protocol, similar to the protocol employed for SARS-CoV-2 sequence analysis, was designed for HAV. This will also allow WGS for samples with a relatively low virus load.

8.1.6 International developments

An Argentinian study investigated the cellular memory response at least ten years after vaccination [3]. Subjects were immunocompetent children, born in 2004-2005, who had been vaccinated with Havrix® or Vacqta® at the age of 12 months (+/- 1 month) and in 2015-2016 participated in the ten-year-evaluation of the implementation of single-dose universal vaccination against HAV in Argentina. Two groups of individuals were approached between September 2018 and March 2019: individuals with unprotective anti-HAV antibody levels (UAL) and individuals with protective anti-HAV Ab levels (PAL) in the 2015 evaluation. UAL were confirmed in 41/54 (76%) individuals from the unprotected group of 2015, and 25/27 (93%) individuals from the protected group of 2015 had maintained seroprotection. The UAL group received a booster dose and were followed-up with 30 days later, which was completed by 52 (96.2%) participants. From these, 48 (92%) reached post-booster PAL and 4 remained below the 10 mIU/mL threshold. The T cell memory response was assessed with flow cytometry analysis at admission in both groups, and again 30 days after the booster dose in the UAL group. The presence of the T cells appeared to be independent of the level or presence of

anti-HAV antibodies: HAV-specific memory CD4+ and CD8+ T cells responses were detected in 11 (52.4%) and 9 (42.9%) PAL individuals (n=21), and in 14 (53.8%) and 7 (26.9%) UAL individuals (n=26), respectively.

In Thailand, the effectiveness of the two- and three-dose regimens of hepatitis A vaccination (Havrix) among kidney transplant recipients was examined in a randomised controlled trial with a 2:1 allocation ratio, August 2017-December 2018 [4]. A total of 285 out of 401 participants (71.1%) were already anti-HAV IgG positive. Out of 77 subjects, 60 allocated to the 2-dose regime completed vaccination series, as did 33 out of 39 subjects allocated to the 3-dose regime. Reasons for not completing the study were loss to follow-up, switch to chronic hemodialysis due to allograft failure, having already been vaccinated with hepatitis A vaccine before enrolment, and death due to other underlying diseases. No difference in seroconversion rates one month after complete vaccination was seen: 51.7% (2-dose regime) and 48.5% (three-dose regime). Higher overall seroconversion rates were seen in participants with high estimated glomerular filtration rate, high serum albumin level, and on low intensity immunosuppressive regimens.

A phase 3, single blind, parallel, randomised, active-controlled, two-arm study was conducted comparing Biological E inactivated hepatitis A (BE-HAPIBEV™) vaccine with Havrix 720® vaccine in 1-15-year-old children in India, May 2019-August 2020 [5]. BE-HAPIBEV is based on the Healive® vaccine from China, which then is fill-finished in India. The vaccines were administered intramuscularly, six months apart. Both groups consisted of 260 initial subjects, out of whom 233 (BE-HAPIBEV) and 234 (Havrix) completed vaccination. Seroconversion was 100% at day 210 in both groups.

In China, 3,515 HAV-susceptible children were included in a randomised trial between 1996 and 1999 [6]. The children were aged between 1-12 years (mean age: 5.4 years) at enrolment, where they received a single dose of the live-attenuated HAV vaccine (Pukang Biotechnological Co. China) or served as controls. After 17 years of follow-up, 2,132 (61%) of the participants remained available. Loss to follow-up was mainly caused by having received additional doses of hepatitis A vaccine (62%) and emigration (25%). The seropositive rate and geometric mean concentration (GMC) were 94.9% and 131.3 mIU/ml, respectively, at two months after immunisation, and then gradually declined. At 12 years and 17 years after immunisation, excluding natural infection and vaccine boosting, seropositive rates and GMC were 54.1% and 43.5 mIU/ml (95% CI: 32.0–59.1 mIU/ml), and 55.6% and 41.1 mIU/ml (95% CI: 27.8– 61.0 mIU/ml), respectively. The overall median predicted duration of antibody levels above the threshold of 10 mIU/ml was estimated at 293.5 months (IQR: 247.0-330.0 months). The pooled cumulative infection rate in 17 years was not significantly different between the vaccine groups (3.1%; 95% confidence interval: 1.3%–5.7%) and the controls (4.2%; 95% CI: 2.6% - 6.2%).

A total of 450 hepatitis A outbreaks in Spain during 2010-2018 were analysed: 120 outbreaks in regions with a universal vaccination strategy were compared to 330 outbreaks in regions with a risk-group vaccination strategy [7]. The cumulative outbreak incidence rate was lower in regions with universal vaccination with 16.04 per million persons compared with 20.76 per million persons in regions with risk-group vaccination (RR 0.77; 95%CI 0.62–0.94). In regions

with universal vaccination, imported outbreaks accounted for 65%, whereas this was 28.7% in regions with risk-group vaccination (aOR 3.88; 95%CI 2.13–7.09). Adolescents and young adults aged 15-44 years (31.0% versus 43.1%) and men who have sex with men (23.8% versus 67.5%) were less frequently the first case of the outbreak in regions with a universal vaccination strategy versus regions with risk-group vaccination.

In the United States, the public health impact and cost-effectiveness of a hepatitis A catch-up vaccination of persons aged 2-18 years was calculated with a dynamic transmission model [8]. Routinely, children in the age 12-23 months are vaccinated within the vaccination programme. The incremental cost per quality-adjusted life year (QALY) gained from a societal perspective over a 100-year time horizon, using a 3% annual discount rate, was estimated and converted into 2020 US dollars. The catch-up programme would prevent 70,072 additional symptomatic infections, 51,391 outpatient visits, 16,575 hospitalisations, and 413 deaths in the 100-year time period. The catch-up vaccination strategy was cost-saving, especially when focusing on unvaccinated children and adolescents and maximising their first dose coverage.

8.1.7 Literature

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* RIVM publication.

8.2 Respiratory Syncytial Virus

A.C. Teirlinck, P.B. van Kasteren, M. van Boven, H.E. de Melker, A. Meijer

8.2.1 Key points

- While in the winter of 2020/2021 hardly any RS-virus circulated, an out-off season RSV epidemic started in week 23 of 2021, which still continued at the end of this reporting period (week 20/2022).
- After the summer peak, the number of detections reported in the virological laboratory surveillance remained stable above the epidemic threshold. In winter, the number of detections was lower than usual, with no distinct winter peak. After a gradual decline from week 52/2021, the number of detections increased again from week 11/2022 and remained high, even increasing slightly until the end of this reporting period (week 20/2022, n=121). The total number of detections in the 2021/2022 season (week 40/2021 until week 20/2022, n=2514), is higher than in previous seasons.
- In the period of week 21/2021 up to week 20/2022, the overall percentage of RSV positive ARI specimens taken by the GPs was highest in children in the age group 0-1 years, where 36% of the sampled children of 0-1 years was positive for RSV, followed by age group 2-4 years (15%) and >65 years (7%). The percentage was lowest in the age groups 5-64 years (range 1 – 5%).
- While in 2021, RSV-A was dominant, this shifted to RSV-B dominance in 2022.

8.2.2 Figures

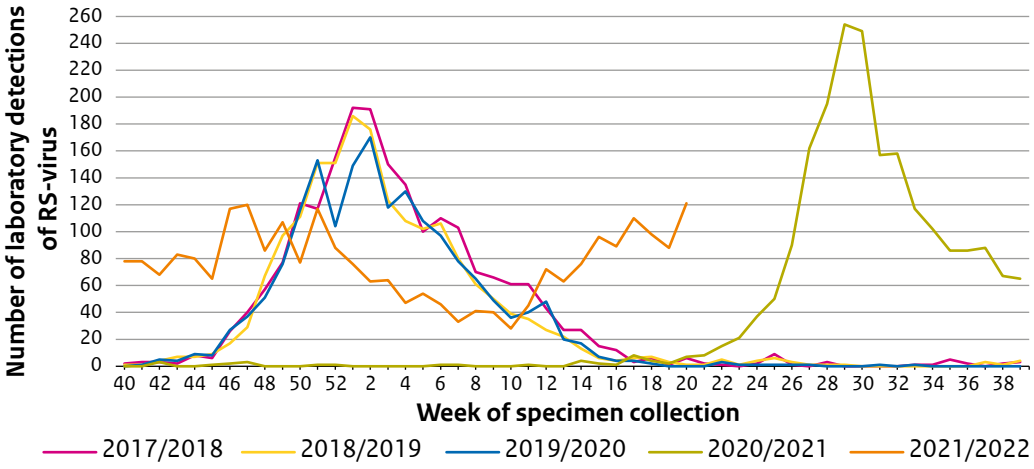

Figure 8.2.1 Number of weekly reported RSV diagnoses in the virological laboratory surveillance for the period 2017/2018-2021/2022 Source: virological laboratory surveillance, NWKV.
(NWKV = Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).)

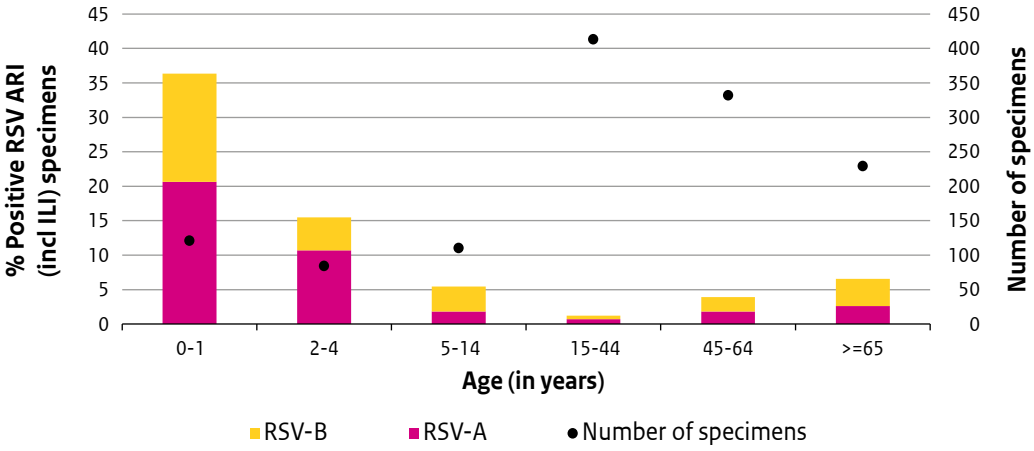

Figure 8.2.2 Percentage of RSV-A and RSV-B positive specimens from patients with ARI (including ILI), and the number of tested specimens, sentinel influenza surveillance during the respiratory season of 2021/2022 (week 21 of 2021 up to and including week 20 of 2022), displayed for six age groups.
Source: Nivel Primary Care Database, RIVM

Because of the extraordinary out-of-season circulation of RS-virus, this figure displays the characteristics from week 21 of 2021 onwards instead of the usual week 40 of 2021.

8.2.3 Epidemiology and pathogen

Studies show that RSV is a common cause for respiratory infections in young children [1] and in older adults [2, 3], causing outbreaks in elderly care facilities [4]. RSV is subdivided in RSV-A and RSV-B, mainly on the basis of the variation in the attachment protein, the G-protein.

The current Dutch RSV surveillance is based on 1) general practitioner (GP) sentinel surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI) and 2) virological laboratory surveillance. For the Nivel/RIVM GP sentinel surveillance, nose and throat swabs are collected from a subset of patients and analysed by National Influenza Centre (NIC) location RIVM for influenza viruses, RSV, rhinoviruses, enteroviruses, since February 2020 for SARS-CoV-2, and since January 2021 for parainfluenza virus types 1-3, human metapneumovirus and human seasonal coronaviruses. RSV detections in the virological laboratory surveillance mainly represent RSV laboratory analysis from hospitalised paediatric patients who are tested for clinical purposes [5, 6].

While hardly any RS-virus circulated in the winter of 2020/2021, an out-of-season RSV epidemic started in week 23 of 2021 (determined by the Moving Epidemic method (MEM) [7], which still continues at the end of this reporting period (week 20/2022). The number of virus detections reported in the virological laboratory surveillance peaked in July 2021, with 254 detections reported in week 29 of 2021 (Figure 8.2.1). This was higher than the peaks of

the past nine years, when peaks never exceeded 200 detections. After this summer peak, the number of detections declined, but remained stable above the epidemic threshold. In winter, the number of detections increased slightly, but was lower than usual with no distinct winter peak. After week 51/2021, the number of detections declined gradually until week 10/2022 (28 detections). In week 11 however, the number of detections increased again and remained high and even slightly increasing until the end of this reporting period (week 20/2022, n=121) and still stays above the epidemic thresholds.
In the period of week 21/2021 up to week 20/2022, the overall percentage of RSV-positive ARI specimens taken by GPs was highest in children in the age group 0-1 years, where 36% of the sampled children of 0-1 years was positive for RSV, followed by age group 2-4 years (15%) and >65 years (7%) (Figure 8.2.2). The percentage was lowest in the age groups 5-64 years (range 1 – 5%). While in 2021, RSV-A was dominant, this shifted to RSV-B dominance in 2022.

Since early May 2021, the Wilhelmina Children's Hospital (WKZ) of UMC Utrecht registers the number of (RSV-)bronchiolitis admissions of children <2 years old in 45 hospitals in the Netherlands on a weekly basis. This data is collected and analysed in the context of the *SPREAD*-study, which aims to compare characteristics of children being admitted during earlier winter epidemics with characteristics of children being admitted since summer 2021, and is also used for modelling purposes. RIVM can use the aggregated data for RSV surveillance, to get a broader perspective on RSV circulation, both in mild and in severe patients. For these results, and more information and data on epidemiology in the Netherlands, please refer to the annual report 'Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2021/2022' [8], and the *RIVM website on RSV surveillance* (only available in Dutch).

8.2.4 Research

RIVM is a partner in the *RESCEU* and *PROMISE* projects, both funded by the Innovative Medicines Initiative Joint Undertaking, under grant agreements 116019 and 101034339, receiving support from the European Union's Horizon 2020 Research and Innovation Programme and the European Federation of Pharmaceutical Industries and Associations. Both projects aim to explore the clinical, economic, and social burden of RSV and strengthen European collaboration through the various disciplines working on RSV. The aim is to create a sound epidemiological and virological baseline before introducing a vaccine to identify appropriate target groups for vaccination. THE PROMISE project is expected to build on and extend the analyses initiated in the RESCEU project, and is particularly focussed on the design of public health strategies as well as on the development and use of vaccines and therapeutics in both children and older people. In addition, PROMISE aims to develop an EU-wide surveillance network on RSV.

RIVM is also a partner (subtopic and work package lead) in the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking *INNO4VAC*. Funded under grant agreement No 101007799, this Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This consortium aims to harness advances in the fields of immunology, big data and artificial intelligence, 3D tissue models and human infection models,

and incorporate them into the vaccine industry to accelerate and de-risk the development of new vaccines. Within this consortium, RIVM is specifically involved in the development of in vitro differentiated epithelial models to study infection with and immunological protection against RSV and influenza virus, aiming to reduce the need for animal models. The project will run from September 2021 to February 2027.

8.2.5 International developments

Following an interim safety assessment, GSK has decided to stop enrolment and vaccination in several late-stage trials (NCT04605159, NCT04980391, NCT05229068) evaluating its potential RSV maternal vaccine candidate in pregnant women (press releases on February 18th and 28th, 2022). No data has been presented to date on the specifics of the safety assessment.

Moderna is initiating a phase 3 trial (NCT05127434) for its mRNA-based RSV vaccine candidate in older adults, after obtaining Fast Track status from the FDA (press releases February 22nd, 2022 and August 3rd, 2021). A phase 1 trial including, amongst other groups, RSV seropositive children aged 12 to 59 months is still ongoing (NCT04528719).

A phase 3 trial by Astra-Zeneca/Sanofi concerning an improved anti-F monoclonal antibody (Nirsevimab) for prophylactic therapy, which requires only a single dose due to its longer half-life, in term infants is close to completion (NCT03979313) and is currently under assessment at the EMA (press release February 17th, 2022).

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8.3 Rotavirus

R. Pijnacker, E.A. van Lier, H. Vennema, M. Hooiveld, H.E. de Melker

8.3.1 Key points

- Rotavirus circulation in 2021 had a remarkable seasonal pattern, with a low number of rotavirus detections during the usual rotavirus season in the first half of the year. This was probably due to COVID-19 control measures. In October 2021, however, an increase in rotavirus detections was observed, marking an early start of the 2022 rotavirus season.
- The 2022 rotavirus season, which already started at the end of 2021, peaked in March, after which the number of laboratory rotavirus detections started decreasing.
- G9P8 was the most prevalent genotype in 2021, although a shift towards G3P8 was observed at the end of the year.
- The State Secretary of Health, Welfare and Sport decided on September 20th, 2022, that universal rotavirus vaccination would be added to the Dutch NIP from 2024 onwards.

8.3.2 Tables and figures

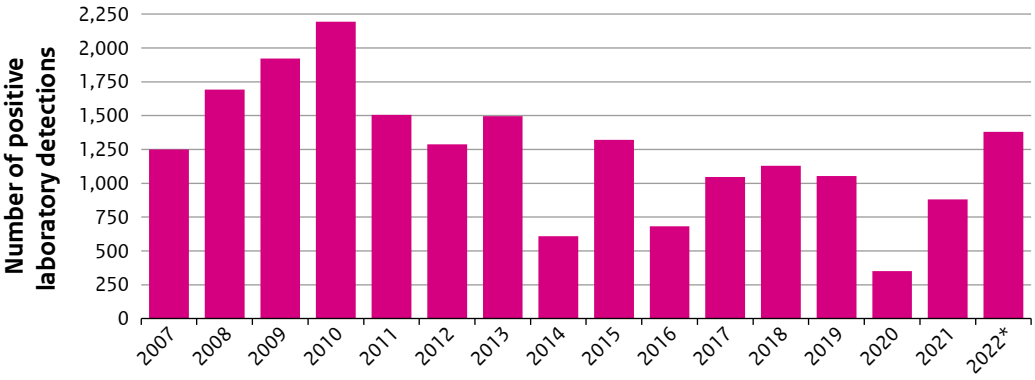

Figure 8.3.1 Number of reported laboratory rotavirus detections per year in the Netherlands, 2007-2022.

* Data for 2022 are available until week 26.

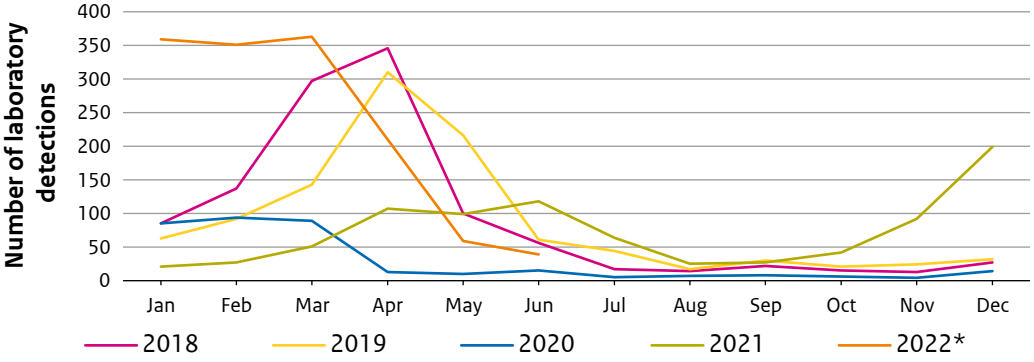

Figure 8.3.2 Number of reported laboratory rotavirus detections per month in the Netherlands, 2018-2022.

* Data for 2022 are available until week 26.

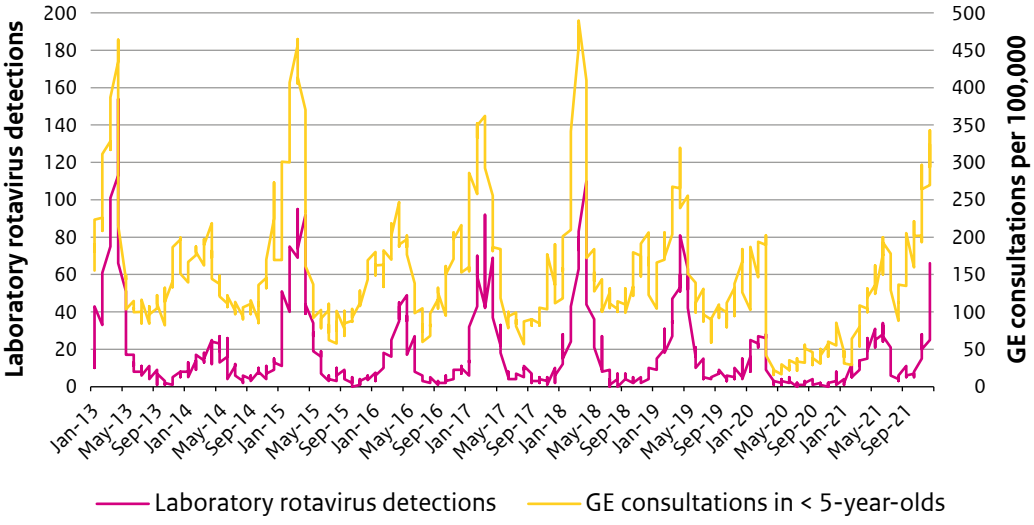

Figure 8.3.3 Overall number of rotavirus laboratory detections and general practice all-cause gastroenteritis consultations in children under 5 years old per week, the Netherlands, 2013-2021.

Table 8.3.1 Number of rotavirus samples typed per year and identified genotypes, the Netherlands, 2018-2022*.

Type	2018	2019	2020	2021	2022*	Total
G12P8	1.1%	0.7%	0.0%	2.7%	3.9%	**8**
G1P8	3.9%	8.3%	9.1%	17.3%	6.5%	**39**
G2P4	3.4%	9.0%	22.7%	14.7%	2.6%	**37**
G3P8	**31.3%**	**27.6%**	13.6%	**25.3%	**75.3%**	**176**
G4P8	1.7%	0.0%	0.0%	0.0%	0.0%	**3**
G9P8	**33.5%**	**26.2%**	**50.0%**	**38.7%**	10.4%	**146**
G9P4	16.2%	16.6%	4.5%	1.3%	0.0%	**55**
Other	8.9%	11.7%	0.0%	0.0%	1.3%	**34**
Total	**179**	**145**	**22**	**75**	**77**	**498**

* Data for 2022 are available until week 26.
** Predominantly found at the end of 2021, during the early start of the 2022 season. The value of 10.6% represents 19 samples in total, 16 of which were found in November (4) and December (12) of 2021.

8.3.3 Epidemiology

Rotavirus infections are not notifiable in the Netherlands. Therefore, data sources other than those for notifiable diseases were used, namely the weekly virology report and the Nivel Primary Care Database.

8.3.3.1 Laboratory detections

In 2021, 870 rotavirus detections were reported, which is more than in 2020 (n=350), when the number of rotavirus infections was at an all-time low (Figure 8.3.1). The latter was most probably due to COVID-19 control measures, such as the closure of schools and day care centres, limited numbers of visitors per day, social distancing, and increased handwashing. Although the number of rotavirus detections in 2021 was comparable to 2016-2019, averaging 981 annual detections (range: 682-1,054), it had a remarkable seasonal pattern. Usually, the number of rotavirus detections peak in February or March, but a clear peak was absent in 2021 (Figure 8.3.2). Instead, the season was delayed, with fewer detections. As in 2020, this probably resulted from COVID-19 control measures. However, there was an early start of the 2022 rotavirus season in October 2021, which is believed to be due to an increase in the number of children susceptible to rotavirus due to the absence of a rotavirus season in 2020.

8.3.3.2 Consultations in primary care

Nivel Primary Care Database provided data on all-cause gastroenteritis (GE) in children under the age of 5 years consulting their general practitioner [2]. GE was defined as a diagnosis of presumed gastrointestinal infection (ICPC code D73).
In 2021, 7,945 all-cause GE consultations were reported per 100,000 children below 5 years of age (on average 152 per 100,000 per week) (Figure 8.3.3). This was higher than in 2020, which was a year with an abnormally low number of GE consultations, when about half that number

of all-cause GE consultations was recorded (3,419 per 100,000), but comparable to 2016-2019, when the annual number of GE consultations ranged between 7,827.2 and 9,839.8. While 2020 was a year with abnormally low GE consultations, the increase relative to 2020 could also be due to increased healthcare-seeking behaviour and/or increased rotavirus incidence.

Consultations in 2021 had no pronounced seasonal pattern, opposed to pre-COVID-19 years where they were most frequent from January through March. Interestingly, the number of consultations seemed to gradually increase until week 27, followed by a decreasing trend for several weeks, after which the gradual increase resumed. This is in line with the number of rotavirus detections (Figure 8.3.3), which increased until week 27 and dropped afterwards, without a clear seasonal peak. The subsequent increase in consultations, from week 31 onwards, follows the increasing norovirus incidence, followed by the unusually early start of the 2022 rotavirus season in October 2021.

8.3.4 Rotavirus genotypes

IDS/RIVM receives faecal samples throughout the year from the Working Group Clinical Virology laboratories for rotavirus genotyping. The results are given per calendar year and are shown in Table 8.3.1. In 2021, all received samples could be typed. G9P8 was the most prevalent genotype in 2021 (29/75, 39%), which is in range with previous years (2020=50%; 2019=26%; 2018=36%). The second most prevalent genotype was G3P8 (19/75, 26%). Although this was in line with previous years (2020=14%; 2019=28%; 2018=31%), it was predominantly found in November and December of 2021, when the unusually early 2022 rotavirus season started. It continued to be the most dominant genotype in 2022 (data available up to and including week 26, 2021), accounting for 75% (58/77) of all typed samples.

8.3.5 (Inter)national developments

On May 23rd, 2022, the new State Secretary decided that vaccination against rotavirus would not be added to the Dutch NIP on the short term due to a lack of available funds [3]. However, on September 20th, 2022, the State Secretary amended this decision because financial coverage was found, adding universal rotavirus vaccination to the Dutch NIP from 2024 onwards [4].

As of January 2022, 114 countries worldwide have introduced rotavirus vaccination in their national immunisation programmes. Three of these countries have either phased or sub-national introductions [5]. Although 70% of sub-Saharan Africa have introduced rotavirus vaccines, more than half of all rotavirus deaths occur in African countries due to the high disease burden in this region [6]. The World Health Organization (WHO) prequalified four available rotavirus vaccines, namely ROTASILL®, ROTAVAC®, Rotarix®, and RotaTeq® [7]. Only Rotarix® and RotaTeq® are licensed for use in Europe.

8.3.6 Literature

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8.4 Varicella zoster virus (VZV) infection

E.A. van Lier, A. Buisman, C. Kampshoff, H.E. de Melker

8.4.1 Key points

- The epidemiology of herpes zoster (incidence of GP consultations, hospitalisations and deaths) in the Netherlands did not change in 2020 and was comparable to that in previous years; GPs recorded about 92,000 herpes zoster episodes (550 episodes per 100,000 population).
- For varicella, the incidence of GP consultations and hospitalisations in 2020 was significantly lower; GPs recorded about 23,000 varicella episodes (130 episodes per 100,000 population). The incidence was approximately half less than in previous years. This is probably linked to the COVID-19 measures, which also have limited transmission of VZV.
- Preliminary data showed an increase in varicella in the Netherlands since the beginning of 2022 also affecting older children between 5 and 15 years of age (higher risk of complications), which may be a catch-up effect after the corona years.
- Interim results showed that the adjuvanted recombinant zoster vaccine (RZV) confers long-term protection against HZ at least seven years post-vaccination. The efficacy against HZ remained high (>84%).

8.4.2 Tables and figures

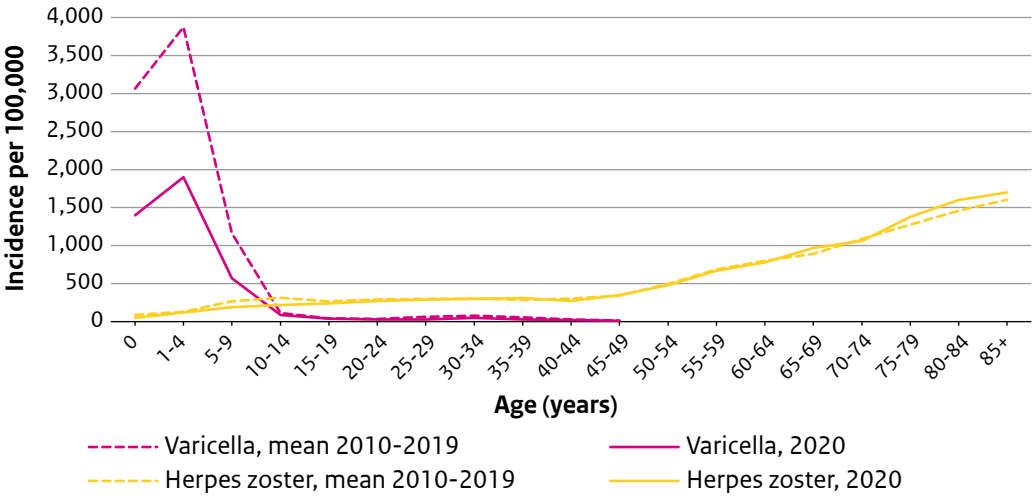

Figure 8.4.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2020 versus mean 2010–2019 by age group [1].
Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and therefore not included.
Source: NIVEL

Table 8.4.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on NIVEL-Primary Care Database (PCD), using the old (2009–2011) and new methods (2010–2020) (rounded to nearest 10).

Syndrome	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Varicella*	(110)	(180)										
Varicella**	180	210	230									
Varicella***		310	270	250	280	270	250	240	280	260	300	130
Herpes zoster**	360	360	360									
Herpes zoster***		480	490	510	510	530	530	530	530	540	550	530

* Dutch Sentinel General Practice Network (CMR) [2]; since 2008, this network has switched from paper registration to electronic reporting, which may have resulted in under-reporting of the weekly number of varicella patients. We therefore used data from NIVEL-PCD from 2008 onwards.
** NIVEL-PCD, old method [3].
*** NIVEL-PCD, new method from 2012 onwards [1]; 2010–2012 recalculated.
Source: NIVEL

Table 8.4.2 Incidence per 100,000 population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2009–2020* [4].

Syndrome	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Varicella	1.5	1.9	1.7	1.5	1.7	1.9	1.8	2.0	2.0	1.7	1.9	0.9
Herpes zoster	2.4	2.1	2.2	2.1	2.1	2.7	2.9	2.8	2.8	3.0	3.1	3.0

In 2006/2007, a number of hospitals ceased registration, causing an underestimation of hospital admissions from 2006 until 2014 (see Appendix 1).
Admissions for a single day have been excluded.
The number of admissions may be higher than the number of hospitalised patients reported here because some patients have been admitted more than once within the same year.
In 2015-2019, number of admissions were rounded off to the nearest 5. Corrected for non-participating hospitals. Data retrieved from Dutch Hospital Data/Statistics Netherlands; this may have resulted in a trend break compared to previous years.
* Data for 2020 are preliminary.
Source: DHD, CBS

Table 8.4.3 Absolute number of deaths with varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) as primary cause of death, 2009–2021* [5].

Syndrome	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Varicella	1	2	1	2	1	2	2	4	3	2	3	2	4
Herpes zoster	20	25	20	21	21	26	33	27	33	36	32	43	36

* Data for 2021 are preliminary.
Source: CBS

8.4.3 Epidemiology

In 2020, general practitioners (GP) recorded about 23,000 varicella and 92,000 herpes zoster (HZ) episodes (130 and 530 episodes per 100,000 population, respectively). The incidence of GP consultations due to varicella episodes per 100,000 population was highest in children under 5 years of age, whereas the incidence of GP consultations due to HZ episodes was highest in those aged 50 years and over (Figure 8.4.1).

The epidemiology of HZ (incidence of GP consultations, hospitalisations, and deaths) in the Netherlands in 2020 was similar to previous years (Tables 8.4.1, 8.4.2, and 8.4.3). However, for varicella, the incidence of GP consultations and hospitalisations in 2020 was significantly lower. The incidence was approximately half less than in previous years. This is probably linked to the COVID-19 measures, which have limited transmission of VZV, too. An effect of the COVID-19 pandemic on the incidence was also observed for other vaccine-preventable diseases in the Netherlands [6, 7], as well as for varicella in other countries (for example China, South Korea, Japan and France [8-13]). France stated that the lack of immune stimulation due to the reduced circulation of microbial agents and to the related reduced vaccine uptake induced an 'immunity debt' which could have negative consequences for varicella as well when the COVID-19 pandemic is under control [13]. This phenomenon is illustrated by preliminary data showing an increase in varicella in the Netherlands since the beginning of 2022, also affecting older children between 5 and 15 years of age (who have a higher risk of complications), which may be a catch-up effect after the corona years [14].

According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards [15], the incidence of HZ is higher than reported previously (Table 8.4.1). Mahamud *et al.* found that national death certificate data tends to overestimate the number of deaths in which HZ is the underlying or contributing cause of death [16]. If we apply their rate of deaths for which HZ was validated as the underlying cause of death (0.25 (range 0.10–0.38) per 1 million population) to the Dutch population in 2020 and 2021, we would expect 4.4 deaths (range 1.7–6.6) in both years, instead of the 43 and 36 deaths reported in 2020 and 2021 respectively (Table 8.4.3).

8.4.4 International developments

8.4.4.1 Varicella

Fontoura-Matias *et al.* studied the burden of varicella from 2000 to 2015 in Portugal, where varicella vaccination is not included in the NIP. A total of 1,520 hospitalisations were registered (annual rate of 17.3 hospitalisations per 100,000 inhabitants). During the summer period and in Southern regions, a higher number of hospitalisations was observed. The median length of stay was 4 days (interquartile range 3.0–7.0), and complications were mostly dermatologic (19.6%), neurologic (6.0%), and respiratory (5.1%) [17]. Vandenhaute *et al.* reported high rates of complications (12.6%) and antibiotic use (27.3%) due to varicella based on a retrospective observational study in a primary care setting in Belgium, where no universal varicella vaccination is implemented [18]. Pawaskar *et al.* showed that in the United States, universal varicella vaccination was associated with significant reductions in the use of antibiotics and

antivirals for varicella management among children and their associated costs [19]. Piazza *et al.* studied the burden of varicella from 2010 to 2017 in Liguria (Italy), where universal varicella vaccination was introduced in 2015. The annual incidence rate of varicella cases and hospitalisations declined from 2015 while vaccination coverage at 24 months increased from 11% in 2015, 49% in 2016 to 68% in 2017 [20]. Widgren *et al.* conducted a medical record study among people hospitalised with varicella in 2012-2014 in Stockholm and Gothenburg, Sweden. They found that 87.2% of children and 63.0% of adults had complications. In children, dehydration (31.7%), bacterial skin infections (29.8%) and neurological involvement (20.6%) were the most frequent complications. 63% of the adults were born abroad. A separate seroepidemiological analysis showed a VZV seroprevalence of 66.7% at 5 years and 91.5% at 12 years of age [21]. Arnheim-Dahlström *et al.* showed that parents in Sweden, where varicella vaccination is available privately, generally viewed varicella infection as a mild disease. While 65% of respondents were aware of the varicella vaccine, only 15% had started vaccination as of February 2019. If offered within the NIP, 85% of parents would be highly likely to vaccinate their child [22]. A multi-country Phase III study over a ten-year period showed high efficacy of two varicella vaccines in Norwegian and Swedish populations, consistent with overall study results of ten European countries. Vaccine efficacy in the two-dose group (MMRV) was ≥92.1% in both Norwegian and Swedish children, compared to 72.3% in Norway and 58.0% in Sweden in the one-dose group (monovalent varicella vaccine) [23].

8.4.4.2 Herpes zoster

Interim results of an extension study of the phase 3 clinical trials ZOE-50 and ZOE-70 showed that the adjuvanted recombinant zoster vaccine (RZV) confers long-term protection against HZ at least 7 years post-vaccination. The efficacy against HZ remained high (>84%) from approximately 5 to 7 years after the 2-dose vaccination course administered at the age of ≥50 years (mean, 67.2 years) [24]. Bruxvoort *et al.* showed that the risk of HZ was not significantly different between RZV recipients with and without concomitant vaccination, supporting current recommendations on concomitant vaccination. The HZ incidence rate was 2.2 (95%CI: 1.6–3.0 per 1,000 person-years) among individuals with concomitant vaccination and 3.4 (95%CI: 2.9–4.0 per 1,000 person-years) among individuals without concomitant vaccination. The adjusted hazard ratio (HR) for HZ comparing RZV recipients with and without concomitant vaccination was 0.75 (95%CI: 0.53–1.08). The most common vaccines that were given concomitantly with RZV were influenza vaccines (65.9%), pneumococcal vaccines (20.2%), Td/Tdap (12.3%), and hepatitis vaccines (10.2%) [25]. Carryn *et al.* studied humoral and cell-mediated immunity, as markers of VZV exposure, in adults aged ≥50 years. They found that VZV-specific humoral immunity from 17 countries (12 high, 2 moderate and 3 low VZV circulation) varied significantly between countries but not by VZV circulation [26]. Widgren *et al.* conducted a mathematical modelling study in which they explored various alternative forms of exogenous boosting. They found that a strong or durable protection from boosting does not necessarily cause an extensive surge in HZ incidence following introduction of universal varicella vaccination [27].

In a meta-regression of HZ incidence worldwide, incidence rates varied by age (increase with age), gender (lower in males), continent (lower in Europe and North America compared to Asia and Oceania) and year of study data (increase with year) [28]. In England, where the lifetime prevalence of HZ was estimated at 11.5%, age, gender, ethnicity, and digestive disorders may be related to the risk of HZ [29]. Between 2009 and 2019, the number of HZ patients treated as full inpatients in German hospitals increased from 17,333 to 27,295 cases per year corresponding to a significant linear increase of 57.5%. The increase was significant in all age categories (0–20, 21–40, 41–60 and over 60 years). Possible causes may be the changing age distribution of the German population and a trend toward a higher number of sunshine hours (UV exposure) for Germany over the period 2009-2019 [30]. In Australia, two years after implementation of HZ vaccination, an estimated 7,000 cases were prevented. The incidence fell steadily in those aged 70–79 years, with an estimated decrease of 2.25 (95%CI: 1.34– 3.17) per 1,000 person-years per year. In the two non-vaccine-programme-targeted groups, there was no evidence of reduction in zoster incidence: 60–69 years, 0.46 (95%CI: -0.46–1.38) and 80–89 years, 0.11 (95%CI: -1.64–1.87) [31]. Amodio reported a decline in HZ hospitalisation rates in Italy in the period 2003–2018. Hospitalisation rate was 10.4 per 100,000 persons/year with a significant decreasing trend from 13.9 in 2003–2006 to 7.8 in 2015–2018 ($p < 0.001$). This decline may be due to a changing of hospitalisation criteria instead of a true reduction in the burden of disease [32]. A prospective cohort study conducted by Díez-Domingo *et al.* in Spain showed that during days 0–30 post-HZ diagnosis, the mean EQ-5D utility score was 0.738 (utility loss of 0.138). The most affected ADL component was sleep [33].

In the United States, overall cumulative completion rates of the 2-dose schedule of RZV were 70.4% and 81.8% at 6 and 12 months respectively for adults ≥50 years of age with a first RZV prescription filled between October 2017 and September 2019. The adherence with the recommended administration schedule (2-6 month interval between first and second RZV dose) was 67.6% [34]. Another study in the US also showed that adherence and completions rates for RZV are suboptimal (adherence rate 71,8%, completion rate 72.3% after 6 months and 86.2% after 24 months) [35]. Curran *et al.* estimated the impact of reduced RZV use due to COVID-19. In 2020, 3.9 million RZV series initiations were missed, resulting in 31,945 HZ cases, 2,714 postherpetic neuralgia cases, and 610 lost QALY [36].

In Thailand, Bakker *et al.* found strong seasonal incidence in both varicella and HZ, with a three-month lag between the peak of varicella and the peak of HZ notifications. Their models suggested that the seasonal cycles of varicella and HZ have different underlying mechanisms and that there is a strong correlation between seasonal UV radiation and HZ incidence [37].

Sim *et al.* analysed the association between HZ and increased cancer risk in a large population-based retrospective study. HZ is associated with decreased immune function, a factor involved in cancer development. The HZ group showed a slightly decreased overall cancer risk compared with the non-HZ group (HR=0.94, 95%CI: 0.90–0.97). The HRs for specific cancer risk were 0.41 (95%CI: 0.33–0.50); 0.86 (95%CI: 0.81–0.91); 0.87 (95%CI: 0.78–0.97); 0.80 (95%CI: 0.73–0.87); 1.20 (95%CI: 1.07–1.34); and 1.66 (95%CI: 1.35–2.03) for cancers of the lips, mouth, and pharynx; digestive system; respiratory system; unknown secondary and

unspecified sites; thyroid and endocrine glands; and lymphoid and hematopoietic systems, respectively. The HZ with PHN group showed higher HRs for specific cancer risk, such as lymphoid and hematopoietic systems (95%CI: 1.27–2.39). These results suggest that HZ and PHN were associated with the development of certain cancers [38].

Different articles discuss a possible relationship between COVID-19, COVID-19 vaccines, and HZ but causality has not yet been established. A possible cause of VZV reactivation is a transient lymphopenia with T-cell immune dysfunction that occurs after vaccination, similar to that in COVID-19 [39-44]. Data from a retrospective cohort study conducted by Birabaharan *et al.* suggested mRNA COVID-19 vaccination is not associated with increased rates of VZV reactivation [45]. In their systematic review and meta-analysis, Chu *et al.* also concluded that there is no evidence that COVID-19 vaccination was associated with increased risk of HZ (RR 1.06, 95%CI: 0.91–1.24) [46]. Patil *et al.* did not find evidence for an association between COVID-19 vaccination and a new diagnosis of HZ [47] either. Gringeri *et al.* reported a slightly higher risk of HZ following the Pfizer-BioNTech vaccine (ROR=1.49, 95%CI: 1.42–1.57) based on the VAERS database. However, almost all cases were of non-serious nature. For the vaccines of Moderna (ROR=0.75, 95%CI: 0.71–0.79) and Janssen (ROR=0.64, 95%CI: 0.57–0.71), the risk was slightly lower [48]. Hertel *et al.* found a higher incidence of HZ post-COVID-19 vaccination (OR=1.8, 95%CI: 1.7–1.9); most patients received the Pfizer-BioNTech vaccine [49]. Bhavsar *et al.* found in a large retrospective cohort study that COVID-19 diagnosis in ≥50-year-olds was associated with a 15% (aIRR 1.15, 95%CI: 1.07–1.24) increased risk of developing HZ. The risk was more pronounced (21%; aIRR, 1.21; 95%CI: 1.03–1.41) following COVID-19 hospitalisation [50]. In Germany, there was no evidence for an increased risk of HZ requiring hospitalisation during the first year of the COVID-19 pandemic [51]. Merzon *et al.* found a decreased likelihood of being tested positive for COVID-19 among ZVL vaccinated individuals ≥50 years of age (adjusted OR=0.47, 95%CI: 0.33–0.69) [52]. Bruxvoort *et al.* found that RZV vaccination was associated with a 16% lower risk of COVID-19 diagnosis and 32% lower risk of hospitalisation (aHRs for COVID-19 diagnosis and hospitalisation were 0.84 (95%CI: 0.81–0.87) and 0.68 (95%CI: 0.64–0.74), respectively) [53].

Johannesdottir Schmidt *et al.* found no association between HZ and the risk of dementia in Denmark (HR=0.98, 95%CI: 0.92–1.04 during the first year and 0.93, 95%CI: 0.90–0.95 thereafter) [54]. Warren-Gash *et al.* concluded that in the UK, HZ was not associated with increased dementia diagnosis (HR=0.92, 95%CI 0.89–0.95) [55] and Choi reported similar findings for South Korea (OR=0.90, 95%CI: 0.84–0.97) [56]. Lophatananon *et al.* also reported that in the UK a history of HZ was not associated with an increased risk of dementia (OR=1.088, 95%CI: 0.978–1.211) but in people eligible for HZ vaccination and vaccinated with Zostavax® they saw a decreased risk of developing dementia (OR=0.808, 95%CI: 0.657–0.993) [57]. Scherrer *et al.* also found a decreased risk of dementia following HZ vaccination in two patient cohorts in the United States (Veterans Health Affairs HR=0.69, 95%CI: 0.67–0.72, and MarketScan HR=0.65, 95%CI:0.57–0.74) [58]. A review and meta-analysis of Huang *et al.* also suggested that there is an association between diabetes mellitus and the risk of HZ. Individuals with diabetes mellitus had a higher risk of developing HZ than individuals in the general population (pooled relative risk: 1.38; 95%CI: 1.21–1.57) [59].

8.4.4.3 Cost-effectiveness

Pawaskar *et al.* estimated the economic burden of varicella in Europe in the absence of universal varicella vaccination. The overall annual total costs were estimated to be €662,592,061 (range: €309,552,363 to €1,015,631,760) and are mainly driven by caregiver work productivity loss [60]. Carrico *et al.* studied the cost benefit of vaccination against HZ among US adults aged 50 years and older. Compared with no vaccination, current vaccination coverage is associated with 3.9 million averted disease cases, $24.5 billion averted costs of cases, and $15.5 billion in incremental vaccination costs over a 30-year period from a societal perspective (benefit-cost ratio (BCR) = 1.6). Increased vaccination coverage (vs. current coverage) is associated with 5.6 million additional averted disease cases, $34.1 billion additional averted costs of cases, and nearly $23.6 billion in incremental vaccination costs, resulting in a societal BCR of 1.5 over 30 years. This highlights the economic value of HZ vaccination and indicates that efforts to further increase vaccination coverage may be warranted and economically justifiable [61]. Helm *et al.* conducted a health impact analysis of HZ vaccination in Norway. The model analysed six vaccination scenarios with the live-attenuated vaccine (ZVL) at different ages (60, 65, and 70 years) compared with no vaccination, including a catch-up programme in the first year of the vaccination in three of the scenarios. They concluded that vaccinating adults at 65 years of age with catch-up to 70 years in the first year of the programme was the most cost-effective strategy (ICER = NOK (Norwegian Krone) 245,459 per QALY from societal perspective or NOK 248,637 from the health care system perspective) [62]. Health impact and cost-effectiveness analyses of RZV in the German population ≥50 years of age were updated by Curran *et al.* with the latest vaccine efficacy estimates against HZ. The ICER ranged from €26.000 per QALY in 60-year-olds to €35.000 in 70-year-olds. Compared to previous analyses, public health and cost-effectiveness results improved due to the higher, sustained vaccine efficacy of RZV [63]. Pieters *et al.* concluded that in Belgium, RZV is cost-effective in the 50-year-old age cohort at the unofficial Belgian threshold of €40,000 per QALY gained, if its price drops to €55.40 per dose but is never cost-effective at its current market price [64]. A system review and meta-analysis by Udayachalerm et al., including 37 studies, concluded that RZV may be cost-effective for vaccination in ages of 60–70 years, while ZVL might be cost-effective in some age groups. Based on the societal perspective, ZVL was cost-effective compared with no vaccine when vaccinated at ages of 50–59 and 70–79 years with incremental net benefits of $0.61 (95%CI: 0.37–0.85) and $9.67 (95%CI: 5.20–14.14), respectively. RZV was cost-effective for those aged 60–69 and 70–79 years with incremental net benefits of $75.61 (95%CI: 17.98–133.23) and $85.01 (95%CI: 30.02–140.01), respectively. Under the third-party payer perspective, ZVL was cost-effective compared to no vaccine when vaccinated at the age of 70–79 years with incremental net benefits of $7.57 (95%CI: 0.27–14.86) and RZV was cost-effective at 60–69 years with incremental benefits of $220.87 (95%CI: 47.80–393.93) [65]. Meredith *et al.* conducted a systematic review to evaluate the cost-effectiveness evidence of HZ vaccines in the United States. All studies that compared RZV vaccination with no vaccination concluded that RZV is a cost-effective strategy to prevent HZ and postherpetic neuralgia, and RZV consistently dominated ZVL. According to the authors, this supports removal of ZVL from the US market [66].

8.4.5 Literature

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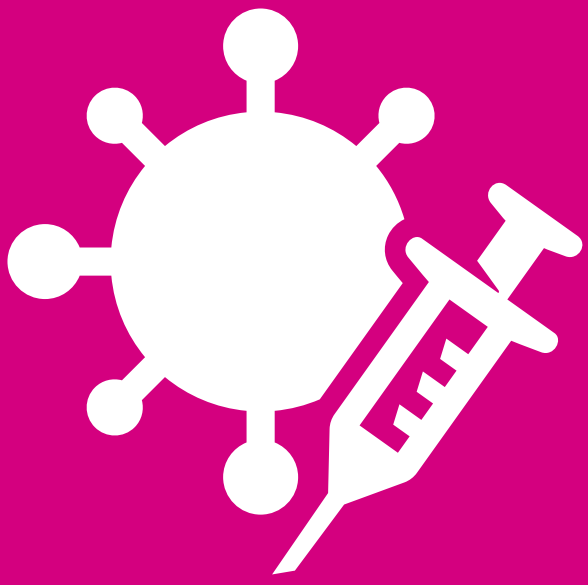
9
COVID-19



9.1 The epidemiological situation of SARS-CoV-2 in the Netherlands

A.J.M. Pluijmaekers, D.S.F. Berry, F. Jongenotter, S.J.M. Hahné

9.1.1 Key points

- The tail-end of the second COVID-19 period in 2020, continued through the first few weeks of 2021. The second period in the Netherlands started with an increase in notifications in younger age groups (10-29 years), followed by an increase in their parents (people 40-50 years of age), and subsequently the older age groups (70+).
- The third period lasted from February 2021 until June 2021. COVID-19-related deaths did not increase during this wave, probably as a result of the vaccination campaign.
- The fourth period occurred in the summer of 2021 (weeks 27 through 39) with a small peak, most probably due to a combination of introduction of the virus from holiday destinations and the re-opening of dance venues where recipients of the Janssen vaccine were allowed access immediately after being vaccinated.
- The fifth period lasted from week 40 of 2021 until the end of 2021. At the end of September 2021, measures were re-introduced and repeatedly strengthened.
- At the beginning of 2022, the sixth and, as of week 26 of 2022, current period started. At the beginning of this period, measures were relieved due to greatly decreased numbers of deaths despite high amounts of notifications and hospitalisations. This decrease probably resulted from the booster vaccination campaign and the spread of the less severe Omicron-variant.

9.1.2 Tables and figures

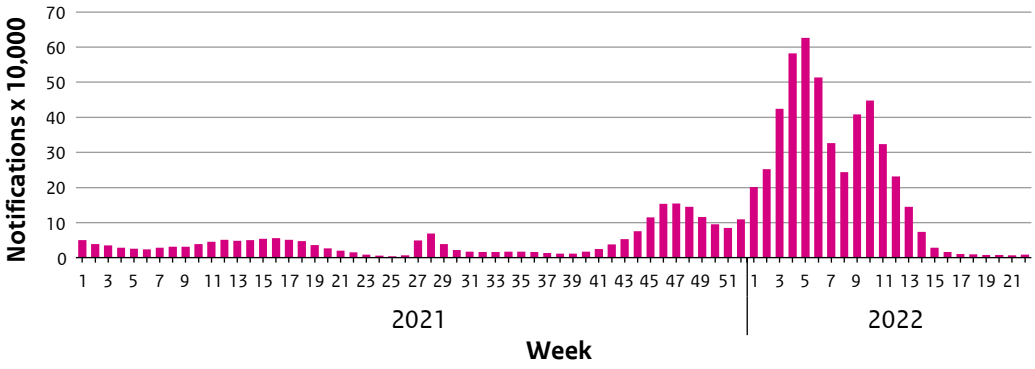


Figure 9.1.1 Total number of notifications per 10,000 for week 1, 2021, until week 22, 2022. Hospitalisations and mortality can be found on the *Dutch Corona dashboard website*.

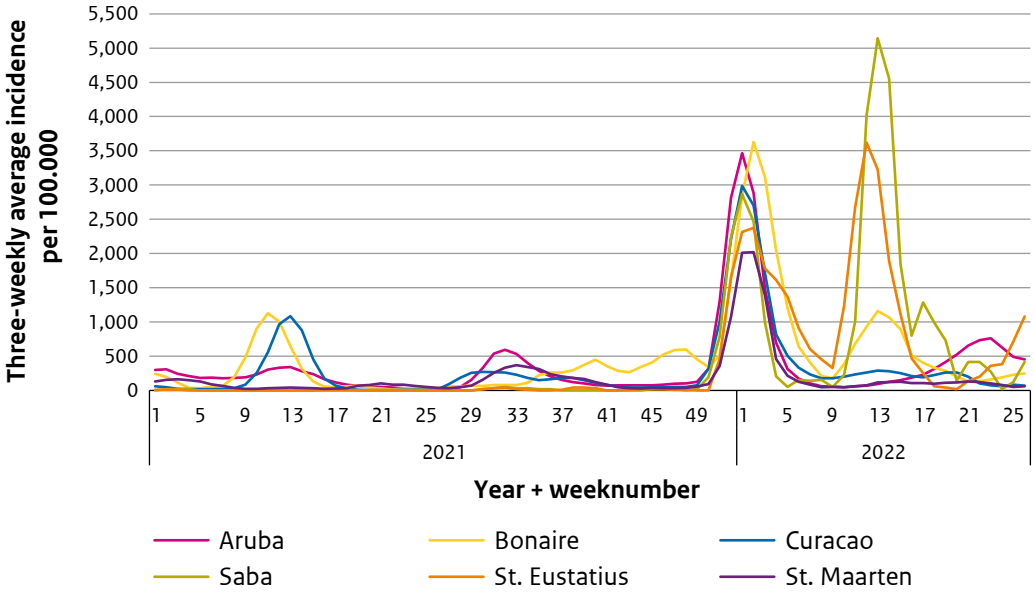


Figure 9.1.2 Incidence per 100,000 (three-weekly rolling average) on the Dutch Caribbean islands. Please note that the testing policy on St. Maarten and Curaçao changed in the course of the reporting period. Consequently, after respectively April 26th, 2022, and June 4th, 2022, their trends are not comparable to the period before.

9.1.3 SARS-CoV-2 surveillance in the Netherlands in 2021 and 2022

Figure 9.1.1 shows the total number of SARS-CoV-2 tests and the proportion of positive test results, by week, from week 1 in 2021 until week 22 in 2022.

Official tests were carried out by the municipal health services (GGD), and were either a PCR, loop-mediated isothermal amplification (LAMP), or antigen test. From December 1st, 2020, onwards, anyone who had been in close contact with a SARS-CoV-2 positive person could request to be tested, regardless of whether they experienced any COVID-19-related symptoms. From April 11th, 2022 (week 15), it was no longer mandatory to confirm a positive self-test with an official test. While the amount of performed tests had already been decreasing from the end of January 2022, this change to testing-guidelines led to a further decrease in performed tests, as can be seen in Figure 9.1.1.

In addition to nation-wide reporting on positive tests, a few groups of interest are monitored separately: people living at elderly care facilities, people living at disabled care facilities, people over 70 years of age who live independently, healthcare workers, and teachers and day-care workers. Summaries on the spread of SARS-CoV-2 in these groups can be found in the *weekly update on the SARS-CoV-2 epidemiological situation in the Netherlands* as prepared by RIVM's epidemiology department.

The day-to-day changes in the number of positive cases as found by the GGD together with data on the number of hospitalisations and intensive-care admissions provided by the COVID-19 hospital registry from the National Intensive Care Evaluation (NICE) are used to calculate the R-number. See the weekly updated *RIVM page on the SARS-CoV-2 figures*.

Alongside testing activities and vaccination duties, the GGD has also taken on the source and contact-tracing role in the Netherlands. The goal of source and contact tracing changed throughout the pandemic, but overall, it is used to limit further spread of the virus by looking for common sources of infection, and warning people who have been in close contact with an individual who tested positive for SARS-CoV-2. Because contacts are warned of their possible exposure to SARS-CoV-2 early on, they can go into quarantine before symptoms develop, thereby limiting transmission of the virus.

For more in-depth data on the epidemiology of the SARS-CoV-2 virus and COVID-19 in the Netherlands, please refer to the weekly update on the epidemiological situation in the Netherlands as prepared by RIVM's epidemiology department. For more general overviews of all epidemiological data related to SARS-CoV-2 and COVID-19 summarised from the beginning of the pandemic, please refer to the *Dutch Corona dashboard website*. The weekly updates and dashboard can also be consulted to stay up-to-date on the SARS-CoV-2 epidemiological situation in the Netherlands.

9.1.4 The SARS-CoV-2 timeline in the Netherlands in 2021 and 2022

January 6th, 2021, marked the kick-off of the SARS-CoV-2 vaccination campaign in the Netherlands, starting with healthcare workers and continuing with nursing-home residents. At the same time, the Netherlands' second period of the COVID-19 pandemic, which had started in September 2020, was coming to an end. A few weeks into the start of the vaccination campaign, daily deaths began to decrease steadily. Therefore, from March 1st, 2021 (week 9) onwards, measures aimed at preventing the spread of SARS-CoV-2 were gradually eased. A five-step plan was used to further scale down the measures on a regional basis.

Simultaneously with the easing of measures, the third period of COVID-19 began in week 5, with an increase in cases sweeping through the country and peaking in week 16 with 56,111 notifications and 1,853 hospitalisations. Deaths had however continued to decrease, down to 15 in week 25.

The Netherlands experienced its fourth period from weeks 27 until 39, 2021. There was an increased influx of new cases, likely resulting from a combination of imported cases from holiday destinations and from the re-opening of dance venues where recipients of the Janssen vaccine were allowed access immediately after being vaccinated. This period peaked in week 28, with 69,451 notifications. After week 26, hospitalisations also began to rise, peaking in week 29 with 579 new hospitalisations. The number of deaths began to rise slowly, and peaked in week 34, when 43 people deceased as a result of COVID-19.

Notifications started to increase again in week 39, heralding the start of the fifth period in week 40, and leading to a reintroduction of control measures in week 44. These focussed on decreasing interpersonal contacts by limiting visitors and urging to work from home, as well as limiting access to shops and hospitality services on the basis of the so-called corona pass. These measures were made more stringent at the end of weeks 45 and 48, after which the country entered a full lockdown at the end of week 50.

After the re-introduction of measures, notifications temporarily peaked in week 47 (154,548), and then decreased until the end of the year with 109,523 notifications in week 52. Along with the increase in positive tests, hospitalisations increased as well, with deaths following suit from week 41 onwards. Hospitalisations peaked in week 47 (2,178) and deaths steeply peaked in weeks 49 (443) and 50 (354).

Notifications again increased from week 1 in 2022 (the start of the sixth COVID-19 period in the Netherlands), peaking in week 5 (626,300). Likely circumstances leading to this increase were Christmas and New Year's celebrations, the upcoming spread of the Omicron variant, and the re-opening of shops, education, sports clubs, and contact-dependent professions from the end of week 2. In week 4, despite the rise in notifications, measures were eased further, after which notifications decreased until week 8 (243,444). Notifications temporarily increased in week 9, possibly resulting from further easing of measures and the yearly Carnival celebrations, peaking in week 10 (448,159), and then decreased again to 73,707 in week 14. Since week 15 (starting from April 11th), official testing after a positive self-test is no longer mandatory.

Hospitalisations showed a similar trend to notifications, reaching a temporary low in week 2 of 2022 (805) and again increasing until week 5. Unlike the notifications, which temporarily decreased after week 4, hospitalisations plateaued for two weeks and even decreased for a week (week 8), before continuing their increase. Hospitalisations peaked in week 11 (1,878 new admissions), one week after the peak in notifications. Ever since, hospitalisations have steadily decreased until the end of May (week 21, 184), after which figures seem to indicate a slow rise again.

Deaths showed a different trend than hospitalisations and notifications, by decreasing until week 3 (53) and then remaining relatively stable. This is probably a result of the emergence of the Omicron variant, which causes less severe disease, and the start of the booster campaign, which started on November 18th, 2021, with people over 80 years of age and people living or working in eldercare facilities. The booster campaign was ramped up towards the end of the year in order to vaccinate as many people aged 60 years and over before the start of 2022. This momentum was carried on into the younger age groups, although uptake of booster vaccination decreased by age group.

In weeks 6 through 7 and weeks 10 through 13 of 2022, deaths did increase slightly (on average 80 and 102, respectively) following the increase in hospitalisations, after which they have continued to decrease until the beginning of June (week 22). Just like the hospitalisations, deaths seem to increase again from week 23 onwards.

For a more detailed description of SARS-CoV-2 epidemiology in the Netherlands, please see the last two Annual Reports Surveillance of COVID-19, influenza, and other respiratory infections in the Netherlands, both for winter 2020/2021 and winter 2021/2022 [1, 2]. For more information on the international SARS-CoV-2 and COVID-19 situation, please refer to the ECDC and WHO web pages.

9.1.5 SARS-CoV-2 surveillance in the Dutch Caribbean

Figure 9.1.2 shows the three-week average incidence rate (per 100,000 including the estimated population of undocumented residents), by week, from week 1 in 2021 until week 22 in 2022.

The Caribbean part of the Kingdom of the Netherlands entails the countries Curaçao, Aruba, and Dutch Sint Maarten (CAS islands), as well as the overseas municipalities Bonaire, St Eustatius, and Saba (BES islands). Throughout the pandemic, surveillance data of SARS-CoV-2 cases has been collected on each island in collaboration with local public health departments, laboratories, and medical professionals. The coordination of SARS-CoV-2 surveillance was carried out in close collaboration with the Dutch National Institute for Public Health and the Environment (RIVM), the Dutch Ministry of Health, Welfare and Sport, the Caribbean Public Health Agency (CARPHA), British overseas territories (UKOTS), Santé Publique France, and the WHO regional office for the Americas (PAHO).

On the BES islands, SARS-CoV-2 diagnostics (PCR) were carried out by the municipal health services (GGD) via testing centres. On the CAS islands, diagnostics were carried out by local laboratories in collaboration with the local public health departments: Directie Volksgezondheid (DVG) on Aruba, the Epidemiology & Research Unit of the Ministry of Health of Curaçao, and the Collective Prevention Services (CPS) on Dutch Sint Maarten. By the end of 2021, rapid antigen tests were also used by local laboratories in addition to PCR testing to diagnose SARS-CoV-2 infections on all islands. Self-tests became available on the islands early 2022, although accessibility was limited due to the local pricing and dependency on overseas supply.

Testing guidelines differed between islands and were amended over time, depending on European Netherlands, WHO/PAHO, and CDC testing guidelines, local burden of disease, as well as locally available public health capacity and resources. In addition, testing obligations also existed for tourists returning to their country of residence. There was no separate monitoring of SARS-CoV-2 positive test results from people living at elderly care or disabled care facilities, teachers, or day-care workers. SARS-CoV-2 positive test results from healthcare workers in local hospitals were monitored until early 2022, when source and contact tracing efforts were no longer feasible given the high amount of SARS-CoV-2 positive test results reported due to the Omicron wave.

Until summer 2021, modelling of the Ro and COVID-19 hospitalisation scenarios for the CAS islands was carried out in close collaboration between RIVM and local stakeholders, leading the Dutch Ministry of Health, Welfare and Sport to provide these islands with additional support in terms of healthcare personnel, equipment, and medical supplies whilst at the same time coordinating accelerated vaccine supply.

To aid the pandemic response and support outbreak investigations, RIVM sequenced RT-PCR positive samples from the islands as part of the overall national genomic-based SARS-CoV-2 variant surveillance ('kiemsurveillance'), using NGS/WGS. In September 2021, the Netherlands received the HERA Incubator Action Area 1 grant to enhance the overall WGS and RT-PCR infrastructure and capacity. RIVM applies this to support the BES/CAS by equipping two laboratories (on Aruba and Curaçao) for WGS, and training its laboratory personnel and offering WGS-training to all laboratory and public health personnel of the six islands.

For more in-depth data on the epidemiology of the SARS-CoV-2 virus and COVID-19 on the CAS-BES islands, please refer to the *weekly update on the epidemiological situation in the Dutch Caribbean*, as prepared by RIVM's epidemiology department.

9.1.6 Literature

1.* Reukers DFM, van Asten L, Brandsema PS, Dijkstra F, Donker GA, van Gageldonk-Lafeber AB, et al. Surveillance of influenza and other respiratory infections in the Netherlands: winter 2017/2018. Bilthoven: RIVM; 2019. Report No.: 2018-0049.

2.* Reukers DFM, van Asten L, Brandsema PS, Dijkstra F, Hendriksen JMT, Hooiveld M, Jongenotter F, de Lange MMA, Teirlinck AC, Willekens G, Meijer A, van Gageldonk-Lafeber AB. Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2021/2022. Bilthoven: RIVM; 2022. Report No.: 2022-0098.

* RIVM publication.

Table continues on next page.

9.2 Recommendations from the Health Council of the Netherlands

A.J.M. Pluijmaekers

9.2.1 Key points

- The vaccination strategy focused on reducing severe illness and death, and on keeping the healthcare system from becoming overtaxed. Therefore, persons most at risk of becoming severely ill or dying from SARS-CoV-2 should be first in line for vaccination, with their healthcare workers and caregivers next in line.
- In addition, employees of long-term care facilities, hospital employees providing direct COVID-19 care, and general practitioners were prioritised.
- Eventually, all persons aged 12 years and over were eligible for COVID-19 vaccination with priority given to risk groups and invitations being sent in descending order, from old to young.
- At the end of 2021, the Health Council of the Netherlands advised to invite risk-group children aged 5-11 years for vaccination, followed by a positive vaccination advice for all children aged 5-11 years.
- At the end of 2021, the Health Council also advised to provide boosters to the entire eligible population, by first inviting vulnerable groups and inviting people for vaccination in descending order, from old to young.

9.2.2 Tables

Table 9.2.1 Overview of all Health Council (HC) recommendations regarding SARS-CoV-2 vaccination in the Netherlands, for the period up to and including September 8th, 2021. The complete list of recommendations can be found on the *Health Council's website*. Please refer to this page for full descriptions and any future additions.

Date	Links	Title
19/11/20	NL, EN	COVID-19 vaccination strategies
07/12/20	NL	Prioritering vaccinatie COVID-19 voor de CAS-landen
24/12/20	NL, EN	COVID-19 vaccination: BioNTech/Pfizer
04/01/20	NL	Advies uit eerste gezamenlijk overleg OMT en Gezondheidsraad over COVID-19-vaccinatiestrategie
11/01/21	NL, EN	COVID-19 vaccination: The Moderna vaccine and the vaccination strategy
14/01/21	NL	Advies uit tweede gezamenlijk overleg OMT en Gezondheidsraad over COVID-19-vaccinatiestrategie
03/02/21	NL	Interval BioNTech/Pfizer
04/02/21	NL, EN	Ethical and legal considerations COVID-19 vaccination

Date	Links	Title
04/02/21	NL, EN	COVID-19-vaccination: AstraZeneca vaccine
08/03/21	NL	Spoedvragen COVID-19-vaccinatie
17/03/21	NL, EN	COVID-19 vaccination: Janssen vaccine
22/03/21	NL	Aanvulling hoog-risicopatiëntgroepen COVID-19-vaccinatie en toedieningsvormen COVID-19-vaccins
09/04/21	NL	Inzet AstraZeneca-vaccin
09/04/21	NL	Vaccinatie van kinderen
12/04/21	NL	Interval tussen de eerste en tweede vaccinatie
20/05/21	NL	Transmissie na vaccinatie
20/05/21	NL	Interval AstraZeneca-vaccin
02/06/21	NL	Leeftijdsgrens en tweede dosis AstraZeneca-vaccin
02/06/21	NL	Inzet vaccins in huidige fase COVID-19-vaccinatieprogramma
09/06/21	NL	Vaccinatie van kinderen met een medisch risico en ringvaccinatie
17/06/21	NL	Advies Gezondheidsraad en OMT over COVID-19 vaccinatiestrategie voor de korte en middellange termijn
29/06/21	NL	Vaccinatie van adolescenten tegen COVID-19
05/07/21	NL	Heterologe vaccinatie
29/07/21	NL	Vaccinatie van adolescenten tegen COVID-19 met het Moderna-vaccin
14/09/21	NL	Boostervaccinatie tegen COVID-19
02/11/21	NL	Boostervaccinatie tegen COVID-19; vervolgadvies
17/11/21	NL	Boostervaccinatie tegen COVID-19 voor mensen met downsyndroom
25/11/21	NL	Boostervaccinatie tegen COVID-19 bij personen van 18 tot 60 jaar
03/12/21	NL, EN	COVID-19 vaccination for young children belonging to clinical risk groups
10/12/21	NL, EN	COVID-19 vaccination of children aged 5 to 11
23/12/21	NL	Vaccinatie tegen COVID-19 met het Novavax-vaccin bij volwassenen
24/12/21	NL	Inzet vaccin van Janssen als booster
19/01/22	NL	Actualisatie advies vaccinatie van 5- tot en met 11-jarigen tegen COVID-19
04/02/22	NL	Boostervaccinatie van adolescenten tegen COVID-19
18/02/22	NL, EN	Second booster vaccination against COVID-19
25/03/22	NL, EN	Application framework for revaccination against COVID-19
25/03/22	NL	Vervolgadvies tweede boostervaccinatie tegen COVID-19
07/04/22	NL	Inzet Moderna-vaccin bij kinderen van 6 tot en met 11 jaar

9.2.3 Recommendations regarding SARS-CoV-2 vaccination strategy

On November 19th, 2020, the Health Council of the Netherlands (HC) published their first advice on COVID-19 vaccination strategies, focussed on reducing severe disease and death. To this end, persons most at risk of falling severely ill or dying from SARS-CoV-2, i.e., individuals over 60 years of age and individuals suffering from serious health complications, or their healthcare workers and caregivers, should be first in line for vaccination. Healthcare workers who came in close contact with their patients could be considered for vaccination as well. On December 7th, 2020, the HC expanded this recommendation to the CAS countries, favouring a switch to age-based priority; older age translated to higher priority.

As with non-COVID-19-related HC advice, the Dutch Ministry of Health, Welfare and Sport (HWS), through their Minister or State Secretary, will decide if and/or to what degree the HC recommendations are translated into policy. Thus, there may be differences between the HC's recommendations and the actual execution, which can be found in Chapter 9.3: COVID-19 vaccination campaign.

9.2.3.1 Allocation of vaccines

On December 24th, 2020, and January 11th, 2021, the HC recommended that the BioNTech/Pfizer and Moderna vaccines should be used primarily for the elderly. Healthcare workers vital to the continuation of care should be offered other vaccines. On March 22nd, the HC recommended that patients in need of an organ transplant should be vaccinated before their surgery with an mRNA vaccine, simultaneously with the 70-year-old age group.

On February 4th, 2021, the AstraZeneca vaccine was recommended for seniors of 60-64 years of age and persons in medical risk groups. On March 8th, the HC expanded this recommendation to include persons over the age of 65. On April 9th, after EMA added thrombosis with thrombocytopenia syndrome (TTS) to the adverse events from the AstraZeneca vaccine, the HC stated that this vaccine should only be offered to persons over 60 years of age. Anyone younger than 60 years who had already received their first dose could still receive their second dose. On June 2nd, the HC indicated that its advice remained unchanged.

The Janssen vaccine was recommended on March 17th, 2021, for seniors over 60, followed by specific risk groups, i.e., individuals with Down Syndrome, morbid obesity (BMI>40), and/or neurological afflictions that could lead to respiratory issues. After TTS was recognised as a rare but possible adverse event after vaccination with the Janssen vaccine, the Health Council restated the safety of the Janssen vaccine on June 2nd, yet recommended exclusive use of mRNA-vaccines due to their better cost-benefit ratio. The HC did leave room for use of the Janssen vaccine in specific populations in which only one vaccine dose could be attained. The determination of this was best left to the different health professionals who worked with these populations.

Although EMA approved the Novavax vaccine, the HC advised on December 23rd, 2021, to continue preferentially vaccinating unvaccinated people with the mRNA vaccines. The main reason for this was that the SARS-CoV-2 Omicron variant was becoming dominant, while insufficient data was available about the effectiveness of the Novavax vaccine against the

delta and Omicron variants. The mRNA vaccines, on the other hand, were proving to be effective. The HC did indicate however, that the Novavax vaccine, being a peptide vaccine, would be valuable specifically for people who did not want to receive an mRNA vaccine.

9.2.3.2 *Changes proposed to intervals between doses*

On January 14th, 2021, the HC and the Dutch Outbreak Management Team (OMT) recommended increasing the BioNTech/Pfizer vaccine interval to six weeks in order to provide as many people as possible with their first dose of the vaccine. This strategy was reaffirmed on February 3rd and again on March 8th, although persons who had been infected in the six months prior to their first vaccination would no longer require a second dose.

On April 12th, the HC advised that the BioNTech/Pfizer and Moderna intervals could be stretched to 12 weeks after all. The recommended interval for AstraZeneca remained 12 weeks and was reaffirmed in the May 20th advice.

9.2.3.3 *Changes proposed to the vaccination strategy*

On June 2nd, 2021, the HC recommended that people under 60 years should continue to receive mRNA vaccines. However, Janssen's vaccine, which had also been found to potentially cause TTS yet only required a single dose, was recommended for persons who could not be contacted through regular routes.

On July 5th, the HC indicated that they did not object to heterologous vaccination, in which a first dose of the AstraZeneca vaccine was followed by the BioNTech/Pfizer vaccine.

9.2.3.4 *Booster vaccination*

The HC and OMT delivered a joint advice on June 17th, 2021, about possible booster vaccinations. On September 14th, the first full advice on booster vaccinations followed, judging boosters as not yet required for the general public. The moment at which booster vaccinations would become worthwhile, would depend on the effectiveness of the vaccine in protecting against severe illness. However, while not technically functioning as a booster, a third dose was advised for people with a severely compromised immune system, who typically had no or inadequate immune responses after two doses of a COVID-19 vaccine.

On November 2nd, the HC advised to start providing booster vaccinations to people over 60 (starting with the oldest age groups) and people living in care facilities because primary vaccination in people over 60 leads to lower protection, while they are also at a higher risk of severe illness. In care facilities, booster vaccines would help stem the increase in infections and prevent severe illness, especially as many care facilities are home to elderly people. Booster vaccines were to be mRNA vaccines, regardless of the vaccine received in the primary series, and the interval after the last dose should be at least six months.

This first advice on booster vaccinations was followed on November 17th by the recommendation to include people with Down syndrome in the booster campaign. Similar to the elderly, their immune response to the primary series was shown to be lower, while they ran an increased

risk of severe illness and death. Next, on November 25th, the HC recommended including all people between the ages of 18 and 60 into the booster campaign, after booster vaccines had been offered to all people over 60, people residing in care facilities, and healthcare workers who came into close contact with their patients. As per the general rule, the HC advised to first invite older age groups for their booster vaccine.

Regarding the use of Janssen's vaccine as a booster, the HC recommended on December 24th, 2021, that it would be preferable to continue the booster campaign with mRNA vaccines only. The Janssen vaccine appeared to lead to a smaller increase in antibody levels compared to the mRNA vaccines, especially in people who had received Janssen as their primary vaccine. Further research should be awaited to see if antibody levels would increase in the months following a Janssen booster vaccine, just as this was the case for primary vaccination with the Janssen vaccine. If this would turn out to be the case, the Janssen vaccine might turn out to be a valuable booster option after all. Reasons to include the Janssen vaccine in the booster campaign were less stringent demands during transportation and storing of the vaccine, and being able to offer a booster vaccine to people who did not want to receive an mRNA vaccine.

On February 18th, 2022, the HC advised to offer a second booster vaccination (minimum interval of three months) to people over 70 years of age, people residing in care facilities, adults with Down syndrome, and/or adults with a severe immune disorder. On March 25th, this was expanded to include everyone aged 60 to 69. This recommendation was based on the consideration that, although the Omicron variant leads to less severe illness, these vulnerable groups still ran a greater risk for severe illness, while the improved protection against SARS-CoV-2 they had gained after the first booster, would have waned after three months.

The same two recommendations indicated that people who did not fall into any of those vulnerable categories did not need a second booster vaccine, as this would lead to limited health gains due to Omicron leading to less severe illness. However, on March 25th, the HC did point out the value of being able to quickly offer booster vaccinations to specific target populations, if the epidemiological situation indicated this to be of value. To this end, the HC provided a framework to quickly determine at which moment certain groups should become eligible for booster vaccination.

9.2.4 Recommendations for vaccination of children

9.2.4.1 Primary vaccination strategy

On April 9th, 2021, the HC recommended that 16- and 17-year-olds at risk of severe COVID-19 disease should be vaccinated with the BioNTech/Pfizer vaccine, expanding to risk group children aged 12 and over on June 9th. Children who could not be vaccinated due to medical reasons could be protected through ring vaccination.

On June 29th, the HC further expanded their recommendation for children by also including non-risk group children of 12 years and over, because of both health-based and social benefits. For the same reasons, Moderna's vaccine was recommended for children aged 12-17, on July 29th.

EMA approved the lowered-dose BioNTech/Pfizer SARS-CoV-2 vaccine for children aged 5 to 11 on November 25th, 2021. Subsequently, on December 3rd, 2021, the HC recommended to indeed offer this vaccine to risk-group children aged 5-11 because of their increased risk of hospitalisation and development of a severe inflammatory response affecting multiple organ systems (MIS-C). Selection of high-risk children would best be carried out by the relevant medical specialists.

On December 10th, 2021, this recommendation was expanded to include all children aged 5 to 11. This recommendation was again aimed at decreasing incidence of MIS-C (estimated at about 150 cases), but also at indirectly improving children's (mental) health by improving access to school, sports, and other avenues of social contact. Simultaneously, the HC stressed the importance of ensuring both parents and children had access to clear information about the vaccination, and that any and all forms of insistence had to be avoided.

On January 19th, 2021, the December 10 advice was upheld after it was re-evaluated in light of the Omicron variant, which caused less severe disease. Vaccination still protected against severe and (to a lesser degree) mild illness due to Omicron, and while MIS-C might occur less often after an Omicron infection, incidence was still estimated at 100 cases (instead of 150), thus still posing a substantial health risk. However, children who had already had COVID-19, as evidenced by a PCR test, would be protected against MIS-C, and would not have to be vaccinated with the aim of preventing the inflammatory syndrome.

The Moderna vaccine was approved by EMA for use in children aged 6 to 11 on February 24th, 2022, yet on April 7th, 2022, the HC recommended to continue use of the lower-dose BioNTech/Pfizer vaccine in children. The reason for this was because the BioNTech/Pfizer vaccine was still available and had been shown to confer good protection, while effectiveness and safety data on the Moderna vaccine were still limited.

9.2.4.2 Booster vaccinations

On February 4th, 2022, the HC advised not to offer booster vaccinations to adolescents aged 12 to 17 years, as data showed it led to only limited health gains, especially relating to the decreased severity of COVID-19 resulting from the Omicron variant, even in high-risk adolescents. Vaccinated adolescents proved well protected against severe illness and/or MIS-C due to an Omicron infection, while receiving another vaccination carried the rare yet possible risk of myocarditis, and the effect on viral spread was expected to be minimal. Furthermore, EMA had not yet approved the vaccine for use as a booster for adolescents, which would mean this specific use would be off-label. However, the HC did recommend to allow tailoring to specific adolescents with severe immune disorders and adolescents who wanted to receive a booster to protect vulnerable family members. Booster vaccinations for adolescents who wanted to travel to a destination that required a booster for entry into the country, were not part of this advice.

9.3 COVID-19 vaccination campaign

A. Valk, S.J. Lanooij, A.A.A. Maxwell, H.E. de Melker, S.J.M. Hahné

9.3.1 Key points

- The COVID-19 vaccination campaign in the Netherlands started on January 6th, 2021. The mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevac® (Moderna) have been used from week 1 and 3 2021, respectively. The vector vaccines Vaxzevria® (AstraZenaca) and Jcovden® (Janssen) were used from week 6 and 16 2021, respectively. The protein substitute vaccine Nuvaxovid® (Novavax) is used from week 11, 2022. From November 2021 onwards, Vaxevria® was not longer used in the Netherlands.
- In the Caribbean part of the Kingdom of the Netherlands, two COVID-19 vaccines were used in 2021: Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna). The Comirnaty® vaccine was used as from November 2021 for the booster vaccination campaign on the islands.

9.3.2 Tables

Table 9.3.1 Characteristics of the COVID-19 vaccines that were used in the Netherlands, week 1, 2021-week 21, 2022.

Manufacturer	Brand name	Minimum age in years	Type	Doses for primary series[1]	Interval target in weeks (window)	In use since	Offered as booster or repeat (since week)
BioNTech/ Pfizer[4]	Comirnaty ®	5[2]	mRNA	2	3 (3-6)	Week 1, 2021	Yes (47, 2021)
Moderna[5]	Spikevax ®	12	mRNA	2	4 (3-6)	Week 3, 2021	Yes, half a dose (47, 2021)
AstraZeneca	Vaxzevria ®	18	Recombinant vector	2	6-12 (4-14)	Week 6, 2021[3]	No
Janssen	Jcovden®	18	Recombinant vector	1	-	Week 16, 2021	Yes (25, 2022)
Novavax	Nuvaxovid ®	18	Protein subunit	2	3	Week 11, 2022	No

1 The primary series is completed when the required number of doses has been received. If someone has had a SARS-CoV-2 infection prior to the first dose, one dose for all vaccines is considered sufficient to complete the primary series.
2 A lower dose for ages 5 to 11, compared to the 12-year-olds and over.
3 From 15 to 23 March and 2 to 5 April 2021, Vaxzevria® was temporarily not in use. On April 8, 2021, the Minister of Health, Welfare and Sport decided to discontinue the use of Vaxzevria® for people younger than 60 years of age [1]. From the first of November 2021 onwards, Vaxzevria® was not longer used in the Netherlands.
4 Comirnaty® (BioNTech/Pfizer) was also used in the Caribbean part of the Netherlands, for both the primary series and, as of November 2021, also for the booster series.
5 Spikevax® (Moderna) was also used in the Caribbean part of the Netherlands for the primary series.

Table 9.3.2 Overview of all specified target groups and the dates from which they either were vaccinated, and/or could make an appointment for vaccination. Most, but not all, links lead to the corresponding news update in English.

Date	Group
Jan 6, 2021	• Employees of long-term care facilities • Hospital employees providing COVID-19 care
Jan 18	• Residents of long-term care facilities • Persons with an intellectual disability living in an institution
Jan 22	General practitioners and employees at general practices
Jan 25	Residents of long-term care facilities vaccinated by their GPs
Jan 26 – Feb 5	Mobile persons* living at home: persons born; *before 1931* *1931 – 1935* *1936 – 1940*
Feb 12	Employees of rehabilitation facilities
Feb 15	• Persons living at home, born between 1956 – 1960 • Employees of disability care facilities
Feb 22	Intramural mental healthcare clients and employees
Feb 25	District nursing employees
Mar 2	Employees covered by the Social Support Act
Mar 6	Mobile persons* living at home, born between 1941 and 1946
Mar 17	Mobile adult medical risk groups; persons: • with a haematological malignancy • with severe renal failure • with a severe congenital immune disorder • after organ-, stem cell-, or bone marrow transplant • with a neurological disorder that compromises breathing
Apr 5	Immobile persons* living at home, including risk group adults with a neurological disorder that compromises breathing
Apr 6	Mobile persons* living at home, born between 1947 and 1951
Apr 16	Medical risk groups; persons born between 1961 and 2003: • with Down syndrome • with morbid obesity

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Date	Group
Apr 19	Minors belonging to medical risk groups that are at least 16 years old; persons born between 2003 and 2005: • Living in an institution; - with a haematological malignancy - with severe renal failure - with a severe congenital immune disorder - after organ, stem-cell or bone-marrow transplant - with a neurological disorder that compromises breathing - with Down syndrome - with morbid obesity (grade 2 or higher) • Living at home; - with Down syndrome - with morbid obesity (grade 2 or higher)
Apr 19 – Apr 30	Mobile persons* living at home, born between or in *1952* *1953 – 1955* *1961* *1962*
May 6	Medical risk groups; persons who receive annual invitations for influenza vaccination born between 1961 and 2003
May 18	Minors belonging to medical risk groups that are ast least 16 years old and living at home; persons born between 2003 and 2005: • with a haematological malignancy • with severe renal failure • with a severe congenital immune disorder • after organ, stem-cell or bone-marrow transplant • with a neurological disorder that compromises breathing
May 25	Military personnel born between 1961 and 2003
May 16 – June 19	Anyone born between or in the years *1963* – *2003*, invited in ascending order of birthyear***
June 22	Minors belonging to medical risk groups, that are at least 12 years old; persons born between 2004 and 2009: • with Down syndrome • who are invited for annual influenza vaccination
July 2 – July 11	All minors born between or in *2004* – *2009*, who are at least 12 years old
Oct 6	Immunocompromised people invited for a 3rd dose
Nov 24	Booster vaccination offered to persons with Down syndrome, living in an institution

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Date	Group
Nov 25 – Jan 4, 2022	Booster vaccinations offered to all adults born before or in the years *1939* – *2003*, in ascending order of birthyear***
Dec 2	Booster vaccination offered to: • Persons with Down syndrome, who live at home • Immobile persons* living at home
Dec 10	Booster vaccination offered to all healthcare and social welfare personell who come in close contact with patients or clients, and have not yet been invited through the route for the general population
Dec 18	Primary vaccination for minors belonging to medical risk groups, that are at least 5 years old; persons born between 2010 and 2016
Jan 18, 2022	Primary vaccination for all minors born between or in 2010 – 2016, who are at least 5 years old
Feb 26	Additional vaccination for vulnerable groups, three months after their most recent vaccination: • Persons aged 70 or older • Immunocompromised adults • Adults with Down syndrome
Mar 11	Novavax vaccine as vaccination for persons who cannot be vaccinated with, or are hesitant to be vaccinated with, an mRNA- or vector-vaccine
Mar 23	Janssen vaccine as booster vaccination for adults who: • Could not be vaccinated with an mRNA-vaccine because of medical reasons • Did not want to receive an mRNA-vaccine as a booster
Apr 19	Additional vaccination for immunocompromised adults, three months after their most recent vaccination
July 18	Reminders sent out for booster and additional vaccinations
Sep 13	Additional vaccination for all persons aged 12 and over, three months after their most recent vaccination, in order of: • Persons aged 60 or older, starting with oldest age groups • Healthcare personell who come in close contact with patients or clients • Persons aged 59 or younger who are at risk for severe COVID-19 • All persons aged 12 and over

* Mobile persons= persons who are able to reach the location at which vaccinations are administered, either by themselves or aided by others.
** Immobile persons with a neurological disorder that compromises breathing will be vaccinated alongside other home-living immobile persons.
*** The news messages related to invitations for these groups can be found at *https://www.rivm.nl/en/news*.

9.3.3 The COVID-19 vaccination campaign in the Netherlands

This chapter partly overlaps with the National Immunisation Programme report of 2020-2021 [2], as the COVID-19 vaccination campaign is described from the start of the campaign. The COVID-19 vaccination campaign in the Netherlands started on the 6th of January, 2021. The Netherlands uses five different COVID-19 vaccines, which have all been approved by the European Medicines Agency (EMA). An overview of the various COVID-19 vaccines and their characteristics are shown in Table 9.3.1. There were five vaccines in use for the primary series, which include the mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna), the vector vaccines Vaxzevria® (AstraZeneca) and Jcovden (Janssen) and the protein vaccine Nuvaxovid (Novavax). Vaxzevria® was used until November 2021 [1]. The recommended number of doses to complete the primary series is two doses, except for Jcovden® for which one dose is considered sufficient, and for individuals who have been infected with SARS-CoV-2 in the past six months, one dose is sufficient to complete the primary series. An additional dose was recommended in the primary series for immunocompromised patients. Immunocompromised patients were invited for a third dose on 6 October 2021 by their medical specialist.

The booster campaign started on the 18th of November, 2021. The additional vaccination after the primary series was intended to improve the level of protection. People were advised a booster vaccination six months after their previous COVID-19 vaccination or six months after their last SARS-CoV-2 infection. The mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna) are used for booster vaccinations. For Spikevax® (Moderna) half a dose is sufficient. Since March 25th, 2022, the vector vaccine Jcovden® is offered as a booster vaccination. It is available for people who, for medical reasons, cannot receive a booster vaccination with a mRNA vaccine or for people who do not want an mRNA vaccine.

On February 26th, 2022, people aged 70 or over were invited for the repeat vaccination (second booster). In addition, residents of long-term care facilities, adults with Down Syndrome, and immunocompromised patients were invited. On March 23rd, 2022, people aged 60 to 69 were invited for a repeat vaccination as well. The two mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna) are used for the repeat vaccination. For Spikevax® (Moderna) half a dose is sufficient.

Vaccinations in the primary series and during the booster campaign were provided by different organisations, including the Municipal Health Services (GGD), the general practitioners (GPs), hospitals, and long-term care facilities. Repeat vaccinations were provided by GGD and long-term care facilities.

9.3.3.1 The COVID-19 vaccination campaign in the Caribbean part of the Kingdom of the Netherlands

RIVM distributed the COVID-19 vaccines to the CAS and BES islands. The islands handled the storage of the COVID-19 vaccines and were responsible for the implementation of the vaccination strategy and registration of the administered COVID-19 vaccine doses. Two COVID-19 vaccines were used for the primary series on the islands: Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna). As of November 2021, the Comirnaty® vaccine was also used for the booster vaccination campaign on the islands.

9.3.4 Indication for COVID-19 vaccination

In general, people were eligible for a COVID-19 vaccination six months after a SARS-CoV-2 infection minimal or six months after completing their primary series (till December 2021). From December 2021, this changed to a minimum of three months after a SARS-CoV-2 infection or after their last vaccination, due to the Omicron variant [3]. On the CAS and BES islands, the eligibility for the primary series, booster vaccination, and repeat vaccination was similar to the European Netherlands.

9.3.4.1 Primary series

All adults and children aged 5 years and older (birth year 2016 and before) living in the Netherlands and registered in the Personal Records Database (BRP) [4] were eligible for the primary series of vaccination. The vaccination advice for children aged between 5-11 years was different from the advice for persons aged 12 years and older, as the medical need was less high for this group. In addition to persons registered in the BRP, also (labour) migrants without documentation, unregistered persons staying in the Netherlands for more than one month, Dutch diplomats, military personnel who are abroad, persons in detention centres, and asylum seekers were eligible for vaccination. Persons living in Belgium or Germany who work in Dutch healthcare were eligible for vaccination in the Netherlands as well. The eligible population was not invited all at once (Table 9.3.2). For immunocompromised persons aged 12 years or over, three vaccine doses in the primary series were advised for medical reasons, as two doses were shown to provide inadequate protection for this group [5].

9.3.4.2 Booster vaccination

All adults and children aged 12 years and over (birth year 2009 and before) living in the Netherlands and registered in the BRP were eligible for a booster vaccination after their primary series. For persons aged 12-17 years there was no medical need for a booster vaccination [6]. The eligible population was not invited all at once (Table 9.3.2).

9.3.4.3 Repeat vaccination

Adults aged 60 years and over (birth year 1961 and before), people living in long-term care facilities and people with Down Syndrome were eligible for a repeat vaccination after their booster vaccination.

9.3.5 COVID-19 vaccination strategy

The vaccination strategy in 2021 was based on the advice of the Health Council of the Netherlands and the decisions of the Minister of Health, Welfare and Sport. An overview of the advice given by the Health Council of the Netherlands can be found in Chapter 9.2. The focus of the strategy was to reduce severe illness and death due to COVID-19. Therefore, older age groups and high-risk groups, such as residents of long-term care facilities and individuals with a learning disability who are living in an institution, were prioritised. Additionally, health-care workers were prioritised for the primary series, because of their increased risk of infecting risk groups and overtaxing the healthcare system due to illness-related absenteeism. During the booster vaccination campaign and the repeat vaccination campaign, the older age groups were prioritised. Table 9.3.2 shows an overview of the target groups and the dates for when they were invited for vaccination.

9.3.6 Literature

1. De Jonge H. Stand van zakenbrief Covid-19. In: VWS, editor. 2021.
2.* Pluijmaekers AJM, de Melker HE. The National Immunisation Programme in the Netherlands. Surveillance and developments in 2020-2021. RIVM; 2021. Report No.: 2021-0055.
3. RIVM-LCI. COVID-19-vaccinatie, Uitvoeringsrichtlijn: RIVM; 2022 [updated 9 August 2022]. Available from: *https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie*.
4. Government of the Netherlands. Personal Records Database (BRP) 2022. Available from: *https://www.government.nl/topics/personal-data/personal-records-database-brp*.
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6. Gezondheidsraad. Advies Boostervaccinatie van adolescenten tegen COVID-19. 2022.

* RIVM publication.

9.4 COVID-19 vaccination coverage

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9.4.1 Key points

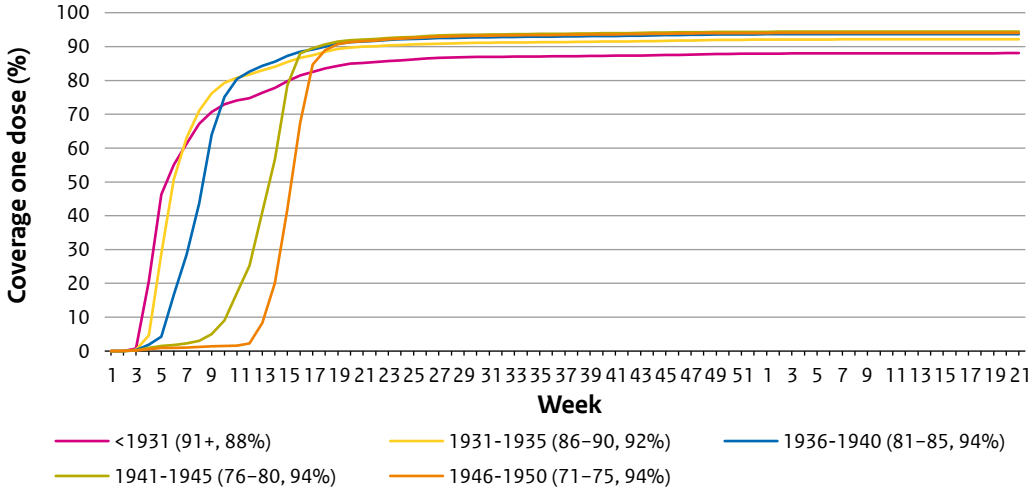
- Data in this chapter differs from data in the Vaccination Monitoring reports published before the 24th of May, 2022 because all results in this report are based on an optimised monitoring method, which is used from 24 May onwards.
- In general, vaccination coverage was higher in older age groups compared to younger age groups.
- The highest vaccination coverage is in the east- and south-east region of the Netherlands. The larger cities and Bible Belt show the lowest vaccination coverage.
- The highest vaccination coverage for both the primary series and the booster vaccinations in the Caribbean part of the Kingdom of the Netherlands is on Saba.

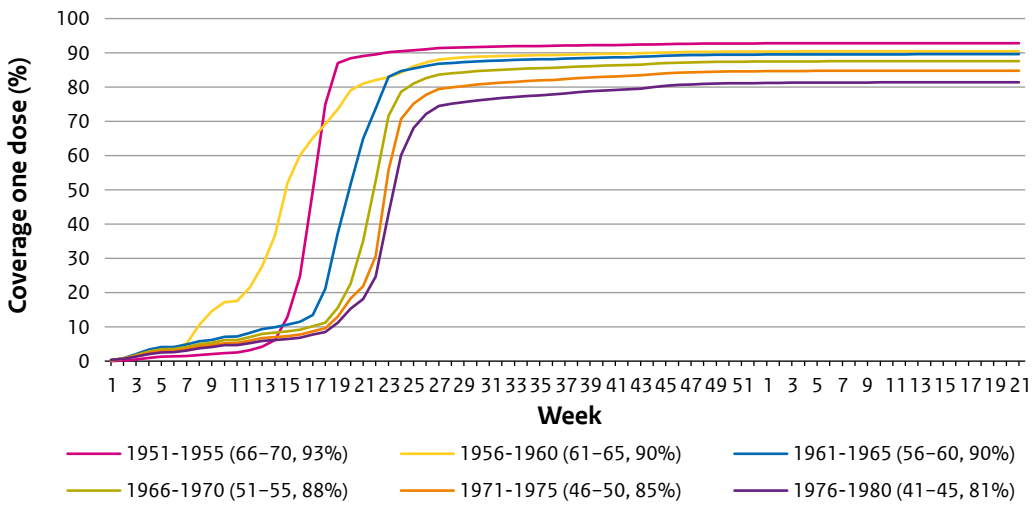
9.4.2 Tables and Figures

Table 9.4.1 Registered coverage for at least one dose and primary series completed COVID-19 vaccination for birth years 2009 and before and 2003 and before, up to and including week 21, 2022.[1-4]

Birth year	Coverage for at least one dose	Coverage for primary series completed
2009 and before	82.8%	82.0%
2003 and before	84.0%	83.2%

1. Data: Numerator: CIMS supplemented with GGD vaccination data that is not registered in CIMS. The number of vaccine doses administered by other organisations will be calculated using assumptions based on the GGD data. People who died or emigrated were excluded. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.
2. Persons who were infected with SARS-CoV-2 prior to their first vaccination only need one vaccine dose to complete their primary series.
3. 'At least one dose' means the part of the Dutch population that received at least one dose of their primary series. 'Coverage primary series' means the part of the Dutch population that completed their primary series (one dose of Janssen vaccine, one dose after a SARS-CoV-2 infection, two doses of Comirnaty®, Spikevax®, Vaxzevria®, Nuvaxovid®).
4. When age was unknown, persons are only included in the numerator of the birth years 2009 and before and not in the numerator of the birth years 2003 and before.





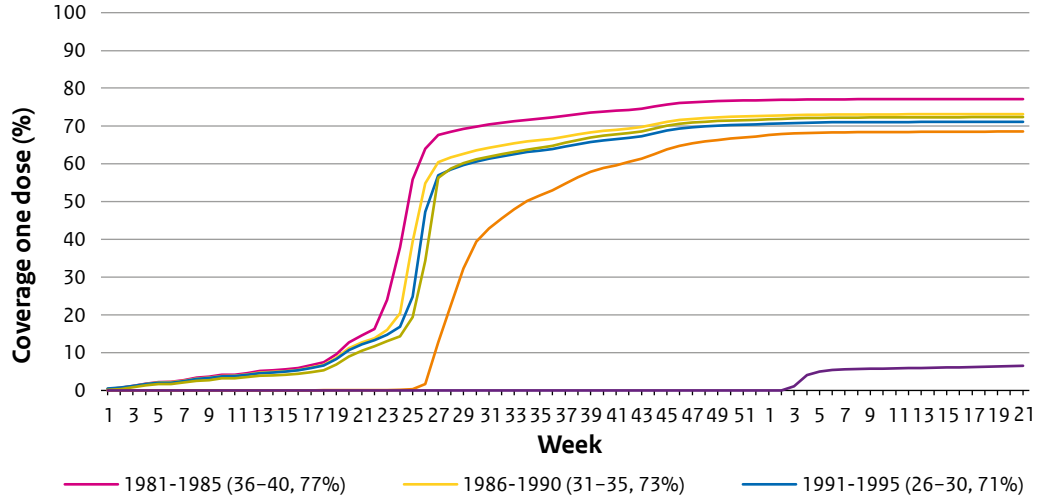
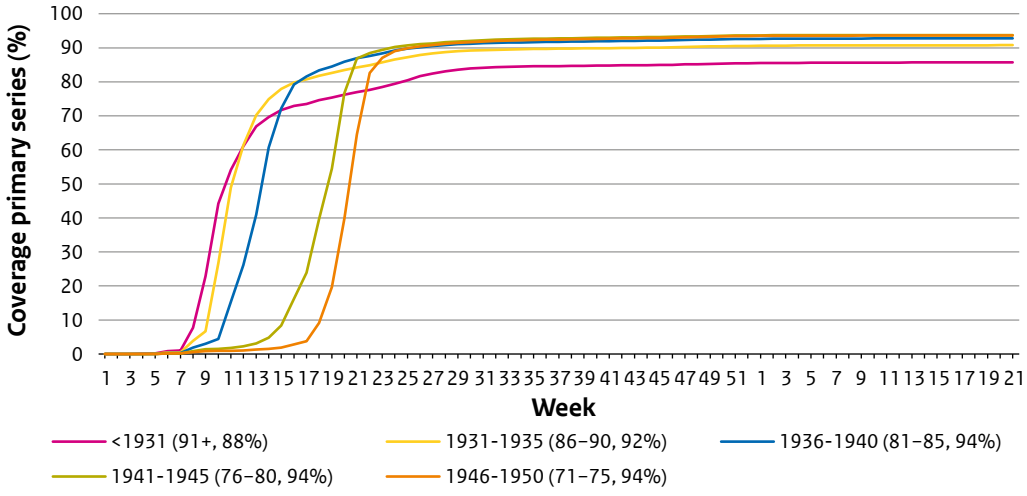
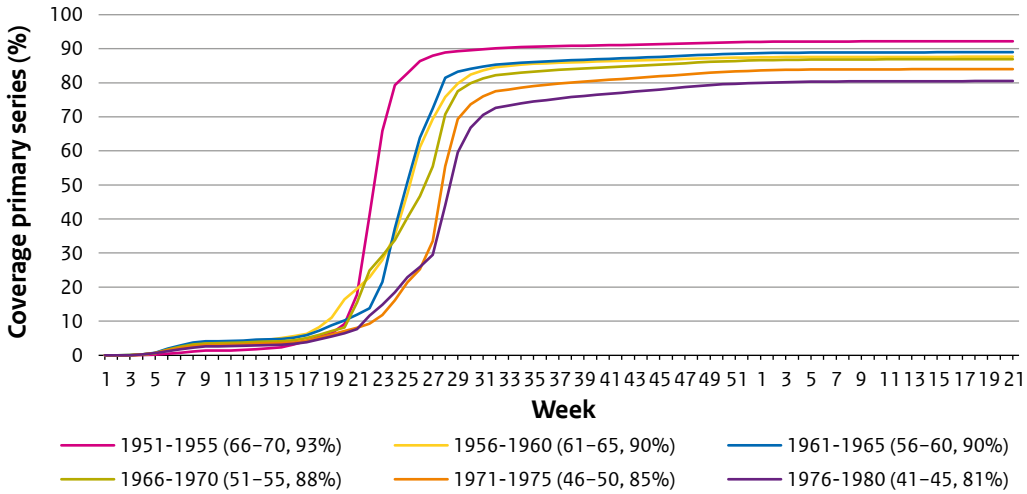


Figure 9.4.1 Coverage for at least one dose COVID-19 vaccination, stratified by birth year, for week 1, 2021 up to and including week 21, 2022.[1-6]

1. Week numbers are calendar weeks (ISO 8610); week 1, 2021 = January 4th to 10th, 2021, etc.
2. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: people who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.
3. People born between 1956-1960 were mainly vaccinated by their GP with Vaxzevria®. Vaccinations performed by GPs were based on vaccinations registered in CIMS. From March 15th until March 23rd, 2021 and from April 3rd until April 5th, Vaxzevria® was temporarily not administered.
4. 'Cumulative coverage for at least one dose' means the part of the population that received at least one vaccination in their primary series.
5. Children born in 2017 could make an appointment for vaccination after their birthday.
6. Children born between 2010-2017 with a high medical risk were invited for their primary series from the end of December 2021. Due to traceability, children who received their first vaccine dose before January 18th, 2022 are not included in this figure.





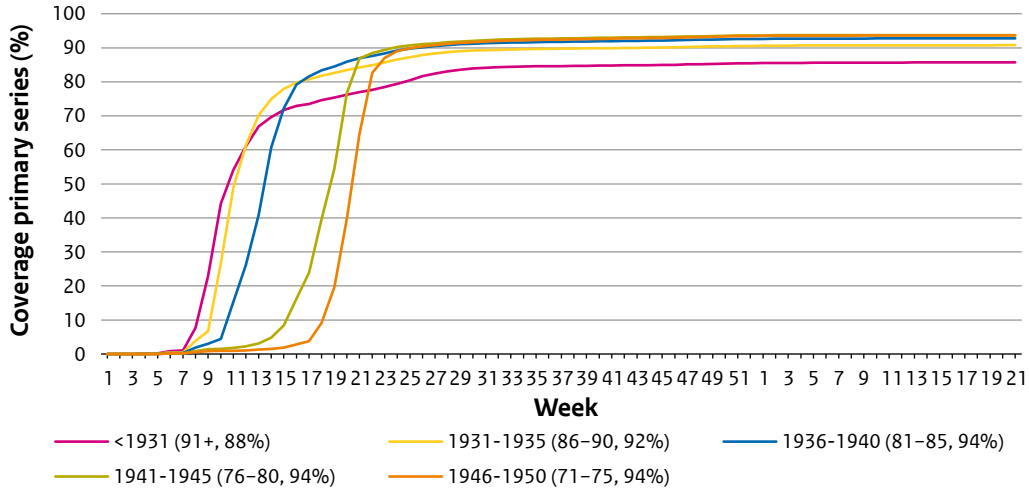
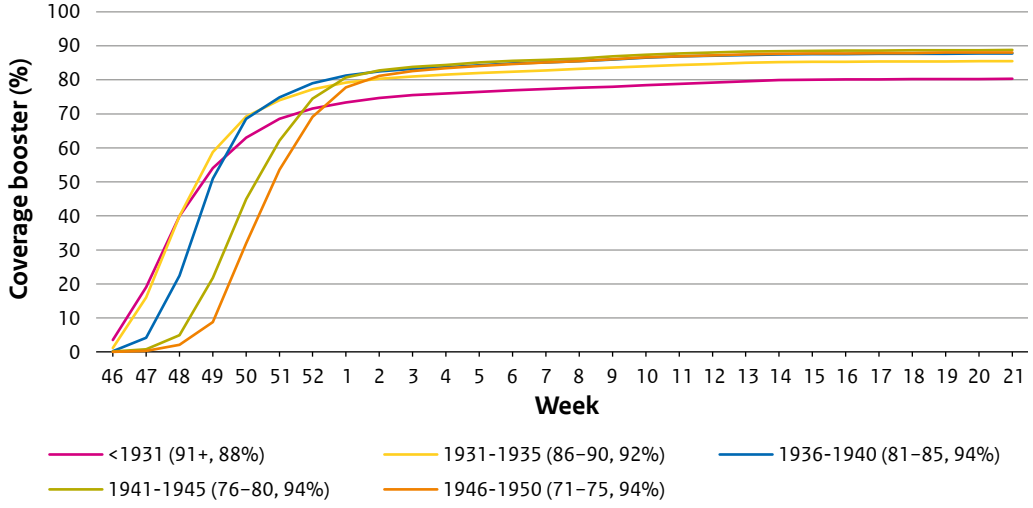
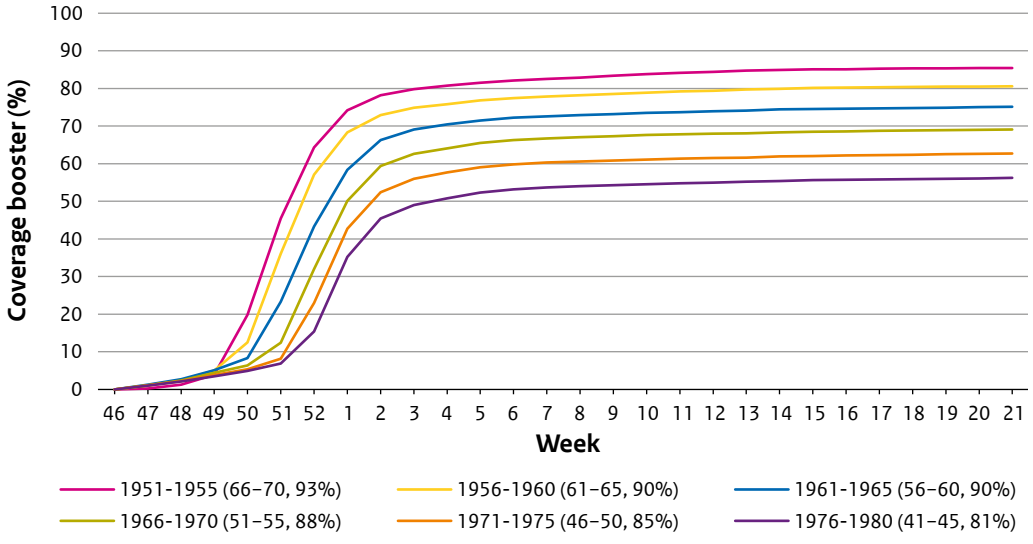


Figure 9.4.2 Coverage for completing the primary series of COVID-19 vaccination, stratified by birth year, for week 1, 2021 up to and including week 21, 2022.[1-7]

1. Week numbers are calendar weeks (ISO 8610); week 1, 2021 = January, 4th to 10th, 2021, etc.
2. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: people who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.
3. People born between 1956-1960 were mainly vaccinated by their GP with Vaxzevria®. Vaccinations performed by GPs were based on vaccinations registered in CIMS. From March 15th until March 23rd, 2021 and from April 3rd until April 5th, Vaxzevria® was temporarily not administered.
4. 'Coverage primary series' means the part of the Dutch population that completed their primary series (one dose of Janssen vaccine, one dose after a SARS-CoV-2 infection, two doses of Comirnaty®, Spikevax®, Vaxzevria®, Nuvaxovid®).
5. Children born in 2017 could make an appointment for vaccination after their birthday.
6. Children born between 2010-2017 with a high medical risk were invited for their primary series from the end of December 2021. Due to traceability, children who received their first vaccine dose before January 18th, 2022 are not included in this figure.
7. Children born between 2010-2017 without a medical risk do not need a second dose after a SARS-CoV-2 infection to complete their primary series. This is not visible in the data. Therefore, the cumulative coverage for completing the primary series is slightly underestimated for this group.





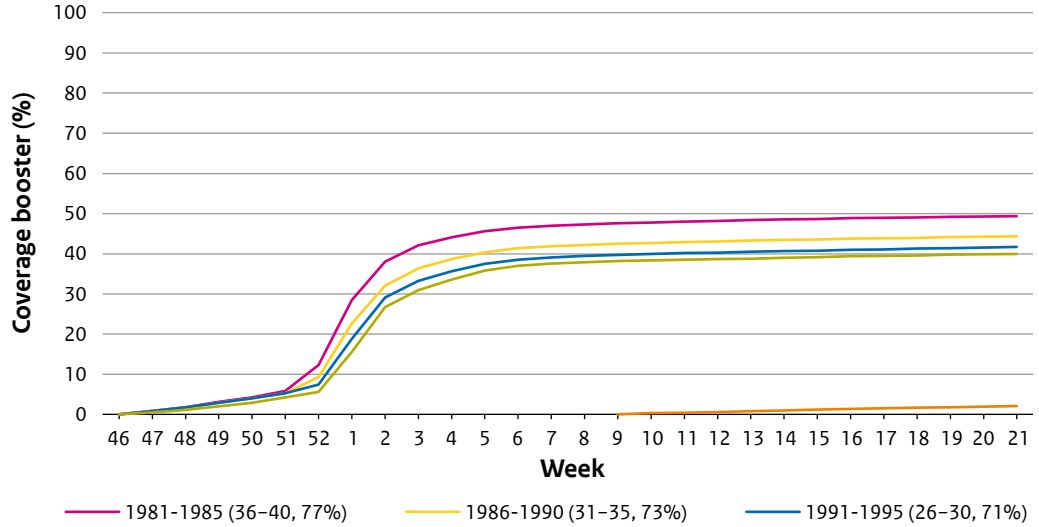


Figure 9.4.3 Coverage booster vaccination, stratified by birth year, for week 46, 2021 up to and including week 21 2022.[1-2]

1. Week numbers are calendar weeks (ISO 8610); week 1, 2021 = January 4th to 10th, 2021, etc.
2. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: people who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.

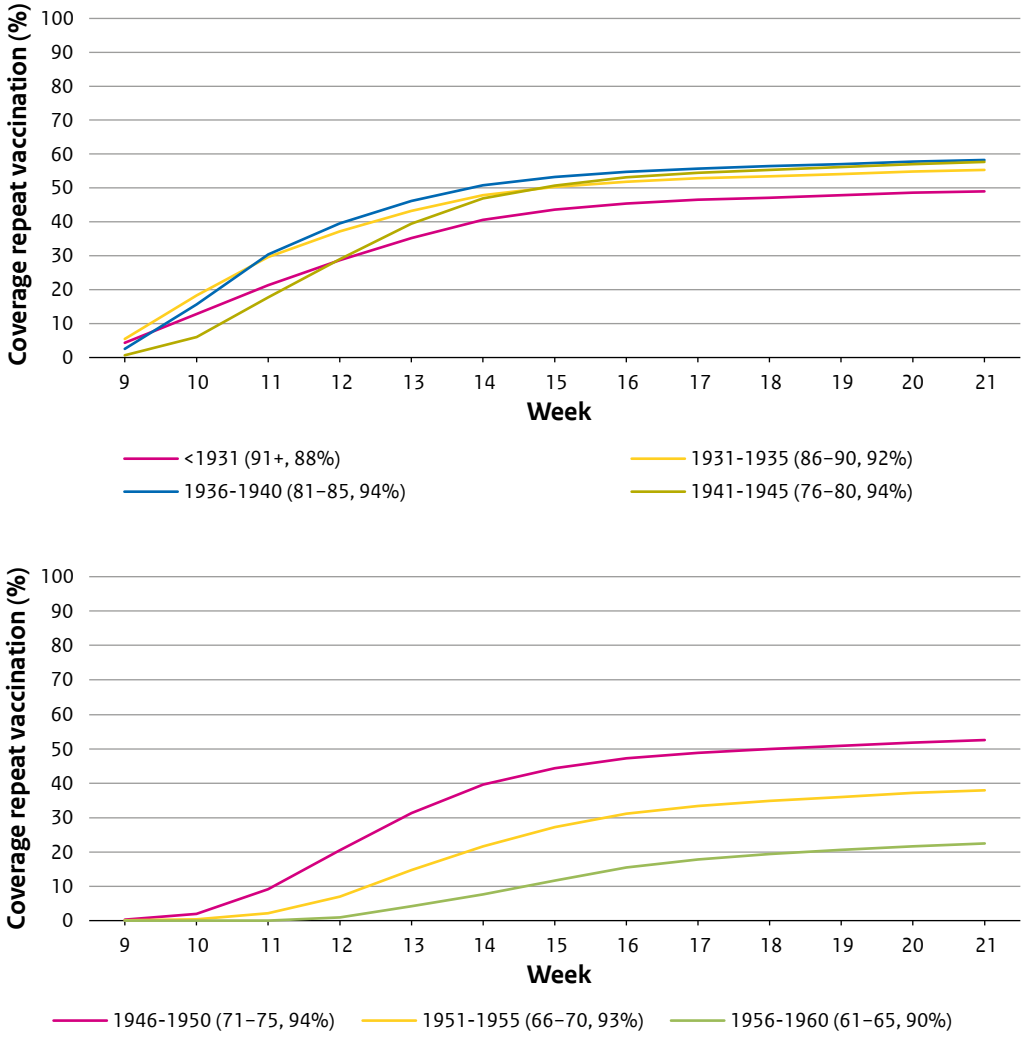


Figure 9.4.4 Coverage booster vaccination, stratified by birth year, for week 46, 2021 up to and including week 21 2022.[1-2]

1. Week numbers are calendar weeks (ISO 8610); week 1, 2021 = January 4th to 10th, 2021, etc.
2. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: people who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.

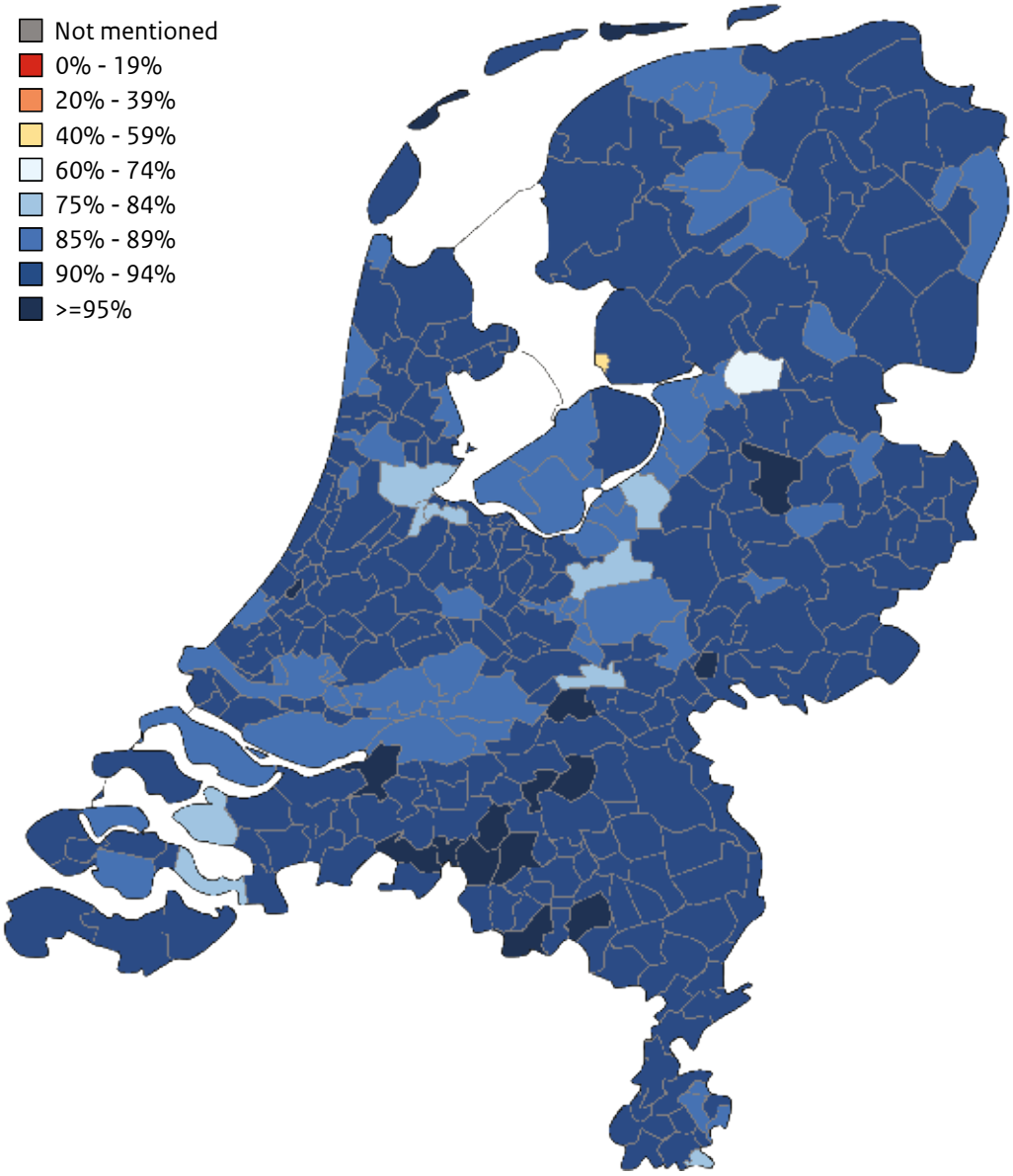


Figure 9.4.5 Coverage primary series COVID-19 vaccination completed, birth years 1961 and before, week 1, 2021 up to and including week 21, 2022.[1-2]

1. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.
2. 'Coverage primary series' means the part of the Dutch population that completed their primary series (one dose of Janssen vaccine, one dose after a SARS-CoV-2 infection, two doses of Comirnaty®, Spikevax®, Vaxzevria®, Nuvaxovid®).

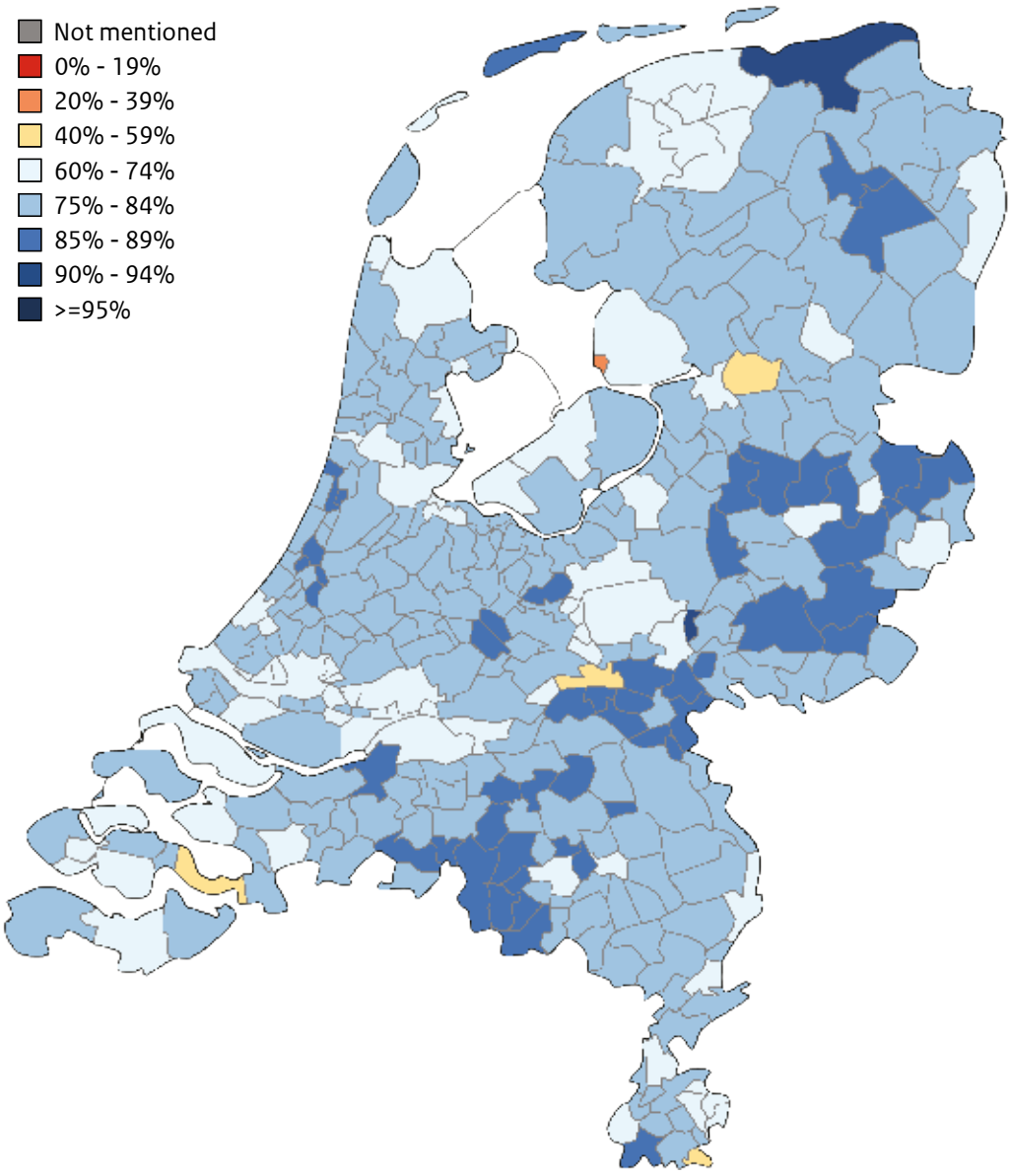


Figure 9.4.6 Coverage primary series COVID-19 vaccination completed, birth years 1962-2009, week 1, 2021 up to and including week 21, 2022.[1-2]

1. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.
2. 'Coverage primary series' means the part of the Dutch population that completed their primary series (one dose of Janssen vaccine, one dose after a SARS-CoV-2 infection, two doses of Comirnaty®, Spikevax®, Vaxzevria®, Nuvaxovid®).

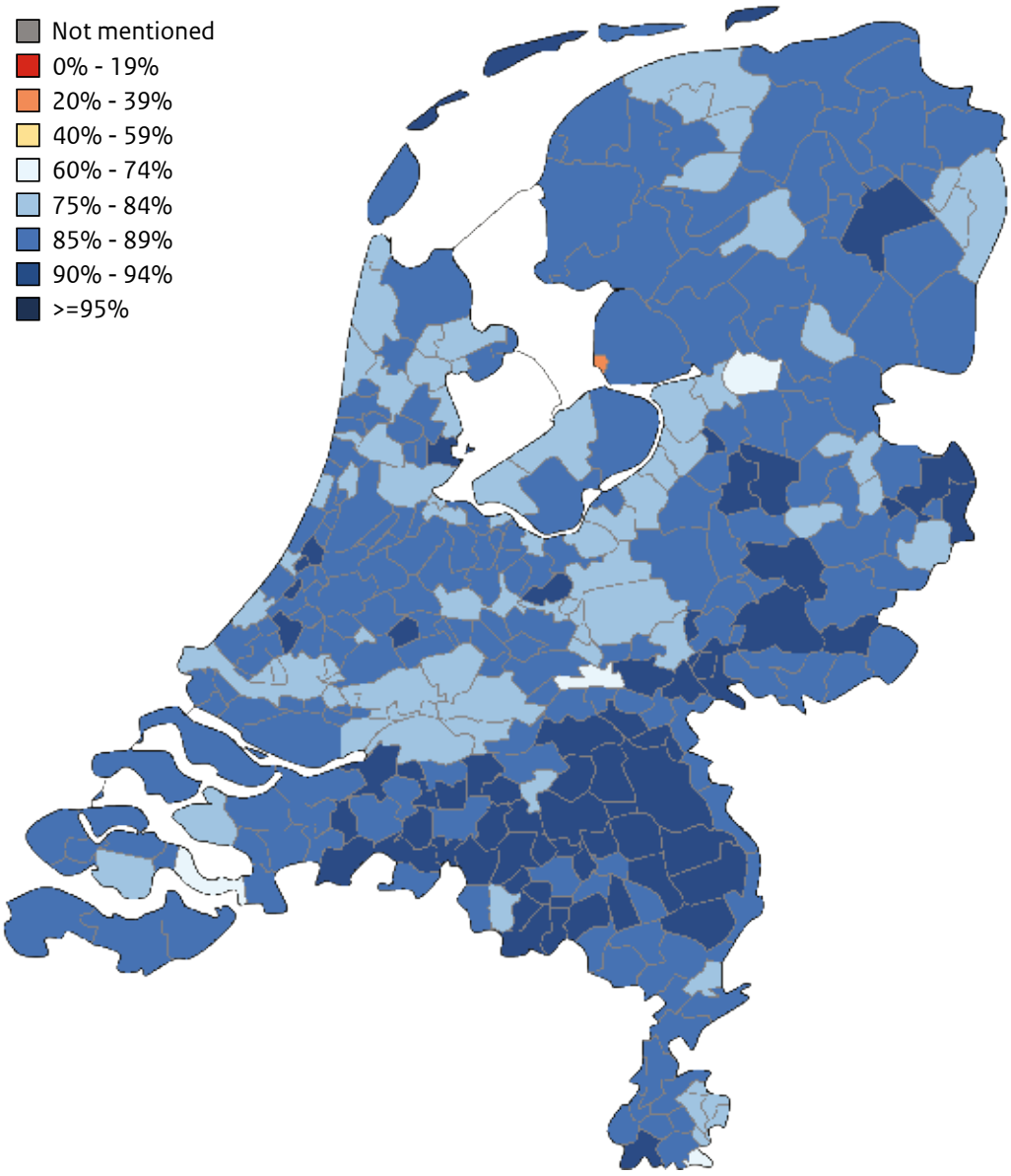


Figure 9.4.7 Coverage booster vaccination, birth years 1961 and before, week 46, 2021 up to and including week 21, 2022.[1]

1. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.

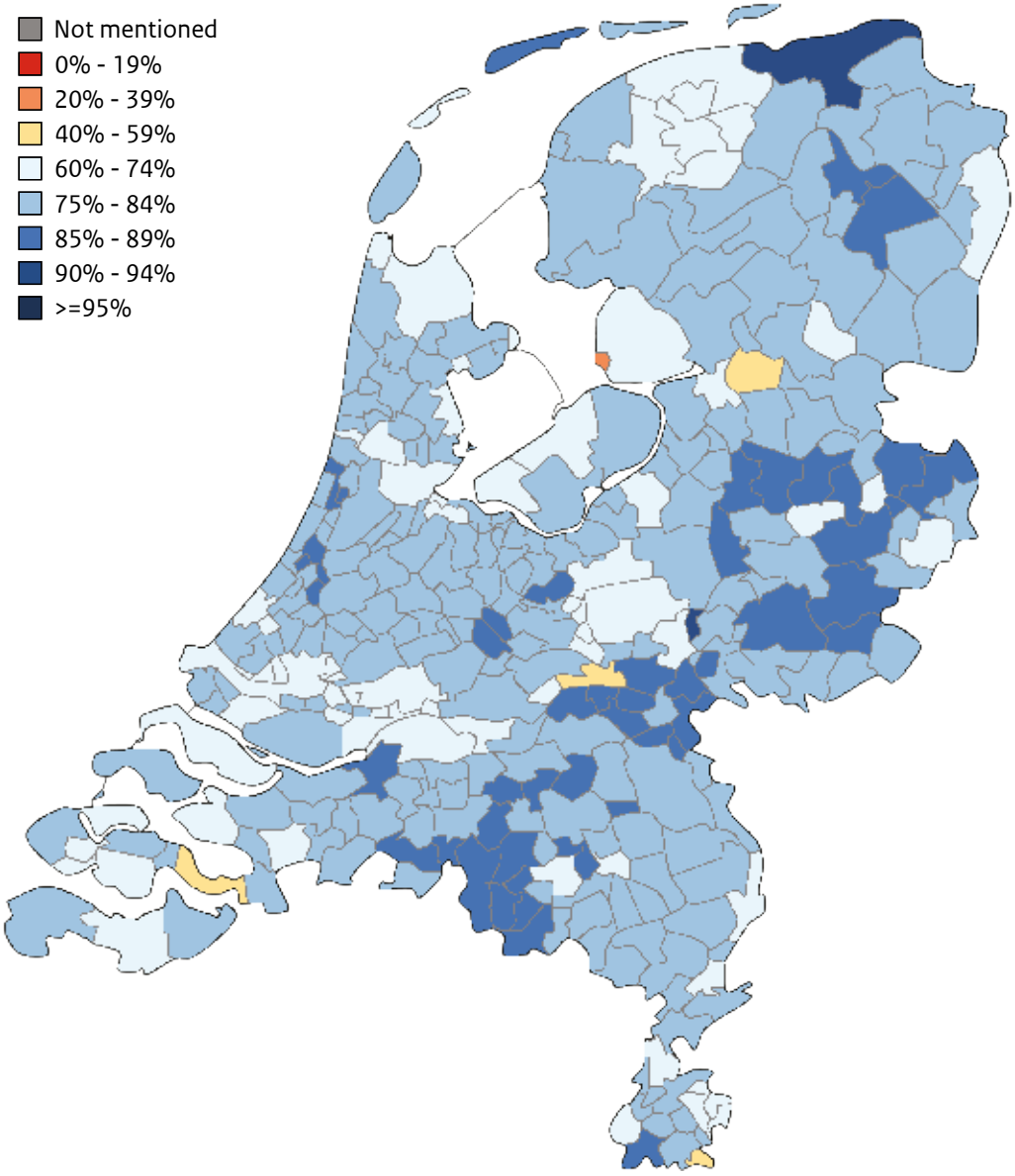


Figure 9.4.8 Coverage booster vaccination, birth years 1962-2009, week 46, 2021 up to and including week 21, 2022.[1]

1. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.

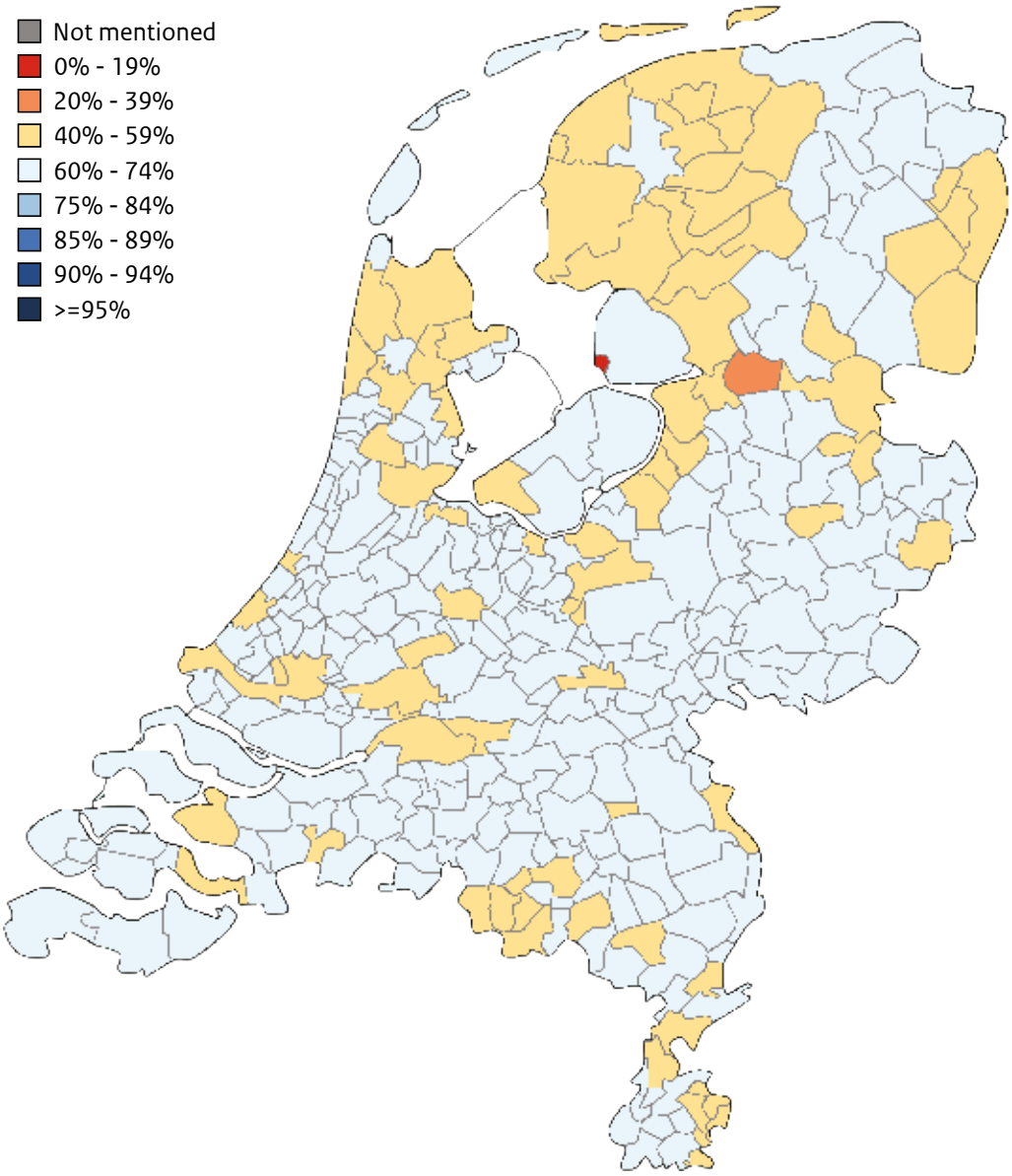


Figure 9.4.9 Coverage repeat vaccination, birth years 1961 and before, weeks 9-21, 2022.[1]

1. Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) supplemented with GGD vaccination data that is not registered in CIMS. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of April 6th, 2022.

Table 9.4.2 Estimated coverage for at least one dose and primary series completed COVID-19 vaccination in the Caribbean part of the Kingdom of the Netherlands for birth years 2009 and before up to and including week 21, 2022.[1-3]

Island	At least one dose	Coverage primary series completed	Coverage booster vaccination series
Curacao	74.4%	69.7%	31.4%
Aruba	81.0%	75.6%	30.4%
Sint Maarten	52.1%	46.2%	15.5%
Bonaire	86.2%	78.5%	39.2%
Sint Eustatius	62.9%	59.4%	27.9%
Saba	94.7%	93.8%	65.6%

1. Data: Numerator: weekly first and second vaccination dose registrations from the CAS and BES islands shared with RIVM. People who died or emigrated could not be excluded. Denominator: people who were registered citizens on the islands along with an estimate for the undocumented individuals living on the islands.
2. Persons who were infected with SARS-CoV-2 prior to their first vaccination only need one vaccine dose to complete their primary series.
3. 'At least one dose' means the part of the island population who received at least one dose of their primary series. 'Coverage primary series' means the part of the island population that completed their primary series (one dose after a SARS-CoV-2 infection, two doses of Comirnaty® or Spikevax®).

9.4.3 Methods

The described period in this chapter partly overlaps with the National Immunisation Program report of 2020-2021 [2], since data from the start of the COVID-19 vaccination campaign is presented. Data in this chapter differs from data in the report 'Vaccination coverage COVID-19 vaccination the Netherlands, 2021' (forthcoming) and from the *vaccination monitoring reports* published before the 24th of May, 2022. The method used to monitor vaccination coverage was optimised and population data has been updated [3]. In this new method, we rely on the COVID-19 vaccination Information and Monitoring System (CIMS) database, which is supplemented with data from the Municipal Health Services (GGD) that is not registered in CIMS. The use of CIMS makes it possible to exclude people who have emigrated or died, because this database is linked to the Personal Records Database (BRP) [1]. RIVM no longer uses estimates based on the number of vaccine doses that were supplied. Source data from CIMS will be supplemented with GGD vaccination data that is not registered in CIMS. The number of vaccine doses administered by other organisations will be calculated using assumptions based on the GGD data. This method also takes into account that a single vaccination following a COVID-19 infection counts as a completed primary series of vaccinations.

It should be noted that this chapter reports the COVID-19 vaccination coverage, which is not synonymous with the actual immunity reached in the population. In Chapter 9.6, more information is provided on the COVID-19 seroepidemiology in the Netherlands.

9.4.3.1 *Methods for the Caribbean part of the Kingdom of the Netherlands*

For the monitoring of the vaccination campaigns on the CAS and BES islands, each island kept a register of the total number of weekly administered vaccinations, and these were shared with RIVM. People who were not registered citizens on the CAS and BES islands were also included in the vaccine registrations and included in the calculations for the vaccine coverage on the islands.

9.4.4 Vaccination coverage

In week 21, 2022, coverage for at least one dose of COVID-19 vaccination and primary series completed for individuals born in 2009 or before had reached 82.8% and 82.0% respectively (Table 9.4.1). For individuals born in 2003 or before, the coverage had reached 84.0% and 83.2% respectively.

For children between 5 and 11 years of age, the vaccination strategy differed from the vaccination strategy for people of 12 years and over (see Chapter 9.3). Therefore, the coverage for at least one dose and for completing the primary series was lower in children between 5-11 years.

9.4.4.1 *By age*

In general, the vaccination coverage (primary series, booster and repeat vaccination) is higher in older age groups compared to younger age groups (Figures 9.4.1 to 9.4.4). Older age groups were often invited for COVID-19 vaccination earlier, except for the primary series where healthcare workers were invited first. People who passed away or emigrated were excluded from the numerator (every day) and the denominator (once per quarter of a year). Research done by the RIVM Corona Behaviour Unit [4] showed that the willingness for vaccination was lower among younger age groups [5].

9.4.4.2 *By municipality*

The vaccination coverage at municipality level is shown in Figures 9.4.5 to 9.4.9. Only people registered in the Personal Records Database (BRP) are included in the numerator and denominator. This means that people living in an asylum seekers' centre, homeless people and seafarers are not included in the vaccination coverage. The highest vaccination coverage is in the east- and south-east region of the Netherlands. The larger cities and Bible Belt show the lowest vaccination coverage. In the Bible Belt, a larger proportion of persons reject vaccination in general, on religious grounds. Additionally, border areas generally have a lower vaccination coverage. A possible explanation is people who live in border areas could have been vaccinated in neighbouring countries, such as Belgium or Germany. Their vaccinations are not registered in the Netherlands and are therefore not included in the numerator.

9.4.4.3 *Vaccination coverage in the Caribbean part of the Kingdom of the Netherlands*

Due to the differences in the implemented COVID-19 vaccination strategies per island and differences in vaccine registration and reporting, it is difficult to make comparisons between the islands on the vaccination coverage. Saba has the highest vaccination coverage of all the islands for both the primary series and the booster vaccinations (Table 9.4.2). In general, the vaccination coverage for the booster vaccinations on the islands remains relatively low when compared to the vaccination coverage in the primary series. This indicates a possible decrease in the willingness in the region to receive additional doses of the COVID-19 vaccine after the primary series.

9.4.5 Literature

1. Government of the Netherlands. Personal Records Database (BRP) 2022. Available from: *https://www.government.nl/topics/personal-data/personal-records-database-brp*.
2.* Pluijmaekers AJM, de Melker HE. The National Immunisation Programme in the Netherlands. Surveillance and developments in 2020-2021. RIVM; 2021. Report No.: 2021-0055.
3. RIVM. COVID-19 vaccination figures more up-to-date due to optimised monitoring 2022 [updated May 23 2022]. Available from: *https://www.rivm.nl/en/news/covid-19-vaccination-figures-more-up-to-date-due-to-optimised-monitoring*.
4. RIVM Corona Gedragsunit. Publicaties Corona Gedragsunit 2022. Available from: *https://www.rivm.nl/gedragsonderzoek/publicaties*.
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* RIVM publication.

9.5 Vaccine effectiveness

M.J. Knol, B. de Gier, C. van den Ende, S.P. Andeweg, C.E. van Ewijk, J.A. Backer, C. Hoeve, A.J. Huiberts, C.H. van Werkhoven, T. van der Maaden, S. van den Hof, S.J.M. Hahné, H.E. de Melker

9.5.1 Key points

- RIVM uses surveillance data and dedicated studies to monitor vaccine effectiveness (VE) against SARS-CoV-2 infection and transmission, and severe COVID-19.
- VE against hospitalisation and ICU admission was generally very high (80-95%), although it was lower for elderly and certain medical risk groups, lower during the Omicron period compared to the Delta period, and decreased with increasing time since vaccination; after the first and second booster, VE increased to levels observed shortly after the previous dose.
- VE against SARS-CoV-2 infection was generally high (60-80%), with lower VE among elderly and medical risk groups, lower VE against Omicron vs. Delta infection and decreasing through time since vaccination; additional exposure to SARS-CoV-2, either through vaccination or infection, increases protection.
- VE against transmission in case of infection was generally moderate (30-70%) and lower for Delta infection than for Alpha infection; similar VE against Omicron and Delta transmission given infection was observed.
- Results from RIVM analyses are consistent with the international literature on VE estimation.

9.5.2 Figures

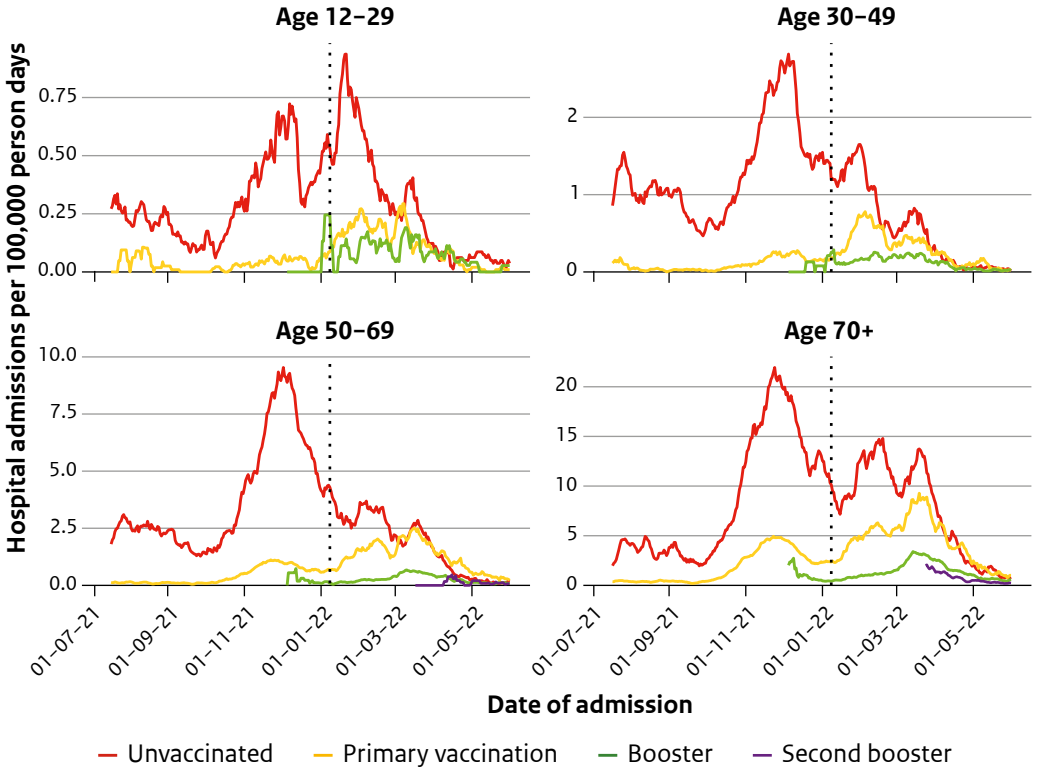

Figure 9.5.1 Seven-day moving average of the incidence of COVID-19 hospitalisations per 100,000 person days, by vaccination status and age group in the period 18 July 2021 to 31 May 2022. From July 18, nearly all COVID-19 hospitalisations were due to the Delta variant. The vertical dotted lines reflect when approximately 50% of the COVID-19 hospitalisations were caused by the Omicron variant, based on pathogen surveillance data of hospital samples from persons aged 70+ years. Note that the y-axes have different scales. Sources: NICE, CIMS.

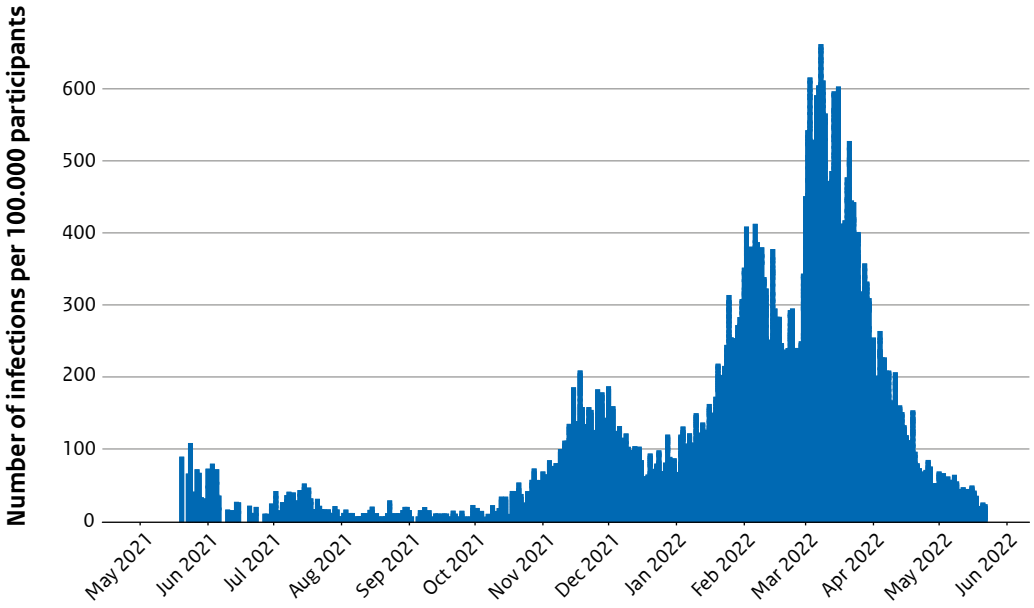

Figure 9.5.2 Number of SARS-CoV-2 infections per 100,000 participants in VASCO (VAccine Study COVID-19). Infections are self-reported by participants through the study app or through the monthly questionnaire. Figure is based on data until May 23rd, 2022.

9.5.3 Vaccine effectiveness against hospital admission

9.5.3.1 Hospital register data (NICE)

The effectiveness of COVID-19 vaccines against hospital and intensive care unit admission is monitored bi-weekly by enriching the hospital register data (NICE) with data from the central COVID-19 vaccination Information and Monitoring System (CIMS). The association between vaccination status and hospital admission is estimated using negative binomial regression adjusted for age and calendar time yielding relative risks (RR). Vaccine effectiveness (VE) is expressed as (1-RR) * 100%. The reports describing VE in different periods can be found at *Bescherming coronavaccins tegen ziekenhuisopname | RIVM* [1].

During the period when the Delta variant dominated (July-November 2021), VE against hospitalisation and ICU admission was very high, with an overall VE of 93% (95% CI 93-94) against hospitalisation and 97% (95% CI 96-97) against ICU admission [2]. The VE was lower in persons aged 70 years and over (87% (95% CI 86-88). From November 2021 onwards, a decrease in VE of primary vaccination against hospitalisation became apparent with increasing time since vaccination [3]. As the subsequent rollout of the booster vaccination campaign coincided with the emergence of the Omicron BA.1 variant (December-January), booster VE estimates against Delta are not available. From February 2022 onward, Omicron BA.1 and BA.2 variants dominated, resulting in much lower VE compared to Delta. In the period February-March 2022, VE of primary vaccination was 35% (95% CI 30-39) against hospitalisation and

45% (95% CI 34-55) against ICU admission. Booster vaccination increased VE substantially to 81% (95% CI 80-82) against hospitalisation and 90% (95% CI 88-92) against ICU admission, although even after booster vaccination, waning of VE by time since vaccination was visible [4]. Since the end of February 2022, vulnerable groups including persons aged 60 years and over and nursing home residents have been invited for a second booster. This second booster increased VE again to levels comparable to shortly after booster vaccination, and the VE of the second booster was 88% (95% CI 73-92) against hospitalisation in persons aged 70 years and over during February-April 2022 [5]. The incidence of hospital admission has been highest in the oldest age groups and in unvaccinated persons during July 2021 – May 2022 (Figure 9.5.1). Due to the reduced pathogenicity of Omicron variants compared to Delta, incidence of hospitalisation remained relatively low in vaccinated as well as in unvaccinated persons during January-April 2022.

The analyses on VE against hospital admission based on NICE and CIMS data have some important limitations. CIMS only includes data of vaccinated persons giving informed consent to use the data for research or surveillance purposes. Resulting misclassification leads to underestimation of the VE. Until 25 January 2022, no distinction was made between admission with or admission due to COVID-19. This may also have resulted in underestimation of the VE. From 25 January 2022 onward, clinicians were asked to record whether COVID-19 was the reason for admission, but this information was still missing in a relevant share of the dataset (around 37% since January 25 and no retrospective data). The percentage of patients admitted for other reasons than COVID-19 but testing positive for SARS-CoV-2 was probably higher in the Omicron than in the Delta period, resulting in a larger bias in VE estimates during the Omicron than during the Delta period. Information about SARS-CoV-2 infections that did not result in admission was unavailable for this analysis. As a result, individuals may have been incorrectly classified as partly vaccinated when they had received a single dose after infection; after infection, only one dose is necessary to complete the primary vaccination series, if this dose is given within six months after infection. Secondly, it was not possible to adjust for underlying comorbidities as these data are unavailable in this dataset. Lastly, no data was available on previous SARS-CoV-2 infections. Due to the increasing importance of infection-induced and hybrid immunity in the risk of severe outcomes in current SARS-CoV-2 infections, VE estimates have increasingly been confounded by previous infections. In other words, the differences in hospitalisations between unvaccinated and vaccinated persons has, over time, become less indicative of vaccine effectiveness. Therefore, since August 2022, we no longer report VE estimates in reports on COVID-19 hospitalisations by vaccination status, but we do describe relative risk differences, to quantify the differences in disease burden between groups with different vaccination statuses.

9.5.3.2 VECTOR study

In a test-negative case-control study, detailed information was collected from patients hospitalised with respiratory symptoms in nine different hospitals. Vaccine effectiveness against hospitalisation was assessed, adjusting for underlying comorbidities. Besides, vaccine effectiveness was assessed in several subgroups. Data was collected from both the Alpha-dominant period (March 1st to July 5th 2021) and the Delta-dominant period (October 1st, 2021,

to January 29th, 2022). A total of 1,250 patients were included in the study, of which 614 admitted during the Alpha-dominant period (367 COVID-19 cases and 247 controls) and 636 during the Delta-dominant period (336 COVID-19 cases and 300 controls). VE was calculated using multivariable logistic regression adjusted for calendar week, sex, age, comorbidity, and nursing home residency. During the Alpha-dominant period, the VE was 67% (95% CI 45-80) for partial vaccination and 90% (95%CI 75-96) for primary vaccination. During the Delta period, VE for partial vaccination was 96% (95% CI 80-99), 76% for primary vaccination (95% CI 63-84) and 90% for booster vaccination (95% CI 77-96). Previous infection was not taken into account, overestimating VE of partial vaccination during the Delta period. VE decreased over time, as was seen when stratifying VE by time since vaccination. VE for primary vaccination decreased from 82% (95% CI 52-94) 3-6 months after vaccination to 63% (95%CI 36-79) 6-9 months after vaccination during the Delta period. VE was lower in patients with malignancy, with cardiac condition and aged >75 years.

9.5.4 Vaccine effectiveness against infection

9.5.4.1 Community testing data

VE against infection (defined as a positive SARS-CoV-2 test) was monitored using the community testing data. Vaccination status of positive and negative tests were analysed using a test-negative case-control design to estimate VE. In the Delta period, high VE (over 80%) against infection was observed, with waning over time since vaccination. Older age groups, close contacts of confirmed cases and people having received vector vaccines showed a lower VE [6].

VE against infection by variant (Delta, Omicron BA.1, and BA.2) was estimated using community testing data from two diagnostic laboratories that perform variant-PCR, which gives a proxy for the circulating variant (see section 9.7 Pathogen surveillance) [7]. Protection of primary vaccination against Omicron infection was much lower compared to Delta (~35% vs ~70% at >=7 months after vaccination). In contrast, protection against Omicron BA.2 infection was comparable to BA.1. Previous infection by pre-Omicron variants also offered limited protection against Omicron infection (~35%). Higher protection was observed against all variants in individuals with both vaccine- and infection-induced immunity compared to either one. Waning immunity was observed against all variants after both vaccination and infection. Booster vaccination increased VE against Omicron infection to around 65% at one month post-vaccination, but since booster vaccinations are being offered, this VE decreased rapidly over time.

9.5.4.2 CONTEST study

The aim of the CONTEST study was to determine the VE of COVID-19 vaccination against SARS-CoV-2 infection among adults testing at community facilities, and whether risk of exposure to SARS-CoV-2 confounded these VE estimates. All adults of 18 years and over who attended the GGD testing locations across the Netherlands were invited to participate in the study by filling out a questionnaire before receiving their test result. Information was collected on demographics, signs and symptoms, test results, vaccination history, underlying chronic conditions, and exposure-related variables such as the number of close contacts, or whether

someone had visited busy locations indoors or outdoors. A total of 7,842 adults who were tested for SARS-CoV-2 between July 4th and December 8th, 2021 (Delta period) were included, of whom 7,127 (91%) were SARS-CoV-2 negative and 715 (9%) positive. We calculated the VE of COVID-19 vaccination against SARS-CoV-2 infection after primary vaccination, both with and without taking risk of exposure into account. The VE against SARS-CoV-2 infection was 64% (95% CI 50-73) when taking risk of exposure to SARS-CoV-2 into account. The VE was 68% (95% CI 58-76) without taking risk of exposure into account. These results suggest that SARS-CoV-2 exposure only slightly influences the COVID-19 VE against infection during the studied period, and that VE may be accurately estimated using routinely collected data without the knowledge about people's exposure to SARS-CoV-2.

9.5.4.3 VAccine Study COvid-19 (VASCO)

VAccine Study COvid-19 (VASCO) is a cohort study with a five-year follow-up, which aims to estimate the real-world vaccine effectiveness (VE) of COVID-19 vaccines in the Netherlands [8]. Participants are requested to complete monthly online questionnaires in the first year, and three-monthly online questionnaires in years two-five, including questions on sociodemographic factors, health status, COVID-19 vaccination, SARS-CoV-2 related symptoms and testing results, and behaviour regarding COVID-19 measures. Every six months, participants take a finger prick blood sample, in which nucleoprotein (N) and spike protein receptor binding domain (RBD)-specific antibody concentrations are determined. Between May and December 2021, 45,271 participants with a median age of 61 years (range 18-85) have been enrolled in VASCO. More women (62.9%) than men participate in the study. By the end of March 2022, 33,857 (74.8%) participants had reported having received a booster vaccination, 9,267 (20.5%) participants reported having been fully vaccinated without a booster, 486 (1.1%) participants reported being partly vaccinated and having had a previous infection, 504 (1.1%) participants reported being partly vaccinated without a previous infection, and 1,157 (2.5%) participants reported being unvaccinated. During the first eleven months of the study, a total of 11,345 new infections were reported by participants (10.98 per 1,000 person weeks) (Figure 9.5.2).

Cox proportional hazard models with vaccination status as time-varying exposure and calendar time as underlying timescale were used to calculate VE, adjusted for age, gender, educational level, and medical risk condition. Models were stratified by Delta- and Omicron-dominant period, age and medical risk group, and time since vaccination. Participants who reported a previous SARS-CoV-2 infection were excluded in the current analysis. At total of 34,610 participants with a mean age of 58.5 years and a median follow-up time of 24.9 weeks were included in the current analysis. In the Delta period, VE decreased from 82% (95% CI 74-87) within 3 months to 67% (95% CI 54-77) 6-9 months after primary vaccination and increased to 85% (60-95 95% CI) within 1 month after booster vaccination. In the Omicron period, these estimates were 36% (95% CI 6-56), 35% (95% CI 2-45), and 61% (95% CI 55-66), respectively; VE decreased to 51% (95% CI 42-58) 3-4 months after booster vaccination. In the Omicron-dominant period, VE within one month after booster vaccination was 51% (95% CI 18-71) and 63% (95% CI 55-69) in participants 18-59 years with and without medical risk condition, respectively, and 47% (95% CI 1-72) and 66% (95% CI 53-76) in participants 60-85 years with and without medical risk condition, respectively.

9.5.4.4 *Long-term care facilities*

Persons living in long-term care facilities (LTCFs) are not tested in community testing facilities and are generally not hospitalised because of a SARS-CoV-2 infection. They are therefore not well represented in surveillance data monitoring VE. Data was collected on SARS-CoV-2 outbreaks to estimate disease severity and VE in collaboration with GGD Twente and the SNIV (Surveillance Netwerk Infectieziekten Verpleeghuizen) network. Fourteen outbreaks in LTCF were included with onset date of the first case between July and December 2021 (Delta period). A total of 277 residents were exposed in these 14 outbreaks and 134 SARS-CoV-2 infections (attack rate 47%) were reported. Among 134 residents with an infection, 29 (22%) needed oxygen and 24 (18%) died. Among exposed residents, 96% (range 82-100%) were vaccinated. Attack rate among unvaccinated residents was 71% (5/7) and among residents with primary vaccination was 45% (120/264), resulting in a crude VE of 37% (95% CI –3-61). VE against death was 79% (95% CI 47-92).

One specific COVID-19 outbreak at an LTCF that occurred in November 2021 in the Netherlands was further investigated. This outbreak continued despite measures and the initiation of the booster COVID-19 vaccination campaign. A retrospective cohort study was conducted to describe the outbreak and to assess VE of the primary COVID-19 vaccination series against SARS-CoV-2 infection and mortality 30 days after testing positive in residents. The overall attack rate was 67% (70/105) and varied per ward. The VE of primary vaccination series at more than 6 months after vaccination was low against SARS-CoV-2 infection (17%; 95% confidence interval (CI) -28%; 46%) and moderate against mortality (70%; 95% CI -44%; 96%), highlighting the vulnerability of elderly LTCF residents and the need of booster vaccinations. There were few cases in the second and none in the third week after introduction of the booster despite the presence of susceptible residents with zero case fatality compared to a case fatality of 33% in unvaccinated and 12% in fully vaccinated residents. These data are consistent with the positive impact of the booster vaccination in curbing transmission.

9.5.5 Vaccine effectiveness against transmission in case of infection

9.5.5.1 *Source and contact tracing data*

Comprehensive source and contact tracing data, including vaccination status of both index cases and contacts, provided the opportunity to estimate VE against transmission of SARS-CoV-2 among those infected, and those infected despite vaccination. Secondary attack rates among household contacts of vaccinated and unvaccinated index cases were compared. During the period February-May 2021, when the Alpha variant was dominant, the secondary attack rate among household contacts was lower for fully vaccinated than for unvaccinated index cases (11% vs 31%), with an adjusted VE against transmission of 71% (95% confidence interval: 63–77) [9]. This analysis was repeated after the emergence of Delta, with data collected in August and September 2021. This analysis showed a VE against transmission to unvaccinated and fully vaccinated household contacts of 63% (95% confidence interval (CI): 46–75) and 40% (95% CI: 20–54), respectively [10].

An alternative method to estimate VE against transmission confirms the trends found above. Transmission pairs consisting of infectors and infectees with known vaccination status and age group, were compared to the vaccination coverage of these age groups, i.e., akin to the screening method. In all age groups, the VE against transmission dropped from 59-72% in April-June 2021 to 32% in October 2021.

9.5.5.2 *VASCO*

In VASCO (see 9.5.4.3), data is also collected on transmission of SARS-CoV-2. Following infection, participants are invited to complete a questionnaire on infections in their household. With this data we can determine the transmission rate of SARS-CoV-2 in the household and the effects of vaccination on transmission. If the participant is the first infected case in the household, we follow the household members for infections from the second day after the index case date until 14 days after. Using logistic regression, we estimate the VE against transmission adjusting for age of index case, calendar week, vaccination status of the contact and household size. Generalised estimating equations were used to control for dependencies within the household. Preliminary analyses over the study period August 2021 to May 2022 were performed. 1,226 index cases and 1,599 contacts were included in the analysis. The median age was 58 (IQR: 46-64) for index cases and 52 (IQR: 27-63) for household members. Index cases were vaccinated more (37% primary series, 58% booster, 4% unvaccinated) than household members (35% primary series, 46% booster, 28% unvaccinated). The overall secondary attack rate was 45%. The VE of primary vaccination against transmission was 64% (95% CI: 15-84%) in the Delta-dominant period and 64% (95% CI: 37-79) in the Omicron-dominant period. The VE of booster vaccination against transmission was 63% (95% CI: 36-79) in the Omicron-dominant period; VE of booster vaccination in the Delta-dominant period was very uncertain due to low numbers.

9.5.6 Vaccine effectiveness against death

Through linkage of the CIMS vaccination registry to causes of death and other registry data in the remote access facility of Statistics Netherlands (CBS), VE against COVID-19 mortality was estimated for the period January 2021-January 2022. In all age groups, including elderly people in long-term care facilities, VE against death from COVID-19 was over 90% in the first two months after completion of the primary series. VE gradually decreased in the following months, to around 80% at 7-8 months post-primary series for most age groups and to around 60% for people aged 90 years or over and people aged 70 years or over receiving a high level of long-term care. After the first booster vaccination, VE was restored to over 85% in all groups [11].

9.5.7 Vaccine effectiveness against long COVID

The LongCOVID-study assessed the effect of vaccination prior to infection with SARS-CoV-2 on self-reported symptoms three months after infection in COVID-19 cases [12]. Data was analysed from COVID-19 cases that were infected between May 19th and December 13th, 2021, mainly with the Alpha or Delta virus variant. The prevalence of 13 symptoms was compared between fully vaccinated cases (n=6466) and cases that were partially vaccinated (n=868) or unvaccinated (n=1604) at the time of their positive SARS-CoV-2 test, using permutation tests stratified for the predefined confounders of age, sex, level of education, and number of

comorbidities. The effect of vaccination on long-term symptoms could only be assessed for cases aged <65 years, since almost all cases >65 years had been vaccinated. Cases <65 years old that were fully vaccinated had a significantly lower prevalence of loss of smell and loss of taste three months after infection. Other symptoms did not significantly differ between fully, partially, or unvaccinated cases.

9.5.8 International research

Several online resources are available that provide collections and/or summaries of the international literature on COVID-19, including the effectiveness of COVID-19 vaccination. Examples are LitCovid (containing articles from PubMed categorised by research topic) [13], EPPIcentre (a living map of research articles on COVID-19) [14] and the COVID-19 rapid reviews conducted by the UK Health Security Agency (UKSHA) [15]. To monitor VE estimates in the grey, preprint, and published literature, RIVM uses results of an ongoing systematic search by the International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health and the World Health Organization. They publish updated summary tables with the findings of COVID-19 vaccine effectiveness and impact studies on a weekly basis [16]. In addition, RIVM performs a weekly search in Embase.

9.5.8.1 Vaccine effectiveness against severe COVID-19

International studies show that effectiveness of two vaccine doses against COVID-19 associated hospitalisation was generally lower during the period of Omicron predominance, compared to the Delta period [17, 18]. In both periods, waning of VE with time since vaccination is observed. For example, a study from the US found that nine months or longer after the second dose, VE against hospital admission due to the Omicron variant was 41% (95% CI 21-55) [19]. A booster (third dose) restores protection to 80-90%, but waning is apparent after approximately four months [17-19]. Until now, most studies on the effectiveness of a second booster (fourth COVID-19 vaccine dose) are from Israel and have short observation periods. The available evidence indicates that, in persons aged 60 years and over, the risk of severe disease caused by the Omicron (BA.1) variant is substantially decreased by a fourth vaccine dose compared to receiving a third dose at least 3 months before [20-22].

9.5.8.2 Vaccine effectiveness against infection

Overall, VE against infection with the Omicron BA.1 and BA.2 variant appears to be lower compared to previous variants, and protection of both primary and booster vaccination wanes over time [23]. In their weekly COVID-19 vaccine surveillance reports, the UKHSA provides VE consensus estimates by taking estimates from the UK as well as international data into account [24]. They find that 0-3 months after the first booster dose, VE estimates against infection are around 50% (40-60%). After 4-6 months, this is approximately 30% (20-40%). Data from Israel shows that after a second booster, VE against infection improves, but this protection seems to wane quickly, starting from week 5 after vaccination [21].

9.5.8.3 *Vaccine effectiveness against transmission*

Several studies have been published investigating transmission rates of SARS-COV-2. Most of these studies were conducted in household settings. Two studies compared transmission within households to transmission outside households. Both studies showed that vaccination of the index had a stronger effect on transmission within households compared to outside households [9, 25]. The reported secondary attack rates (SAR) differed widely between studies within households. During the predominance of the Alpha variant, SARs between 40-64% have been reported [26-28], during the Delta period SARs varied between 11-81% [25, 26, 29-31], and during the Omicron period between 15-51% [25, 29, 30, 32]. In studies that compared the results for more than one variant it was observed that the SAR among contacts of indexes infected with the Delta variant was higher than the SAR among contacts of Alpha-infected indexes, and the SAR was higher when the index case was infected with the Omicron variant compared to the Delta variant [25, 26, 29, 30]. In all studies where vaccination status was included it was observed that vaccination of the index reduced the SAR [9, 10, 28, 29, 31, 33].

Effectiveness of vaccination of the index case, i.e., VE against transmission, of the Alpha variant has been estimated between 35% and 88% [9, 26, 33-35]. Studies investigating both Alpha and Delta variants showed reduced VE against transmission of the Delta variant compared to the Alpha variant [26, 33]. This could be due to stronger immune evasion of the Delta variant or increased time since vaccination during the Delta-prevalent period. VE estimates against transmission of the Delta variant vary between 24% and 82% [10, 26, 29, 31, 33, 36]. Limited studies have been published on VE against transmission of the Omicron variant. The results until now indicate low protection from primary vaccination of the index [29, 30]. The available data suggests that a booster dose offers better protection than only the primary series, but the effect is still lower against transmission of the Omicron variant compared to the Delta variant.

9.5.8.4 *Vaccine effectiveness against long COVID*

COVID-19 vaccines may also reduce the risk of long COVID when vaccinated persons get infected with SARS-CoV-2. Most studies that assessed the effect of vaccination prior to infection showed that vaccinated cases were less likely to develop symptoms of long COVID than unvaccinated cases [37]]. All studies had an observational design and were very heterogenous in terms of the definition of long COVID. A recently published paper among veterans suggests that vaccination only partially reduces the risk of long COVID (by 15%) [38].

9.5.9 Literature

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9.6 Seroepidemiology and immunogenicity of SARS-CoV-2 in the Netherlands

E.R.A. Vos, C.C.E. van Hagen, L.L. van den Hoogen, A. Buisman, J. Brummelman, H. Korthals Altes, A. Huiberts, C. Hoeve, D. Wong, G. Smits, A.J. Wijmenga-Monsuur, M. van Boven, J. de Wit, R.S. van Binnendijk, N.Y. Rots, F.R.M. van der Klis, M.J. Knol, M.C. Boer, G. den Hartog, H.E. de Melker

9.6.1 Key points

- Up until the end of 2021, six rounds have been performed in the seroepidemiology PIENTER Corona (PICO) study, providing valuable insights into SARS-CoV-2 humoral immunity in the general population of the Netherlands. Monitoring will continue in the coming years.
- In November 2021, 87% of the Dutch population had antibodies against SARS-CoV-2, of which 26% had serological evidence of infection. Hence, despite multiple large waves of infections, the largest part of the population acquired immunity in 2021 solely due to vaccination, which was rolled out since the start of the year. Seroprevalence was >90% in all (vaccine-eligible) age groups from 12 years. Relatively speaking, young adults were infected most across the pandemic (with peaks over 40% in November 2021), followed by middle-aged adults (30%). The lowest rates were seen in the elderly (20%). Infection in school-aged children increased particularly during the waves caused by the alpha and delta variants of concern (VOC). Differences between GGD-regions were observed over time.
- The PICO study also showed that in the majority of people infection-induced antibodies persist for at least 1.5 years. Moreover, nearly all people seroconvert after the primary vaccination series, regardless of vaccine type. However, IgG antibody levels are lower with increasing age. People with a history of infection seem to induce higher levels of antibodies after vaccination, which also may persist longer, indicative of a booster effect.
- On the Dutch Caribbean Island of Aruba, overall seroprevalence was approximately 20% in the beginning of 2021, with highest rates in adolescents and young adults. Particularly in the older age groups a large discrepancy was observed between cumulative confirmed PCR-tests in the population and seropositivity. This may require attention, as the elderly might be undertested.
- The Vaccine Study Corona (VASCO) showed a large increase in anti-N-seropositivity between January and May 2022: up to 40-60%, with higher seropositivity in 18-59 year-olds compared with 60-85 year-olds. Similar seropositivity rates were seen in people with and without a medical risk condition.
- RIVM vaccination studies also demonstrated higher IgG levels in participants with a history of SARS-CoV-2 infection compared to infection-naïve participants after primary series vaccination, and age was a strong indicator of IgG acquisition. The strength of this correlation decreased between the 1st and 2nd vaccinations, and kept declining months thereafter. Three months after the primary vaccination series, all participants above 50 years were still seropositive.

- Half a year post primary vaccination series with Comirnaty®, IgG antibody concentrations in nursing home residents were lower compared to age-matched home-dwelling elderly, and 19% of the residents were seronegative. One month after booster vaccination antibody levels increased sharply, although they were still lower in the residents.
- A robust T cell response is elicited upon vaccination among all age groups and vaccines. However, in those over 75 years, more variation was found. Additionally, vastly similar T cell responses against the Spike-protein of the different VOCs are observed following vaccination with Comirnaty® or Spikevax®, suggesting a high level of cross-reactivity.
- Vaccination studies in collaboration with RIVM, contributed to the advice given to the minister to offer a 3rd primary series vaccination to specific immunocompromised groups only.

9.6.2 Tables and figures

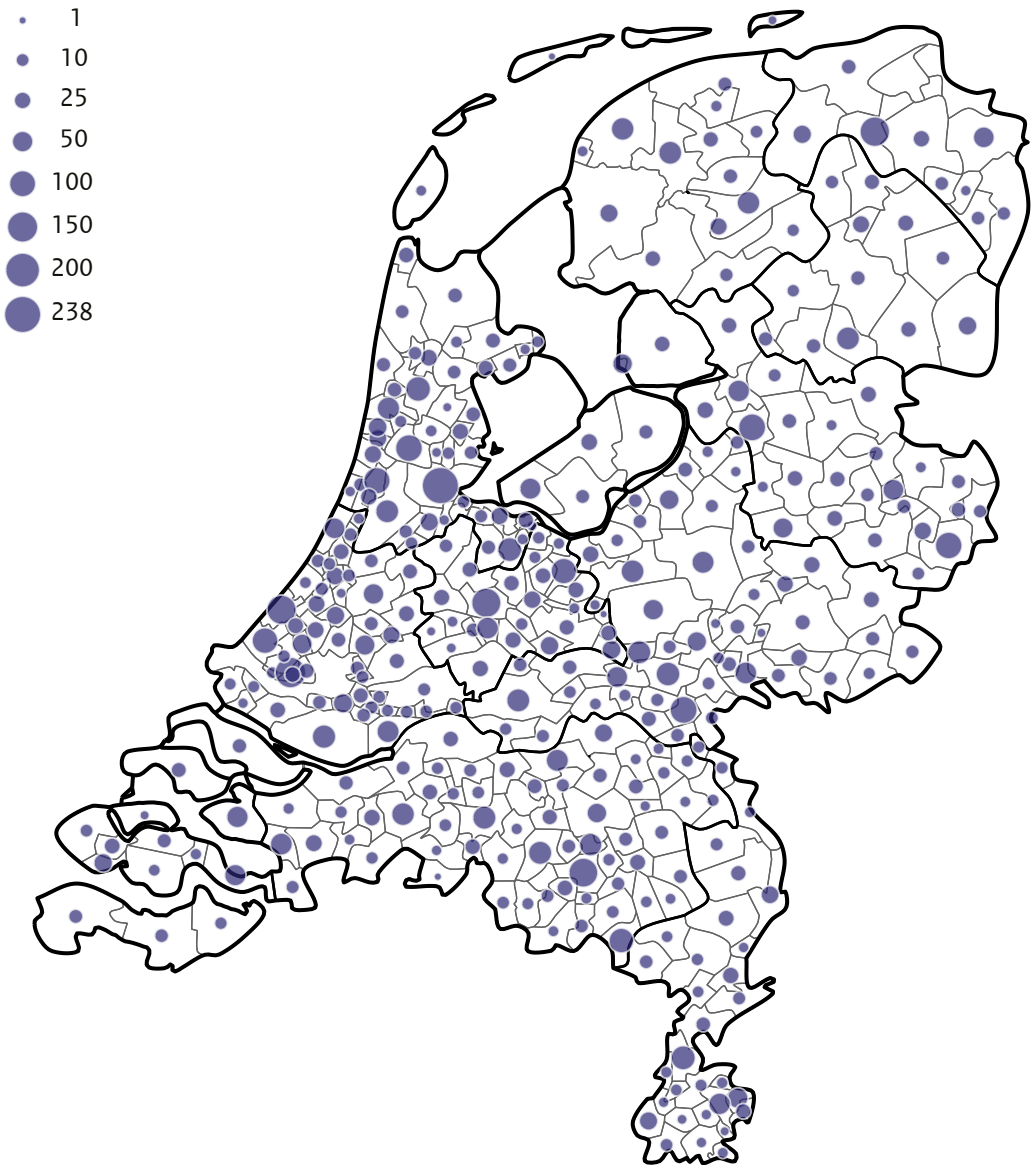

Figure 9.6.1 Number of participants by municipality in the 6th PICO round (November 2021).

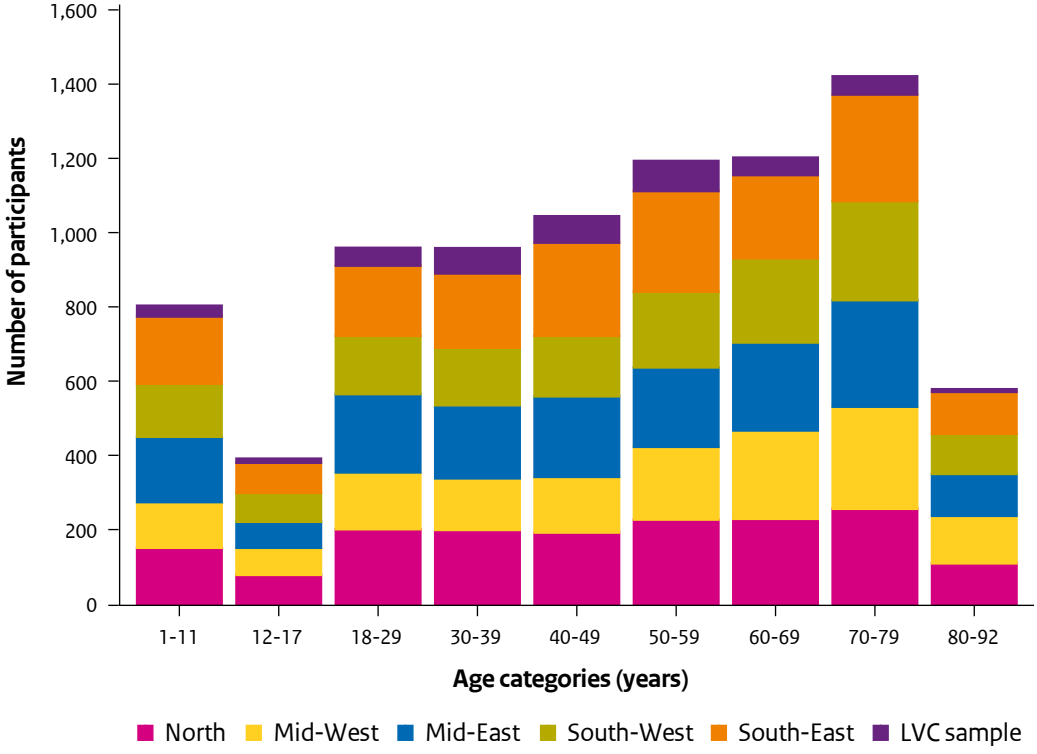

Figure 9.6.2 Number of participants by age category and region in the 6th PICO round (November 2021). Regions consist of the following provinces: North = Groningen, Friesland, Drenthe and Overijssel; Mid-West = Noord-Holland and Flevoland; Mid-East = Utrecht and Gelderland; South-West = Zuid-Holland and Zeeland; South-East = Noord-Brabant and Limburg; LVC = sample of low vaccination coverage municipalities.

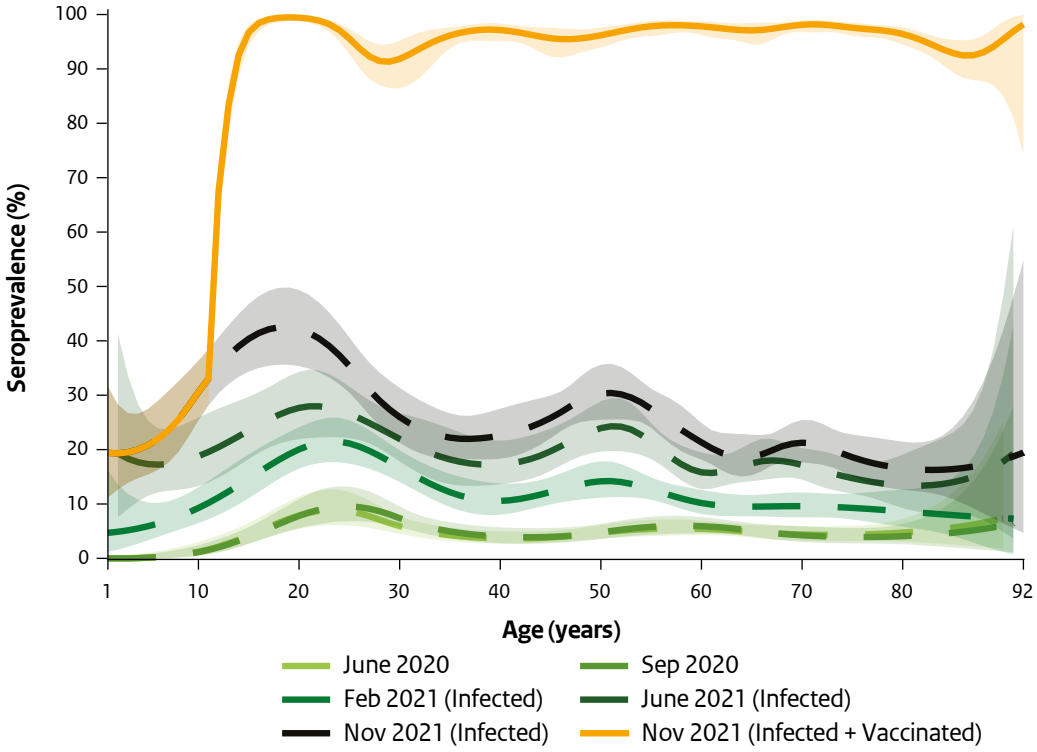

Figure 9.6.3 Weighted SARS-CoV-2 seroprevalence (with 95% confidence intervals) in the general population of the Netherlands, from PICO rounds 2, 3, 4, 5 and 6 (June 2020, September 2020, February 2021, June 2021, and November 2021, respectively), by age (years). Note: seroprevalence of PICO round 6 (November 2021) is subdivided into infection-related seroprevalence and seroprevalence resulting from both infection and/or vaccination (total).

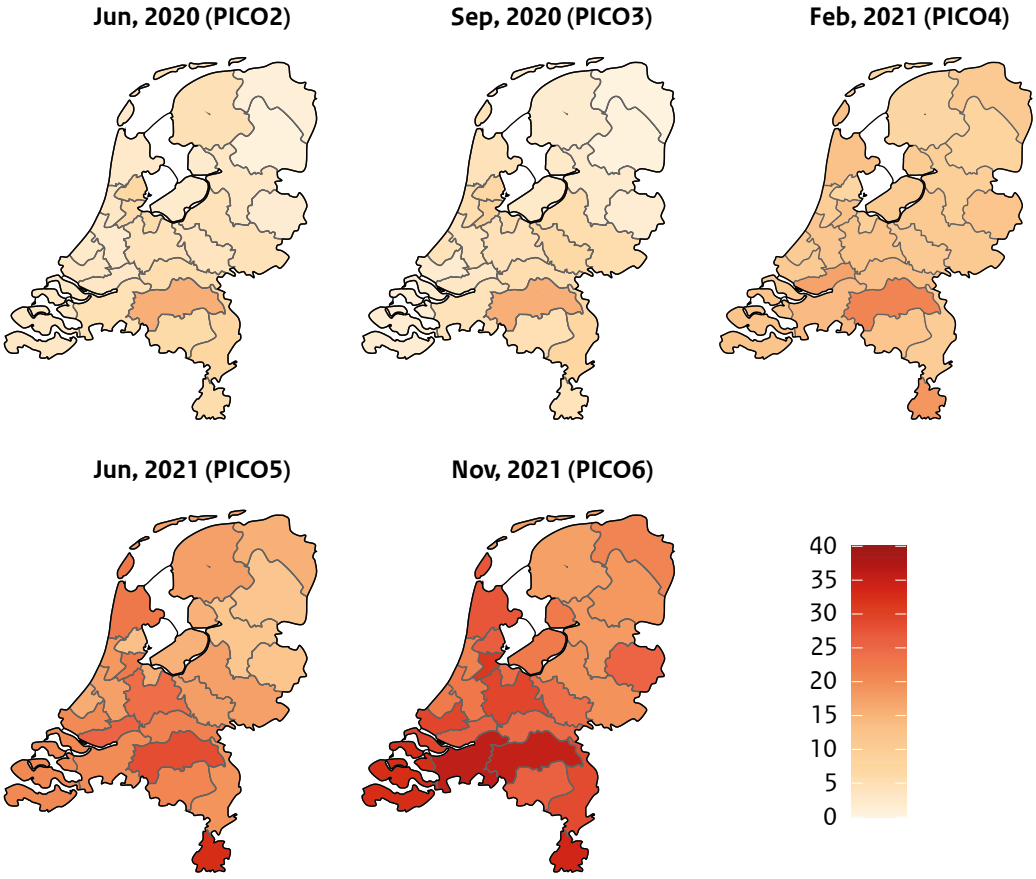

Figure 9.6.4 Weighted SARS-CoV-2 infection-related seroprevalence in the general population of the Netherlands, from PICO rounds 2, 3, 4, 5 and 6 (June 2020, September 2020, February 2021, June 2021, and November 2021, respectively), by GGD region.

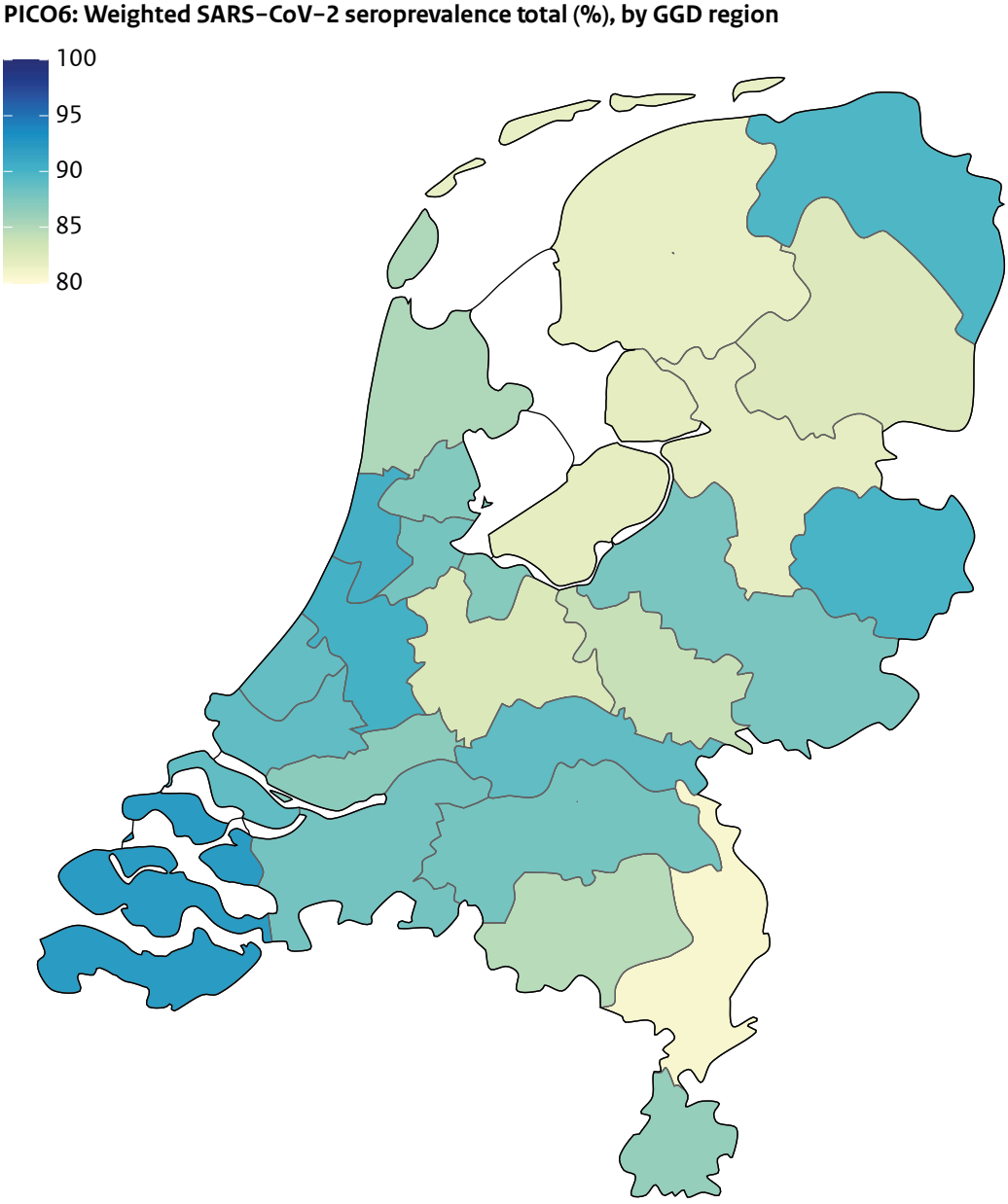

Figure 9.6.5 Weighted SARS-CoV-2 total seroprevalence (infection- and vaccination-induced) in the general population of the Netherlands in PICO round 6 (November 2021), by GGD region.

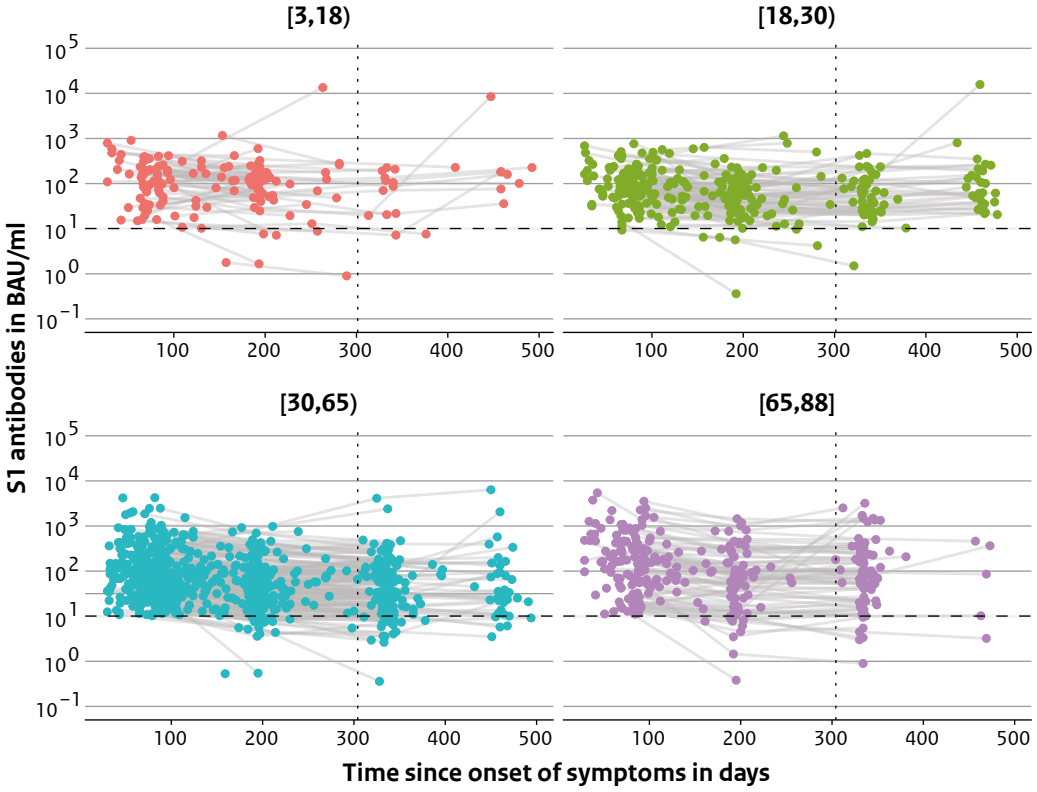

Figure 9.6.6 The level of IgG antibodies to SARS-CoV-2 Spike S1 by time since infection in different age groups (in years; see headers). Note: people receiving a vaccination were excluded. The horizontal dashed line represents the threshold for seropositivity to Spike S1.

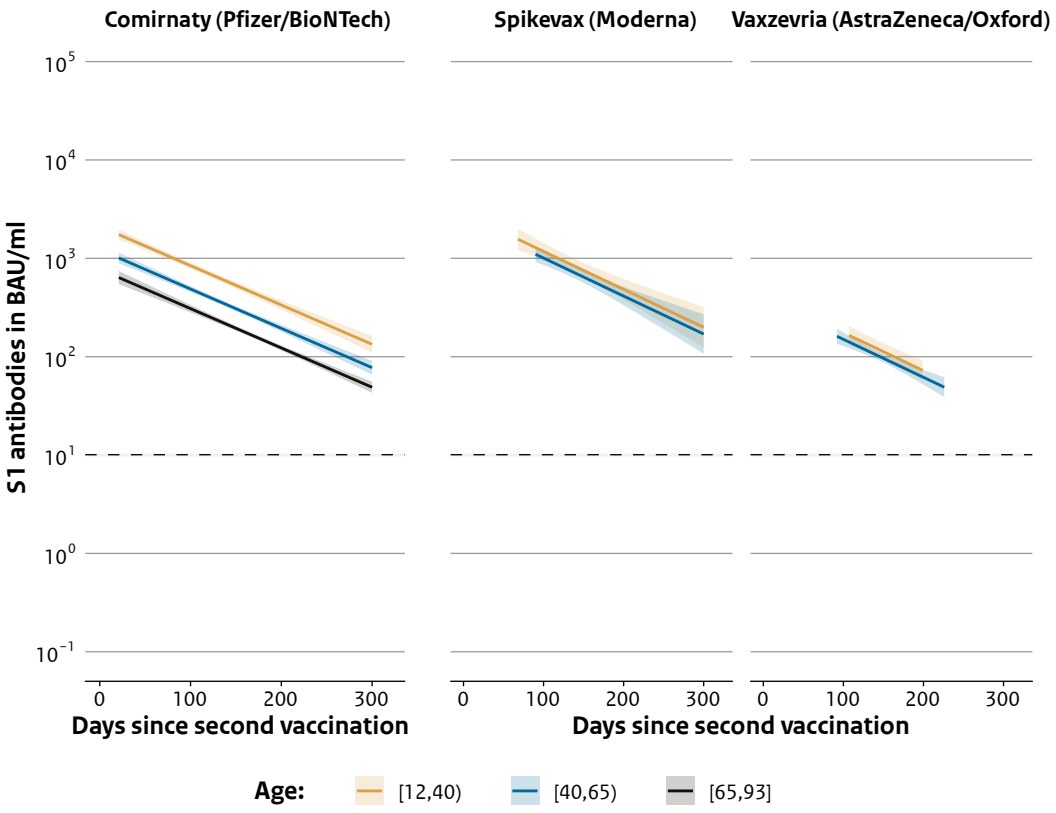

Figure 9.6.7 The decay of SARS-CoV-2 Spike S1-specific IgG after vaccination with three different vaccines (Comirnaty® (Pfizer/BioNTech), Spikevax® (Moderna), and Vaxzevria® (AstraZeneca/Oxford). Data are stratified for age groups of 12-40, 40-65 and 65-92 years of age where applicable. Insufficient numbers were available for Janssen, and people with a history of infection were excluded for this analysis. The horizontal dashed line represents the threshold for seropositivity to Spike S1.

Table 9.6.1 Number (%) of uninfected individuals with Spike S1 IgG antibodies by age group, 100-200 days after completing the primary series of vaccination with Comirnaty®, Spikevax®, Vaxzevria® (2 vaccinations), or Janssen (1 vaccination).

	Number of vaccinations	Age (years)	Number of participants	% Positive at 100-200 days	95% Confidence interval
Comirnaty (Pfizer/BioNTech)					
	2	12 - 40	264	100	98.6-100
		40 - 65	779	99.7	99.1-100
		65 - 93	930	98.6	97.6-99.3
Spikevax (Moderna)					
	2	12 - 40	74	100	95.1-100
		40 - 65	181	100	98.0-100
		65 - 93	9	100	66.4-100
Vaxzevria (AstraZeneca)					
	2	12 - 40	41	100	91.4-100
		40 - 65	363	98.1	96.1-99.2
		65 - 93	123	98.4	94.2-99.8
Janssen					
	1	12 - 40	58	100	93.8-100
		40 - 65	114	96.5	91.3-99.0
		65 - 93	1	-	-

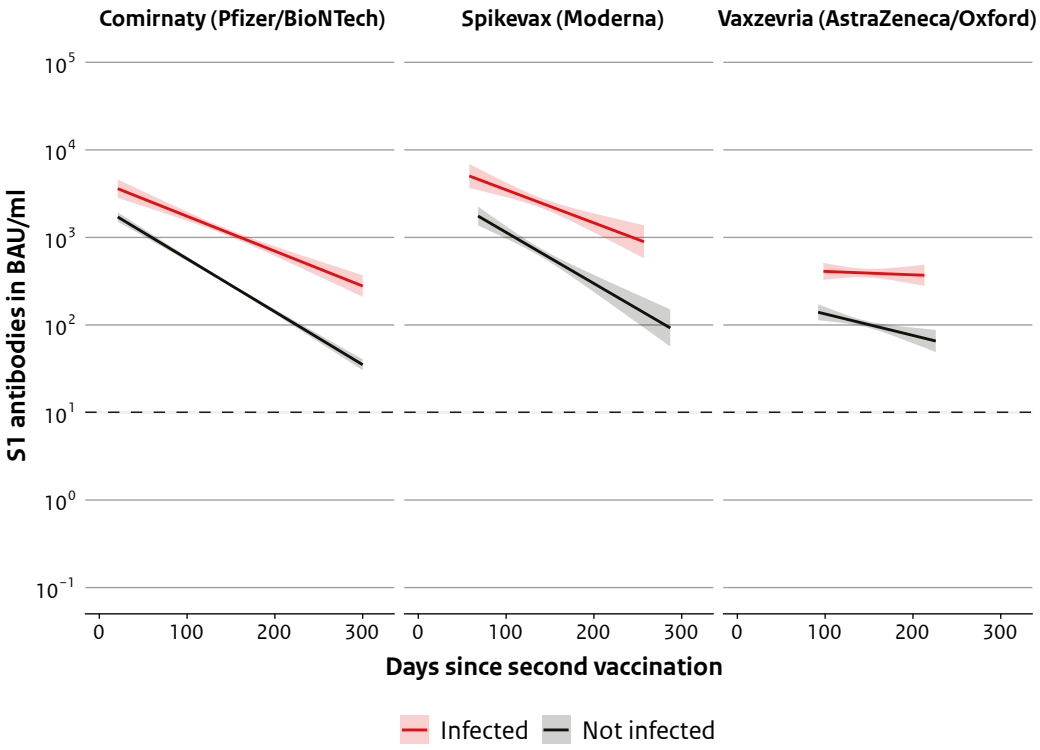

Figure 9.6.8 The decay of SARS-CoV-2 Spike S1-specific IgG antibodies in people with (red) and without (black) a history of infection, for three different vaccines (Comirnaty® (Pfizer/BioNTech), Spikevax® (Moderna), and Vaxzevria® (AstraZeneca/Oxford). The horizontal dashed line represents the threshold for seropositivity to Spike S1.

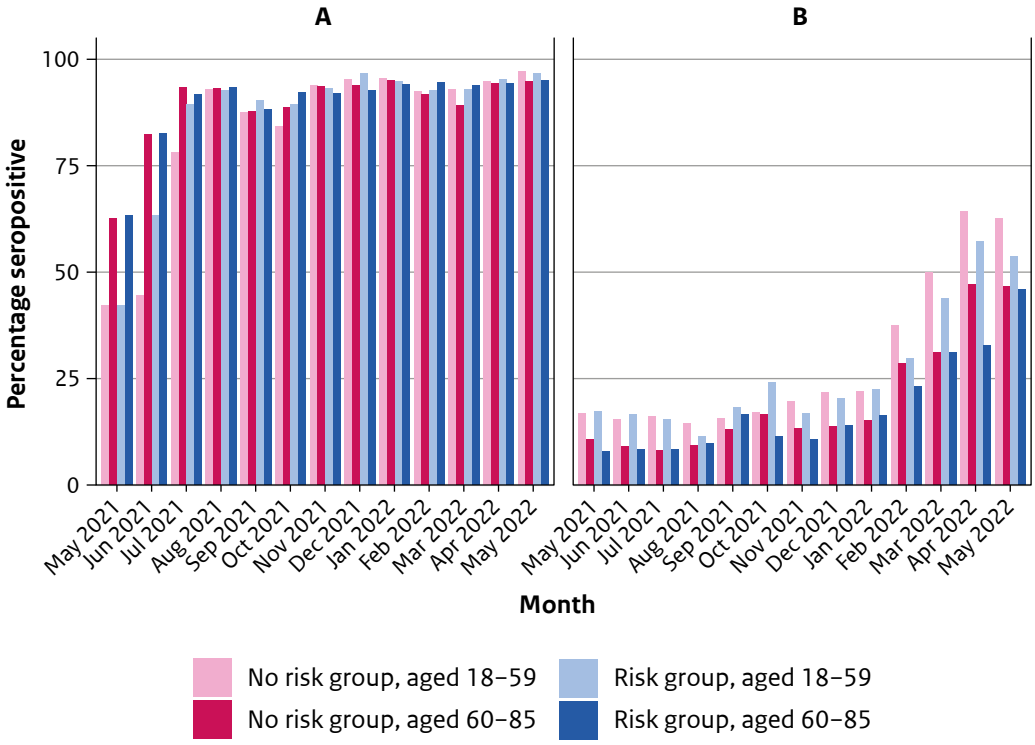

Figure 9.6.9 Percentage of VASCO participants with antibodies against the receptor binding domain (RDB) of the spike protein (panel A) and against the nucleoprotein (panel B) by age group and medical risk group from May 2021 to May 2022 based on ~38,000 serum samples of ~26,000 participants. Note that samples over time are largely from different participants.

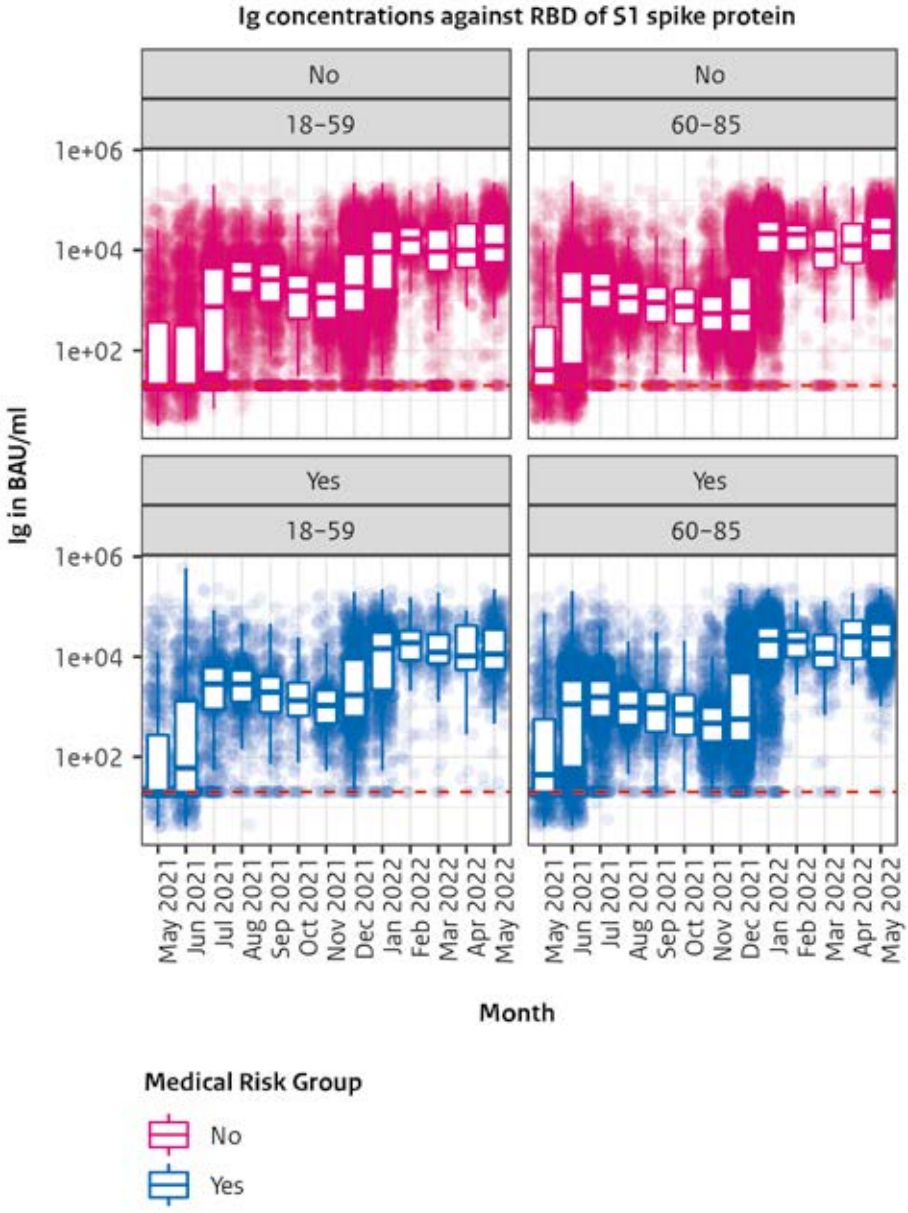

Figure 9.6.10 Antibody concentrations against the receptor binding domain (RDB) of the spike protein in BAU/mL by age group and medical risk group from May 2021 to May 2022, based on ~38,000 serum samples of ~26,000 participants. Note that samples over time are largely from different participants. Individual datapoints are displayed, and boxplots represent the median (horizontal line) and interquartile range.

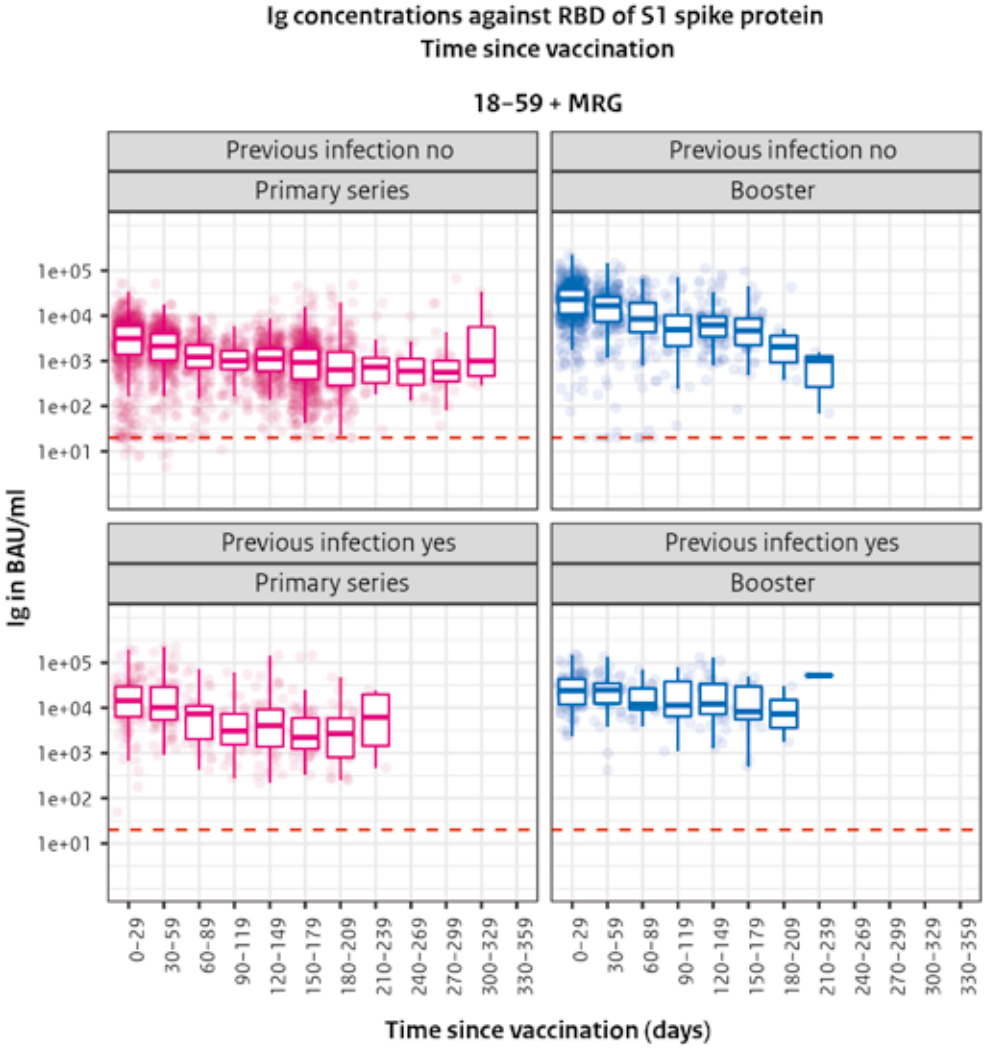

Figure 9.6.11.A Antibody concentrations against the receptor binding domain (RDB) of the spike protein in BAU/mL by time since primary, first booster and second booster vaccination in persons without and with a SARS-CoV-2 infection before vaccination (based on self-report or presence of N-antibodies) among 18-59 year-olds with medical risk condition.

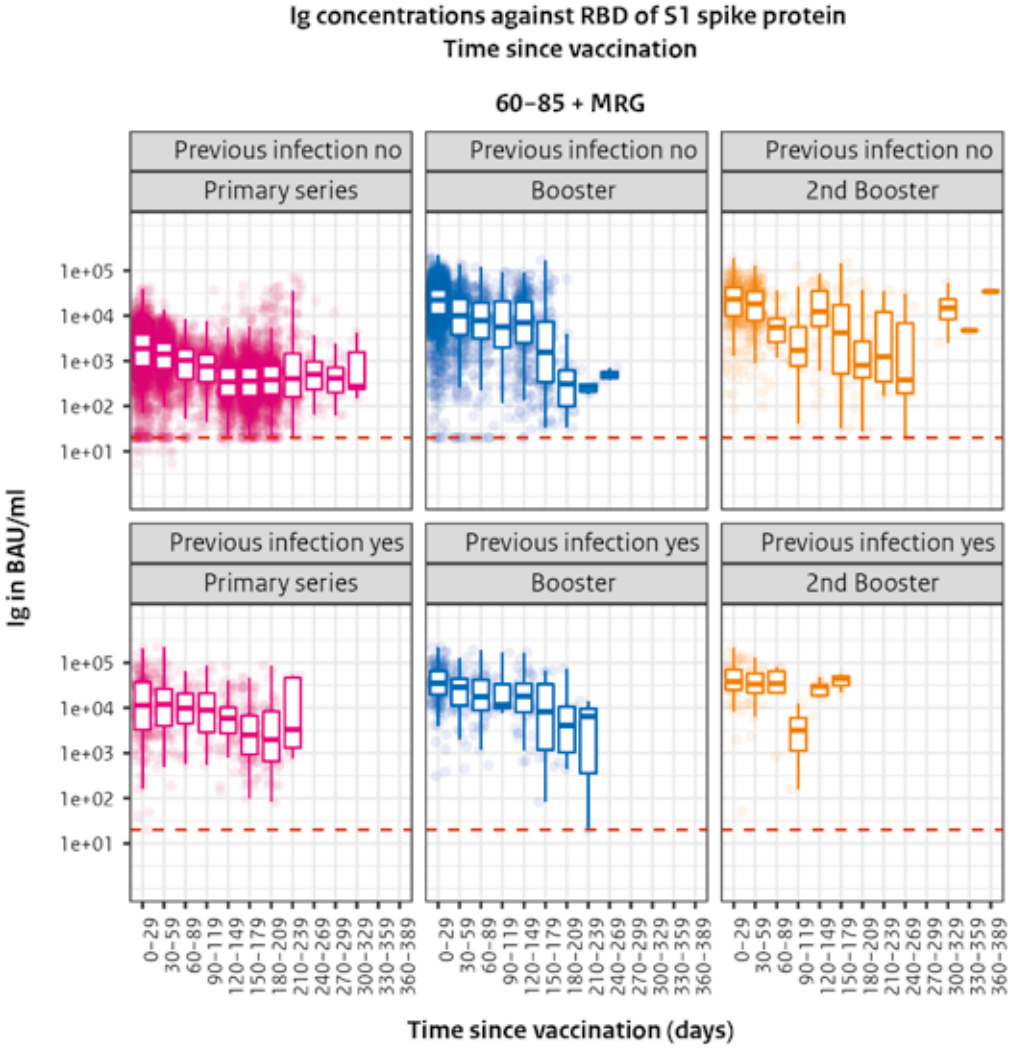

Figure 9.6.11.B Antibody concentrations against the receptor binding domain (RDB) of the spike protein in BAU/mL by time since primary, first booster and second booster vaccination in persons without and with a SARS-CoV-2 infection before vaccination (based on self-report or presence of N-antibodies) among 60-85 year-olds with medical risk condition.

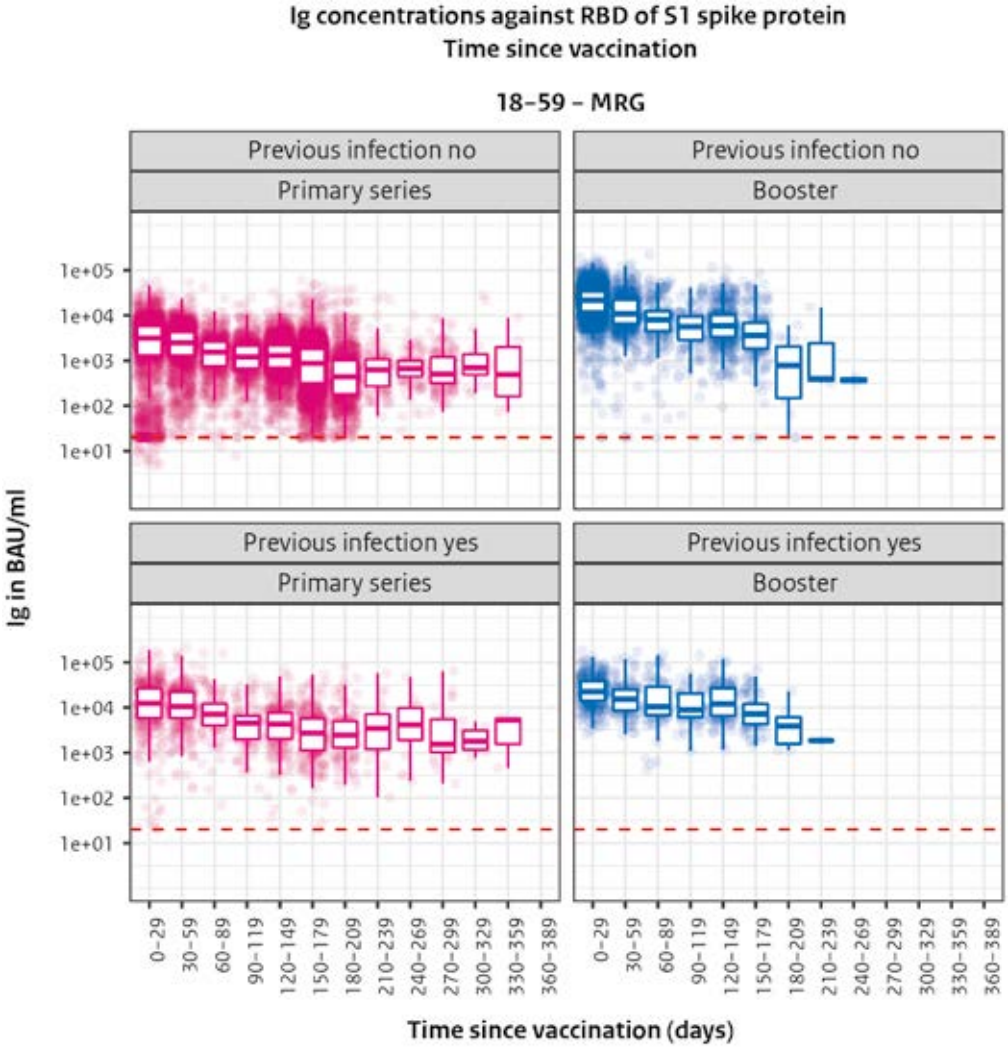

Figure 9.6.11.C Antibody concentrations against the receptor binding domain (RDB) of the spike protein in BAU/mL by time since primary, first booster and second booster vaccination in persons without and with a SARS-CoV-2 infection before vaccination (based on self-report or presence of N-antibodies) among 18-59 year-olds without medical risk condition.

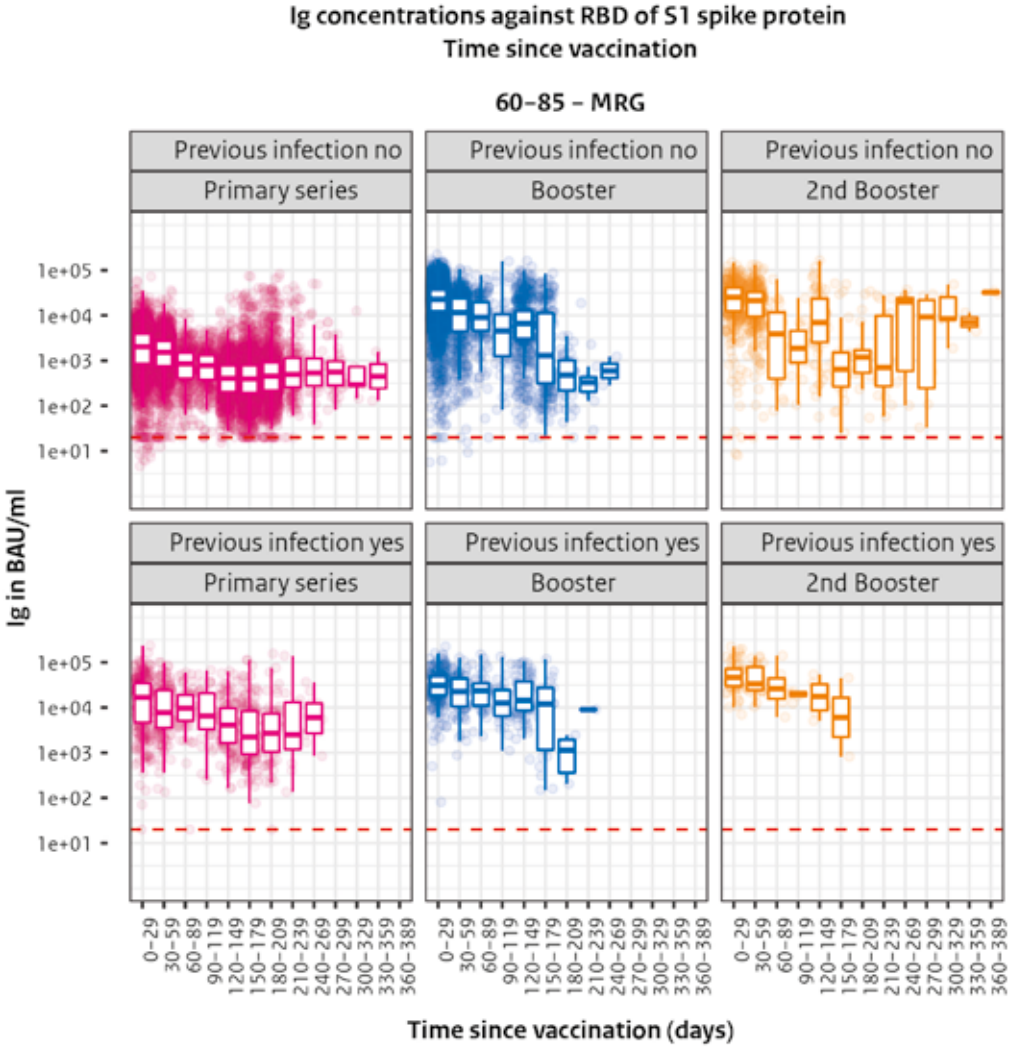

Figure 9.6.11.D Antibody concentrations against the receptor binding domain (RDB) of the spike protein in BAU/mL by time since primary, first booster and second booster vaccination in persons without and with a SARS-CoV-2 infection before vaccination (based on self-report or presence of N-antibodies) among 60-85 year-olds without medical risk condition.

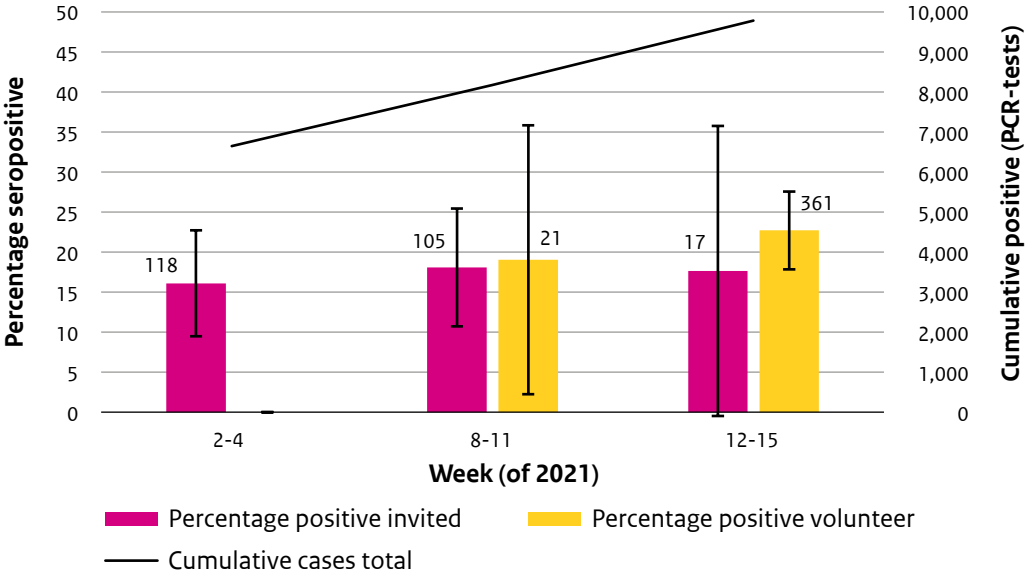

Figure 9.6.12 Percentage of seropositive individuals (with 95% CIs) in samples collected over three time periods in the invited and voluntary groups (pink and yellow bars, respectively) in the first months of 2021, with total number of participants above the bars; total cumulative cases test via PCR in the Aruban population over the same time period illustrated with the black line.

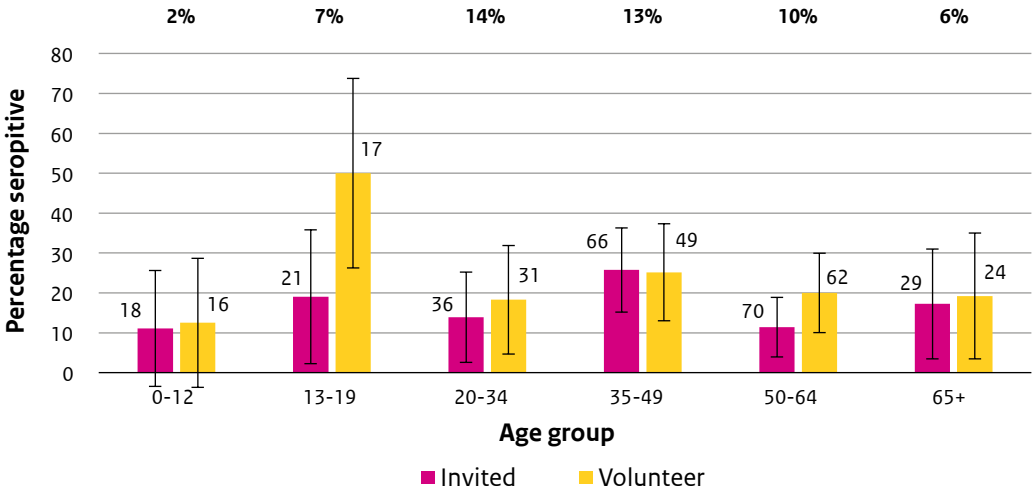

Figure 9.6.13 Percentage of seropositive individuals in the invited and voluntary groups by age groups (pink and yellow bars, respectively); the percentages above the bars refer to the cumulative (PCR-) positively tested individuals in the corresponding age group in the Aruban population at the same time.

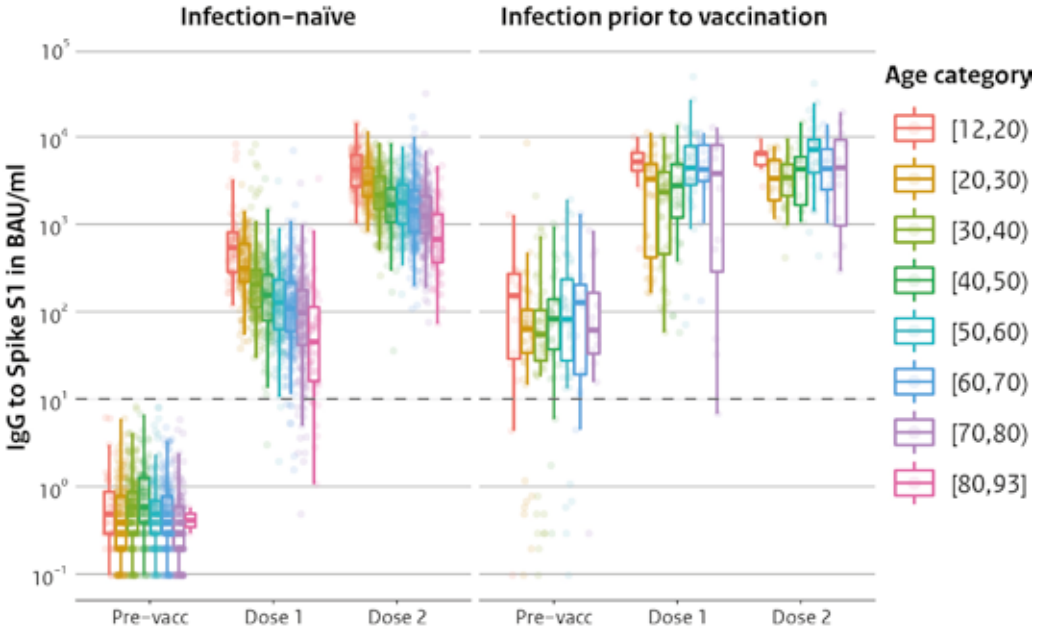

Figure 9.6.14 Spike S1-specific IgG kinetics by age category following the primary series of Comirnaty® (Pfizer/BioNTech) vaccination in infection-naïve participants (A) and participants with a SARS-CoV-2 infection prior to vaccination (B). Results are shown for 1,500 infection-naïve participants and 235 participants with a SARS-CoV-2 infection history prior to vaccination (Pre-vacc), one month after the first (Dose 1) and one month after the second vaccination dose (Dose 2). The horizontal dashed line represents the threshold for seropositivity to Spike S1.

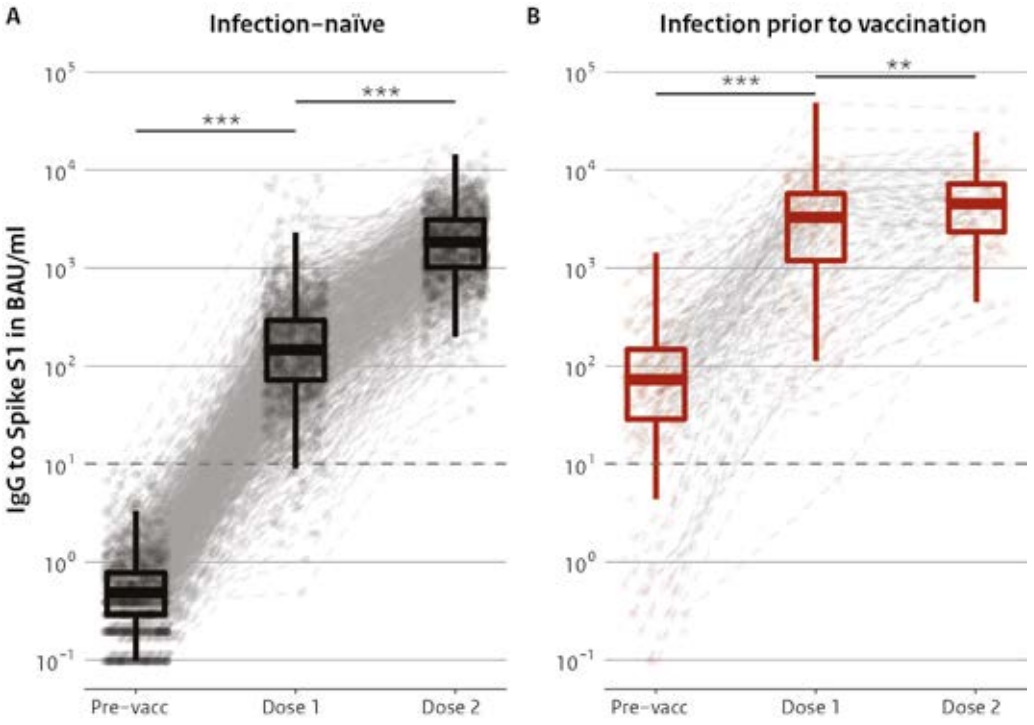

Figure 9.6.15 Spike S1-specific IgG kinetics following the primary series of Comirnaty® (Pfizer/BioNTech) vaccination in infection-naïve participants (A) and participants with a SARS-CoV-2 infection prior to vaccination (B). Results are shown for a total of 1,500 infection-naïve participants and 235 participants with a SARS-CoV-2 infection history prior to vaccination (Pre-vacc), one month after the first (Dose 1) and one month after the second vaccination dose (Dose 2). The horizontal dashed line represents the threshold for seropositivity to Spike S1
***: $p<0.001$; **: $p=0.002$.

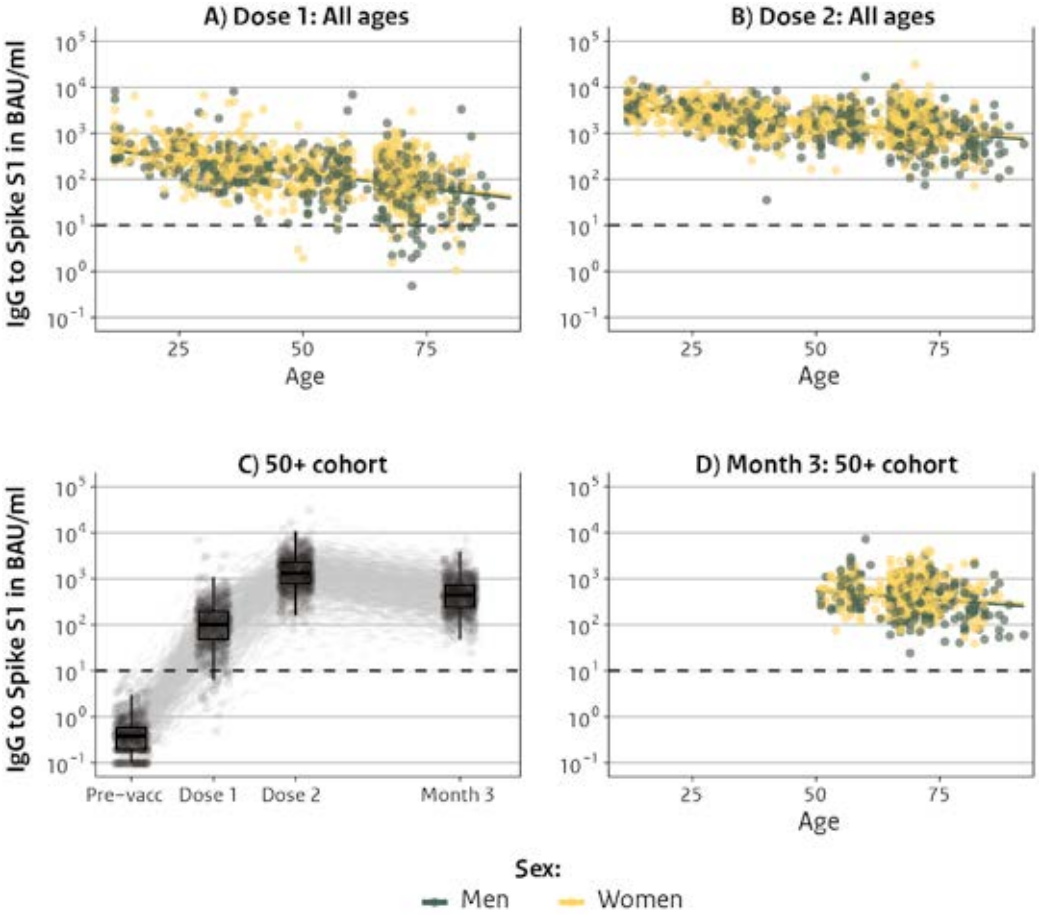

Figure 9.6.16 Spike S1-specific IgG by age in years per timepoint (panels A, B, D) and kinetics following the primary series of Comirnaty® (Pfizer/BioNTech) vaccination in infection-naïve participants up to three months after the second vaccination dose (panel C). In (A, B, D) fitted lines represent the linear association between IgG concentration and age, while dots represent individual measurements prior to vaccination (Pre-vacc), one month after the first (Dose 1), one month after the second (Dose 2) or three months after the second vaccination dose (Month 3). Results are shown separately for men (green) and women (yellow). In (C) boxplots show results for all participants at each timepoint. In (A-B) results are shown for 1,448 unique, infection-naïve participants across all ages, with S1 IgG measurements available at Dose 1 and/or Dose 2, while in (C-D) results are shown for >720 participants in the 50+ cohort.

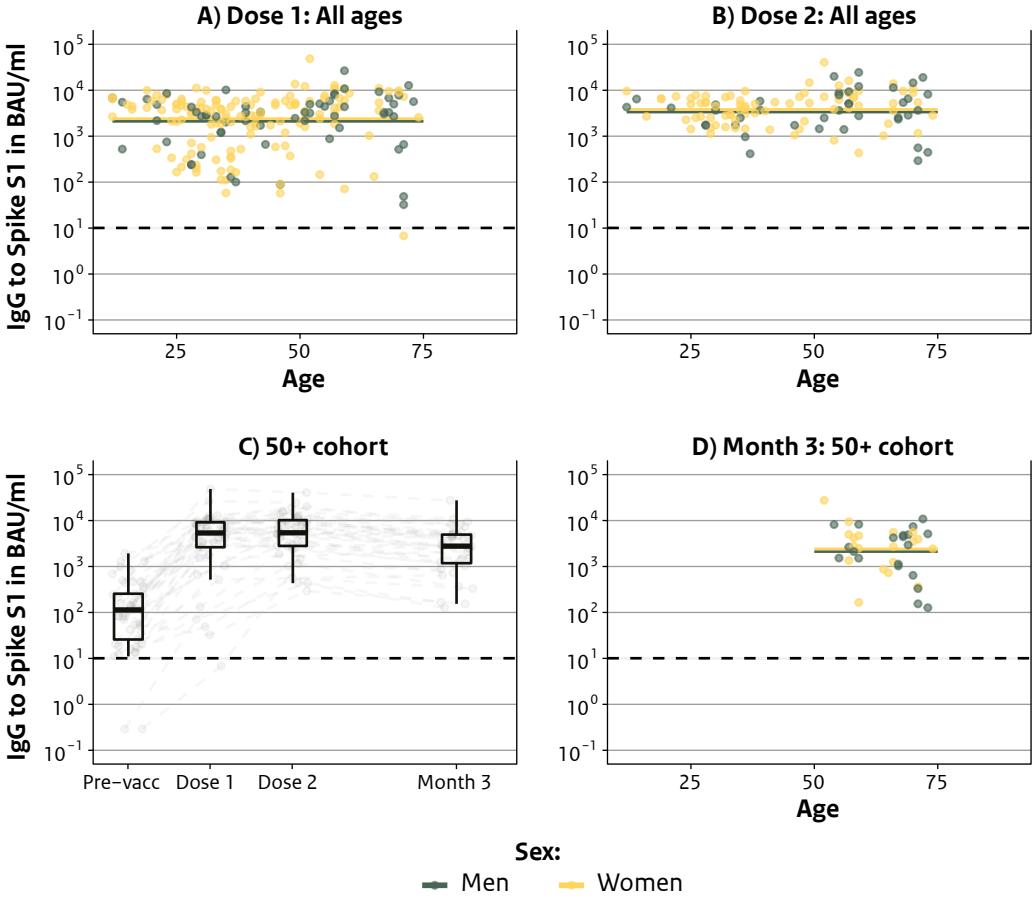

Figure 9.6.17 Spike S1-specific IgG by age in years per timepoint (panels A, B, D) and kinetics following the primary series of Comirnaty (Pfizer/BioNTech) vaccination in participants with a history of SARS-CoV-2 infection up to three months after the second vaccination dose (panel C). In (A, B, D) fitted lines represent the linear association between IgG concentration and age, while dots represent individual measurements pre vaccination (Pre-vacc), one month after the first (Dose 1), one month after the second (Dose 2) or three months after the second vaccination dose (Month 3). Results are shown separately for men (green) and women (yellow). In (C) boxplots show results for all participants at each timepoint, while dots and dashed grey lines show measurements and their trajectory between timepoints per participant. In (A-B) results are shown for a total of 204 participants across all ages while in (C-D) results are shown for 46 participants in the 50+ cohort.

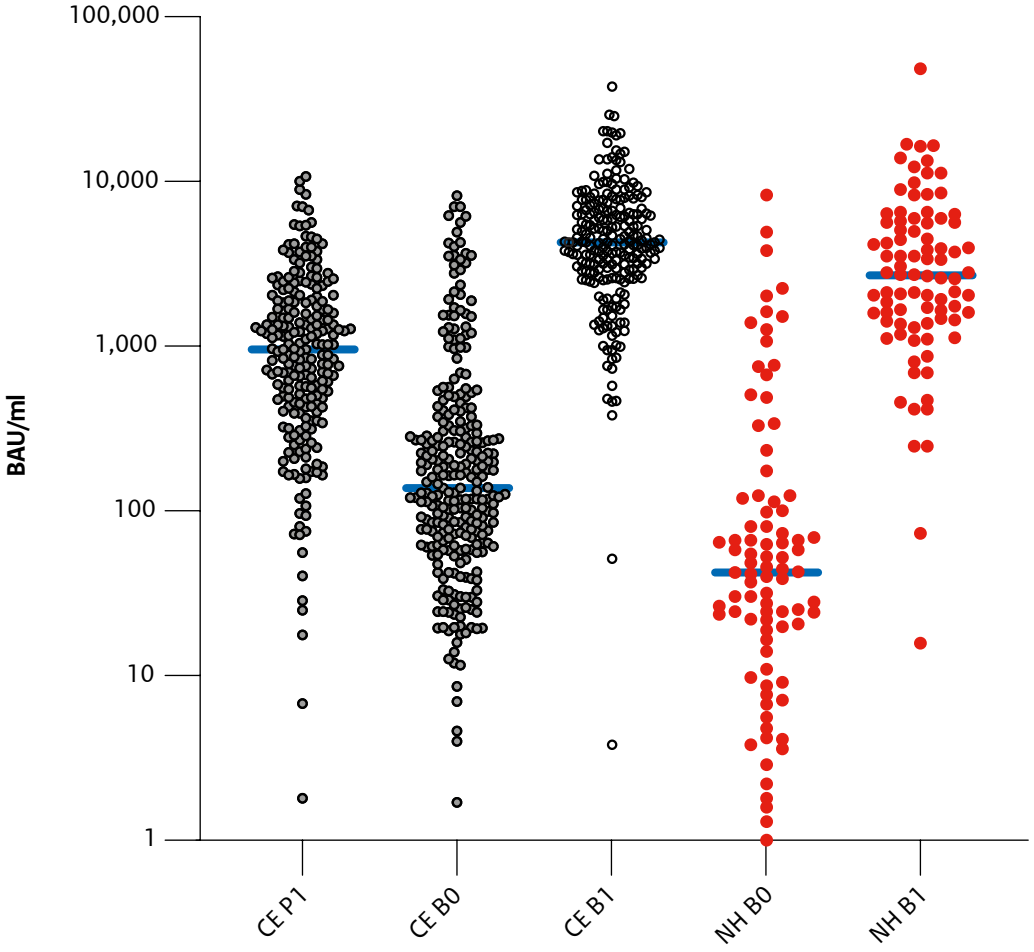

Figure 9.6.18 Spike S1-specific IgG concentrations in control-group elderly persons living at home (CE) and nursing home residents (NH) at 1 month post primary series of Comirnaty® (Pfizer/BioNTech) vaccination (P1), pre booster vaccination (B0) and 1 month post booster vaccination (B1). Results are shown in red for nursing home residents. Data pre booster vaccination are 8-9 months post primary vaccination series. Blue lines indicate the median value per group.

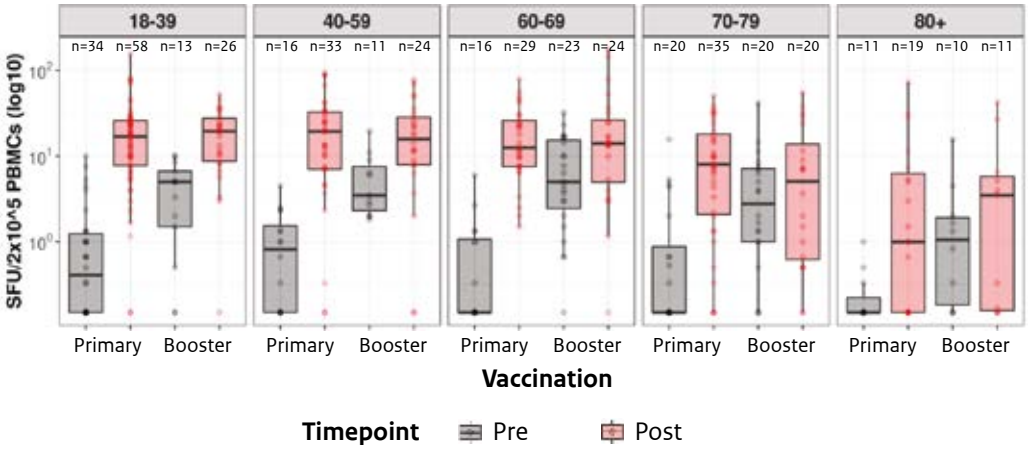

Figure 9.6.19 SARS-CoV-2 Spike-specific T cell responses in different age groups before and after primary and booster COVID-19 vaccination, as measured by the Interferon-gamma (IFNγ) T cell ELISpot assay. T cell responses were measured before or 1 month post completion of the primary series and before or 1 month post booster vaccination in infection-naïve participants. Data from participants who received different vaccine types were pooled in the analysis. These included 179 participants who were vaccinated during their primary series with Comirnaty® (Pfizer/BioNTech), Spikevax® (Moderna), Vaxzevria® (AstraZeneca), or JCOVDEN® (Janssen), ranging from 18-99 years of age. Number of participants per age group and per timepoint (n) are shown. Results are given in IFNγ-Spot Forming Units (SFU) per 2x105 PBMCs, median and IQR are provided, and individual data are presented as dots.

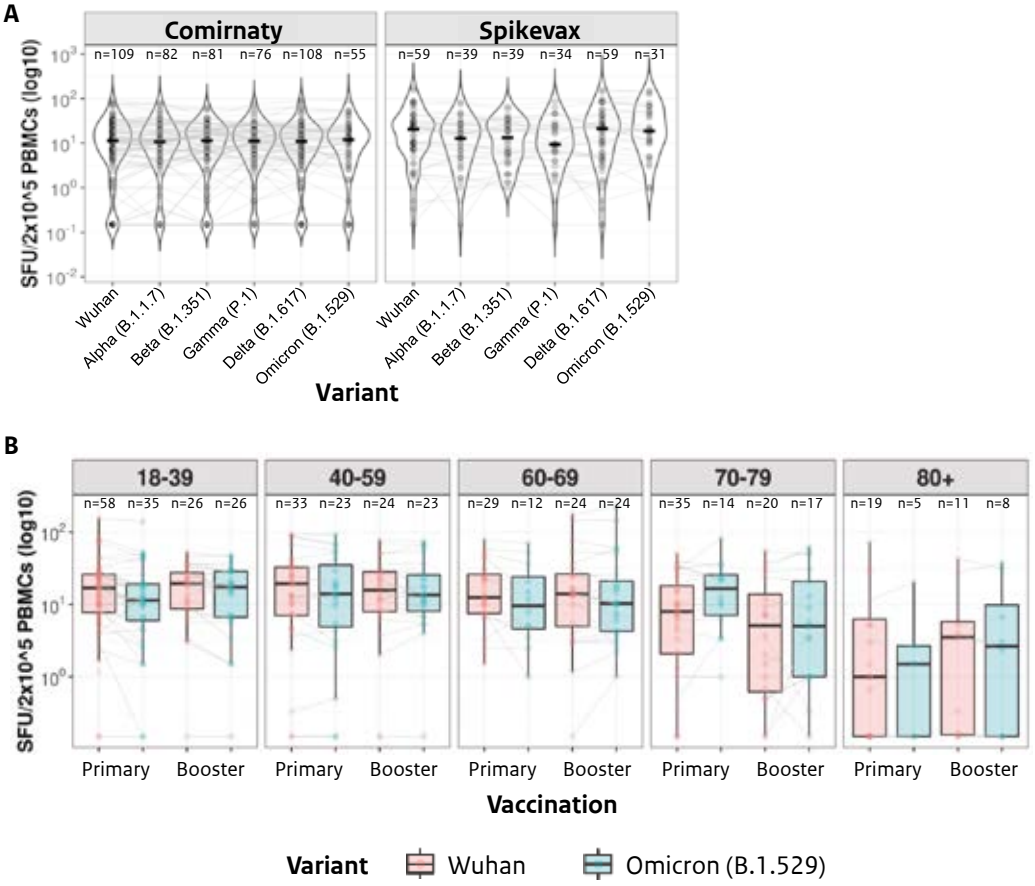

Figure 9.6.20 Cross-reactivity of T cell responses to Spike-protein from different SARS-CoV-2 VOCs in vaccinated infection-naïve adults. T cell responses were measured 1 month post completion of the primary series with the Comirnaty® (Pfizer/BioNTech) or Spikevax® (Moderna) vaccine (A). Data for Wuhan- and Omicron-specific responses upon 1 month post completion of the primary series as well as booster vaccination, stratified by age group (B). Data from participants who received different vaccine types and combinations were pooled in this analysis. Results are given in IFNγ-Spot Forming Units (SFU) per 2x105 PBMCs, median and IQR are provided, and individual data are presented as dots. Number of participants per group (n) are shown.

9.6.3 PIENTER Corona (PICO): a nationwide prospective population-based seroepidemiological study of SARS-CoV-2 in the Netherlands

The PIENTER Corona (PICO) study is a nationwide, prospective, population-based study on immunity against SARS-CoV-2. The primary aim is to detect antibodies to SARS-CoV-2 in repetitive blood samples from a large cohort, representative for the Dutch population. These data are used widely during the course of the epidemic, for instance to estimate the proportion of the population infected and/or vaccinated, as input for modelling purposes, to assess the severity of disease, to determine risk factors for infection, and to study the duration of immunity after infection as well as vaccination (stratified by several groups and types of vaccines).

In the early stages of the COVID-19 pandemic in the Netherlands, participants from the PIENTER-3 study (conducted in 2016/2017 [1]) who had consented to be approached for follow-up were contacted for participation in PICO. The first sampling round was carried out in April 2020, and over 3,200 persons participated. Thereafter, additional sampling took place, randomly selecting people aged 1-89 years across the Netherlands from the Dutch population registry, proportional to municipality size and age-stratified, resulting in over 7,300 participants [2, 3]. Four sampling rounds followed: the 2nd in June 2020, the 3rd in September 2020, the 4th in February 2021 (i.e., at the start of the alpha variant of concern (VOC)), and the 5th in June 2021 (i.e., at the end of the alpha VOC) For the 6th sampling round in November 2021 (i.e., at the beginning of the delta VOC in term of absolute cases), additional random sampling from the Dutch population registry was repeated as before, resulting in over 8,500 participants (see distribution of participants across the Netherlands by municipality in Figure 9.6.1).

Data on potential risk factors for SARS-CoV-2 infection and COVID-19 vaccination data are retrieved via self-completed (online) questionnaires. These documented data from the questionnaires are linked to laboratory measurements regarding humoral immunity obtained from self-sampled fingerstick blood, and measured by a validated bead-based multiplex immunoassay (MIA) developed at RIVM [4] (with a cut-off for IgG seropositivity of 10 binding antibody units (BAU)/mL using the NIBSC 20/136 WHO standard). In the 6th round, the participants' age ranged from 1 to 92 years (mean 50 years, see also Figure 9.6.2, number of participants by age group and region), and slightly more women participated than men (57% vs. 43%). Results were weighted to represent the Dutch population and corrected for laboratory test specifics. The study will proceed in the coming period: a 7th and 8th round were carried out in March and June 2022, respectively. The data from these rounds has yet to be analysed. A 9th round will be held in the autumn of 2022, and additional rounds are planned for the coming years.

9.6.3.1 Epidemiological characteristics

9.6.3.1.1 Overall seroprevalence due to infection and/or vaccination

In the first three PICO rounds (from April 2020 up to and including September 2020), SARS-CoV-2 anti-spike S1 was used to determine infection. SARS-CoV-2 vaccines in the Netherlands are being administered since early of 2021, and all target the spike antigen.

Hence, since the 4th PICO round, anti-nucleocapsid (N) – induced solely via natural infection – and self-reported test positivity (PCR/antigen rapid tests) as well as fold-increases in concentration were used additionally to distinguish antibodies derived from infection and/or vaccination. The overall weighted seroprevalence of IgG antibodies targeted against the spike S1 antigen of SARS-CoV-2 in the Dutch population was 2.8% (95% CI 2.1-3.7) in the 1st round (April 2020). This estimate rose to 4.5% (95% CI 3.8-5.2) in the 2nd round (June 2020), and 4.9% (95% CI: 4.1-5.6) in the 3rd round (September 2020). In February 2021 (round 4), the overall weighted total seroprevalence (i.e., IgG antibodies induced by both infection and/or vaccination) had risen to 14.3% (95% CI 13.1-15.5). Seropositivity increased to 64.5% (95% CI 62.7-66.3) in the 5th round (June 2021) and 86.5% (95% CI 85.4-87.7) in the 6th round (November 2021). Slight differences – albeit not statistically significant – were observed in the total seroprevalence in November 2021 between men (85%) and women (88%), and between those from Dutch (87%) and non-Western ethnic backgrounds (82%), the latter resulting from a lower vaccination uptake. Since the Netherlands started SARS-CoV-2 vaccination in January 2021, distinction was made in 2021 between SARS-CoV-2 infection-induced seropositivity and seropositivity resulting from vaccination only, namely: February/4th round: 12.2%, vs. 2.1%, resp.; June 2021/5th round: 19.8% vs. 44.7%, resp.; and November/6th round: 26.0% vs. 60.5% resp.

With regards to serological proof of infection across the different time points in 2021, estimates from the low vaccination coverage (LVC) region in the Netherlands were generally higher than in the general Dutch population (4th round: 20%; 5th round: 29%; 6th round: 38%), whereas the total seroprevalence (infection and vaccination-induced humoral immunity combined) was lower (4th round: 22%; 5th round: 63%; 6th round: 82%), resulting from lower vaccination uptake.

9.6.3.1.2 Seroprevalence by age

Infection-induced seroprevalence by age is estimated in each round of the PICO study, and shows similar patterns between the different study rounds (Figure 9.6.3, dashed lines). Young adults display the highest seroprevalence at each timepoint, followed by middle-aged adults, and seroprevalence is generally lowest in the very young and in the oldest people. Between June and November 2021, during the start of the delta VOC wave, a relatively steep increase in infections was seen in younger people: from children of primary school age up until young adults of up to 25 years of age, peaking at rates above 40% in 20-year-olds. Middle-aged people around 50 years reached infection levels up to 30%, and seroprevalence remained lowest in the elderly (20%). Total seroprevalence by age in November 2021 (Figure 9.6.3, continuous orange line) shows a pattern that differs from infection-induced seroprevalence. A steep increase was observed in those aged 12 and over, in line with the age-dependent vaccination rollout in the Netherlands (all age groups above 90%). Although seroprevalence among children of primary school age rose in November 2021 in comparison to previous rounds, the percentage of individuals with antibodies in this group remains lower than in older age groups, as a result of vaccinations. Note that many infections occurred after the 6th PICO round was conducted, following relatively high circulation of the Delta VOC in the Netherlands, particularly in the last two months of 2021 (approximately 1.1 million confirmed cases were reported in November and December 2021, as per the RIVM/EPI surveillance). Additionally,

following the introduction of the Omicron VOC at the end of the year, correspondingly resulting in very high numbers of cases due to immune escape mechanisms, large increases in infection-induced antibodies are expected in the subsequent rounds in the first half of 2022, across all age groups, yet particularly in unvaccinated children.

9.6.3.1.3 Seroprevalence by region

Geographical distribution of SARS-CoV-2 seroprevalence in the Netherlands is also monitored in the PICO study. Figure 9.6.4 shows SARS-CoV-2 infection-related seroprevalence per GGD region as of the first wave in the Netherlands. These results clearly show that seroprevalence during the first wave was lower in the northern provinces than in the central regions, and much lower than in the south of the Netherlands. Although seroprevalence was still highest in the southern provinces after the 2nd wave (February 2021, PICO round 4) and 3rd wave (June 2021, PICO round 5), the difference compared to the other regions became smaller with each round. However, during the 4th wave (November 2021, PICO round 6), there still was a difference between northern and southern provinces in terms of infection-related seroprevalence. In November 2021, the highest infection-induced seroprevalence was observed in the GGD regions of Amsterdam, Zeeland, Zuid-Limburg, Hart voor Brabant, and West-Brabant, with the largest increases since June 2021 observed in the GGD regions West-Brabant, Zaanstreek/Waterland, and Twente.

The geographical distribution of the weighted total SARS-CoV-2 seroprevalence (infection and/or vaccination) in November 2021 showed varying estimates between GGD regions in the Netherlands, ranging between 81% (GGD Limburg-Noord) and 92% (GGD Zeeland) (Figure 9.6.5).

9.6.3.2 Antibody responses

9.6.3.2.1 Antibody levels after infection

Data from the 2nd-6th PICO rounds showed that although SARS-CoV-2 Spike S1-specific IgM and IgA antibodies declined rapidly after disease onset, IgG antibodies (also targeted against the spike S1 antigen) were still present in 90% of seropositive participants after sixteen months as per internal analyses (see Figure 9.6.6; and to note, analyses up till and including 7 months after infection are described in [5]). Furthermore, it was observed that avidity of these IgG antibodies, an important indicator of antibody-binding strength, increased over time.

9.6.3.2.2 Antibody levels post vaccination

After initial induction of antibodies following vaccination, levels peak swiftly and start to decline thereafter [6]. Figure 9.6.7 shows this decline of SARS-CoV-2 Spike S1-specific IgG antibodies post second vaccination in uninfected individuals. The levels, and therefore the expected duration of immunity, are higher in younger age groups, particularly for Comirnaty®. In addition, initial levels of antibodies differ considerably between the vaccines. High percentages of seropositivity were observed for all vaccines in all age groups (Table 9.6.1).

People with a history of infection, develop higher levels of IgG antibodies to Spike S1 compared to people without a history of infection who receive the same primary vaccine series (Figure 9.6.8). In addition to the higher levels, the decay is slower, resulting in longer persisting immunity in people with a history of infection prior to vaccination. This is observed for all three types of vaccines, with the lowest initial levels but also the slowest decay observed in individuals vaccinated with Vaxzevria®.

9.6.4 Vaccine Study Corona (VASCO)

The Vaccine Study Corona (VASCO) is a population-based cohort study, aimed at assessing the long-term effectiveness of COVID-19 vaccines among ~45,000 community-dwelling persons aged 18-85 years (see also Chapter 9.5). Participants in VASCO are asked to provide finger prick blood samples at baseline, and 6 months and 12 months after entering the study. An additional sample is requested one month after completing the primary vaccination series. Samples are analysed for Ig antibody concentrations against the receptor binding domain (RBD) of the spike protein (S-antibodies), and against the nucleoprotein (N-antibodies). Here we report on 38,000 samples from 26,000 participants, collected between May 2021 and May 2022. Analyses are stratified by age group (18-59 and 60-85 years) and medical risk group (including people with common comorbidities, such as diabetes, cardiovascular disease, cancer).

Figure 9.6.9 shows seropositivity for S- and/or N-antibodies and seropositivity for N-antibodies over calendar time, by age and medical risk group. Seropositivity based on S- and N-antibodies combined increased from around 50% in May 2021 to >90% in August 2021, when all adults were eligible for COVID-19 vaccination. The age group 60-85 years and younger people with a medical risk condition reached higher seropositivity earlier, which is in line with the age and medical risk group prioritisation of the vaccination program. Seropositivity remained high in all groups up to May 2022. Seropositivity based on N-antibodies, indicative for a relatively recent SARS-CoV-2 infection, was 10-20% from May to November 2021, and increased thereafter to 40-60% in April and May 2022, caused by the Omicron VOC wave in early 2022. N-seropositivity was higher in younger age groups; no clear differences were seen between people with and without a medical risk condition.

S-antibody concentrations decreased over time from August to November 2021, consistent with waning immunity after primary vaccination, and showed an increase in January 2022 after the implementation of booster vaccinations in December 2021 and January 2022 (Figure 9.6.10). In May 2022, S-antibody concentrations were very high in all age- and medical risk groups.

S-antibody concentration decreased with time passed since vaccination (Figure 9.6.11). This is visible after primary and booster vaccination; follow-up time was too short to observe this for the second booster vaccination. After booster vaccination, antibody concentrations increased to a higher level than shortly after primary vaccination. After the second booster, antibody concentrations increased to a similar level as shortly after the first booster. Antibody levels are higher and wane less rapidly in people who had a SARS-CoV-2 infection before vaccination.

After the primary series, antibody concentrations were lower in 60-85-year-olds compared with 18-59 year-olds. After booster vaccination, this difference between age groups is less evident. There are no clear differences in antibody concentrations between people with and without comorbidity after primary or booster vaccination.

9.6.5 Aruba SARS-CoV-2 serosurveillance study

The SARS-CoV-2 Aruba serosurvey was set up to gain insight in the distribution of infections in this island population in the first months of 2021. The main research question was how infection prevalence in different (age-)groups related to the incidence as observed through regular testing.

Participants were randomly drawn by Bureau of Statistics on Aruba, and were stratified on age, sex, and district. The response in this 'invited' sample was about 10% instead of the 25% anticipated. Therefore, a month after the start of the initial study, additional volunteers were recruited through an open invitation. The study spanned the period of weeks 2-15, 2021. Antibodies were measured by detection of total antibodies (including IgG, IgA and IgM) against the S1 receptor binding domain of SARS-CoV-2, isolated from bloodserum obtained by venepuncture. In addition, participants answered a questionnaire about health, exposure to SARS-CoV-2, symptomatology, living conditions, socioeconomic status, travel history, observance of COVID-19-rules, fear and stigma regarding COVID-19, and vaccine acceptance.

The weighted percentage of seropositive people was higher in the volunteers than in the invited sample (not statistically significant; 22.5% (95% CI 18.3-26.7) vs. 17.1% (95% CI 12.3-21.8)). Volunteers were sampled at a somewhat later stage (several weeks to a few months), hence this increase could be related to the cumulative increase in cases as the pandemic unfolded, and the swift increase in the incidence of the Alpha VOC at the time (Figure 9.6.12).

Females were more often seropositive than males, although not statistically significant. Females in the invited sample were 18.1% (95% CI 11.9-24.3) seropositive vs. 15.4% (95% CI 8.0-22.8) males in the invited sample; female volunteers were 24.5% (95% CI 19.2-29.8) seropositive and male volunteers 18.6% (95% CI 11.9-25.3). In the same period, females in the general population also tested (PCR-)positive more often than males: 9% vs. 8%. Seroprevalence was highest in the adolescent and young adult age groups (reaching 50% in the voluntary group), followed by people from 35-49 years (approaching 30%), and lowest in children <12 years (slightly above 10%) (Figure 9.6.13). In adult age-classes younger than 65 years, the cumulative percentage testing positive was 10-14%, as opposed to 6% in people 65 years and older. However, the percentage of seropositive people measured in the serosurvey, was comparable across age classes 20-34, 50-64 and 65 and older (all around 20%). This may indicate that the group >65 years is undertested. This idea appears to be confirmed by the high percentage of test positives among those tested in the group of 75 years and older (22%), the highest percentage when compared to other age classes.

Of the seropositive participants, 43-45% had experienced COVID-like symptoms (in the invited group, n=61 were seropositive, whereas in the voluntary group this was n=126). Note that in seronegative participants, these percentages were 26% and 39% respectively, out of a total group of n=201 seronegative people in the invited group, and n=280 in the voluntary group. Of the participants who (PCR-)tested positive, 72-74% had symptoms (volunteers n=46 and invited n=35). The results of the serosurvey, in combination with the percentage of cumulative positive individuals, suggest that about 32% of the SARS-CoV-2 seropositive participants in both samples who report symptoms, would be missed by testing. Of the seropositive participants without symptoms, about 79-83% would not be found through testing (in the invited and volunteer samples, respectively). These numbers only suggest a trend, as the small sample sizes are associated with large 95% confidence intervals, limiting the statistical significance of differences between groups.

Future studies could focus on investigating the highest age categories, as the results suggest a large discrepancy between cumulative test positivity and seropositivity in this group, which is particularly evident as they have the highest disease burden due to COVID-19. Is this oldest age group less inclined to get tested, and if so, how can their propensity to get tested be increased? Is the discrepancy related to vaccine hesitancy in this group? And if so, could this justify a targeted approach to remove the barriers preventing them from accessing healthcare?

9.6.6 Monitoring & evaluation of immune responses induced by COVID-19 vaccination in the Netherlands

9.6.6.1 Introduction

IIVAC, VITAL-corona, VIDO, VIVO, and VOCAAL are longitudinal observational vaccination studies, performed in the general population of the Netherlands, to monitor and evaluate immune responses induced by COVID-19 vaccination and booster vaccination. These vaccination studies are designed to follow up on all age groups invited to receive a vaccine in the national vaccination program (currently from 5 years of age), and to follow up on all the different vaccines that have been used for the primary vaccination series. Amplitude and kinetics of humoral, cellular, and innate immune responses induced by (booster) vaccination are evaluated to support further evidence-based vaccination strategies to maintain optimal immunity against COVID-19 across the population. Also, vaccine responses in these generally healthy subjects will provide a comparison for vaccine responses in risk groups that are being assessed in other trials (overview in Dutch on the ZonMw page). Across the studies, 3,356 participants aged 5-101 years have been included. In the primary vaccination series they were vaccinated with either Comirnaty® (Pfizer), Spikevax® (Moderna), Vaxzevria® (AstraZeneca), or JCOVDEN® (Janssen).

9.6.6.2 Longitudinal antibody analyses in serum across ages

Longitudinal antibody determinations in serum were carried out using the bead-based multiplex immunoassay (MIA), conferring Spike S1-specific antibody (IgG) concentrations. Antibody concentrations are expressed as international BAU/mL units of specific IgG measured before vaccination, at 1 month after the first vaccination, 1 month after completion of (the second) vaccination, and subsequently pre and post booster vaccination(s).

A total of 1,730 Comirnaty® (or BNT162b2, manufactured by Pfizer/BioNTech) vaccinated participants, aged 12-92, were included for the first data analyses [Van den Hoogen L. et al., paper submitted] of the primary vaccination series (Figure 9.6.14, analyses by age groups). A high percentage of participants seroconverted after the first vaccination already: 97% of infection-naïve participants, as did 100% of those who had been infected prior to vaccination. Higher Spike S1-specific IgG was demonstrated in participants with a history of SARS-CoV-2 infection, compared to infection-naïve participants (Figure 9.6.15). Importantly, age is a strong indicator of Spike S1-specific IgG acquisition following vaccination. After the first vaccination, Spike S1-specific IgG concentrations were lower in older participants compared to younger ones (Figure 9.6.14). Across all vaccinated age groups included in the analyses, Comirnaty®-induced S1 IgG peak concentration after vaccination decreased with age, with the highest concentration in the (youngest) age group of 12-19 years old. Gradual decreases were observed per age decade, down to a median concentration of 45 BAU/mL (interquartile range (IQR) 16-113) after first vaccination and a median concentration of 672 BAU/mL (IQR 366-1,304) after second vaccination in the age group of 80-92 years (Figure 9.6.14). The negative association between increasing age and IgG concentration after the first vaccination, was also demonstrated after the second vaccination (Figure 9.6.16). However, the strength of this negative association decreased between the first and the second vaccination, indicating greater antibody acquisition for those with lower levels after the first vaccination (as seen in older people). Women had higher S1-specific IgG concentrations compared to men after the first vaccination, but this difference was smaller after the second vaccination. Notably, in participants with an infection history, both age and sex were not associated with peak S1-specific IgG concentrations after a first and second dose (Figure 9.6.17). In general, the differences induced by infection status, age, and sex, appear to decrease after a second vaccination dose.

Following the primary vaccination series, median S1-specific IgG decreased from 1,304 (IQR 772-2,318) 1 month after the second vaccination to 440 (IQR 239-736) 3 months after the second vaccination in infection-naïve persons aged 50 years and older. Note that all these participants were still seropositive 3 months after completion of the primary vaccination series (Figure 9.6.16). The negative association between age and S1 IgG was weaker at 3 months after the second vaccination, compared to 1 month after, indicating slower antibody decay between dose 2 and month 3 for those with lower levels at dose 2 (as seen in older people; Figure 9.6.16). Taken together, although Spike S1-specific IgG waned over time, antibody levels remained above seropositivity cut off levels three months after completion of the primary vaccination series.

Analyses of antibody responses following the booster and primary vaccination series for four different vaccines are ongoing.

9.6.6.3 Antibody analyses in serum from nursing home residents

A group of 110 nursing home residents has been followed to evaluate Spike S1-specific IgG concentrations from 6 months post primary Comirnaty® vaccination series onwards. Half a year after the primary vaccination series, antibody concentrations in nursing home residents are lower (geometric mean concentration (GMC) 70.5 BAU/mL) than in age-matched home-dwelling elderly people (GMC 170 BAU/mL) (Figure 9.6.18), and 19% of nursing home residents had antibody concentrations under the cut off level for seropositivity (10 BAU/mL). However, after booster vaccination, antibody levels showed a sharp increase in both groups, leading to a GMC of 2,567 BAU/mL in nursing home residents and a GMC of 3,994 BAU/mL in home-dwelling elderly people, one month post booster vaccination. In home-dwelling elderly participants antibody concentrations were five times higher after booster vaccination in comparison to antibody concentration after the first two vaccinations (GMC 802 BAU/mL).

Apart from the evaluation of Comirnaty vaccination, analyses of antibody concentrations after vaccination with Spikevax®, Vaxzevria®, and JCOVDEN®, as well as of the effects of booster vaccination, are ongoing. Preliminary results in older participants have indicated higher antibody concentrations after 2 vaccinations with Spikevax® (GMC: 1,795 BAU/mL in people over 65 years of age at 1 month post vaccination, N=89) and lower antibody concentrations after Vaxzevria® vaccinations (GMC 101 BAU/mL in people over 60 years of age at 1 month post vaccination, N= 129) compared to Comirnaty® vaccination. Correlation analysis of antibody response upon booster vaccinations and heterologous vaccine combinations is ongoing, as is analysis of the relation with memory B cell responses (memory cells that are pivotal for long term antibody response and long-term antibody production).

9.6.6.4 T cell responses after vaccination across ages

T cells play an important role in protection against infectious diseases, including COVID-19. CD4 (helper) T cells provide help to B cells to start producing antibodies, while CD8 (cytotoxic) T cells kill cells that have been infected with SARS-CoV-2. Evaluating these T cell responses after vaccination is therefore a crucial component of monitoring vaccine responses.

Using the Interferon-gamma (IFNγ) ELISpot assay, T cell responses were determined in peripheral blood of SARS-CoV-2-vaccinated adult participants. T cell responses were measured before vaccination and 1 month after completion of the primary vaccination series and/or booster vaccination.

In the vast majority of the participants, a robust anti-Spike T cell response is induced by the primary vaccination series, regardless of the vaccine that was received. To investigate the impact of age on the ability to elicit T cell responses against the Spike protein of the virus, vaccination responses were evaluated across all adult age groups (range 18-99 years). In the older age groups (i.e., 70 years and older), lower median levels of T cell responses with more variation were notable. Nevertheless, in all age groups T cell responses increased upon booster vaccination (Figure 9.6.19).

9.6.6.5 T cell responses after vaccination across variants

It has been speculated that SARS-CoV-2-specific T cell responses are less susceptible than antibodies to immune escape mechanisms of VOCs. Indeed, when investigating T cell responses following vaccination with Comirnaty® or Spikevax® against the Spike protein of different VOCs, the observed levels are vastly similar (Figure 9.6.20A). This suggests that in general there is a high level of cross-reactivity of the T cell response with VOCs, including Delta and Omicron, following vaccination with mRNA vaccines. Additionally, similar levels of T cell responses between the Wuhan and Omicron (B1.529) variants after primary and booster vaccination were observed within age groups. Overall however, lower T cell responses were seen in older (70+) age groups, irrespective of VOCs (Figure 9.6.20B).

Evaluation of kinetics of T cell responses upon SARS-CoV-2 infection before and after (booster) vaccination is ongoing.

9.6.6.6 Comparison of vaccine responses in immunocompromised people

In addition to the RIVM studies investigating the quantity and the quality of the COVID-19 vaccine-induced immune response in the general Dutch population, ZonMw funded trials are being conducted in (academic) hospitals to investigate the response in different groups that are susceptible to severe COVID-19. These include patients who are immunocompromised due to disease [7], due to the use of specific medication, or due to an inherited immune deficiency, as well as people with Down Syndrome. RIVM (IIV department) has coordinated harmonisation of the study design of these studies, as well as the assays used for analyses of humoral and cellular immune responses, allowing comparisons between different vulnerable groups (cancer patients [8, 9], haematology patients [10] and people with Down Syndrome) and with healthy controls. Together with ZonMw, RIVM is working on an infrastructure for data sharing and cross-project data analyses for all COVID-19 vaccine response studies.

The data have been used to advise the minister to offer a third primary series vaccination to specific immunocompromised groups. Based on the observation that the majority of immunocompromised individuals were able to mount an immune response that was comparable to healthy controls, only a small subset that did not respond or had a low response were offered an additional 3rd baseline vaccination. The subset includes, but is not limited to, organ, bone marrow, and stem cell-transplant patients, patients with solid tumours within three months after chemo- and/or immune therapy with checkpoint inhibitors, and patients treated with specific immunosuppressive agents.

9.6.7 Literature

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* RIVM publication.

9.7 Pathogen surveillance

M.J. Knol, S.P. Andeweg, C.H. van Werkhoven, D. Eggink

9.7.1 Key points

- Based on whole genome sequencing of random SARS-CoV-2 samples, the following SARS-CoV-2 variants of concern have been dominant in the Netherlands: Alpha in Feb-June 2021, Delta in July-Dec 2021, Omicron BA.1 in Jan-Feb 2022, Omicron BA.2 in Mar-May 2022, Omicron BA.5 from June 2022.
- Using whole genome sequencing of positive SARS-CoV-2 samples (case-only approach), we showed that the Beta, Gamma and Delta variants escaped immunity from vaccination, but not infection, compared to the Alpha variant.
- Using variant PCR data, we showed that the Omicron BA.1 and BA.2 variant escaped immunity from vaccination and previous infection to a large extent, when compared to the Delta variant.
- Using variant PCR data, the Omicron BA.4/BA.5 variant showed some escaped immunity from previous infection compared to the Omicron BA.2 variant. The increased risk of Omicron BA.4/BA.5 compared to BA.2 was most pronounced when the previous infection was with Omicron BA.1.

9.7.2 Figures

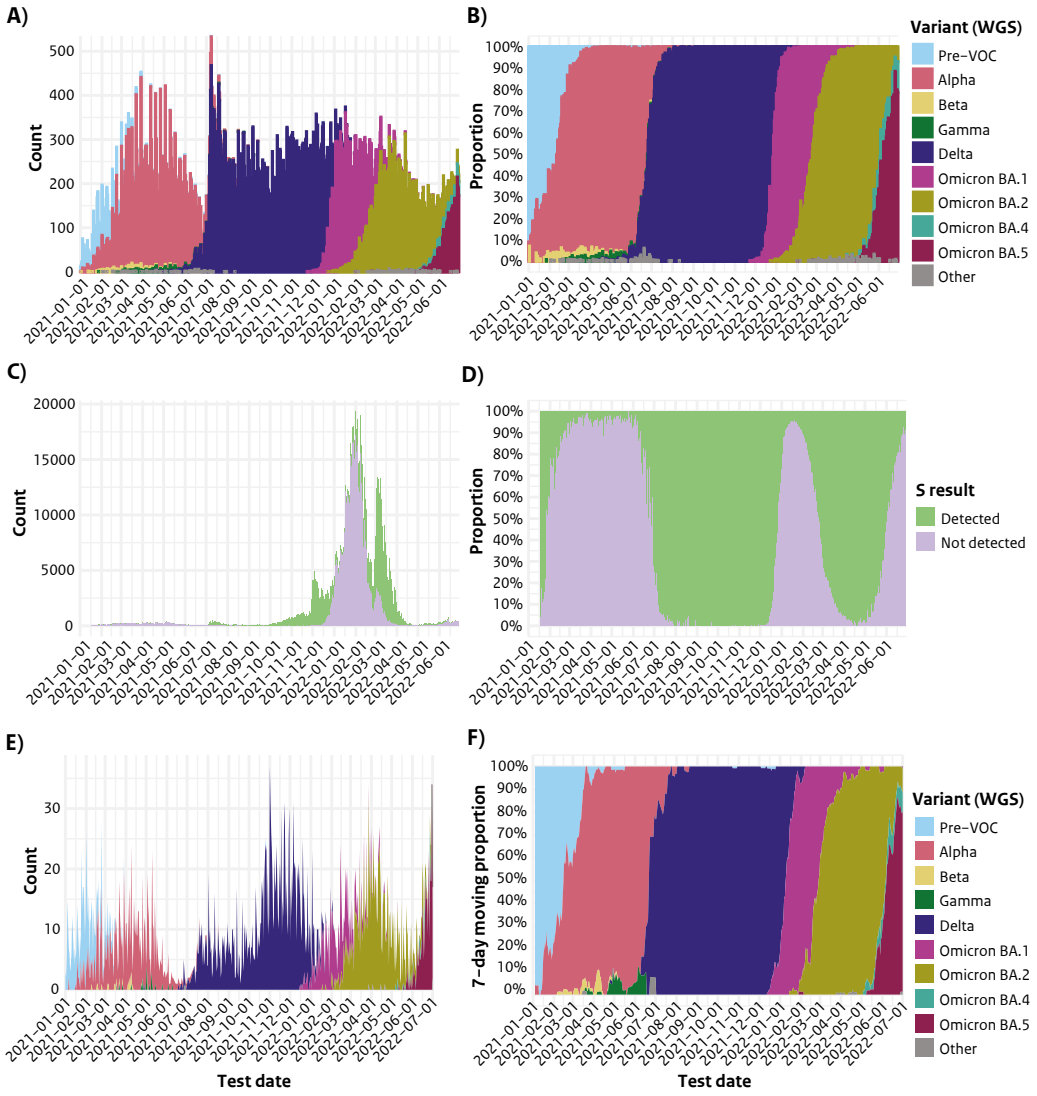

Figure 9.7.1 Time trends for SARS-CoV-2 variants in the Netherlands between 1 January 2021 and 1 July 2022. A, B: Number and proportion of SARS-CoV-2 variants among infections in the community, based on whole genome sequencing (WGS) of positive samples from Municipal Health Centres with and without S-gene target detection by PCR. E, F: Number and proportion of SARS-CoV-2 variants among hospitalisations, based on whole genome sequencing (WGS) of positive samples from hospitals in individuals over 70 years old.

9.7.3 Random pathogen sequencing

Since the world-wide spread of SARS-CoV-2, the virus has been evolving through introduction of mutations in its genome. Several Variants-of-Concern (VOCs) have been defined by the WHO: Alpha (B.1.1.7, first detected in September 2020 in the United Kingdom), Beta (B.1.351, first detected in September 2020 in South Africa), Gamma (P.1, first detected in December 2020 in Brazil), Delta (B.1.5617.2, first detected in December 2020 in India) and Omicron (B.1.1.529, first detected in November 2021 in South Africa).
RIVM sequences randomly selected SARS-CoV-2-positive specimens from both Municipal Health Centres (GGDs) and hospitals, ensuring proper geographical distribution across all provinces (see *Variants of the coronavirus SARS-CoV-2 | RIVM*).

9.7.3.1 Infections

As of January 2021, the Alpha variant started to expand rapidly and quickly became the dominant strain in the Netherlands (Figure 9.7.1 A and B). From March up to May 2021, the Alpha variant caused over 90% of all infections, with only a very small percentage of infections caused by ancestral variants or by the Beta or Gamma variant. From June 2021, the Delta variant started to expand rapidly and caused nearly 100% of all infections from August 2021 to November 2021. From late November 2021, the Omicron variant started to increase, causing nearly all infections from January 2022 onwards. The BA.1 variant of Omicron was dominant until February 2022, then BA.2 was dominant until May 2022. From June 2022, the BA.5 variant has been dominant, while the BA.4 and BA.2.12.1 variant also circulated. Although the prevalence of these latter two variants initially increased similarly to BA.5, BA.5 became dominant.

9.7.3.2 Hospital admissions

A random selection of positive SARS-CoV-2 samples from hospitals is also sequenced. These can be both from hospital personnel and from hospitalised patients. Therefore, to assess variant circulation in hospitalised patients, only samples from persons of 70 years or over are used. Circulating variants among elderly people who were hospitalised with COVID-19 show trends that are similar to variant circulation among infections in the general population (Figure 9.7.1 E and F). However, because some time passes between infection and hospital admission, prevalence of variants in hospitalised patients show some delay compared to prevalence of variants in samples analysed from community testing. Furthermore, because the Omicron variant caused less severe disease than the Delta variant, the Omicron increase shows a further delay for hospital admissions as compared to the variant distribution for infections. Also, age differences (all ages for infection, 70+ years for hospital admissions) can lead to some differences in variant circulation over time.

9.7.4 Variant PCR

Variant PCR is a method that makes use of characteristics of a certain variant. This technique can detect either the presence of specific mutations or the presence of a deletion in the genome that is indicative for a specific variant. Variant PCR is faster and less costly than whole genome sequencing. Although it does not provide detailed genomic data, it can be used as a proxy for the prevalence of specific variants in addition to the regular genomic surveillance. Two high-volume laboratories incorporate this PCR method in community testing for SARS-CoV-2, obtaining results for large numbers of samples.

9.7.4.1 *S-gene target failure*

Omicron BA.1 and BA.5 possess a deletion at amino acid positions 69 and 70 of the spike protein that has been associated with failure of the probe targeting the S-gene, while the Orf1ab and N probe result in proper signal (S-gene target failure (SGTF), also referred to as S-drop-out or S-gene not detected). In contrast, the Delta variant and Omicron BA.2 do not contain this particular deletion. Therefore, failure to detect the S-gene target in an otherwise positive PCR test can be used as a proxy for certain variants, depending on the circulation of other variants at the same period of time.

SGTF has consecutively been used to discern the Delta (S-gene detected), Omicron BA.1 (S-gene not detected), Omicron BA.2 (S-gene detected), and Omicron BA.4/BA.5 (S-gene not detected) (Figure 9.7.1 C and D). As certain variants lead to the same SGTF result, the predictive value of SGTF is dependent on the variant combination circulating at a certain time, as measured by whole genome sequencing of the regular genomic surveillance and conformational sub-sampling of specimens included in SGTF analyses.

9.7.5 Immune escape

9.7.5.1 *Beta, Gamma and Delta variant*

A case-only approach was employed, in which the immune status among cases infected with the Beta, Gamma, or Delta variants was compared to the immune status among cases infected with the Alpha variant [1]. Thereby, the relative effectiveness of vaccination against Beta, Gamma or Delta compared to Alpha variant was assessed. Also, the relative protective effect of previous SARS-CoV-2 infection against a new infection with Beta, Gamma or Delta vs Alpha variants was assessed. For absolute protective effects of vaccination and previous infection, see Chapter 9.5. A total of 28,578 sequenced SARS-CoV-2 samples from individuals with known immune status (vaccination and/or previous infection), obtained through national community testing in the Netherlands from March to August 2021, was analysed. There was an increased risk of infection by the Beta (B.1.351), Gamma (P.1), or Delta (B.1.617.2) variants compared to the Alpha (B.1.1.7) variant after vaccination (adjusted odds ratio (aOR): 3.1 (95% CI: 1.3-7.3), 2.1 (95% CI: 1.1-4.2), 1.8 (95% CI: 1.4-2.4) respectively). The effect was larger in the first 14-59 days after complete vaccination than after >60 days (aOR: 2.3 (95%CI 1.6-3.4) vs 1.4 (95%CI 0.9-2.0)). In contrast to vaccine-induced immunity, there was no increased risk for reinfection with Beta, Gamma or Delta variants relative to Alpha variant in individuals with infection-induced immunity (aOR: 1.4 (95% CI 0.5-3.8), 0.3 (95%CI 0.0-1.8), 0.9 (95%CI 0.6-1.5) respectively). These results indicate that effectiveness of COVID-19 vaccination was lower against Beta, Gamma or Delta infection than against Alpha infection.

9.7.5.2 *Omicron variant*

A similar case-only approach was used to rapidly assess possible immune escape for infection by the Omicron SARS-CoV-2 variant [2]. SGTF was used as proxy for the Omicron variant (BA.1 subvariant at that time). Data from 174,349 infected individuals tested between 22 November 2021 and 19 January 2022 was used. An increased risk of infection with the Omicron variant compared to the Delta variant was found in vaccinated (odds ratio: 3.6; 95% confidence interval: 3.4-3.7) and previously infected individuals (OR: 4.2; 95% CI: 3.8-4.7) compared to

infected naïve individuals. This suggests a substantial decrease in protection from vaccine- or infection-induced immunity against SARS-CoV-2 infections caused by the Omicron BA.1 variant compared to protection against infection with the Delta variant.

Protection from vaccination and previous infection against Omicron BA.1 and BA.2 infection using SGTF data is described in Chapter 9.5.4.1 [3]. In short, similar protection was found against Omicron BA.1 and BA.2 infection after vaccination or previous infection.

A case-only approach was used to assess possible immune escape for infection by Omicron BA.4 and BA.5 [4]. SGTF data from 2 May to 24 July 2022 show that there is an increased risk of BA.4/BA.5 infection compared to BA.2 infection in persons with a previous infection (OR: 1.4 (1.3-1.5)). No difference was observed in the distribution of vaccination status between BA.2 and BA.4/5 cases (OR: 1.1 for primary and booster vaccination). Among persons with reinfections, those newly infected with BA.4/5 had more often had a previous infection caused by BA.1, compared to those newly infected with BA.2 (aOR: 1.9 (95% CI: 1.5-2.6)). This suggests that immunity induced by BA.1 infection is less effective against BA.4/5 infection than against BA.2 infection.

9.7.6 Literature

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* RIVM publication.

9.8 Safety of COVID-19 vaccines

C. van den Ende, C. Hoeve, B. de Gier

9.8.1 Key points

- National and international health authorities continually monitor adverse events following immunisation (AEFI) in people who have received a vaccine.

9.8.2 Tables and figures

Table 9.8.1 Number of reports associated with COVID-19 vaccination up to May 29th, 2022*.

	Number of reports after number of doses					
Vaccine	1st dose	2nd dose	3rd dose	4th dose	5th dose	Total
AstraZeneca	34,712	3,618	27	-		38,357
Pfizer/BioNTech	55,795	47,906	20,762	150	4	124,617
Moderna vaccine	13,495	16,445	17,777	971	8	48,696
Janssen vaccine	15,158	14	1	1	-	15,174
Novavax	11	11	-	1		23
Vaccine unknown	278	78	127	6	-	489

*For the most recent information, see the Lareb page on *side effects after corona vaccination*.

Table 9.8.2 Most frequently reported local reactions and systemic events up to May 29th, 2022*.

Adverse event	Number of reports	Adverse event	Number of reports
Fatigue	107,373	Pain at injection site	69,854
Headache	106,713	Fever	57,271
Malaise	105,949	Nausea	55,935
Myalgia	98,398	Joint pain	55,385
Chills	79,923	Swelling at injection site	29,438

*For the most recent information, see the Lareb page on *side effects after corona vaccination*.

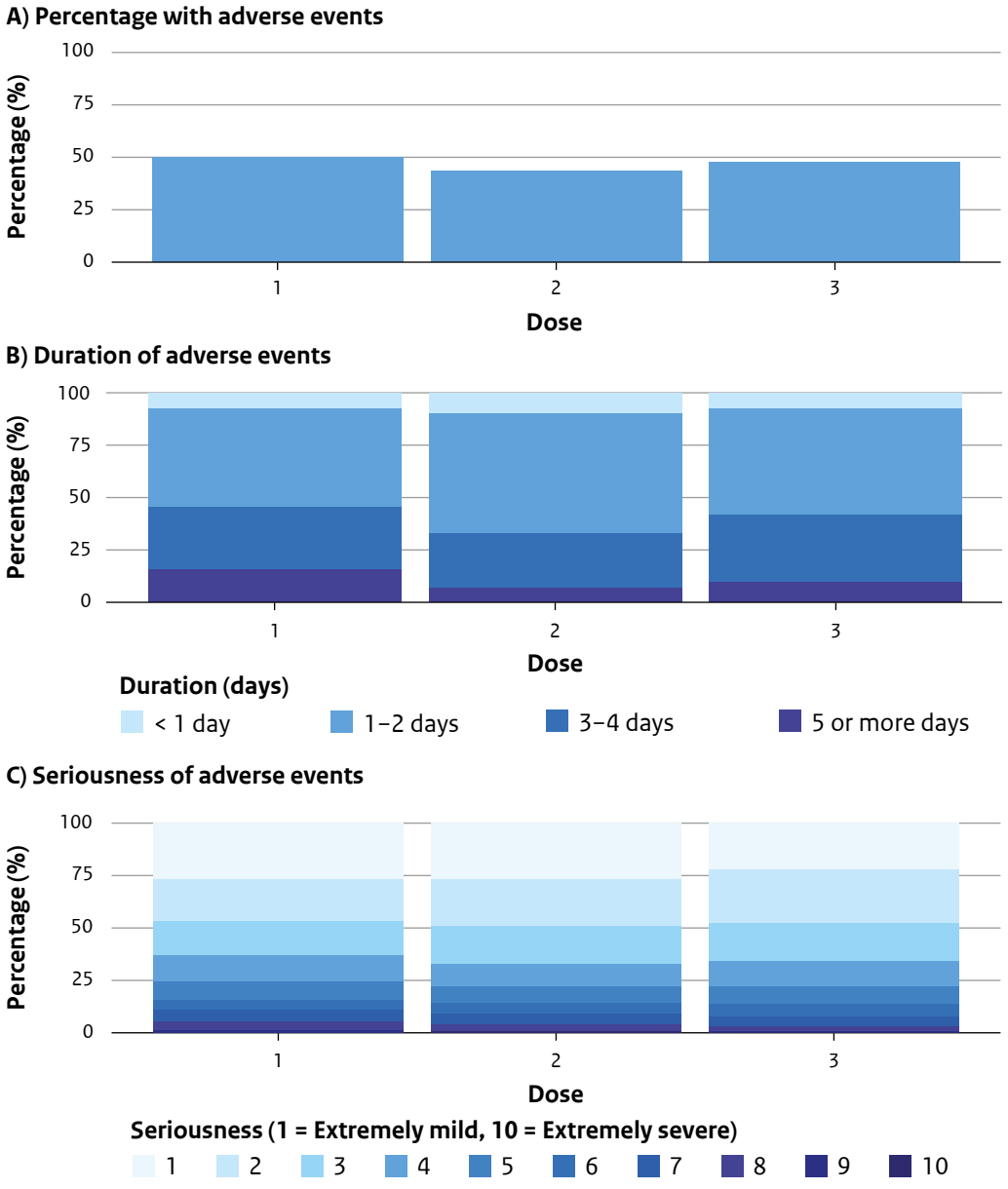

Figure 9.8.1 A) The percentage of participants in the VASCO study who reported injection-site reaction after the first, second and third dose. B) The duration of reported injection-site reactions in days after the first, second and third dose. C) The seriousness of the reported injection-site reactions on a scale of 1 (extremely mild) to 10 (extremely severe) after the first, second and third dose.

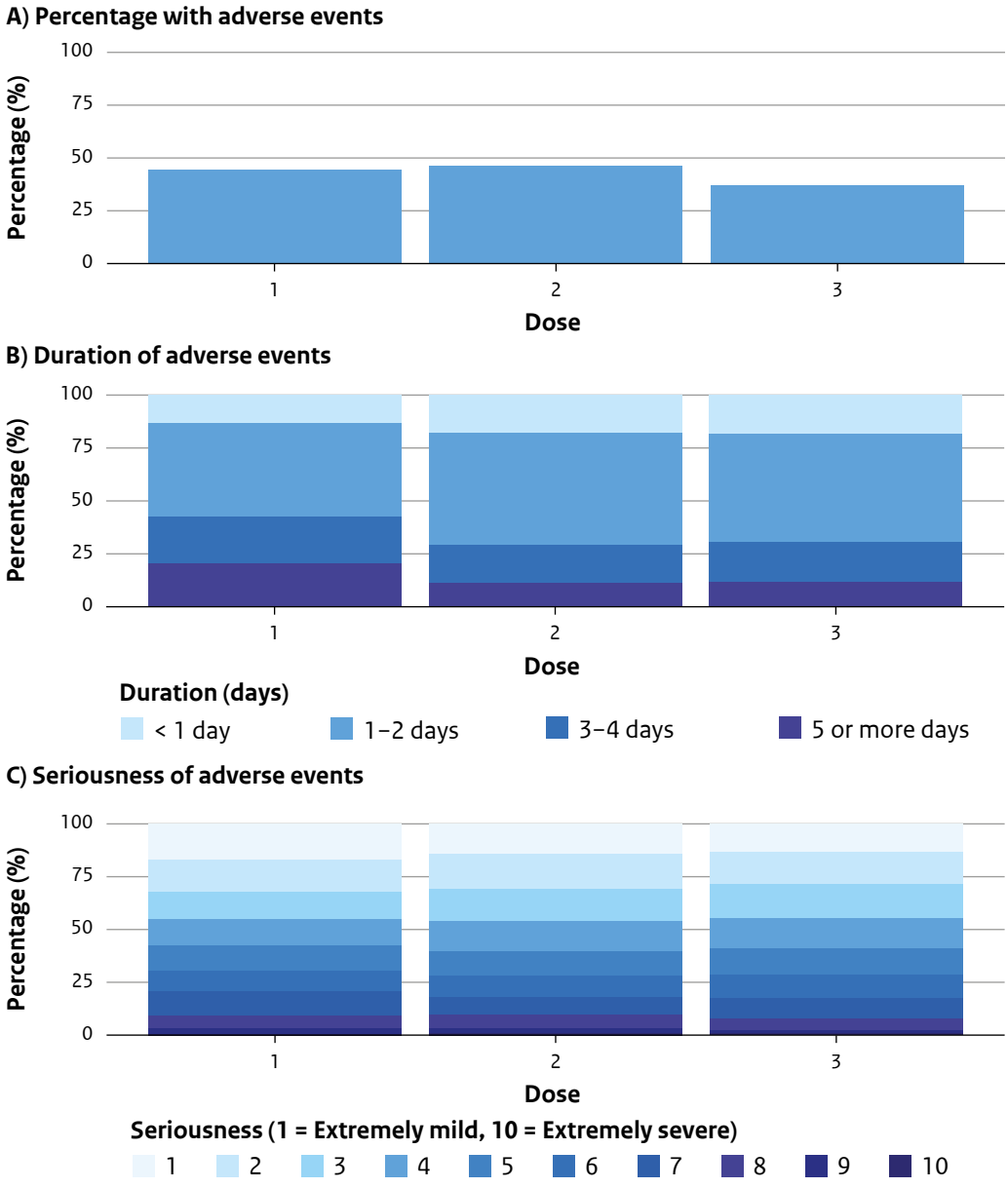

Figure 9.8.2 Reported adverse events other than injection-site reactions in the VASCO study. A) The percentage of participants who reported adverse events after the first, second and third dose. B) The duration of reported adverse events in days after the first, second and third dose. C) The seriousness of the reported adverse events on a scale of 1 (extremely mild) to 10 (extremely severe) after the first, second and third dose.

9.8.3 Number of reports in the Netherlands

The spontaneous reporting system managed by the National Centre for Pharmacovigilance Lareb receives adverse events following immunisation (AEFI) reports for all COVID-19 vaccines. Up to May 29th, 2022, Lareb received 227,356 reports (see Table 9.9.1). The reports relate to about 36.3 million vaccinations, approximately 24.6 million doses from Pfizer/BioNTech (Comirnaty®), 8 million from Moderna (Spikevax®), 2.8 million from AstraZeneca (Vaxzevria®), 850,000 from Janssen (Jcovden®) and 1,500 from Novavax (Nuvaxovid®). These figures are based on the Corona dashboard of the central government (see *this link*).

9.8.4 Reactogenicity

9.8.4.1 Overview from Lareb

All reports received by Lareb contain a total of 1,096, 548 AEFIs. Table 9.9.2 shows the most frequently reported local reactions and systemic events.

In general, the most common AEFIs are reported equally often following the first, second and booster dose. Compared to the first and second dose, lymphadenopathy (lymph nodes that are abnormal in size or consistency) is reported relatively more often than other side effects after booster vaccination [1]. This also applies to reactions at the injection site.

9.8.4.2 VASCO study

Participants in the VASCO study are requested to complete a questionnaire one month after vaccination. In this questionnaire, questions are included about potential adverse events after vaccination. Participants were asked how serious the reactions were and how long they lasted. In the period between 10 May 2021 and 11 April 2022, a total of 36,313 participants completed the questionnaire.

In 47% (43%-50% per dose) of the questionnaires, participants reported injection-site reactions after COVID-19 vaccination (Figure 9.9.1). Injection-site reactions were most commonly reported after vaccination with Pfizer/BioNTech (47%) and Moderna (48%) vaccines. The frequency of injection-site reactions did not differ between the first, second or third dose. Participants under the age of 60 years reported injection-site reactions more frequently (45%-56% per dose) than participants over 60 years (36%-43% per dose). Women reported injection-site reactions more frequently than men (55% vs. 33%). For more than half the participants, injection-site reactions lasted a maximum of two days. Half the participants rated the events between 1 and 3 in seriousness (with 1 being extremely mild and 10 extremely severe).

A total of 38% of the participants reported other adverse events such as fever, headache or myalgia following vaccination (Figure 9.9.2). Adverse events were most frequently reported following administration of the Janssen vaccine (49%). Participants under 60 years reported more adverse events than participants over 60 years. Among participants under the age of 60 years, the proportion of adverse events declined with the number of doses. This trend was not seen among participants over 60 years. Women reported more adverse events than men (43% vs. 29%).

For more than half the participants, adverse events lasted a maximum of two days after the first dose. For the subsequent doses the adverse events lasted a maximum of two days for approximately two-thirds of the participants. Half of the participants rated the seriousness of the adverse events between 1 and 4, and a quarter rated the seriousness with at least a 6 (with 1 being extremely mild and 10 extremely severe). The differences in the duration or seriousness of the reported adverse events were limited between the different vaccines or age groups.

9.8.4.3 International literature

Findings from pre- and post-authorisation monitoring of mRNA-vaccines (Pfizer/BioNTech and Moderna) showed that common reactions following vaccination include injection-site pain, fatigue, headache, myalgia, chills, fever, joint pain, injection-site swelling, and nausea [2-4]. Overall, these reactions were mild and resolved within a few days [5]. The local and systemic reactions following receipt of an mRNA-booster dose were similar to those observed after the primary vaccination series and occurred at a similar or lower frequency [6, 7]. Among adolescents aged 12-17 years, local and systemic reactions were commonly reported after primary Pfizer/BioNTech vaccination but, as in adults, these were usually mild and transient [8, 9]. Similar findings were reported for adolescents after booster vaccination [10]. Reported reactogenicity events after two 50-µg doses of the Moderna vaccine in children 5-11 years were consistent with those in adolescents and adults, mostly injection-site pain, fatigue and headache and generally mild [11].

Results from phase 2/3 trials showed that the AstraZeneca vaccine is well tolerated with a lower reactogenicity profile in older adults than in younger adults [12]. The most commonly reported solicited systemic reactions were similar to those seen after vaccination with mRNA vaccines, including fatigue, headache, feverishness, and myalgia. In a community setting, systemic and local reactions were reported at lower frequencies than in phase 3 trials [13].

Reactogenicity of a single dose of Janssen vaccine in phase 3 trials was similar to the other vaccines [14]. Post-authorisation safety data was in line with the findings from the trials, with headache, pain and fatigue as commonly reported symptoms [15].

Finally, in a phase 3 trial conducted in the United Kingdom, the most commonly reported local adverse events after both the first and second dose of Novavax vaccine were injection-site tenderness or pain [16]. The most commonly reported systemic adverse events were headache (25-40%), muscle pain (21-40%), and fatigue (19-40%), both after the first and second dose. Reactogenicity was generally mild or moderate.

9.8.5 Serious adverse events

Since the introduction of COVID-19 vaccines, certain rare or very rare side effects have emerged. The most severe and/or notable events are described below. The numbers of Lareb as reported below, were obtained at the time of writing of this report. For the most recent numbers, see *this link*.

9.8.5.1 *Anaphylaxis*

9.8.5.1.1 Overview from Lareb

It is possible for a severe allergic reaction (anaphylaxis) to occur immediately after vaccination, although this is quite rare. Until December 19th,2021, Lareb received 348 reports that were consistent with severe allergic reactions, 88 of which were consistent with anaphylaxis. This concerns 13 reports per million vaccinations given, of which 3 in a million are anaphylactic reactions. Severe allergic reactions usually occur within 15 to 30 minutes after the injection. The majority of the reactions occurred after the first dose. Up to December 19th, 2021, one report was received after the third dose, on the background of 1.5 million third vaccinations.

9.8.5.1.2 International literature

The literature on safety monitoring of mRNA COVID-19 vaccines confirms that anaphylaxis following vaccination is a rare event [17, 18]. A report published in March 2022 of surveillance data collected through the Vaccine Adverse Event Reporting System (VAERS, a passive system) and v-safe (a new active system) in the United States showed that the rate of anaphylaxis for both the mRNA vaccines is approximately 5.5 per million doses [5]. In the context of vaccination with AstraZeneca or Janssen vaccine, rare cases of anaphylaxis have also been reported [19, 20].

9.8.5.2 *Myocarditis and pericarditis*

9.8.5.2.1 Overview from Lareb

Myocarditis and pericarditis have been recognised as rare adverse events of the mRNA vaccines of Pfizer/BioNTech and Moderna [22]. There is currently not enough data to determine whether there is a connection with the other COVID-19 vaccines. Until January 24th, 2022, Lareb had received 373 reports of myocarditis (n=99) or pericarditis (n=274). The reports relate to approximately 30 million corona vaccinations (with all available vaccines, including booster vaccination). In the Netherlands, the average reporting rate for pericarditis is 9.2 per million vaccinations, and for myocarditis 3.3 per million vaccinations.

Lareb signalled that the number of reports of myocarditis and pericarditis is higher than expected in some subgroups (with all available vaccines). Lareb found in their reports that for myocarditis, this applies, for example, to: men under 40 years of age on virtually all vaccines and women over 40 years of age after Moderna, the second Pfizer/BioNTech or first AstraZeneca vaccination. The number of reports for pericarditis is higher than expected for, amongst others: men younger than 40 years after Pfizer/BioNTech, Moderna or Janssen vaccination; women younger than 40 years after Pfizer/BioNTech, first Moderna or Janssen vaccination and women older than 40 years after Pfizer/BioNTech and Moderna vaccine.

9.8.5.2.2 *International literature*

Several studies have been published on myocarditis and pericarditis following mRNA COVID-19 vaccination. A systematic review of the literature and a pooled analysis showed that myocarditis and pericarditis mostly affect young males after the second dose, usually within the first five days following vaccination and that the course is often mild [23]. Myocarditis after the first dose of an mRNA vaccine was associated with prior COVID-19.

The literature on myocarditis and pericarditis in the context of the other COVID-19 vaccines is limited. A self-controlled case series in England found an increased risk of myocarditis in the first week after the first dose of AstraZeneca vaccine, but also after a positive SARS-CoV-2 test: an extra 2 (95% CI 0-3) events of myocarditis per 1 million vaccinated persons, compared to an extra 40 (95% CI 38-41) events per 1 million patients in the 28 days following a positive test [24]. The study also found an increased risk of pericarditis following a positive SARS-CoV-2 test, but no association with vaccination. A study that used the VAERS database did not find an association between Janssen vaccine and signals for myocarditis and pericarditis [25]. During a phase 3 trial with the Novavax vaccine, 1 event of myocarditis was reported among 7,020 vaccine participants, 3 days after the second dose [16]. The event was considered to most likely be viral myocarditis.

9.8.5.3 VITT/TTS

9.8.5.3.1 *Overview from Lareb*

Vaccine-induced (immune) thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome (TTS), referring to thrombosis in combination with low platelet counts, was identified as a serious but rare adverse event following immunisation with the viral vector vaccines from AstraZeneca and Janssen [26]. Until January 26th, 2022, Lareb received a total of 75 spontaneous reports of a combination of thrombosis and thrombocytopenia, that relate to approximately 30 million vaccinations. Among these, 26 were confirmed or strongly suspected cases of VITT/TTS following COVID-19 vaccines. The reporting rate of VITT/TTS with the AstraZeneca vaccine is 7.7 per million vaccinations. VITT/TTS has not been associated with mRNA vaccines, but Lareb received a few reports of VITT/TTS following receipt of Pfizer or Moderna vaccine. On the basis of the analysis of these reports no conclusion could be drawn about a causal association.

9.8.5.3.2 *International literature*

The reported incidence of VITT/TTS varies in the literature, partly due to differences between vaccination programmes and the way data was collected and reported [27]. Furthermore, several terms and case definitions have been used to describe this condition [28].
Until 30 September 2021, 1,809 TTS cases have been identified in AstraZeneca post-marketing studies [29]. The overall TTS reporting rate following the second dose was 1.87 cases/million doses, which is lower than the estimated reporting rate after the first dose (14.45/million doses) and also lower than preliminary estimates of the background rate (5.62-10.75/million person-years).

In the United States, approximately 14.1 million doses of the Janssen vaccine were administered through August 31st, 2021, and 54 cases of TTS were identified [30]. This resulted in an overall TTS reporting rate of 3.83 cases per million doses administered.

9.8.5.4 Systemic Capillary Leak Syndrome

9.8.5.4.1 Overview from Lareb

Systemic Capillary Leak Syndrome (SCLS), a rare condition where fluid leaks from the small blood vessels into the body, has been identified as a side effect and contraindication for the vaccines of Janssen and AstraZeneca. The safety committee of the European Medicines Agency (EMA) has recommended that a warning for flare-ups of SCLS should be added to the product information of the mRNA vaccine from Moderna [31]. The committee concluded that there was insufficient evidence to establish a causal association between the mRNA vaccines (Moderna and Pfizer) and the onset of new cases of SCLS. No cases of SCLS after these vaccines have been reported in the Netherlands.

9.8.5.4.2 International literature

Both SARS-CoV-2 infection and COVID-19 vaccination appear to be possible triggering events of SCLS. In a review of the literature available up to October 2021 on cases of SCLS related to SARS-CoV-2 infection or COVID-19 vaccination, a total of seven patients with SCLS after SARS-CoV-2 infection and five patients with SCLS after SARS-CoV-2 vaccination have been described: two with Janssen, one with AstraZeneca, and two with mRNA vaccines (one Moderna and one Pfizer) [32]. Among these patients, six had had episodes of SCLS previously.

9.8.5.5 Menstrual disorders

9.8.5.5.1 Overview from Lareb

In December 2021, Lareb published a signal covering menstrual disorder reports related to COVID-19 vaccination [33]. An update of this signal shows that until March 29th, 2022, Lareb received a total of 24,090 menstrual disorder reports associated with COVID-19 vaccines. Most were reported following vaccination with Pfizer/BioNTech (19,076), followed by Moderna (2,731) and Janssen vaccine (1,646). With an overall 523 reports per 100,000 vaccinations, the Janssen vaccine had the highest reporting rates compared to the other vaccines. Amenorrhoea/oligomenorrhoea was the most reported menstrual disorder (33.3%) followed by heavy menstrual blood loss (29.4%) and irregular blood loss (22.7%), with no major differences between the vaccines.

9.8.5.5.2 International literature

Currently the international evidence on the relationship between COVID-19 vaccination and menstrual disorders is scarce. Edelman *et al.* assessed whether COVID-19 vaccination is associated with cycle length in a vaccinated (n=2,403) and unvaccinated cohort (n=1,556) [34]. After adjusting for confounders, they found that normally cycling individuals experienced small variations in cycle length regardless of vaccination status. The difference in cycle length between vaccinated and unvaccinated individuals was, though statistically significant, less

than one day and therefore not clinically relevant. A larger change in cycle length compared with unvaccinated individuals was seen in a subset of individuals who received both vaccine doses in a single cycle, but after two postvaccine cycles, this difference was no longer apparent.

A preprint by Alvergne *et al.* described the results of a retrospective online survey in the UK [35]. Among 4,989 pre-menopausal women, 80% did not report any changes in their menstrual cycle up to 4 months after their first COVID-19 vaccination. Smoking and a previous history of SARS-CoV-2 infection were found to be risk factors for menstrual cycle changes, whereas using oestradiol-containing contraceptives was found to be a protective factor.

Another preprint from Norway reported on a study that used mobile-phone questionnaires to collect reports of menstrual disturbances from 5,688 women aged 18-30 years, participating in the population-based Norwegian Young Adult Cohort [36]. Prior to vaccination the prevalence of any menstrual disturbance was 37.8%. COVID-19 vaccination was found to be associated with heavier bleeding after vaccination (first dose: relative risk 1.90 [95% CI: 1.69-2.13], second dose: relative risk 1.84 [95% CI: 1.66-2.03]).

The safety committee of EMA continues with the assessment of cases of heavy menstrual bleeding with the mRNA vaccines [37]. On the basis of a review of all available data and literature, they concluded there was insufficient evidence to establish a causal association between the vaccines of Pfizer and Moderna and the absence of menstruation.

9.8.5.6 Death

9.8.5.6.1 Overview from Lareb

Until February 18th, 2022, Lareb received a total of 662 reports of death, that relate to approximately 33.5 million corona vaccinations. There were 471 reports after the Pfizer/BioNTech vaccine (which is the most commonly used COVID-19 vaccine). After AstraZeneca vaccination there were 77 reports, after Moderna 71, and after Janssen 20. In 23 reports the vaccine was unknown.

Three patients almost certainly died because of the rare adverse event TTS after AstraZeneca vaccination. In two other deaths this was not clear but considered possible. Three people died of heart problems after myocarditis or pericarditis following vaccination with the Pfizer/BioNTech vaccine. Infections or other heart conditions may also have played a role in these reports. One patient died after complex disease, which probably also involved capillary leak syndrome. This patient was vaccinated with the Janssen vaccine.
Analysis of cause of death after vaccination is difficult. COVID-19 vaccination coverage was high among the elderly population, a group with, on average, already higher mortality rates.

9.8.5.6.2 Study RIVM and CBS

The Dutch Parliament commissioned a study into causes of death in 2021 in relation to COVID-19 vaccination. CBS (Statistics Netherlands) and RIVM performed this study. One of the study objectives was to explore whether an increased risk in non-COVID-19 mortality exists in the weeks following a COVID-19 vaccine dose. National registries of causes of death, COVID-19 vaccination and long-term care reimbursements were linked by a unique identifier using data from January 1st, 2021 to January 31st, 2022. We used Cox regression with calendar time as the underlying time scale to estimate risk of non-COVID-19 mortality in the eight weeks following a first, second or booster dose, adjusting for birth year, sex and country of origin. The results showed a lower to comparable risk of non-COVID-19 mortality, compared to the vaccination status before the respective vaccine dose. This was true for all ages, including long-term care recipients. No indication was found for an increased risk of death from other causes in the five to eight weeks following immunisation [38].

9.8.5.6.3 International literature

International numbers show that reports of death after COVID-19 vaccination are rare [39]. More than 589 million doses of COVID-19 vaccines were administered in the United States from December 14th, 2020 through June 6th, 2022. During this period, VAERS received 14,980 preliminary reports of death (0.0025%) among people who received a COVID-19 vaccine. Continued monitoring has identified nine deaths associated with the Janssen vaccine.

9.8.6 Literature

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* RIVM publication.

10
Vaccines in development for other potential future NIP target diseases

N.Y. Rots

10.1 Chapter overview

An update of information on vaccines in development for infectious diseases that have reached the clinical testing phase and are relevant for the Netherlands, is given in the table below. In general, vaccine development takes 10 to 20 years, with only a small percentage (6%) of vaccines tested in phase I reaching marketing authorisation. On average, clinical development phase I takes one to two years, phase II two to three years, and phase III four to six years. However, with the SARS-CoV-2 vaccines we have seen that during a pandemic it is possible to develop a vaccine, from research to market authorisation within one year. The mRNA vaccine platform that has been successfully used for the development of SARS-CoV-2 vaccines is also being used for the development of other vaccines, such as for influenza, RSV, CMV and rabies.

The WHO provides an overview of the SARS-CoV-2 vaccines in development on their websites that is being updated twice a week (see the *WHO COVID-19 vaccine landscape*), summarised in a separate table in Chapter 10.4. The number of SARS-CoV-2 vaccines in development has increased to 368, and 170 of these have reached the clinical phase (as of June 14th, 2022). Most of them are RNA (22%) or protein subunit (33%) vaccines, followed by viral vector and inactivated vaccines (both 13%). The European Medicines Agency (EMA) has granted conditional approval for five vaccines, which is only one more than last year. For two vaccines (Valneva and Sanofi Pasteur), marketing authorisation evaluation has started in 2022. The European Commission (EC) has purchase agreements for SARS-CoV-2 vaccines from eight manufacturers. Of these SARS-CoV-2 vaccines, only the vaccines that are relevant for the Netherlands and are being tested in humans have been included in the overview.

10.2 Bacteria

Vaccine	Status, clinical phase
Chlamydia	
• Adjuvanted chlamydia vaccine CTH522 (SSI/Imperial College London)	I completed, safe, humoral and cellular immune response
Clostridium difficile	
• Toxoid inactivated (Pfizer)	III, FDA fast track
• Recombinant toxoid VLA84, genetic fusion (Valneva)	II completed III waiting for partner
• Recombinant protein adjuvant (GSK)	I
Helicobacter pylori	
• HP3 (Chiron/Novartis)	I/II completed, limited protective immunity, not pursued
• Oral recombinant vaccine (China)	III discontinued
Lyme	
• Outer surface protein-based vaccine (GSK)	Licensed but removed from market in 2002 due to poor market performance
• Subunit vaccine VLA15, 6 strains (Valneva/ Pfizer)	II 5-65 year olds started in 2021, FDA fast track, positive pediatric data
Meningococcal ABCWY	
• MenABCWY recombinant conjugated (Novartis/GSK)	IIIB 15-25 year olds booster dose study
• MenABCWY recombinant conjugated, 2nd generation (GSK)	IIa
• MenACWY Bexsero infants (GSK)	III
• MenACWY Menquadfi infants >6wks (Sanofi)	III
• Nimenrix-Trumemba combinations (Pfizer)	III adolescents, young adults
• Multicomponent Men B (Sanofi)	II
Moraxella catarrhalis, non-typeable Haemophilus influenza COPD	
• Recombinant COPD reduction with adjuvant (GSK)	II, completed

Table continues on next page.

Vaccine	Status, clinical phase
Shigella	
• Live attenuated oral single-strain (University Maryland US)	II and IIb challenge study terminated due to safety issues
• Monovalent synthetic carbohydrate based conjugate vaccine (university Maryland)	II
• Inactivated oral whole cell (university Maryland)	II, terminated
• Single-component O-antigen S. sonnei vaccine (Pasteur/GSK)	II completed
• Recombinant glycoconjugate (biconjugate)	III
• Bioconjugate outer membrane tetravalent (Novartis/GSK)	II
Staphylococcus aureus	
• Conjugate (SA4Ag, 4 antigen) (Pfizer)	IIb, failed Previous phase I-III with different single antigen vaccine candidates all failed due to safety concerns and low efficacy
• Recombinant Protein bioconjugated adjuvated (GSK)	II
Streptococcus group A	
• N-terminal M protein-based multivalent vaccines (26-valent and 30-valent)	II
• Conserved M protein vaccines (the J8 vaccine and the StreptInCor vaccine)	I
• C-terminal M-protein DTconjugate, AlOH adjuvanted	I
Streptococcus group B	
• CPS-protein conjugate (mono and trivalent) (Novartis/GSK)	II maternal
• 6-valent polysaccharide CRM197 conjugated vaccine (Pfizer)	II maternal, FDA fast track
• Recombinant fusion antigen (Minervax, APS, GBS-NN)	I

Table continues on next page.

Vaccine	Status, clinical phase
*Pneumococcus**	
• (Killed) whole-cell vaccine	II
• PCV15 children (MSD)	III registration expected fall 2022
• PCV21 adult (MSD)	II, breakthrough therapy designation FDA
• PCV20 (Pfizer)	III, infants and child <18yrs, approved adults
• Protein-based vaccine (GSK)	II
• Protein-based conjuage vaccine (Sanofi)	II
Tuberculosis (all forms, all ages)	
• Live attenuated vaccine BCG	On market but low efficacy
• M72/ASO1 adjuvanted recombinant fusion protein (GSK licensed to Gates, IAVI)	II(b) published VE 54%
• Subunit adjuvanted recombinant fusion protein (H4:IC31®) (Aeras/Sanofi/SSI now IAVI)	II published
• Modified Recombinant BCG	II
• Recombinant Subunit (GSK, Sanofi)	II completed
• Live attenuated (MTBVAC)	III
• Lysate of NTM	III
• Killed whole cell (booster) (Aeras, IAVI)	II
• Viral vector ChAdOx1 85A (Oxford)	I-II

* For conjugate serotype specific vaccines, see section 6.9 on pneumococcal disease.

10.3 Viruses

Vaccine	Status, clinical phase
Chikungunya	
• Live recombinant measles virus-based, Merck V184 (Merck)	II completed
• Virus-like particle (NIAID)	I/II completed
• Live attenuated (Valneva)	III completed positive results, FDA fast track, pre-submission FDA Q2 2022, PRIME designation by EMA
Cytomegalo (CMV)	
• Glycoprotein B bivalent	I and III
• Replication defective V160 (MSD)	II completed
• Recombinant, subunit adjuvant (GSK)	I, females age 16-49
• RNA vaccine (Moderna)	III
Dengue	
• Live recombinant (tetravalent) (Butantan/ NIAID)	III
• Live-attenuated (tetravalent) TDV (Takeda)	III
• Live virus (GSK)	II
• Recombinant Subunit (tetravalent) V180 (GSK/Merck)	II
• Inactivated virus (GSK/Merck)	I
• Live attenuated, Dengavaxia (Sanofi)	Registration approved for 9-45 years of age, for seropositive people only
Ebola	
• rVSVΔG-ZEBOV-GP V920 (Merck/ NewLink Genetics)	III, approved for compassionate use
• CAd3-EBOZ (GSK/NIH/NIAID)	III
• Ad26-EBOV and MVA-EBOV (Johnson & Johnson/Janssen vaccines/Bavarian Nordic)	EMA registration
• Recombinant nanoparticle based (Novavax)	III
• Recombinant Viral vector (GSK, 2019 Sabin vaccine institute)	II
• VRC-EBOADC069-0-VP (Okairos/NIAID)	I

Table continues on next page.

Vaccine	Status, clinical phase
Epstein–Barr	
• Recombinant gp350, glycoprotein subunit	II
• Live attenuated vaccines	On hold
Hepatitis C	
• Recombinant, heterologous viral vector (GSK)	II, not effective in preventing infection
Hepatitis E	
• Recombinant protein (Hecolin®) (Xiamen Innovax Biotech)	IV Approved in China, not registered in EU
Herpes simplex	
• HSV-529 replication defective live attenuated (Sanofi)	I
Herpes zoster (Shingles)	
• Recombinant (Shingrix, GSK)	Approved in US and EU
• Inactivated V212 (Merck)	III, on hold
HIV	
• Recombinant protein (GSK)	II
• Viral vector Prime/boost (Sanofi)	II?
• Ad26 Mos HIV vaccine (Janssen vaccines)	III
• DNA (GeoVax)	II completed
Hookworm	
• iBio	I? not in iBio pipline anymore
Noro	
• Virus-like particles (bi-valent) (Takeda, now Hillvax)	III
• Oral tablet vaccine (Vaxart)	II
MERS-CoV	
• MVA-MERS-S	I booster dose safe and sign NT response
• DNA (GeneOne Life Scinence/Inovio)	II started in August 2021
Parainfluenza type I	
• Live attenuated	I-II?

Table continues on next page.

Vaccine	Status, clinical phase
Respiratory syncytial (RSV) (17 in clinical development)	
• Live attenuated (Sanofi/NIH)	II toddlers
• Live attenuated (Intravacc)	I paediatric
• Inactivated whole cell	0
• Nanoparticle-based (Novavax)	III maternal data 2021, FDA fast track, failed
• Recombinant protein nanoparticle with and without adjuvant(Novavax)	I 2-6 yrs, 60+
• Subunit, F-protein (GSK)	III elderly failed II maternal stopped
• Subunit, F-protein (NIH/NIAID/VRC)	I paediatric
• Subunit, F-protein (Pfizer)	III maternal, fast track FDA, III older adults
• Subunit, F-protein (Janssen)	III elderly
• Subunit, F-protein (Merck)	II elderly-maternal I elderly
• Gene-based vector MVA (Bavarian Nordic	III
• Gene-based vector AV (Janssen)	III elderly
• Gene-based vector AV (Vaxart)	I paediatric
• Gene-based vector AV (GSK)	III older adults
• RNA vaccine (Moderna)	III older adults, pediatric I
Typhoid	
• TT-Conjugate (Bharat Biotech)	III published
West Nile	
• Inactivated (NIAID)	I completed
• Chimeric vaccine; live attenuated recombinant (ChimeriVax) (NIAID/Acambis)	II
• Recombinant subunit (NIAID/Hawaii Biotech)	I completed
Zika	
• DNA (GeneOne Life Scinence/Inovio/NIAID)	II
• RNA (Moderna)	II
• Live attenuated	II
• Whole virus inactivated (Sanofi, Takeda, NIAID)	II (Sanofi did not start phase III limited funding Barda)
• Whole virus inactivated (Valneva)	I completed, on hold priority to vaccines for greater health crisis

Source: WHO and clinicaltrial.gov, websites of pharmaceutical companies.

10.4 SARS-CoV-2 vaccines

Company	Status
Inactivated whole virus	
• Sinovac (China)	EMA rolling review
• Bharat Biotech	III, emergency use listing.list WHO
• Valneva#	EMA revaluation started May 2022, UK approved
Live attenuated virus	
• Meissa vaccines	I
• Intranasal vaccine (Conagenix/SII)	I
Non-replicating Viral vector	
• ChAd# (Oxford University/AstraZeneca)	EMA conditional marketing authorisation
• Ad5 (CanSino Beijing Institute Biotech)	Registration in China
• Ad26# (Janssen Pharmaceutical)	EMA conditional marketing authorisation
• Ad26, Sputnik V (Gamaleya Res. Ins)	EMA rolling review
• ReiThera/Leukocare/Univercells	II/III
• Ad5, adjuvanted, oral vaccine (Vaxart)	II
• hAd5 S + N (immunityBio)	II
• MVA (Ludwich Maximilinas University Munich)	I
Replicating Viral Vector	
• MVA (MSD/Inst Pasteur/Themis/University of Pittsburg)	Development discontinued
• Intranasal flu (Beijing Wantai Bio/Xiamen university)	III
• rVSV (Israel Institute for Biological Research)	II/III
Protein (sub-unit)	
• Matrix M adjuvant# (Novavx)	EMA conditional marketing authorisation
• ASO3 adjuvant# (Sanofi/GSK)	EMA evaluation since March 2022
• with adjuvant* (HIPRA)	EMA rolling review
• ASO3 or CPG and aluminium adjuvant (Clover/GSK/Dynavax)	II/III, EMA registration submission Q3 2022
• MF59 adjuvanted sclamp (University of Queensland)	I, interference with HIV diagnostic

Table continues on next page.

Company	Status
• Plant based KBio holdings Ltd. (former Kentucky Bioprocess)	I/II
• Vaxine Meditox, CinnaGen (Advax adj)	III
• Medigen/NIAID, Dynavax (CpG 1018 adj) Taiwan	III
• TT-conjugate, AlOH adjuvant (Finlay inst. Cuba)	III, Authorized emergency use Cuba
• Vaxxinity, multitope peptide base vaccine (former COVAXX)	III
• UMCGroningen Akston	II booster trial
RNA	
• LNP encapsulated mRNA#, mRNA-1273 (Moderna)	EMA conditional marketing authorisation 6 yrs and older, 6 mos-5yrs and adapted strain vaccines in rolling review
• LNP encapsulated mRNA#, Comirnaty (BioNTech/Pfizer)	EMA conditional marketing authorisation >5years, rolling review 6 mos-4 yrs and adapted strain vaccines
• Imperial College London (LNP)	I
• Curevac#	III, EMA review, VE 49%, failed
• Acturus Duke/NUS	II
• Sanofi Pasteur Translate Bio	II
• GSK, self amplifying RNA, LNP platform	I
DNA	
• DNA plasmid electroporation (Inovio/IVI)	II/III
• Zydus Cadila Healthcare Limited	III
• Genexine consortium	II/III
• Adjuvanted (Osaka University/Takara bio)	II/III
VLP	
• Medicago	III
• SII SpyBiotech (HBsAg RBD S)	I/II
• Radboud University (MF59)	III

COVID-19 vaccines with EC contract.
* COVID-19 vaccines with EC contract negotiations.

11
List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
2vHPV	bivalent human papillomavirus vaccine
4vHPV	quadrivalent human papillomavirus vaccine
95%CI	95% confidence interval
9vHPV	nonavalent human papillomavirus vaccine
AEFI	adverse event following immunisation
AEs	adverse events
AFP	acute flaccid paralysis
AFM	acute flaccid myelitis
aHR	adjusted hazard ratio
aIRR	adjusted incidence rate ratio
aOR	adjusted odds ratio
aP	acellular pertussis
ARI	acute respiratory infection
BAU/mL	binding antibody units per milliliter
BES	Bonaire, St. Eustatius, Saba
bOPV	bivalent oral polio vaccine
BRP	Personal Records Database; Basisregistratie Personen
CAS	Curacao, Aruba, St. Maarten
CBS	Statistics Netherlands; Centraal Bureau voor de Statistiek
CC	clonal complex
CD4/8	cluster of differentiation 4/8
C. diphtheriae	Corynebacterium diphtheriae
C. ulcerans	Corynebacterium ulcerans
CFS	chronic fatigue syndrome
cgMLST	core-genome multilocus sequence typing
CI	confidence interval
CIb	Centre for Infectious Disease Control Netherlands
CIMS	COVID-vaccination Information Monitoring System
CIN	cervical intraepithelial neoplasia
CoP	correlates of protection
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRM	cross-reactive material conjugate
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
cVDPV2	circulating vaccine derived polio virus type 2

DALY	disability-adjusted life years
DHD	Dutch Hospital Data
DNA	deoxyribonucleic acid
DT	diphtheria toxoid
DTaP	combination of diphtheria, tetanus and acellular pertussis vaccines
DTaP-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines
DTP3	third dose of a combination of diphtheria, tetanus and pertussis vaccine
DTaP-IPV-HBV-Hib	combination of diphtheria, tetanus, pertussis, inactivated polio, hepatitis B virus and *Haemophilus influenzae* type b vaccines
ECDC	European Centre for Disease Control and Prevention
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENPEN	European Non-Polio Enterovirus Network
EU	European Union
EUL	Emergency Use Listing
EV	enterovirus
EV-D68	enterovirus D68
FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
FHbp	factor H-binding protein
Fim 2	serotype 2 fimbriae
Fim3	serotype 3 fimbriae
GA	gestational age
GAPIII	Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use
GE	gastroenteritis
GGD	municipal health services; gemeentelijke gezondheidsdiensten
GMC	geometric mean concentrations
GNV	gender neutral vaccination
GP	general practitioner
GPEI	Global Polio Eradication Initiative
GPLN	WHO Global Polio Laboratory Network
GSL	Global Specialized Laboratory
GW	genital warts

HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	Health Council
HCP	healthcare professionals
HepB	hepatitis B virus
Hi	*Haemophilus influenzae*
Hia	*Haemophilus influenzae* type a
Hib	*Haemophilus influenzae* type b
Hie	*Haemophilus influenzae* type e
Hif	*Haemophilus influenzae* type f
HIV	human immunodeficiency virus
HPV	human papillomavirus
HR	hazard ratio
hrHPV	high-risk human papillomavirus
HSIL+	high-grade squamous intraepithelial lesions or worse
HWS	The Netherlands Ministry of Health, Welfare and Sport
HZ	herpes zoster
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IDU	injecting drug use
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IKNL	Netherlands Comprehensive Cancer Organisation; Integraal Kankercentrum Nederland
ILI	influenza-like illness
IMD	invasive meningococcal disease
IMI-2	Innovative Medicines Initiative 2
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rate
IRR	incidence rate ratio
IQR	interquartile range
JGZ	youth health care; jeugdgezondheidszorg
KNCV	Royal Dutch Chemical Organisation; Koninklijke Nederlandse Chemische Vereniging
LINH	Netherlands Information Network of General Practice; Landelijk informatienetwerk huisartsenzorg

MEM	moving epidemic method
MenABCWY	pentavalent meningococcal conjugate vaccine
MenACWY	quadrivalent meningococcal conjugate vaccine
MenACWY-CRM	quadrivalent meningococcal vaccine conjugated to mutant diphtheria toxin
MenACWY-DT	quadrivalent meningococcal vaccine conjugated to diphtheria toxoid
MenACWY-TT	quadrivalent meningococcal vaccine conjugated to tetanus toxoid
MenA/B/C/W	Meningococcal serogroup A/B/C/W
MLST	multilocus sequence typing
MMR	combination of measles, mumps and rubella vaccines
MMRV	combination of measles, mumps, rubella and Varicella vaccines
MNTE	Maternal and Neonatal Tetanus Elimination initiative
mOPV2	monovalent type 2 Oral Polio Vaccine
MPV	maternal pertussis vaccination
MSM	men who have sex with men
NA	Not Available
NIBSC	National Institute for Biological Standards and Control
NICE	Dutch National Intensive Care Evaluation; Nationale Intensive Care Evaluatie
NIP	National Immunisation Programme
Nivel	Netherlands Institute for Health Services Research; Nederlands Instituut Voor onderzoek van de Eerstelijnstgezondheidszorg
NKR	Netherlands Cancer Registry
nOPV2	novel oral polio vaccine type 2
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NRLBM	Netherlands Reference Laboratory for Bacterial Meningitis
nOPV2	novel type 2 oral polio vaccine
NTHi	nontypeable *Haemophilus influenzae*
NWKV	Dutch Working Group for Clinical Virology; Nederlandse Werkgroep voor Klinische Virologie
OMT	Outbreak Management Team
OPV	oral polio vaccine
OR	odds ratio
OSIRIS	Dutch information system for infectious disease surveillance; Online systeem voor infectieziekten registratie binnen ISIS
PCA	principal component analysis
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV12	12-valent pneumococcal conjugate vaccine

PCV13	13-valent pneumococcal conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PEV	parechovirus
PHN	postherpetic neuralgia
PorA	porin A protein
POTS	postural orthostatic tachycardia
PPV	pneumococcal polysaccharide vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
PRAC	Pharmacovigilance Risk Assessment Committee
Prn	pertactin
Ptx	pertussis toxin
PV	poliovirus
QALY	quality-adjusted life year
qPCR	real-time polymerase chain reaction
RBD	receptor binding domain
RCT	randomized controlled trial
RIVM	Netherlands National Institute for Public Health and the Environment
RNA	ribonucleic acid
ROS	reactive oxygen species
RR	relative risk
RSV	respiratory syncytial virus
RZV	recombinant zoster vaccine (Shingrix®)
SAGE	Strategic Advisory Group of Experts on Immunization
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCLS	systemic capillary leak syndrome
SIA	supplementary immunisation activity
SIDS	sudden infant death syndrome
ST	sequence type
Tdap	tetanus, diphtheria and pertussis vaccine
TT	tetanus toxoid
TTS	thrombocytopenia syndrome
UK	United Kingdom
US	United States
USP	Utrecht Science Park

VAERS	Vaccine Adverse Event Reporting System
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VITT	Vaccine Induced Prothrombotic Immune Thrombocytopenia/ Vaccine-Induced Immune Thrombotic Thrombocytopenia
VLP	virus-like particle
VOC	variant of concern
VWS	Ministry of Health, Welfare, and Sport; Ministerie van Volksgezondheid, Welzijn en Sport
VZV	varicella zoster virus
wgMLST	whole-genome multi-locus sequence type
WGS	whole-genome sequencing
WHO	World Health Organisation
wP	whole-cell pertussis
WPV	wild poliovirus
WPV1	type 1 wild poliovirus
WTP	willingness to pay
YHC	youth healthcare
ZVL	zoster vaccine live (Zostavax®)

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Appendix

Appendix 1 Surveillance methodology

A1.1 Disease surveillance

The impact of the National Immunisation Programme (NIP) can be monitored through mortality, morbidity and laboratory data related to the target diseases. We describe the different data sources used for disease surveillance, and the different methods used to estimate vaccine impact, vaccine effectiveness, burden of disease, and cost-effectiveness.

A1.1.1 Data sources

A1.1.1.1 Notification data

Mandatory disease notifications are an important source of surveillance data for the diseases included in the NIP. Notification of infectious diseases was introduced in the Netherlands in 1865. Since then, several changes in the notification procedures have been implemented. Not all diseases targeted by the NIP have been notifiable throughout the entire period (Table A1.1) [1]. In December 2008, a new law (Wet Publieke Gezondheid) was passed that required notification of all NIP-targeted diseases except human papillomavirus (HPV). There are four notifiable disease categories. Diseases in category A have to be reported by telephone immediately following a suspected case. Diseases in categories B1, B2 and C must be reported within 24 hours or one working day after laboratory confirmation. However, under-reporting and reporting delays are issues with regard to several diseases [2]. In each of the first three categories (A, B1 and B2), different intervention measures can be enforced by law to prevent spreading of the disease.

Physicians and clinical laboratories are required to notify cases to the Municipal Health Centres (GGDs). The GGD in question reports cases to the RIVM through the online Osiris platform. In addition to patient characteristics (e.g. year of birth, sex, postal code), epidemiological (e.g. related cases, risk factors) and clinical data (e.g. hospital admission, death, vaccination status) are collected through the notifications.

Table A1.1 Periods and category of statutory notifications for vaccine-preventable diseases (VPDs) included in the current National Immunisation Programme (NIP).

Disease	Category	Periods of notification by legislation
Diphtheria	B1	from 1872 onwards
Pertussis	B2	from 1975 onwards
Tetanus	C	1950–1999, from December 2008 onwards
Poliomyelitis	A	from 1923 onwards
Invasive *Haemophilus influenzae* type b	C	from December 2008 onwards
Hepatitis B disease	B2	from 1950 onwards
Invasive pneumococcal disease	C	from December 2008 onwards (cases born in or after 2006) from April 2021 onwards (cases aged 60+)
Mumps	C	1975–1999, from December 2008 onwards
Measles	B2	1872–1899, from 1975 onwards
Rubella	B2	from 1950 onwards
Invasive meningococcal disease	C	from 1905 onwards

A1.1.1.2 Register-based data

A1.1.1.2.1 Death statistics

Statistics Netherlands (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerns a natural death, a non-natural death, or a stillborn child. In the event of a natural death, the physician is required to report the illness or disease that has led to death (primary cause), any complication directly related to the primary cause that has led to death (secondary cause), as well as additional diseases and specifics present at the moment of death that have contributed to death (secondary causes). The CBS codes causes of death according to the International Classification of Diseases (ICD). This classification is adjusted every ten years or so, which has to be taken into account when identifying mortality trends. Since the statistical year 2013, CBS has used the IRIS programme to automatically code the causes of death [3]. One of the advantages of this procedure is that it increases the international comparability of data. The change in coding did however cause considerable (once only) shifts in the statistics.

A1.1.1.2.2 Hospital admissions

Until 2010, hospital data was managed by the Prismant research institute in the National Medical Register (LMR). After 2011, Dutch Hospital Data (DHD) managed the LMR. Since 2013, the National Register Hospital Care (LBZ) managed by DHD has received the discharge diagnoses of

all patients admitted to hospital. Outpatient diagnoses are not registered. Diseases, including all NIP-targeted diseases, are coded as the main or subsidiary diagnosis according to the ICD-10 coding system. Up to 2012, discharge diagnoses were coded according to the ICD-9 coding system, thereafter according to ICD-10. Coverage of this registration system amounted to about 99% until mid-2005. Thereafter, coverage has fluctuated due to changes in funding (Table A1.2). The data presented in this report relate only to clinical admissions and have not been corrected for changes in coverage, causing an underestimation of hospital admissions from 2006 up to 2014. Hospital admission data are also susceptible to under-reporting, as shown by De Greeff *et al.* in a paper on meningococcal disease incidence [4] and by Van der Maas *et al.* for pertussis [5]. Hospitalisation data from 2015 onwards are retrieved from Statistics Netherlands. These data are corrected for non-participating hospitals, which may have resulted in a trend break compared to previous years. Due to privacy regulations, data are also rounded off to the nearest five. With these numbers, one should take into account that 0 cases is not always actually 0 but may also mean a few cases. Data for 2021 are not available as yet.

Table A1.2 The completeness of LMR/LBZ data through the years*, by day admissions and clinic admissions.

Year	Day admission		Clinic admission	
	% registered	% generated (=missing)	% registered	% generated (=missing)
2007	87	13	89	11
2008	88	12	88	12
2009	87	13	88	12
2010	86	14	89	11
2011	79	21	85	15
2012	72	28	82	18
2013	74	26	84	16
2014	82	18	99	1

*These numbers are an approximation of the exact percentage.
Sources: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards.

A1.1.1.2.3 Primary care data
The Nivel (Netherlands Institute for Health Services Research) Primary Care Database (Nivel-PCD) includes data from routine electronic medical records of general practitioners (GPs). Nivel-PCD uses routinely recorded data from healthcare providers to monitor health and the utilisation of health services in a representative sample of the Dutch population. All symptoms and diagnoses of consulting patients are recorded using the International Classification of Primary Care (ICPC-1). Annual incidence estimates of the total number of new episodes appearing in general practice in the Netherlands are generated by extrapolating the reporting rates in these practices to the total number of Dutch residents, as obtained from CBS. For example, incidence rates of varicella and herpes zoster have been calculated using these data.

The current Dutch RSV surveillance programme is based primarily on general practitioner (GP) surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI). Nose swabs and throat swabs are collected from a subset of patients and tested for influenza virus, RSV, rhinovirus and enterovirus. Furthermore, the weekly reporting of virological laboratory surveillance by 20 virological laboratories yields insights into the number of positive RSV tests, reflecting RSV circulation. These specimens are collected mainly from children [6]. For more information, also on other sources for RSV surveillance, please see the *annual RIVM report on Surveillance of COVID-19, influenza and other respiratory diseases*.

A1.1.1.3 Laboratory data

Laboratory diagnostics are important in monitoring infectious diseases and the effectiveness of vaccination; about 75% of all infectious diseases can only be diagnosed by laboratory tests [7]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting vaccine-preventable diseases. Two laboratory surveillance systems used for NIP disease surveillance are the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) and the virological laboratories, which are part of the Dutch Working Group for Clinical Virology.

A1.1.1.3.1 Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM)

The NRLBM is a collaboration between the National Institute for Public Health and the Environment (RIVM) and the Academic Medical Centre of Amsterdam (AMC). On a voluntary basis, microbiological laboratories throughout the Netherlands send isolates from normally sterile sites (e.g. blood and cerebrospinal fluid (CSF)) of patients with invasive meningococcal disease, invasive pneumococcal disease, and invasive *Haemophilus influenzae* disease to the NRLBM for further typing. Furthermore, for invasive meningococcal disease and invasive *H. influenzae* disease, PCR positive samples are sent to the NRLBM for further typing. This means that we have nationwide coverage of laboratory surveillance for invasive meningococcal disease and invasive *H. influenzae* disease. For invasive pneumococcal disease, nine sentinel clinical laboratories distributed throughout the country have been sending in all invasive isolates positive for *Streptococcus pneumoniae* since 2004. These nine sentinel laboratories cover approximately 28% of the Dutch population. Since 2008, for children aged under 5, all clinical laboratories send in all invasive isolates positive for *S. pneumoniae*, and since 2017, all medical microbiology laboratories are requested to submit all invasive pneumococcal isolates without restriction to age of the patient.

A1.1.1.3.2 Virological laboratories

Every week, virological laboratories that are members of the Dutch Working Group for Clinical Virology send positive results of virological diagnostics to the RIVM. Approximately 22 laboratories submit information on a regular basis. Aggregated results are shown on the RIVM website.

It is important to bear in mind that the presence of a virus does not automatically imply the presence of disease. Since 1 December 2014, information on the total number of tests done can be reported for each week or each year.

A1.1.1.4 *Dedicated studies*

In addition to the data sources described above, dedicated disease surveillance studies are performed to collect data on hospitalisation or mortality. For example, every 2 to 4 years, clinical data for invasive pneumococcal disease (including mortality and comorbidity) are collected retrospectively from the patient dossiers [8]. Furthermore, retrospective studies were performed to collect disease surveillance data for invasive Hib disease, invasive meningococcal disease, and varicella zoster [9-11].

A1.1.1.5 *Validity of the different data sources*

Data from registers on mortality and hospitalisation are not always reliable. For example, tetani cases are sometimes incorrectly registered as tetanus [5] and cases of post-poliomyelitis syndrome are sometimes classified as acute poliomyelitis, even though these occurred many years ago. Furthermore, cases of acute flaccid paralysis (AFP) due to causes other than poliovirus infection are sometimes inadvertently registered as cases of acute poliomyelitis [12]. Thus, for poliomyelitis and tetanus, notifications are a more reliable source of surveillance data. Additionally, for invasive *H. influenzae* disease, invasive pneumococcal disease, and, to a lesser extent, invasive meningococcal disease, data on mortality and hospital admissions based on registration databases are unreliable. This is because these are syndromic diseases (meningitis, sepsis and pneumonia) and the causative pathogen is not always correctly specified when these diseases are coded. Notification data in combination with laboratory data from the NRLBM are more reliable for these diseases.
A specific ICD code is available (ICD-9: 008.61, ICD-10: A08.0) for Rotavirus (RV) disease. However, this code is hardly ever used in the Netherlands as more general ICD categories are felt to suffice. Moreover, gastroenteritis hospitalisations are often not tested in general for all causative pathogens, in particular in very young children. For this reason, the number of gastroenteritis hospitalisations attributable to RV is estimated indirectly according to a method proposed by Harris *et al.* [13]. Using this method, the proportion of hospitalisations for gastroenteritis attributable to RV can be estimated by comparing the weekly RV laboratory detections (surveillance virological laboratories) with the number of hospitalisations for specific gastroenteritis ICD codes using linear regression analysis (ICD-9: 86-93, 5589; ICD-10: A0,-A09, K52, K529). This linear regression model estimates a constant representing the background number of events for gastroenteritis other than RV infection, and a constant scaling factor dependent on the number of RV-positive laboratory detections that varies every week. The number of hospital admissions attributable to RV infection is calculated using the scaling factor times the number of positive laboratory detections per week. For this report, the constant and scaling factor were estimated by imposing the model onto hospitalisation data and weekly laboratory detections (laboratory surveillance) for the five previous years. The scaling factor estimated by this model was used to estimate the RV-attributed hospital admissions for the most recent year by multiplying it with the RV-positive laboratory detections of that year.

In 2012, there was a fourfold increase in the number of general practices participating in Nivel-PCD compared with the previous group of LINH practices, resulting in a representative sample of 386 participating general practices with approximately 1.2 million registered patients

(http://www.nivel.nl/NZR/zorgregistraties-eerstelijn). From 2012 onwards, incidence rates from Nivel-PCD have been calculated using an adjusted procedure: changes were made to the definitions of disease episodes and to calculations of incidence, which caused an increased incidence for many diseases. Episode duration is defined as the time between the first and last consultation registered with the same code, plus an additional period in which patients are considered not susceptible (eight weeks for acute morbidities/complaints). Incidence rates are calculated by using a more specific selection of patient years resulting in a more reliable denominator [14, 15]. Because of these changes, we decided to report previously published incidence rates until 2011 based on the old method [16] and incidence rates from 2012 onwards using the new method [17]. Due to the new estimation method, the data for 2012 (based on 219 practices) and onwards are not comparable with the data for previous years.

A1.1.2 Methods for disease surveillance

A1.1.2.1 Burden of disease

The disability-adjusted life year (DALY) is composite health measure that was developed to compare the impact of diseases. The idea behind this approach is that the impact of a particular disease can be divided between the number of years of life lost (i.e. premature mortality) and the number of years lived at less than full health (i.e. morbidity). The result is a single measurement unit that quantifies the years of healthy life lost due to a certain disease or infection. The full methodology used to estimate the disease burden of infectious diseases in the Netherlands expressed in DALYs is described in the State of Infectious Diseases in the Netherlands, 2013 [18, 19].

A1.1.2.2 Impact of implementation of vaccination

The impact of vaccination (programmes) can be estimated by comparing disease burden after implementation to disease burden before implementation of vaccination. This can be done quite simply by a before/after comparison of incidence. A more complex alternative is by applying time series analysis, in which, for example, time trends before implementation of vaccination, seasonality and vaccination coverage can be taken into account. The vaccination status of individuals is not needed to estimate the impact of a vaccination programme; the vaccination coverage of the population suffices. In addition to effectiveness of the vaccination itself, vaccination coverage and the level of herd protection determine the impact of a vaccination programme.

A1.1.2.3 Vaccine effectiveness

To estimate vaccine effectiveness, the vaccination status of at least the cases is necessary. After the implementation of a vaccination in the NIP, vaccine effectiveness (VE) can be routinely estimated using the 'screening method' [20] with the following equation:
VE (%) = 1- [PCV / (1-PCV) * (1-PPV/PPV)], in which PCV = proportion of cases vaccinated, PPV = proportion of population vaccinated, and VE = vaccine effectiveness.

In addition, several study designs, including case-control and cohort studies, can be used to assess VE after implementation [21]. A specific type of case-control design used to estimate VE is the indirect cohort design or Broome method [22]. This design can be used for a vaccine that protects against specific types of a pathogen, e.g. 10-valent pneumococcal conjugate vaccine, which protects against 10 pneumococcal serotypes. Cases in which the disease is caused by a vaccine type are the 'cases', and cases in which the disease is caused by a type not included in the vaccine serve as 'controls'. Vaccination status is then compared between the 'cases' (vaccine-type cases) and 'controls' (non-vaccine-type cases). The advantage of this design is that it adjusts for ascertainment bias between cases and controls, as both cases and controls are actually ill. An assumption in this design is that vaccinated people are at the same risk of non-vaccine-type infection as unvaccinated people. This means that the VE is underestimated in the case of cross-protection by the vaccine against non-vaccine-type disease. Conversely, if replacement disease occurs only in vaccinated people, the VE is overestimated.
Multiple statistical approaches are available to evaluate the VE against persistent HPV infections through the use of cohort studies. These approaches differ with respect to their underlying assumptions [23]. Based on available literature, absence of violations of the underlying assumptions, and the use of data throughout the follow-up, we suggest the Prentice Williams Peterson Total-Time (PWP-TT) approach as being the most valid method to evaluate vaccine effectiveness against HPV infections in cohort studies conducted among young women. The PWP-TT is a survival analysis method for recurrent events, taking into account the total time at risk. It assumes event-specific hazards, allowing the hazard to be different for each subsequent event [24]. We estimated the VE as one minus the hazard ratio times 100%. If the VE is estimated against a combined endpoint of multiple HPV types, then instead of the total number of infections, being infected with one of these types at that time point is used as outcome.

A1.1.2.4 Pertussis vaccination coverage

In the past a standardised vaccination coverage estimate of 92% was used for the PPV to calculate vaccine effectiveness for the pertussis booster vaccination at the age of 4 years. Nowadays, in response to the changes in vaccination coverage, the vaccination coverage as reported in the national vaccination coverage report is used for each birth cohort. This results in a different PPV for each birth cohort and more accurate VE calculation.

A1.2 Molecular surveillance of the pathogen

Monitoring strain variations due to differences in phenotype and/or genotype is an important part of information gathering on the emergence of (sub)types that may be more virulent or less effectively controlled by vaccination. It is also a useful tool for increasing insights into transmission dynamics.

A1.3 Immunosurveillance

Monitoring the seroprevalence of all NIP-targeted diseases is a way to gather age-specific and sex-specific information on immunity to these diseases, acquired either through natural infection or vaccination. To achieve this, a random selection of people from the general population of the Netherlands is periodically asked to donate a blood sample and complete a questionnaire (PIENTER survey). This survey was conducted in 1995-1996 (N_{blood}=10,128) [25], 2006–2007 (N_{blood}=7,904) [26], and 2016-2017 (N_{blood}=5,745). People living in regions with low vaccine coverage and non-Western migrants are oversampled in order to gain greater insights into differences in immunity among specific groups.

A1.4 Vaccination coverage

Vaccination coverage data can be used to gain insight into the NIP's effectiveness. Furthermore, this information can help identify groups with low vaccine coverage who are at increased risk of contracting one of the NIP-targeted diseases. In the Netherlands, all vaccinations administered within the framework of the NIP are registered in a central electronic (web-based) database at the individual level (Præventis) [27].

A1.5 Surveillance of adverse events following vaccination

Passive safety surveillance through an enhanced spontaneous reporting system was used by the RIVM until 2011. An aggregate analysis of all reported adverse events following immunisation (AEFIs) was published annually. The last report, for 2010, also contains a detailed description of the methodology used and a review of trends and important findings over the previous 15 years [28].
On 1 January 2011, this enhanced spontaneous AEFI reporting system was taken over by the Netherlands Pharmacovigilance Centre (Lareb). Detailed information is available at *www.lareb.nl*. In view of this transition, comparisons between the period before 2011 and the period from 2011 onwards should be made with caution. Furthermore, in 2011, Lareb started a campaign among parents of vaccinated children to promote the reporting of AEFIs.
In January 2017, the procedure for registering AEFIs in the Lareb database was changed. Previously, reports of redness, swelling, pain and warmth at the injection site were recorded as injection-site inflammation. Since January 2017, these local reactions are registered separately. As a result, the number of AEFIs per report is higher.
In addition, the RIVM Centre for Infectious Disease Control (CIb) conducts systematic studies to monitor the safety of the NIP, e.g. questionnaire surveys and linkage studies between different databases.

A1.6 Cost-effectiveness

The decision to include a certain vaccination option in the NIP is based on several factors, including vaccine safety and efficacy, avertable disease burden, acceptability, and cost-effectiveness of vaccination. Cost-effectiveness is defined as the additional cost per additional unit of health benefit produced, compared to an alternative such as the vaccine already in use or no vaccination. In other words, economic evaluation of a vaccination programme provides information on whether the health gain associated with a new vaccine is worth the cost as compared with other options for investing in health improvements or prevention. Most commonly, cost-effectiveness is expressed in cost per quality-adjusted life year (QALY), which is a measure of disease burden comprising both the quality and quantity of life. If provided in a transparent and standardised manner, evidence of cost-effectiveness can contribute to policy recommendations for vaccinations included in the NIP.

A1.7 Literature

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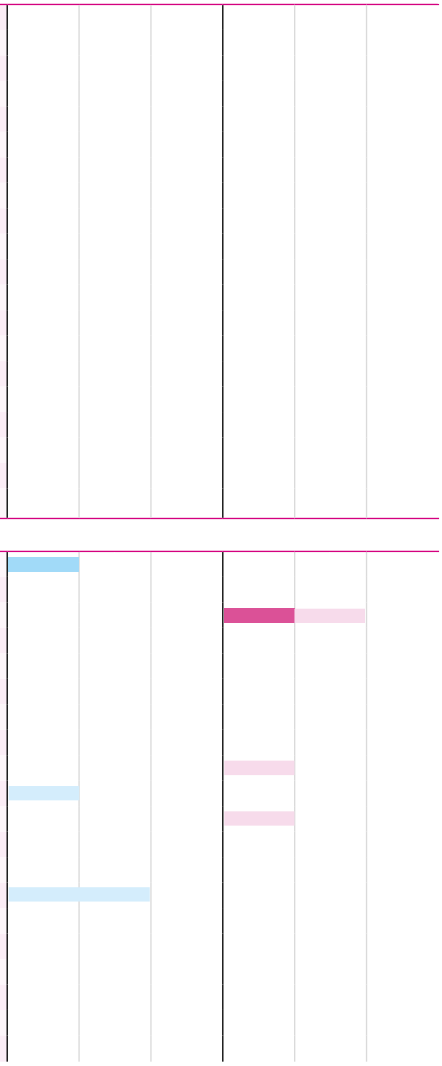
* RIVM publication.

Appendix 2 Morbidity and mortality figures

Diseases included in the current NIP

Diphtheria								ICD10: A36
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021*	0	0	0	0	0	0	**0**	
*Hospitalisations** (source: Prismant/DHD/CBS)*								
2001	0	0	0	1	0	0	**1**	
2002	0	0	0	0	0	0	**0**	
2003	0	1	0	0	0	1	**2**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	1	**1**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	2	**2**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	
2018^	0	0	0	0	0	0	**5**	
2019^	0	0	0	0	0	0	**0**	
2020^	0	0	0	0	0	0	**0**	



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

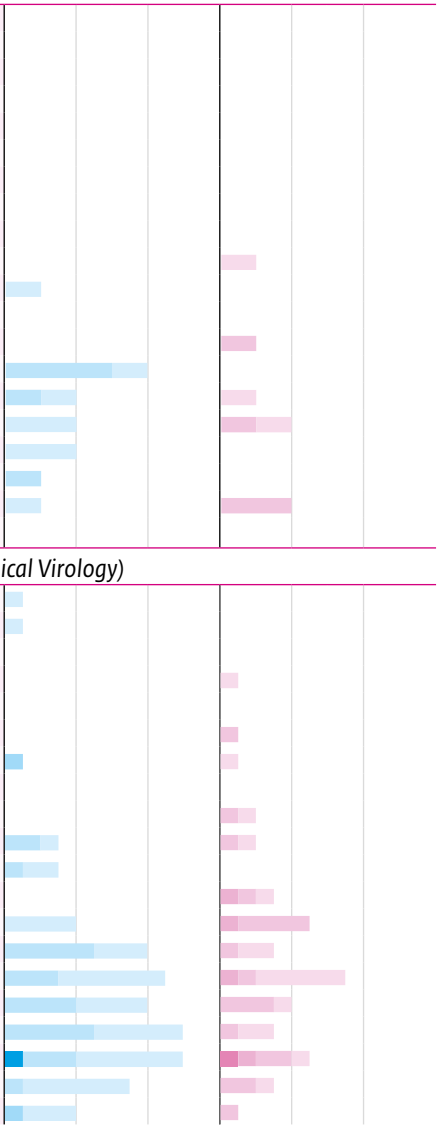
** Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Diphtheria

ICD9: 032
ICD10: A36

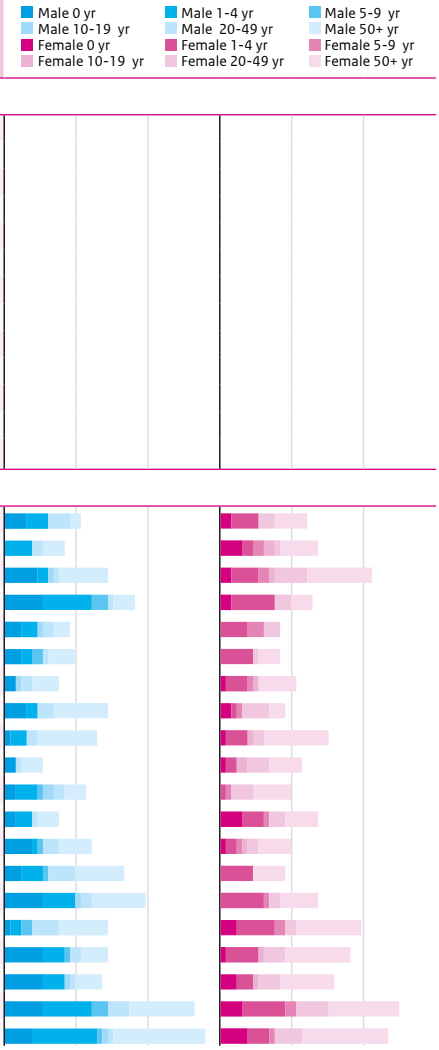
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (source: Osiris)							
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	0	0	**0**
2003	0	0	0	0	0	0	**0**
2004	0	0	0	0	0	0	**0**
2005	0	0	0	0	0	0	**0**
2006	0	0	0	0	0	0	**0**
2007	0	0	0	0	0	0	**0**
2008	0	0	0	0	0	0	**0**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	0	0	**0**
2011	0	0	0	0	0	1	**1**
2012	0	0	0	0	0	1	**1**
2013	0	0	0	0	0	0	**0**
2014	0	0	0	0	1	0	**1**
2015	0	0	0	0	3	1	**4**
2016	0	0	0	0	1	2	**3**
2017	0	0	0	0	1	3	**4**
2018	0	0	0	0	0	2	**2**
2019	0	0	0	0	1	0	**1**
2020	0	0	0	0	2	1	**3**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)*							
2001	0	0	0	0	0	2	**2**
2002	0	0	0	0	0	1	**1**
2003	0	0	0	0	0	1	**1**
2004	0	0	0	0	0	0	**0**
2005	0	0	0	0	0	1	**1**
2006	0	0	0	0	0	0	**0**
2007	0	0	0	0	1	2	**3**
2008	0	0	0	1	0	1	**2**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	1	1	**2**
2011	0	0	0	0	3	2	**5**
2012	0	0	0	0	2	2	**4**
2013	0	0	0	1	3	1	**5**
2014	0	0	0	1	4	5	**10**
2015	0	0	0	0	6	5	**11**
2016	0	0	0	1	5	10	**16**
2017	0	0	0	0	7	5	**12**
2018	0	0	0	0	5	5	**10**
2019	1	0	1	1	5	7	**15**
2020	0	0	0	0	3	7	**10**



* Number of diphtheria isolates.
** Two isolates came from the same patient, but were collected at different times and from different sample types.

Haemophilus influenzae

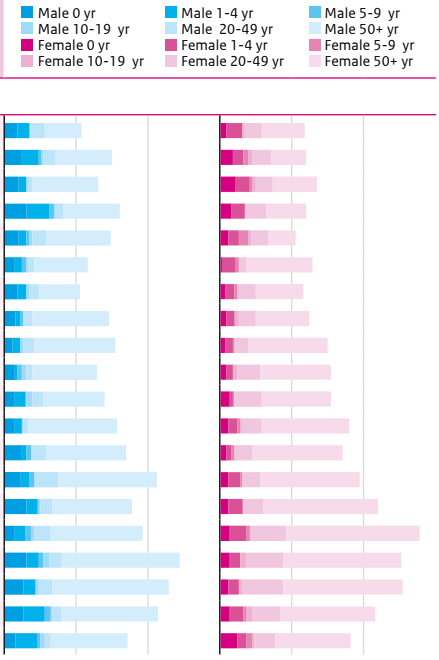
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (serotype b; source: Osiris)*							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	20	**35**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	3	8	0	0	2	7	**20**
2014	4	3	2	1	4	6	**20**
2015	3	5	0	0	5	4	**17**
2016	6	13	0	1	4	9	**33**
2017	4	8	4	0	3	13	**32**
2018	7	11	1	1	4	16	**40**
2019	10	6	1	2	6	16	**41**
2020	12	17	4	1	9	23	**66**
2021	11	13	4	1	6	30	**65**
Laboratory diagnoses (serotype b; source: NRLBM)							
2002	7	9	0	0	7	9	**17**
2003	5	8	2	2	3	11	**30**
2004	8	7	2	2	8	21	**29**
2005	9	17	3	0	4	8	**47**
2006	3	8	3	1	6	3	**41**
2007	3	8	2	0	2	9	**23**
2008	3	5	1	2	2	12	**24**
2009	6	3	1	0	8	14	**24**
2010	2	7	0	1	4	23	**31**
2011	3	2	0	2	5	10	**37**
2012	2	5	2	2	6	11	**22**
2013	6	7	1	0	4	11	**28**
2014	6	3	2	1	6	12	**28**
2015	3	10	1	0	5	15	**29**
2016	7	14	1	1	4	17	**34**
2017	4	10	4	0	7	21	**44**
2018	8	10	1	1	6	17	**45**
2019	10	7	0	2	5	15	**43**
2020	11	17	5	0	10	25	**39**
2021	10	16	2	1	6	33	**68**



* Notifiable since 2009.

Haemophilus influenzae

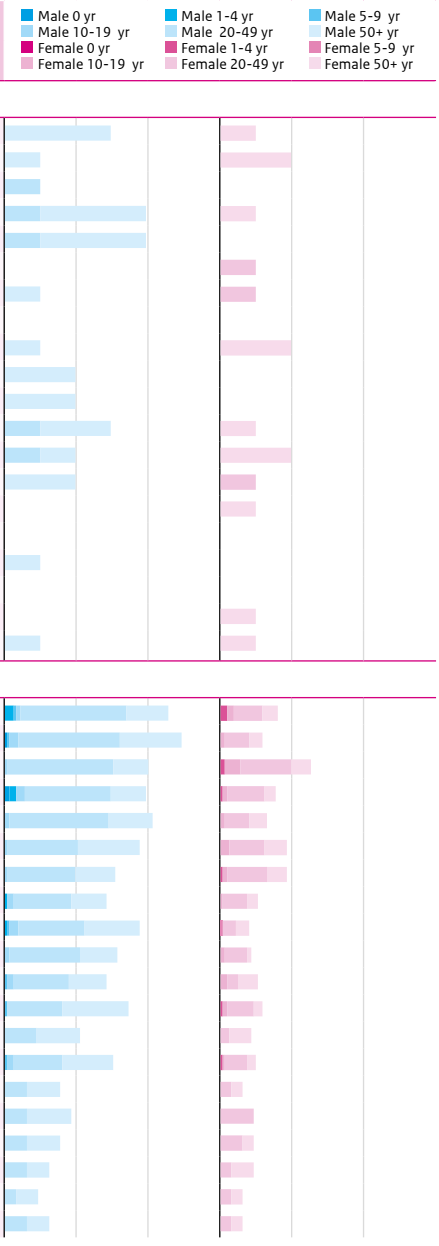
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serotypes; source: NRLBM)							
2002	13	18	0	2	22	53	**108**
2003	21	19	5	4	20	60	**129**
2004	19	14	2	3	15	72	**125**
2005	21	24	3	1	19	64	**132**
2006	14	12	8	4	21	61	**120**
2007	7	14	5	1	9	79	**115**
2008	11	14	2	3	18	60	**108**
2009	11	8	3	2	18	87	**129**
2010	8	10	1	3	15	106	**143**
2011	11	6	3	6	20	93	**139**
2012	12	11	2	4	26	85	**140**
2013	11	11	2	2	16	117	**159**
2014	16	6	5	1	22	111	**161**
2015	15	14	4	1	27	129	**190**
2016	19	16	2	1	22	130	**190**
2017	12	20	6	3	34	149	**224**
2018	21	15	3	8	32	157	**236**
2019	17	15	0	4	36	155	**227**
2020	18	24	7	5	24	125	**203**
2021	18	20	6	4	18	100	**166**



Hepatitis B

ICD9: 070.2-3
ICD10: B16, B17.0, B18.0, B18.1

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (B16: Acute; source: CBS)							
2001	0	0	0	0	0	4	**4**
2002	0	0	0	0	0	4	**4**
2003	0	0	0	0	0	3	**3**
2004	0	0	0	0	1	0	**1**
2005	0	0	0	0	1	4	**5**
2006	0	0	0	0	1	3	**4**
2007	0	0	0	0	1	0	**1**
2008	0	0	0	0	1	1	**2**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	0	3	**3**
2011	0	0	0	0	0	2	**2**
2012	0	0	0	0	0	2	**2**
2013	0	0	0	0	1	3	**4**
2014	0	0	0	0	1	3	**4**
2015	0	0	0	0	1	2	**3**
2016	0	0	0	0	0	1	**1**
2017	0	0	0	0	0	0	**0**
2018	0	0	0	0	0	1	**1**
2019	0	0	0	0	0	0	**0**
2020*	0	0	0	0	0	1	**1**
*Hospitalisations** (source: Prismant/DHD/CBS)*							
2001	0	7	1	5	61	26	**104**
2002	1	0	1	6	57	34	**102**
2003	0	2	0	8	71	25	**106**
2004	2	4	0	6	56	21	**92**
2005	0	0	0	4	56	28	**89**
2006	0	0	0	5	48	38	**92**
2007	0	1	0	3	49	27	**81**
2008	0	1	0	4	37	21	**63**
2009	0	1	2	4	36	31	**74**
2010	0	0	0	4	42	19	**66**
2011	0	0	1	6	30	26	**63**
2012	0	1	1	2	37	34	**76**
2013	0	0	0	0	18	30	**48**
2014	0	1	1	4	32	27	**66**
2015^	0	0	0	0	20	20	**40**
2016^	0	0	0	0	25	25	**50**
2017^	0	0	0	0	20	20	**40**
2018^	0	0	0	0	15	20	**35**
2019^	0	0	0	0	10	15	**25**
2020^	0	0	0	0	20	15	**35**



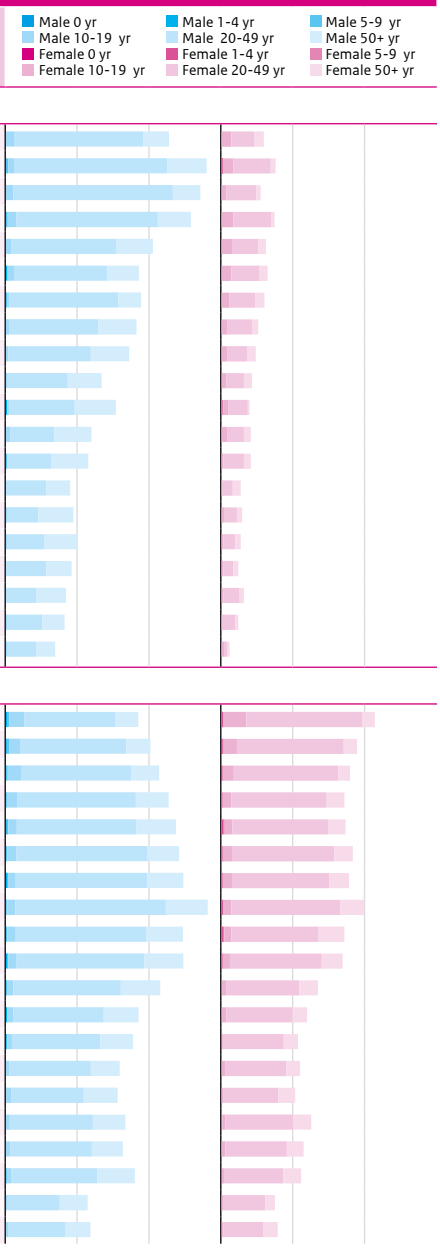
* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

** Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Hepatitis B

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications (Acute; source: Osiris)							
2002	0	0	0	22	193	44	**259**
2003	0	1	3	22	240	56	**322**
2004*	0	1	0	15	240	40	**296**
2005	0	0	2	26	227	46	**301**
2006	0	0	0	20	166	56	**242**
2007	0	1	1	20	154	50	**226**
2008	0	0	1	13	170	41	**225**
2009	0	0	0	11	144	56	**211**
2010	0	0	0	10	129	60	**199**
2011	0	0	1	7	98	53	**159**
2012	0	1	2	9	108	54	**174**
2013	0	0	0	12	77	56	**145**
2014	0	0	1	3	81	56	**141**
2015	0	0	0	1	64	40	**105**
2016	0	0	0	5	55	51	**111**
2017	0	0	0	3	62	50	**115**
2018	0	0	0	2	64	38	**104**
2019	0	0	0	2	58	44	**104**
2020	0	0	0	1	62	32	**95**
2021	0	0	0	4	41	27	**72**
Notifications (Chronic; source: Osiris)							
2002	0	11	15	200	1,099	183	**1,508**
2003	3	7	15	132	1,126	197	**1,480**
2004	2	5	8	128	1,139	208	**1,490**
2005	0	3	9	97	1,134	268	**1,511**
2006	2	18	8	85	1,141	300	**1,554**
2007	0	8	9	95	1,233	265	**1,610**
2008	0	10	6	87	1,215	295	**1,613**
2009	0	7	7	85	1,373	348	**1,820**
2010	0	9	12	77	1,159	328	**1,585**
2011	0	9	10	77	1,162	319	**1,577**
2012	0	3	3	55	959	307	**1,327**
2013	0	4	5	54	829	261	**1,153**
2014	1	5	3	31	788	247	**1,075**
2015	0	1	1	31	758	226	**1,017**
2016	1	0	0	36	674	269	**980**
2017	0	1	1	37	797	269	**1,105**
2018	0	0	0	40	758	253	**1,051**
2019	0	4	4	33	769	291	**1,101**
2020	0	0	0	15	502#	197	**714**
2021	0	0	2	18	513^	210	**743**



* 1 case without information on gender.
# 2 cases without information on gender.
^ 1 case without information on gender

Human papillomavirus								ICD10: C53
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (cervical cancer; source: CBS)								
2002	0	0	0	0	45	142	**187**	
2003	0	0	0	0	47	167	**214**	
2004	0	0	0	0	49	154	**203**	
2005	0	0	0	0	52	183	**235**	
2006	0	0	0	0	44	170	**214**	
2007	0	0	0	0	57	147	**204**	
2008	0	0	0	0	51	193	**244**	
2009	0	0	0	0	40	169	**209**	
2010	0	0	0	0	43	162	**205**	
2011	0	0	0	0	46	143	**189**	
2012	0	0	0	0	42	173	**215**	
2013	0	0	0	0	47	176	**223**	
2014	0	0	0	0	50	148	**198**	
2015	0	0	0	0	49	158	**207**	
2016	0	0	0	0	50	179	**229**	
2017	0	0	0	0	44	162	**206**	
2018	0	0	0	0	50	167	**217**	
2019	0	0	0	0	45	171	**216**	
2020	0	0	0	0	52	178	**230**	
2021*	0	0	0	0	48	165	**213**	
Registrations (cervical cancer; source: NKR)								
2002	0	0	0	0	334	316	**650**	
2003	0	0	0	0	325	292	**617**	
2004	0	0	0	1	376	326	**703**	
2005	0	0	0	0	365	321	**686**	
2006	0	0	0	0	370	320	**690**	
2007	0	0	0	0	416	327	**743**	
2008	0	0	0	0	376	328	**704**	
2009	0	0	0	0	385	339	**724**	
2010	0	0	0	0	399	332	**731**	
2011	0	0	0	0	381	354	**735**	
2012	0	0	0	1	403	328	**732**	
2013	0	0	0	0	379	281	**660**	
2014	0	0	0	0	418	321	**739**	
2015	0	0	0	0	389	321	**710**	
2016	0	0	0	0	451	356	**807**	
2017	0	0	0	1	433	337	**771**	
2018	0	0	0	0	468	376	**844**	
2019	0	0	1	0	513	396	**910**	
2020**	0	0	0	0	452	350	**802**	
2021**	0	0	0	0	558	389	**947**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.
** Preliminary figures.

Human papillomavirus								ICD10: C51
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
*Mortality (vulva cancer; source: CBS)^*								
2002	0	0	0	0	2	89	**91**	
2003	0	0	0	0	3	87	**90**	
2004	0	0	0	0	1	78	**79**	
2005	0	0	0	0	3	73	**76**	
2006	0	0	0	0	5	86	**91**	
2007	0	0	0	0	3	81	**84**	
2008	0	0	0	0	7	92	**99**	
2009	0	0	0	0	3	108	**111**	
2010	0	0	0	0	6	110	**116**	
2011	0	0	0	0	7	134	**141**	
2012	0	0	0	0	1	95	**96**	
2013	0	0	0	0	1	97	**98**	
2014	0	0	0	0	2	115	**117**	
2015	0	0	0	0	8	95	**103**	
2016	0	0	0	0	0	99	**99**	
2017	0	0	0	0	2	112	**114**	
2018	0	0	0	0	4	137	**141**	
2019	0	0	0	0	3	164	**167**	
2020	0	0	0	0	3	147	**150**	
2021*	0	0	0	0	4	140	**144**	
*Registrations (vulva cancer; source: NKR)^*								
2002	0	0	0	0	20	192	**212**	
2003	0	0	0	0	29	215	**244**	
2004	0	0	0	0	34	199	**233**	
2005	0	0	0	0	33	226	**259**	
2006	0	0	0	0	30	241	**271**	
2007	0	0	0	0	37	263	**300**	
2008	0	0	0	0	31	260	**291**	
2009	0	0	0	0	54	298	**352**	
2010	0	0	0	0	41	306	**347**	
2011	0	0	0	1	52	341	**394**	
2012	0	0	0	0	33	317	**350**	
2013	0	0	0	0	38	310	**348**	
2014	0	0	0	0	56	359	**415**	
2015	0	0	0	0	42	335	**377**	
2016	0	0	0	0	37	379	**416**	
2017	0	0	0	0	38	372	**410**	
2018	0	0	0	0	43	384	**427**	
2019	0	0	0	0	51	410	**461**	
2020**	0	0	0	0	41	386	**427**	
2021**	0	0	0	1	33	404	**438**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

** Preliminary figures.

^ While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.

Human papillomavirus								ICD10: C52
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
*Mortality (vagina cancer; source: CBS)^*								
2002	0	0	0	0	2	18	**20**	
2003	0	0	0	0	0	28	**28**	
2004	0	0	0	1	1	17	**19**	
2005	0	0	0	0	3	27	**30**	
2006	0	0	0	0	5	18	**23**	
2007	0	0	0	0	0	17	**17**	
2008	0	0	0	0	2	17	**19**	
2009	0	0	0	0	2	15	**17**	
2010	0	0	0	0	1	21	**22**	
2011	0	0	0	0	0	21	**21**	
2012	0	0	0	0	1	26	**27**	
2013	0	0	0	0	0	27	**27**	
2014	0	0	0	0	1	20	**21**	
2015	0	0	0	0	0	21	**21**	
2016	0	0	0	0	1	22	**23**	
2017	0	0	0	0	0	18	**18**	
2018	0	0	0	0	1	24	**25**	
2019	0	0	0	0	2	23	**25**	
2020	0	0	0	0	0	21	**21**	
2021*	0	0	0	0	1	25	**26**	
*Registrations (vagina cancer; source: NKR)^*								
2002	0	0	0	0	4	44	**48**	
2003	0	0	0	0	7	36	**43**	
2004	0	0	0	0	4	41	**45**	
2005	0	0	0	0	4	36	**40**	
2006	0	0	0	0	6	34	**40**	
2007	0	0	0	0	5	40	**45**	
2008	0	0	0	0	4	35	**39**	
2009	0	0	0	0	7	33	**40**	
2010	0	0	0	0	4	45	**49**	
2011	0	0	0	0	4	54	**58**	
2012	0	0	0	0	8	47	**55**	
2013	0	0	0	0	1	37	**38**	
2014	0	0	0	0	8	33	**41**	
2015	0	0	0	0	4	49	**53**	
2016	0	0	0	0	7	33	**40**	
2017	0	0	0	0	4	48	**52**	
2018	0	0	0	0	1	55	**56**	
2019	0	0	0	0	3	39	**42**	
2020**	0	0	0	0	3	54	**57**	
2021**	0	0	0	0	8	56	**64**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

** Preliminary figures.

^ While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.

Human papillomavirus								ICD10: C60
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
*Mortality (penis cancer; source: CBS)^*								
2002	0	0	0	0	1	12	**13**	
2003	0	0	0	0	1	19	**20**	
2004	0	0	0	0	1	22	**23**	
2005	0	0	0	0	1	20	**21**	
2006	0	0	0	0	1	13	**14**	
2007	0	0	0	0	2	29	**31**	
2008	0	0	0	0	1	25	**26**	
2009	0	0	0	0	2	22	**24**	
2010	0	0	0	0	1	32	**33**	
2011	0	0	0	0	2	31	**33**	
2012	0	0	0	0	4	34	**38**	
2013	0	0	0	0	2	20	**22**	
2014	0	0	0	0	2	33	**35**	
2015	0	0	0	0	2	33	**35**	
2016	0	0	0	0	1	33	**34**	
2017	0	0	0	0	4	30	**34**	
2018	0	0	0	0	2	32	**34**	
2019	0	0	0	0	1	45	**46**	
2020	0	0	0	0	1	50	**51**	
2021*	0	0	0	0	0	37	**37**	
*Registrations (penis cancer; source: NKR)^*								
2002	0	0	0	0	11	89	**100**	
2003	0	0	0	0	8	95	**103**	
2004	0	0	0	0	5	111	**116**	
2005	0	0	0	0	13	96	**109**	
2006	0	0	0	0	11	106	**117**	
2007	0	0	0	0	10	98	**108**	
2008	0	0	0	0	17	111	**128**	
2009	0	0	0	0	13	127	**140**	
2010	0	0	0	0	19	122	**141**	
2011	0	0	0	0	11	136	**147**	
2012	0	0	0	0	10	128	**138**	
2013	0	0	0	0	11	130	**141**	
2014	0	0	0	0	7	116	**123**	
2015	0	0	0	0	11	142	**153**	
2016	0	0	0	0	9	157	**166**	
2017	0	0	0	0	13	152	**165**	
2018	0	0	0	0	12	175	**187**	
2019	0	0	0	0	11	190	**201**	
2020**	0	0	0	0	13	167	**180**	
2021**	0	0	0	0	5	168	**173**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

** Preliminary figures.

^ While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.

Human papillomavirus								ICD10: C10
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
*Mortality (oropharynx cancer; source: CBS)^*								
2002	0	0	0	0	7	63	**70**	
2003	0	0	0	0	11	73	**84**	
2004	0	0	0	0	6	68	**74**	
2005	0	0	0	0	7	52	**59**	
2006	0	0	0	0	3	62	**65**	
2007	0	0	0	0	4	67	**71**	
2008	0	0	0	0	3	63	**66**	
2009	0	0	0	0	3	71	**74**	
2010	0	0	0	0	5	75	**80**	
2011	0	0	0	0	5	89	**94**	
2012	0	0	0	0	2	96	**98**	
2013	0	0	0	0	5	90	**95**	
2014	0	0	0	0	2	95	**97**	
2015	0	0	0	0	2	93	**95**	
2016	0	0	0	0	4	97	**101**	
2017	0	0	0	0	4	96	**100**	
2018	0	0	0	0	2	101	**103**	
2019	0	0	0	0	3	114	**117**	
2020	0	0	0	0	3	114	**117**	
2021*	0	0	0	0	1	122	**123**	
*Registrations (oropharynx cancer; source: NKR)^*								
2002	0	0	0	0	71	396	**467**	
2003	0	0	0	0	75	405	**480**	
2004	0	0	0	0	66	416	**482**	
2005	0	0	0	0	57	397	**454**	
2006	0	0	0	0	40	425	**465**	
2007	0	0	0	0	52	424	**476**	
2008	0	0	0	1	54	499	**554**	
2009	0	0	0	0	52	492	**544**	
2010	0	0	0	0	61	496	**557**	
2011	0	0	0	0	58	561	**619**	
2012	0	0	0	0	44	573	**617**	
2013	0	0	0	0	42	568	**610**	
2014	0	0	0	0	44	591	**635**	
2015	0	0	0	0	40	575	**615**	
2016	0	0	0	0	48	646	**694**	
2017	0	0	0	0	38	629	**667**	
2018	0	0	0	0	35	658	**693**	
2019	0	0	0	1	46	638	**685**	
2020**	0	0	0	0	25	665	**690**	
2021**	0	0	0	1	43	609	**653**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

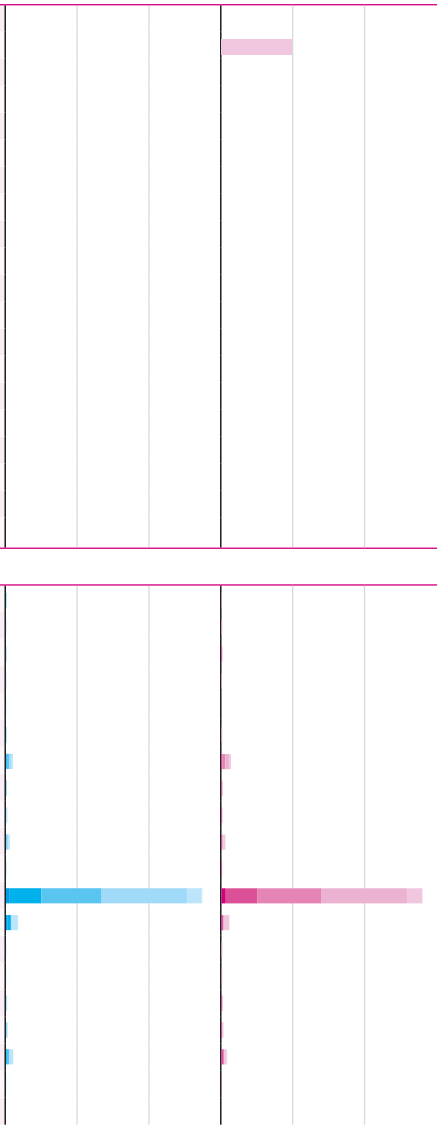
** Preliminary figures.

^ While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.

Human papillomavirus								ICD10: C21
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
*Mortality (anus cancer; source: CBS)^*								
2002	0	0	0	0	1	31	**32**	
2003	0	0	0	0	2	20	**22**	
2004	0	0	0	0	3	21	**24**	
2005	0	0	0	0	1	37	**38**	
2006	0	0	0	0	5	21	**26**	
2007	0	0	0	0	6	20	**26**	
2008	0	0	0	0	3	30	**33**	
2009	0	0	0	0	2	37	**39**	
2010	0	0	0	0	2	39	**41**	
2011	0	0	0	0	1	38	**39**	
2012	0	0	0	0	6	33	**39**	
2013	0	0	0	0	1	35	**36**	
2014	0	0	0	0	2	39	**41**	
2015	0	0	0	0	3	31	**34**	
2016	0	0	0	0	4	49	**53**	
2017	0	0	0	0	2	57	**59**	
2018	0	0	0	0	4	54	**58**	
2019	0	0	0	0	3	61	**64**	
2020	0	0	0	0	3	53	**56**	
2021*	0	0	0	0	6	59	**65**	
*Registrations (anus cancer; source: NKR)^*								
2002	0	0	0	0	27	82	**109**	
2003	0	0	0	0	22	108	**130**	
2004	0	0	0	0	22	87	**109**	
2005	0	0	0	0	25	104	**129**	
2006	0	0	0	0	22	130	**152**	
2007	0	0	0	0	34	108	**142**	
2008	0	0	0	0	29	133	**162**	
2009	0	0	0	0	33	128	**161**	
2010	0	0	0	0	24	152	**176**	
2011	0	0	0	0	28	156	**184**	
2012	0	0	0	0	36	178	**214**	
2013	0	0	0	0	30	187	**217**	
2014	0	0	0	0	30	175	**205**	
2015	0	0	0	0	33	215	**248**	
2016	0	0	0	0	32	225	**257**	
2017	0	0	0	0	25	219	**244**	
2018	0	0	0	0	29	261	**290**	
2019	0	0	0	0	21	234	**255**	
2020**	0	0	0	0	25	239	**264**	
2021**	0	0	0	0	32	266	**298**	

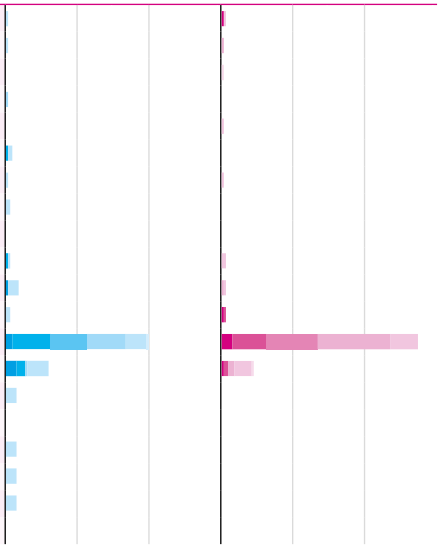
* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.
** Preliminary figures.
^ While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.

Measles								ICD10: B05
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	1	0	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2002	0	2	0	1	0	0	**3**	
2003	0	0	1	2	1	0	**4**	
2004	1	1	0	3	6	0	**11**	
2005	0	0	1	1	1	0	**3**	
2006	0	0	0	0	1	0	**1**	
2007	0	1	0	0	8	0	**9**	
2008	4	8	38	39	21	0	**110**	
2009	1	2	2	3	7	0	**15**	
2010	1	2	2	1	9	0	**15**	
2011	2	2	7	14	26	0	**51**	
2012	1	2	0	1	6	0	**10**	
2013	53	425	840	1,162	199	9	**2,688**	
2014	18	25	6	17	65	3	**134**	
2015	0	0	0	0	6	1	**7**	
2016	0	0	2	0	4	0	**6**	
2017	0	1	1	3	10	1	**16**	
2018	3	4	0	2	14	1	**24**	
2019	4	15	17	10	37	1	**84**	
2020	0	1	0	0	1	0	**2**	
2021	0	0	0	0	0	0	**0**	



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Measles								ICD9: 055 ICD10: B05
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
2001	1	0	0	0	2	0	**3**	
2002	0	0	0	1	1	0	**2**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	1	0	0	**1**	
2005	0	0	0	0	1	0	**1**	
2006	0	1	0	0	2	0	**3**	
2007	0	0	0	0	2	0	**2**	
2008	0	0	0	0	2	0	**2**	
2009	0	0	0	0	0	0	**0**	
2010	0	1	0	0	3	0	**4**	
2011	1	0	0	1	6	0	**9**	
2012	1	1	0	0	2	0	**4**	
2013	8	34	41	52	23	1	**164**	
2014	6	6	0	4	18	1	**35**	
2015^	0	0	0	0	5	0	**5**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	5	0	**5**	
2018^	0	0	0	0	5	0	**10**	
2019^	0	0	0	0	10	0	**10**	
2020^	0	0	0	0	0	0	**0**	

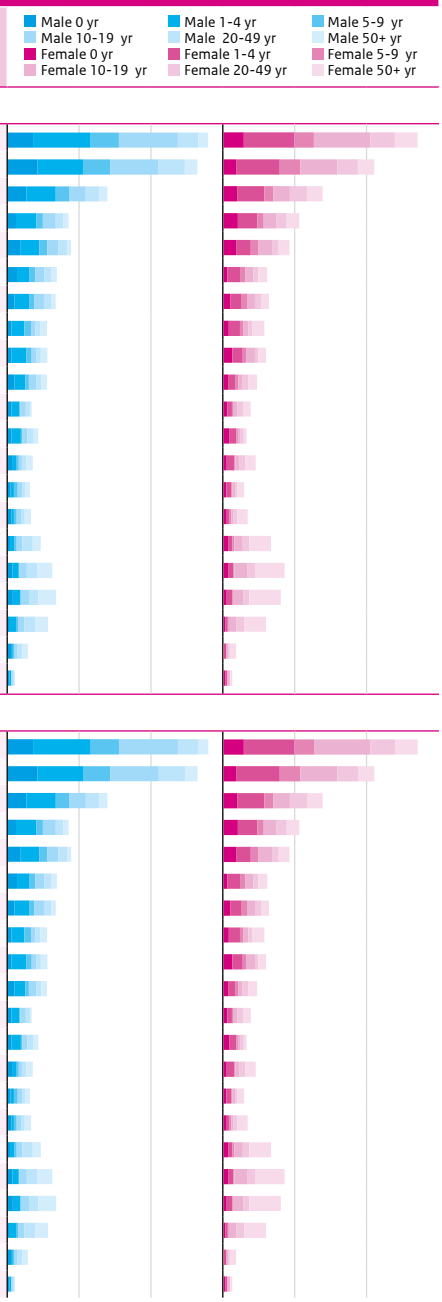


* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Meningococcal disease — ICD10: A39

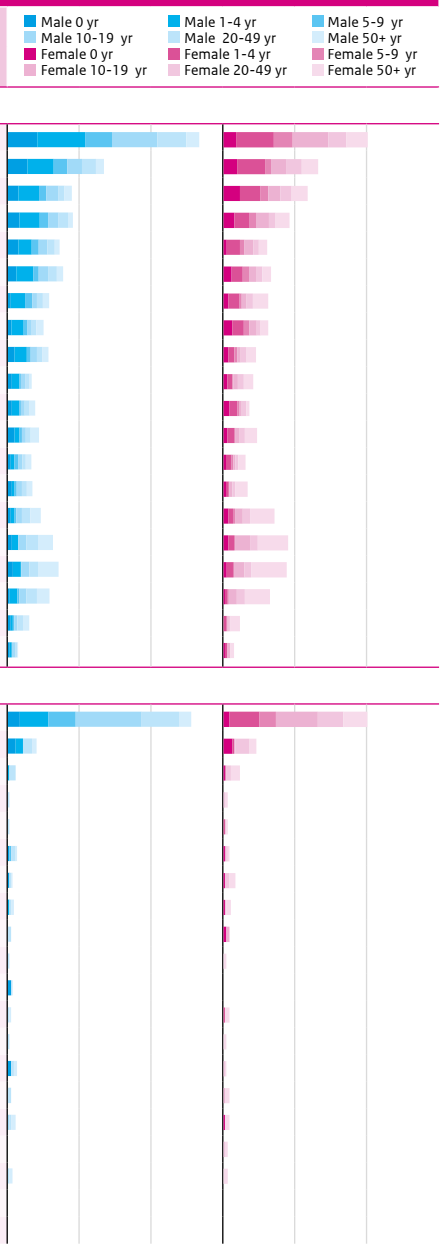
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
2001	4	16	2	16	10	8	**56**
2002	4	14	2	8	4	12	**44**
2003	7	7	0	0	3	3	**20**
2004	0	5	0	0	2	8	**15**
2005	3	3	0	3	0	2	**11**
2006	1	0	1	1	0	1	**4**
2007	2	3	0	1	0	3	**9**
2008	1	1	0	0	2	3	**7**
2009	1	3	0	0	1	1	**6**
2010	3	2	0	1	0	2	**8**
2011	2	0	0	0	1	2	**5**
2012	0	1	0	0	0	0	**1**
2013	0	1	0	1	0	1	**3**
2014	0	1	0	0	0	5	**6**
2015	0	1	0	0	1	2	**4**
2016	0	2	0	1	0	3	**6**
2017	1	2	0	1	2	2	**8**
2018	0	2	0	4	2	5	**13**
2019	1	1	0	1	1	4	**8**
2020	0	0	0	0	0	1	**1**
2021*	0	0	0	0	0	0	**0**
Notifications (source: Osiris)							
2001	88	211	93	224	87	63	**766**
2002	82	173	93	166	91	56	**661**
2003	62	110	44	64	60	46	**386**
2004	45	77	25	50	35	34	**266**
2005	48	67	30	48	30	29	**252**
2006	25	50	20	34	24	27	**180**
2007	26	50	23	32	27	23	**181**
2008	17	47	19	19	17	36	**155**
2009	24	49	18	25	16	28	**160**
2010	22	34	14	21	22	28	**141**
2011	14	24	4	19	20	18	**99**
2012	18	32	6	15	17	16	**104**
2013	16	22	6	14	20	32	**110**
2014	10	17	9	14	10	23	**83**
2015	13	10	9	13	14	33	**92**
2016	13	17	8	27	33	58	**156**
2017	18	22	3	41	34	87	**205**
2018	16	25	2	37	29	96	**205**
2019	5	20	5	26	38	67	**161**
2020	6	9	4	8	13	23	**63**
2021	6	7	0	9	4	5	**31**



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

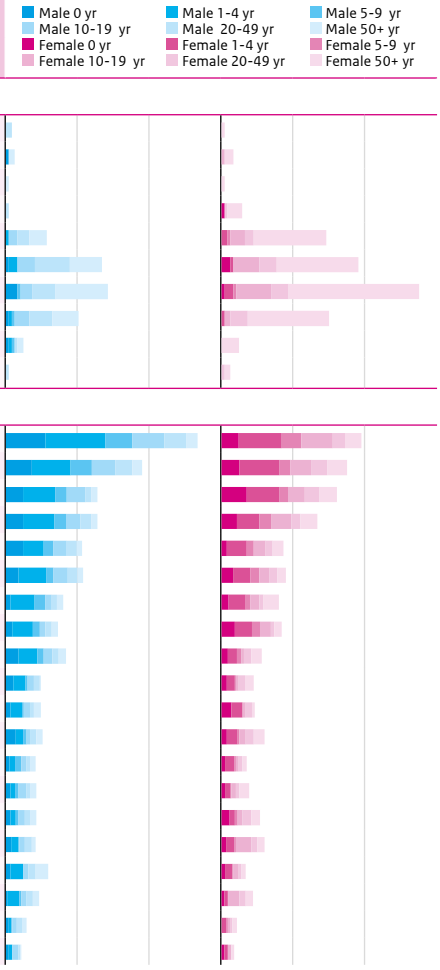
Meningococcal disease

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serogroups; source: NRLBM)							
2002	79	154	84	148	86	62	**613**
2003	61	98	37	54	56	45	**351**
2004	50	75	27	45	31	43	**271**
2005	41	63	29	45	30	34	**242**
2006	25	49	22	32	23	24	**175**
2007	30	51	20	30	27	28	**186**
2008	15	47	18	18	22	39	**159**
2009	25	47	18	23	16	28	**157**
2010	23	34	13	18	21	28	**137**
2011	15	23	4	18	19	22	**101**
2012	18	28	7	11	17	16	**97**
2013	19	21	6	15	19	37	**117**
2014	10	16	10	12	11	23	**82**
2015	12	10	5	14	15	33	**89**
2016	14	15	7	24	28	63	**151**
2017	16	21	3	41	35	82	**198**
2018	15	25	3	33	28	101	**205**
2019	6	19	5	27	34	68	**159**
2020	5	9	4	9	13	28	**68**
2021	6	8	0	12	4	7	**37**
Laboratory diagnoses (serogroup C; source: NRLBM)							
2002	13	39	30	73	42	25	**222**
2003	11	6	0	1	16	8	**42**
2004	1	1	1	0	7	7	**17**
2005	0	0	0	0	2	2	**4**
2006	0	1	0	0	2	1	**4**
2007	2	0	1	1	4	2	**10**
2008	2	0	0	0	4	5	**11**
2009	1	1	0	0	2	5	**9**
2010	2	0	0	2	2	0	**6**
2011	0	0	0	0	1	2	**3**
2012	2	0	0	0	1	0	**3**
2013	0	1	0	0	1	4	**6**
2014	0	0	0	0	1	2	**3**
2015	2	0	0	0	3	3	**8**
2016	0	0	0	1	2	3	**6**
2017	1	0	0	1	1	6	**9**
2018	0	0	0	0	1	2	**3**
2019	0	0	0	0	1	5	**6**
2020	0	0	0	0	0	0	**0**
2021	0	0	0	0	0	0	**0**



Meningococcal disease

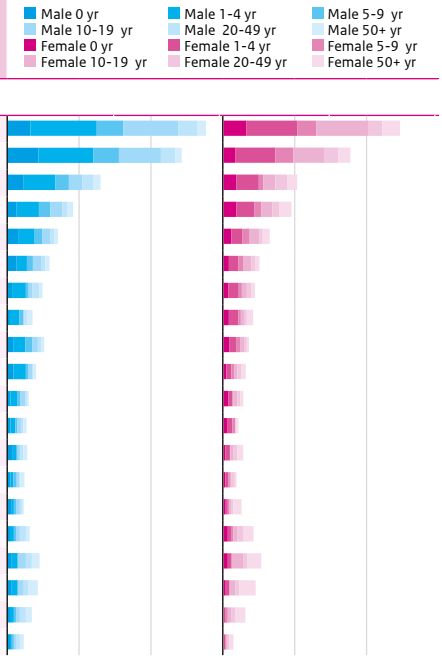
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (serogroup W; source: NRLBM)							
2012	0	0	0	0	2	1	**3**
2013	1	0	0	1	0	5	**7**
2014	0	0	0	0	0	2	**2**
2015	1	0	0	0	2	6	**9**
2016	0	3	1	8	7	31	**50**
2017	4	4	0	15	18	39	**80**
2018	5	3	2	16	14	63	**103**
2019	1	2	1	7	14	37	**62**
2020	1	1	1	0	1	8	**12**
2021	0	0	0	0	2	2	**4**
Laboratory diagnoses (serogroup B; source: NRLBM)							
2002	65	115	53	72	39	31	**375**
2003	49	88	36	49	38	33	**293**
2004	48	73	22	40	22	27	**232**
2005	36	60	27	38	22	26	**209**
2006	25	45	20	28	19	18	**155**
2007	27	50	18	27	20	17	**159**
2008	13	46	17	17	11	24	**128**
2009	23	42	17	18	11	15	**126**
2010	21	31	12	13	15	20	**112**
2011	14	23	3	10	14	11	**75**
2012	16	25	3	10	11	11	**76**
2013	17	20	6	11	16	19	**89**
2014	8	16	9	9	8	11	**61**
2015	9	11	5	14	8	18	**65**
2016	14	12	6	12	16	17	**77**
2017	11	17	3	23	15	12	**81**
2018	9	22	1	12	11	19	**74**
2019	5	17	3	18	14	15	**72**
2020	3	8	3	8	8	10	**40**
2021	6	8	0	11	2	4	**31**



Meningococcal disease

ICD9: 036.0-4, 036.8-9
ICD10: A39

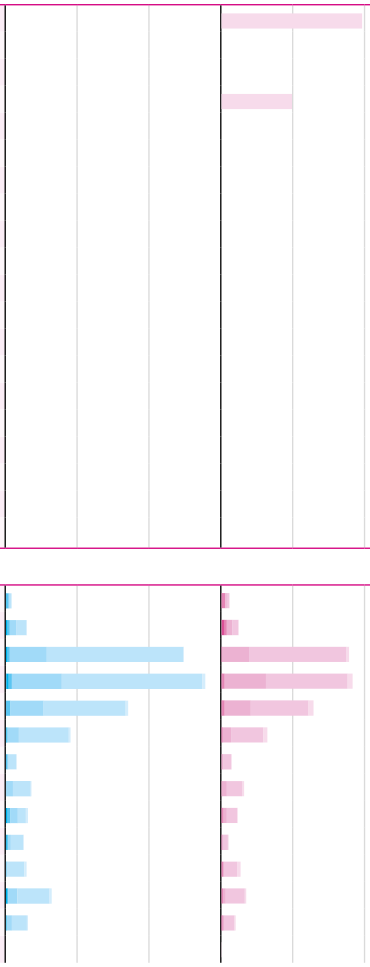
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD/CBS)*							
2001	114	295	113	268	85	66	**949**
2002	106	238	110	182	72	47	**767**
2003	72	135	46	64	57	44	**421**
2004	54	101	46	58	31	45	**336**
2005	45	70	36	45	19	27	**244**
2006	35	50	28	40	20	21	**196**
2007	23	58	17	22	28	18	**166**
2008	18	48	15	14	11	30	**136**
2009	28	49	26	25	14	13	**156**
2010	21	37	12	20	13	18	**122**
2011	18	27	12	20	13	11	**103**
2012	15	26	11	11	9	12	**84**
2013	16	22	4	14	17	25	**99**
2014	10	15	13	11	10	16	**75**
2015^	15	15	10	15	10	25	**90**
2016^	15	20	10	20	30	35	**135**
2017^	15	30	5	50	30	55	**180**
2018^	15	30	5	30	20	65	**160**
2019^	5	15	5	20	25	40	**115**
2020^	5	10	5	5	15	15	**55**



* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Mumps								ICD10: B26
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	0	0	0	0	0	2	**2**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2008	0	2	10	5	7	1	**25**	
2009	0	9	8	22	30	2	**71**	
2010	0	4	5	119	435	6	**569**	
2011	1	6	10	169	412	15	**613**	
2012	0	2	12	110	260	13	**397**	
2013	0	3	2	37	152	11	**205**	
2014	0	0	4	5	28	2	**39**	
2015	0	0	2	21	61	5	**89**	
2016	0	5	7	20	34	5	**71**	
2017	1	3	0	8	32	2	**46**	
2018	0	1	3	5	54	10	**73**	
2019	0	4	3	22	95	7	**131**	
2020	0	3	0	13	44	4	**64**	
2021	0	0	0	0	0	1	**1**	

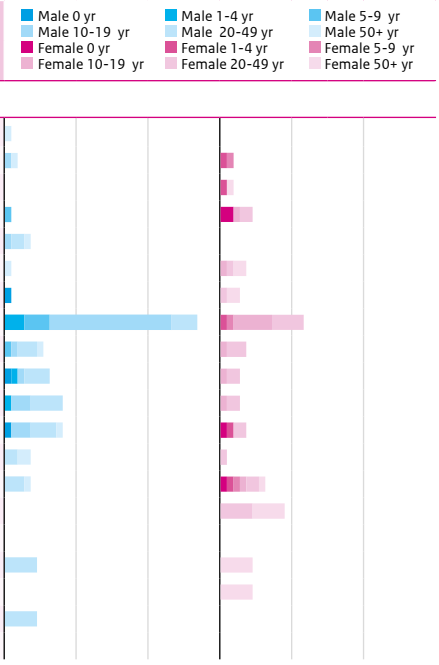


* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Mumps

ICD9: 072
ICD10: B26

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD/CBS)*							
2001	0	0	0	0	0	1	**1**
2002	0	1	1	1	0	1	**4**
2003	0	1	0	0	0	1	**2**
2004	2	0	1	1	2	0	**6**
2005	0	0	0	1	2	1	**4**
2006	0	0	0	1	1	3	**5**
2007	1	0	0	0	1	2	**4**
2008	0	4	5	25	9	0	**43**
2009	0	0	1	2	6	1	**10**
2010	1	1	0	2	6	0	**10**
2011	0	1	0	4	7	0	**12**
2012	2	1	0	3	6	1	**14**
2013	0	0	0	0	3	2	**5**
2014	1	1	1	1	5	2	**11**
2015^	0	0	0	0	5	5	**15**
2016^	0	0	0	0	0	5	**5**
2017^	0	0	0	0	5	5	**10**
2018^	0	0	0	0	5	5	**10**
2019^	0	0	0	0	5	0	**10**
2020^	0	0	0	0	0	0	**5**



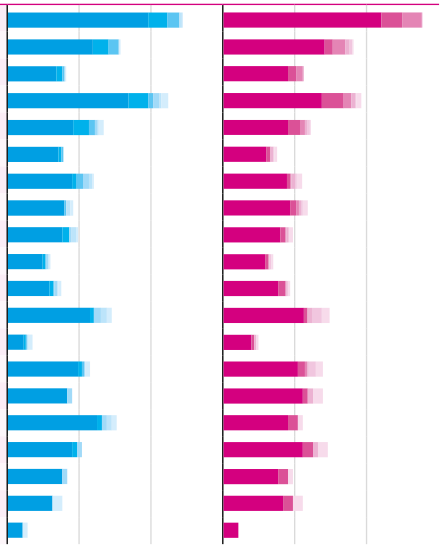
* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Pertussis								ICD10: A37
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	1	0	0	0	0	0	**1**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	1	0	0	**1**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	1	**1**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	1	0	0	0	0	0	**1**	
2012	2	0	0	0	0	0	**2**	
2013	0	0	0	0	0	0	**0**	
2014	1	0	0	0	0	0	**1**	
2015	1	0	0	0	0	0	**1**	
2016	1	0	0	0	0	1	**2**	
2017	1	0	0	0	0	1	**2**	
2018	1	0	0	0	0	0	**1**	
2019	2	0	0	0	0	0	**2**	
2020	1	0	0	0	0	1	**2**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2002	168	511	1,624	1,004	807	438	**4,552**	
2003	134	367	1,070	582	465	245	**2,863**	
2004	367	1,006	2,750	2,390	2,099	1,139	**9,751**	
2005	190	787	1,292	1,586	1,212	850	**5,917**	
2006	143	471	788	1,353	987	622	**4,364**	
2007	190	450	837	2,888	2,057	1,331	**7,753**	
2008	195	346	779	3,154	2,343	1,484	**8,301**	
2009	164	270	658	2,442	1,962	1,064	**6,560**	
2010	115	168	355	1,278	1,212	637	**3,765**	
2011	160	283	1,007	2,531	1,984	1,231	**7,196**	
2012	234	378	1,525	4,192	4,497	3,002	**13,828**	
2013	77	136	315	889	1,054	931	**3,402**	
2014	258	490	788	2,859	2,721	2,138	**9,254**	
2015	174	274	560	1,962	2,053	1,532	**6,555**	
2016	217	402	489	1,426	1,813	1,223	**5,570**	
2017	182	221	416	1,307	1,610	1,146	**4,912**	
2018	193	334	432	1,260	1,534	1,144	**4,897**	
2019	188	311	424	1,608	2,155	1,697	**6,383**	
2020	38	40	77	228	287	271	**941**	
2021	9	7	1	7	23	27	**74**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Pertussis								ICD9: 033 ICD10: A37
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
2001	301	40	32	1	2	2	**378**	
2002	188	24	23	4	3	3	**245**	
2003	114	14	9	2	0	1	**140**	
2004	221	42	13	10	3	12	**301**	
2005	131	28	11	5	4	6	**185**	
2006	94	7	2	3	1	3	**110**	
2007	129	7	8	10	5	7	**166**	
2008	124	6	5	2	6	8	**151**	
2009	112	12	1	4	6	6	**141**	
2010	77	6	2	2	2	4	**93**	
2011	97	11	2	4	2	5	**121**	
2012	164	7	1	11	16	13	**213**	
2013	44	5	1	2	2	6	**60**	
2014	146	11	4	3	7	12	**185**	
2015^	140	10	0	10	5	10	**175**	
2016^	155	15	0	5	5	10	**190**	
2017^	150	10	0	10	0	10	**180**	
2018^	110	10	0	5	0	10	**135**	
2019^	105	10	0	0	5	15	**140**	
2020^	30	5	0	0	0	5	**40**	

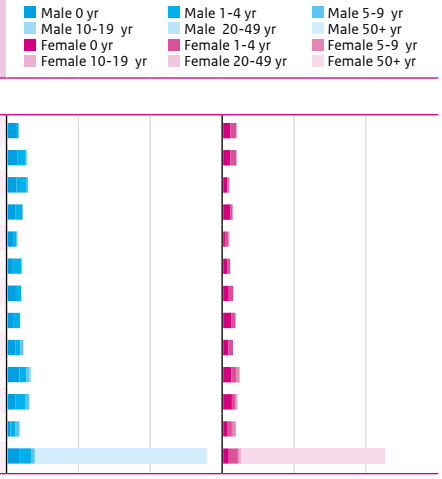


* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

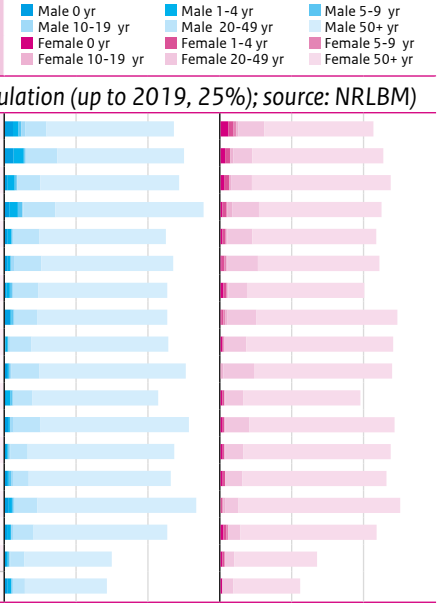
Pneumococcal disease

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications IPD (source: Osiris)*							
2009	28	14	1				**43**
2010	31	24	2				**57**
2011	23	21	3				**47**
2012	27	15	2				**44**
2013	13	11	4				**28**
2014	16	20	2				**38**
2015	25	17	0				**42**
2016	25	18	1				**44**
2017	23	17	4	1			**45**
2018	35	21	12	2			**70**
2019	29	24	9	2			**64**
2020	13	16	14	1			**44**
2021	30	37	10	4		555	**636**
Laboratory diagnoses IPD (nationwide; source: NRLBM)							
2008	40	40					**80**
2009	45	28					**73**
2010	44	34					**78**
2011	38	26					**64**
2012	33	17					**50**
2013	22	12					**34**
2014	22	25					**47**
2015	38	22					**60**
2016	30	19					**49**
2017	26	24	17	9			**76**
2018	40	28	16	10			**94**
2019	33	28	9	12			**61**
2020	15	17	14	3			**32**
2021	33	36	9	10	147	857	**1092**



Pneumococcal disease

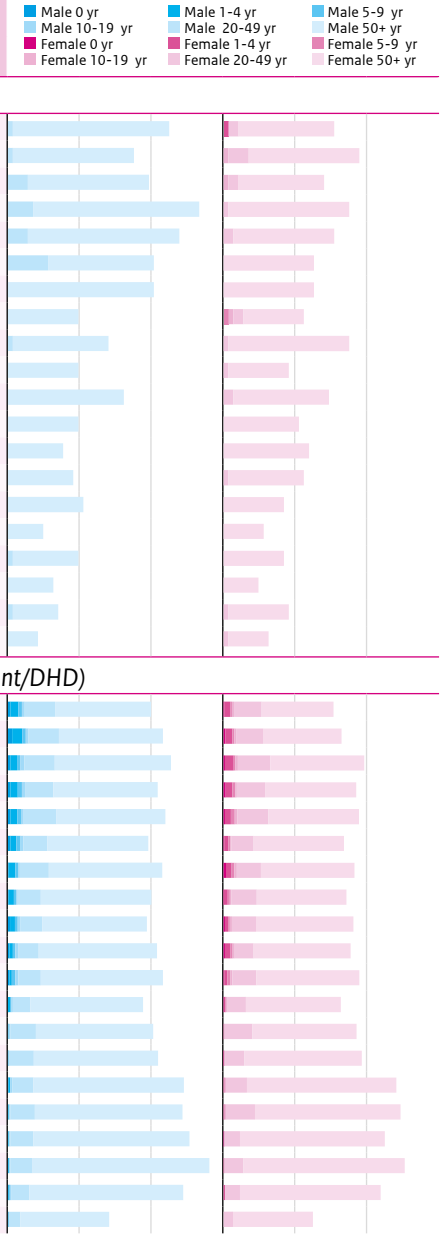
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses IPD (sentinel labs covering 28% of population (up to 2019, 25%); source: NRLBM)							
2004	30	20	10	12	88	444	**604**
2005	24	30	3	8	95	480	**640**
2006	11	23	4	4	83	516	**641**
2007	11	24	10	12	110	519	**686**
2008	10	14	4	5	100	474	**607**
2009	8	10	4	10	110	478	**620**
2010	9	12	6	4	83	459	**573**
2011	11	7	8	7	95	506	**634**
2012	4	7	3	3	81	540	**638**
2013	4	3	4	6	110	525	**652**
2014	5	11	5	5	67	454	**547**
2015	10	5	1	9	95	547	**667**
2016	6	5	3	4	66	547	**631**
2017	8	8	5	4	60	531	**616**
2018	7	9	5	5	67	595	**688**
2019	9	13	3	4	61	503	**593**
2020	5	7	4	2	45	316	**379**
2021	8	7	0	3	42	379	**339**
Mortality IPD (all ages, sentinel labs covering 25% of Dutch population; source: NRLBM)							
2005	3	0	0	0	1	101	**105**
2006	0	1	0	0	3	91	**95**
2007	0	0	0	0	7	82	**89**
2008	0	1	0	0	7	82	**90**
2009	1	1	1	0	4	75	**82**
2010	0	0	0	0	6	52	**58**
2011	0	0	0	0	3	65	**68**
2012	0	0	0	0	6	68	**74**
2013	0	0	0	0	1	75	**76**
2014	0	1	0	1	1	75	**78**
2015	1	0	0	0	4	72	**77**



Pneumococcal disease

ICD9: 481
ICD10: J13

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality pneumococcal pneumonia (source: CBS)*							
2002	0	1	0	0	3	50	**54**
2003	0	0	0	1	5	46	**52**
2004	0	0	0	1	6	41	**48**
2005	0	0	0	0	6	57	**63**
2006	0	0	0	0	6	50	**56**
2007	0	0	0	0	8	39	**47**
2008	0	0	0	0	0	47	**47**
2009	0	0	1	1	2	37	**41**
2010	0	0	0	0	2	43	**45**
2011	0	0	0	0	1	26	**27**
2012	0	0	0	0	2	42	**44**
2013	0	0	0	0	0	29	**29**
2014	0	0	0	0	0	28	**28**
2015	0	0	0	0	1	28	**29**
2016	0	0	0	0	0	27	**27**
2017	0	0	0	0	0	15	**15**
2018	0	0	0	0	1	25	**26**
2019	0	0	0	0	0	16	**16**
2020	0	0	0	0	2	21	**23**
2021*	0	0	0	0	1	14	**15**
*Hospitalisations pneumococcal pneumonia** (source: Prismant/DHD)*							
2001	24	102	39	34	421	1,215	**1,839**
2002	45	123	41	35	414	1,323	**1,987**
2003	28	115	34	49	454	1,523	**2,215**
2004	33	103	51	37	409	1,416	**2,051**
2005	29	95	57	36	461	1,446	**2,130**
2006	25	72	46	28	333	1,388	**1,893**
2007	10	87	41	33	382	1,502	**2,064**
2008	8	68	31	21	352	1,452	**1,938**
2009	28	59	30	36	332	1,465	**1,955**
2010	23	62	37	35	285	1,560	**2,009**
2011	17	40	46	38	337	1,631	**2,111**
2012	4	28	11	20	263	1,506	**1,835**
2013	0	4	7	17	384	1,606	**2,020**
2014	3	4	3	19	309	1,754	**2,095**
2015^	5	10	10	25	305	2,175	**2,525**
2016^	0	5	5	20	380	2,125	**2,540**
2017^	5	5	5	15	270	2,180	**2,485**
2018^	5	10	5	15	290	2,455	**2,785**
2019^	5	15	5	15	235	2,140	**2,410**
2020^	5	0	0	5	155	1,230	**1,395**



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

** Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Poliomyelitis								ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	3	**3**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	

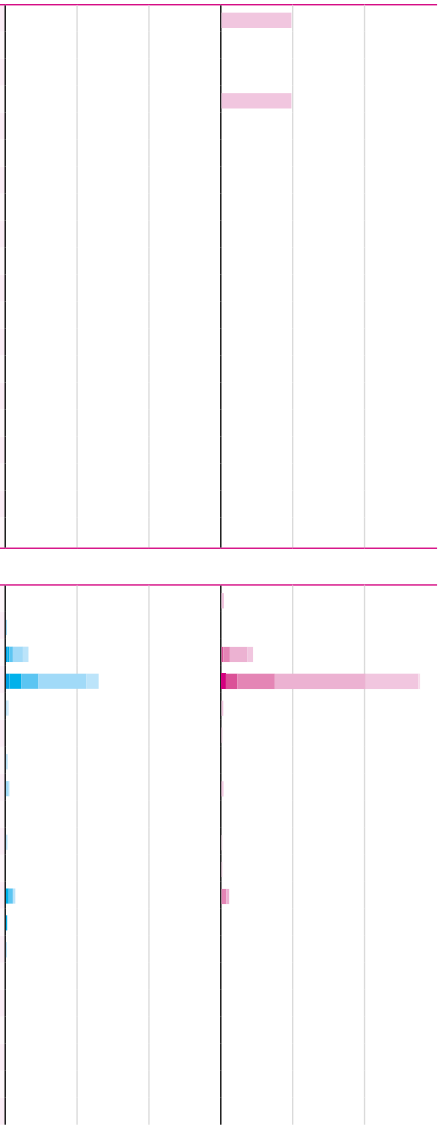
* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Poliomyelitis								ICD9: 045 ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prismant/DHD)*								
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	
2018^	0	0	0	0	0	0	**0**	
2019^	0	0	0	0	0	0	**0**	
2020^	0	0	0	0	0	0	**0**	

* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

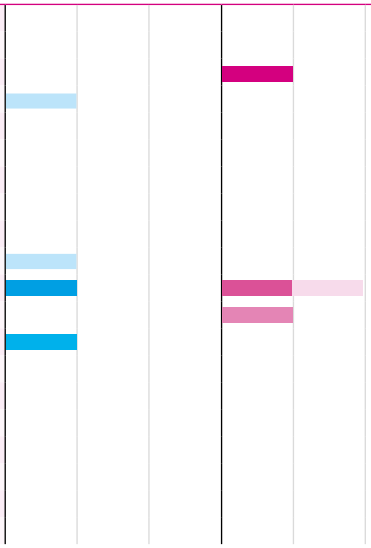
^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Rubella (acquired)								ICD10: B06
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	0	0	0	0	1	0	**1**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	1	0	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2002	0	0	0	0	3	0	**3**	
2003	0	0	0	1	0	0	**1**	
2004	2	4	12	33	14	0	**65**	
2005	9	28	66	166	78	2	**349**	
2006	0	0	0	0	4	1	**5**	
2007	0	0	0	0	1	0	**1**	
2008	0	0	0	0	2	0	**2**	
2009	0	0	0	4	2	1	**7**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	1	2	**3**	
2012	0	0	0	0	1	0	**1**	
2013**	0	10	37	7	3	0	**57**	
2014	0	1	0	0	1	0	**2**	
2015	0	0	0	0	1	0	**1**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.
** Gender unknown for 37 cases.

Rubella (acquired)								ICD9: 056 ICD10: B06
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations (source: Prisman/DHD)*								
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	1	0	0	0	0	0	**1**	
2004	0	0	0	0	1	0	**1**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	1	0	**1**	
2011	1	1	0	0	0	1	**3**	
2012	0	0	1	0	0	0	**1**	
2013	0	1	0	0	0	0	**1**	
2014	0	0	0	0	0	0	**0**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	
2018^	0	0	0	0	0	0	**0**	
2019^	0	0	0	0	0	0	**0**	
2020^	0	0	0	0	0	0	**0**	



* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

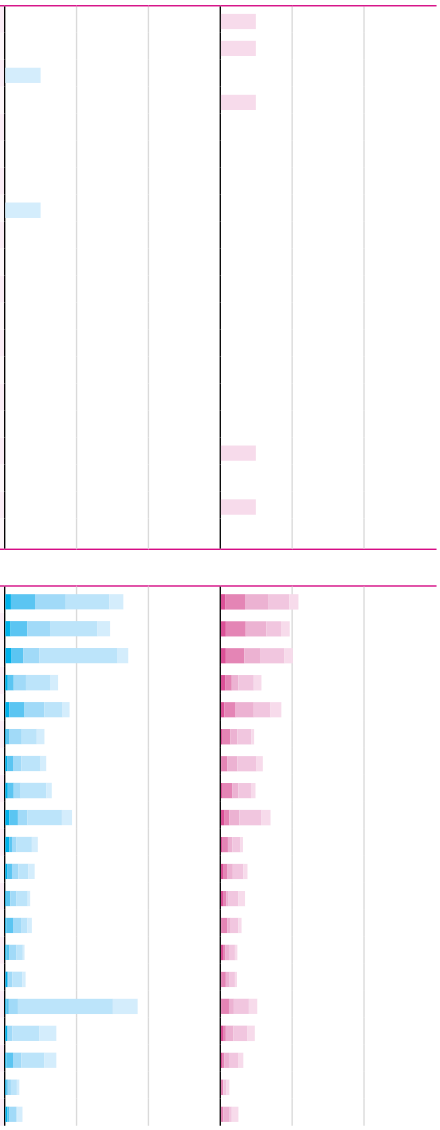
^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Tetanus								ID10: A33-35
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	2	**2**	
2011	0	0	0	0	0	5	**5**	
2012	0	0	0	0	1	1	**2**	
2013	0	0	0	0	1	0	**1**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	1	0	0	**1**	
2016	0	0	0	0	0	1	**1**	
2017	0	0	0	0	0	1	**1**	
2018	0	0	0	0	0	1	**1**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	1	0	1	**2**	
2021	0	0	0	0	0	0	**0**	

* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Potential NIP target diseases

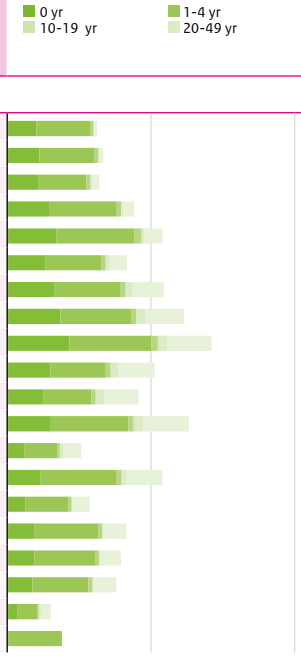
Hepatitis A								ICD10: B15
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	1	**1**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	1	**1**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	1	**0**	
2021*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2002	0	23	97	119	143	51	**433**	
2003	0	23	81	96	137	48	**385**	
2004	1	24	67	71	226	44	**433**	
2005	0	16	27	42	87	35	**207**	
2006	0	17	59	84	77	39	**276**	
2007	0	5	26	43	64	23	**161**	
2008	0	6	25	42	85	27	**185**	
2009	0	9	36	28	85	22	**180**	
2010	0	17	30	43	124	44	**258**	
2011	0	13	18	20	52	18	**121**	
2012	0	9	21	26	45	23	**124**	
2013	0	7	16	18	48	20	**109**	
2014	0	5	26	26	31	17	**105**	
2015	0	8	12	22	28	10	**80**	
2016	1	5	12	18	33	12	**81**	
2017	0	5	21	31	243	74	**374**	
2018	0	9	8	27	89	55	**188**	
2019	0	6	19	29	71	38	**163**	
2020	0	2	9	8	20	11	**50**	
2021	1	4	11	28	7	26	**77**	



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

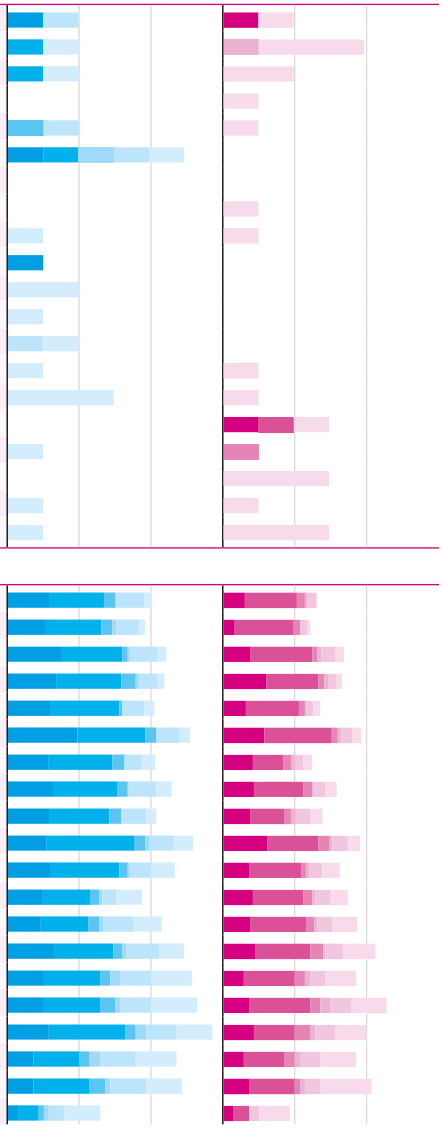
Rotavirus

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations (source: Prismant/DHD)*							
2002	1,180	2,208	148	0	0	160	**3,696**
2003	1,298	2,287	160	0	0	202	**3,947**
2004	1,240	2,011	160	16	51	298	**3,776**
2005	1,729	2,744	199	19	83	443	**5,217**
2006	1,990	3,254	272	26	109	737	**6,388**
2007	1,532	2,323	189	23	139	722	**4,928**
2008	1,933	2,702	211	47	274	1,288	**6,455**
2009	2,171	2,924	220	45	301	1,636	**7,297**
2010	2,534	3,398	262	60	329	1,845	**8,428**
2011	1,754	2,294	167	56	305	1,502	**6,078**
2012	1,470	1,985	148	71	329	1,392	**5,395**
2013	1,774	3,195	218	69	331	1,888	**7,477**
2014	669	1,383	83	26	118	753	**3,030**
2015	1,334	3,139	208	52	152	1,509	**6,394**
2016	704	1,812	110	28	18	712	**3,481**
2017	1,075	2,669	155	25	2	980	**4,905**
2018	1,098	2,502	161	31	0	888	**4,681**
2019^	1,009	2,311	163	42	1	955	**4,480**
2020#	399	804	60	12	85	405	**1,766**
2021†	1,109	2,234	167	34	237	1,125	**4,907**



* Hospitalisations are based on data from 2 years before and 2 years after the concerning year (if available).
^ The estimate for 2019 was based on 2017-2019, to exclude the exceptional COVID-19 pandemic years.
# The estimate for 2020 was based on only 2018 and 2019.
† The estimate for 2021 was based on the estimate for 2020.

Varicella (chickenpox)								ICD9: 052 ICD10: B01
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2002	2	0	0	0	1	1	**4**	
2003	0	1	0	1	0	4	**6**	
2004	0	1	0	0	0	3	**4**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	1	0	1	1	**3**	
2007	1	1	0	1	1	1	**5**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	2	**2**	
2011	1	0	0	0	0	0	**1**	
2012	0	0	0	0	0	2	**2**	
2013	0	0	0	0	0	1	**1**	
2014	0	0	0	0	1	1	**2**	
2015	0	0	0	0	0	2	**2**	
2016	0	0	0	0	0	4	**4**	
2017	1	1	0	0	0	1	**3**	
2018	0	0	1	0	0	1	**2**	
2019	0	0	0	0	0	3	**3**	
2020	0	0	0	0	0	2	**2**	
2021*	0	0	0	0	0	4	**4**	
*Hospitalisations** (source: Prismant/DHD/CBS)*								
2001	62	104	19	3	36	9	**233**	
2002	47	113	17	4	29	9	**219**	
2003	78	121	10	6	41	17	**273**	
2004	89	115	20	7	26	12	**269**	
2005	64	119	9	1	28	17	**238**	
2006	108	132	17	4	33	19	**313**	
2007	69	92	19	4	24	23	**231**	
2008	74	111	19	3	38	26	**271**	
2009	67	92	18	6	37	22	**242**	
2010	81	136	21	7	39	31	**315**	
2011	67	118	13	5	34	40	**277**	
2012	63	96	17	6	29	42	**253**	
2013	58	102	18	7	45	51	**281**	
2014	76	112	22	6	49	56	**321**	
2015^	55	105	15	10	50	70	**305**	
2016^	55	120	25	15	55	75	**345**	
2017^	70	120	25	10	50	60	**335**	
2018^	45	85	20	15	55	75	**290**	
2019^	55	100	20	10	50	85	**325**	
2020^	15	35	5	5	25	65	**155**	



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

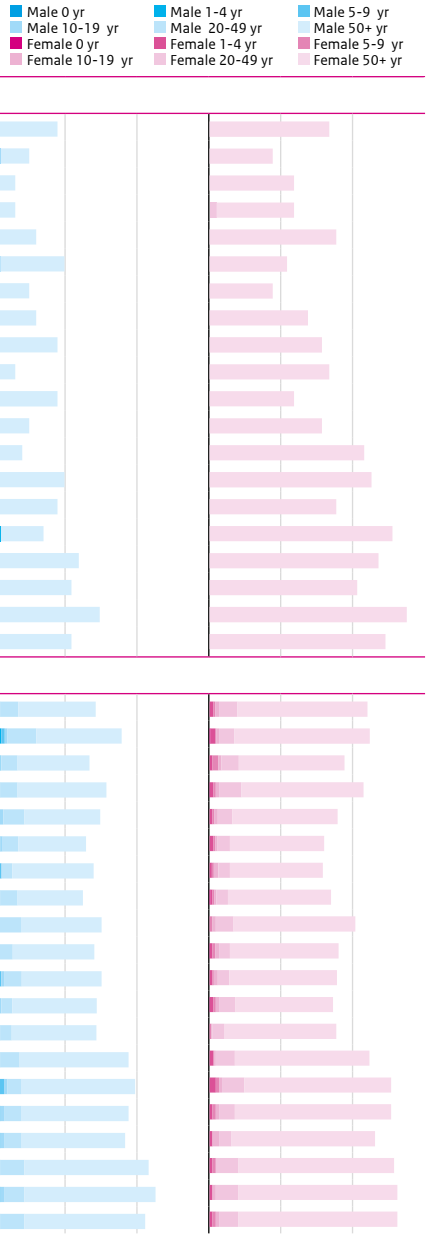
** Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Herpes zoster (shingles)

ICD9: 053
ICD10: B02

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Mortality (source: CBS)							
2002	0	0	0	0	0	26	**26**
2003	0	0	0	1	0	13	**14**
2004	0	0	0	0	0	15	**15**
2005	0	0	0	0	1	14	**15**
2006	0	0	0	0	0	24	**24**
2007	0	0	0	0	1	20	**21**
2008	0	0	0	0	0	14	**14**
2009	0	0	0	0	0	20	**20**
2010	0	0	0	0	0	25	**25**
2011	0	0	0	0	0	20	**20**
2012	0	0	0	0	0	21	**21**
2013	0	0	0	0	0	21	**21**
2014	0	0	0	0	0	26	**26**
2015	0	0	0	0	0	33	**33**
2016	0	0	0	0	0	27	**27**
2017	0	1	0	0	0	32	**33**
2018	0	0	0	0	0	36	**36**
2019	0	0	0	0	0	32	**32**
2020	0	0	0	0	0	43	**43**
2021*	0	0	0	0	0	36	**36**
*Hospitalisations** (source: Prismant/DHD/CBS)*							
2001	1	8	7	9	55	319	**399**
2002	2	18	7	8	67	340	**442**
2003	1	9	14	6	51	273	**354**
2004	4	8	6	7	60	324	**409**
2005	2	9	5	11	54	278	**359**
2006	0	11	7	7	43	249	**317**
2007	1	10	7	8	33	267	**326**
2008	2	8	5	6	43	259	**323**
2009	0	2	6	7	63	311	**389**
2010	1	6	6	8	39	292	**352**
2011	2	9	7	10	44	288	**360**
2012	1	6	11	8	42	279	**347**
2013	1	3	6	5	34	302	**351**
2014	0	9	4	7	58	373	**451**
2015^	0	10	10	15	60	395	**495**
2016^	0	10	10	10	45	405	**480**
2017^	0	15	5	15	45	385	**470**
2018^	0	10	5	5	70	430	**520**
2019^	0	5	5	10	60	445	**530**
2020^	0	5	10	10	60	425	**515**



* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

** Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.

Appendix 3 Overview of vaccine changes in the NIP from 2000

DTaP-IPV-Hib-HBV basic series

Additional DTaP-IPV-Hib-HBV basic vaccination series for risk group children

	DTaP-IPV-Hib	Hepatitis B
2003, March		**HBV vaccination added**
		→ HBVAXPRO (SP MSD)
		🕒 2, 3, 4, and 11 months
		Risk group (1) born on or after January 1st 2003
2006, January		**HBV dose added**
		HBVAXPRO (SP MSD)
		→ 🕒 Birth
		Risk group (2) born on or after January 1st 2006
2006, June	**HBV and DTwP-IPV-Hib vaccination merged + switch from wP to aP**	
	← Pediacel (SP MSD)	**← HBVAXPRO (SP MSD)**
		→ Infanrix hexa (GSK)
	🕒 2, 3, 4, and 11 months	
	Risk group (1) born on or after April 1st, 2006	
2008, January		**Risk group expanded**
		HBVAXPRO (SP MSD)
		🕒 Birth
		→ Risk group (3) born on or after January 1st 2008
2008, September		**Vaccine switch for HBV vaccination at birth**
		← HBVAXPRO (SP MSD)
		→ Engerix-B junior (GSK)
		🕒 Birth
		Risk group (3) born on or after September 1st 2008

Risk groups:

(1) Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

(2) Only for children whose mother tested positive for HBsAg.

(3) Only for children whose mother tested positive for HBsAg and children with Down syndrome.

Tdap-IPV booster vaccinations

	Polio	Diphtheria	Tetanus	Pertussis
2001, July				**aP vaccination added**
				→ Acellular pertussis vaccine (GSK)
				🕒 4 years
				Born or after January 1st, 1998
2006, July	**DT-IPV and aP vaccinations merged**			
	← DT-IPV vaccine (NVI)			**← Acellular pertussis vaccine (GSK)**
	→ Triaxis Polio (SP MSD)			
	🕒 4 years			
	Born on or after July/August 2002			
2008, February	**Vaccine switch for DTaP-IPV booster at age 4**			
	← Triaxis Polio (SP MSD)[1]			
	→ Infanrix IPV (GSK)			
	🕒 4 years			
	Born on or after February 1st, 2004			
2017, January	**Vaccine switch for DTaP-IPV booster at age 4**			
	← Infanrix IPV (GSK)			
	→ Boostrix Polio (GSK)			
	🕒 4 years			
2018, January		**Vaccine switch for DT-IPV booster at age 9**		
		← Revaxis (Sanofi)		
		→ DTP vaccine (BBio)		
		🕒 9 years		

[1] Used until March 2008

Pneumococcal vaccination

2006, June	**Pneumococcal vaccination added at 2, 3, 4, and 11 months of age**
	→ Prevnar (Wyeth)
	🕒 2, 3, 4, and 11 months
	Children born on or after April 1st, 2006
2011, May	**Vaccine switch**
	← Prevnar (Wyeth)
	→ Synflorix (GSK)
	🕒 2, 3, 4, and 11 months
	Children born on or after March 1st, 2011
2013, December	**Vaccine switch + change in dosing schedule**
	Synflorix (GSK)
	← 🕒 2, 3, 4, 11 months
	→ 🕒 2, 4, 11 months
	Children born on or after October 2013
2020, January	**Change in dosing schedule**
	Synflorix (GSK)
	← 🕒 2, 4, 11 months
	→ 🕒 3, 5, 11 months
	Only for children of mothers that received Boostrix after 22 weeks of pregnancy

MMR vaccination

2006, September	**Vaccine switch at age 14 months**
	← MMR vaccine (NVI)
	→ MMR-VaxPro (SP MSD) and Priorix (GSK)
	🕒 14 months
	Children born on or after July/August 2005
2008, October	**Vaccine switch at age 9**
	← Priorix (GSK)
	→ MMR-VaxPro (SP MSD) and Priorix (GSK)
	🕒 9 years
	Children born on or after September 1st, 1999

HPV vaccination

2010, January	**HPV vaccination added at age 12**
	Cervarix (GSK)
	🕒 12 years, girls only
	Children born on or after January 1st, 1997, 3 doses at 0, 1, and 6 months
	Catch-up campaign for children born between January 1st, 1993, to December 31st, 1996
2014, January	**Change in dosing schedule**
	Cervarix (GSK)
	🕒 12 years, girls only
	← 3 vaccines, intervals of 1 and 5 months
	→ 2 vaccines, interval 6 months
	Children born on or after January 1st, 2001
2022, January	**Boys also offered HPV vaccination + age of vaccination lowered to age 10**
	Cervarix (GSK)
	🕒 **Boys *and* girls, at age 10**
	Children born on or after January 1st, 2012
	Catch-up campaign in 2022 and 2023 for children born between January 1st, 2004, to December 31st, 2011

Meningococcal vaccination

2002, September	**Meningococcal type C vaccination added at age 14 months**
	NeisVac-C (Baxter)
	🕒 14 months
	Children born on or after June 1st, 2001
	Catch-up campaign in June 2002 for children born from June 1st, 1983, to May 31st, 2001
2018, May	**Vaccine types expanded with types A, W, and Y**
	← NeisVac-C (Pfizer)
	→ Nimenrix (Pfizer): expansion from MenC to MenACWY
	🕒 14 months
2018, December	**Catch-up campaign meningococcal types A, C, W, and Y for adolescents**
	Nimenrix (Pfizer)
	Catch-up vaccinations in 2018 and 2019 for children born between 2001 and 2005
2020, January	**Meningococcal type A, C, W, and Y vaccination added at age 14 years**
	Nimenrix (Pfizer)
	🕒 14 years

Appendix 4 Composition of vaccines used in the NIP

Vaccine	Composition
M-M-R VaxPro / MSD	
EU/1/06/337 Mumps, measles and rubella vaccine 0.5 ml	Measles virus[1] (Enders' Edmonston)[3], >1000 $TCID_{50}$[4] Mumps virus[1] (Jeryl Lynn, Level B)[3], >12,500 $TCID_{50}$[4] Rubella virus[2] (Wistar RA 27/3)[3], >1000 $TCID_{50}$[4] [1] produced in chick embryo cells [2] produced in WI-38 human diploïd lung fibroblasts [3] live attenuated [4] 50% tissue culture of infectious doses
Boostrix Polio / GSK	
RVG 35123 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine (adsorbed, reduced antigen) 0.5 ml	Diphtheria toxoid[1], >2 IU Tetanus toxoid[1], >20 IU *Bordetella pertussis* antigens Pertussis toxoid (PT)[1], 8 µg Filamentous haemagglutinin (FHA)[1], 8 µg Pertactin (PRN)[1], 2.5 µg Inativated poliovirus type 1 poliovirus (Mahoney)[2], 40 DU type 2 poliovirus (MEF-1)[2], 8 DU type 3 poliovirus (Saukett)[2], 32 DU [1] adsorbed to aluminiumhydroxide ($Al(OH)_3$), hydrated, 0.3 mg Al^{3+} and aluminiumphosphate ($AlPO_4$), 0.2 mg Al^{3+} [2] produced in Vero cells
Boostrix / GSK	
RVG 35121 Diphtheria, tetanus and pertussis (acellular component) vaccine (adsorbed, reduced antigen) 0.5 ml	Diphtheria toxoid[1], >2 IU Tetanus toxoid[1], >20 IU *Bordetella pertussis* antigens Pertussis toxoid (PT)[1], 8 µg Filamentous haemagglutinin (FHA)[1], 8 µg Pertactin (PRN)[1], 2.5 µg [1] adsorbed to aluminiumhydroxide ($Al(OH)_3$), hydrated, 0.3 mg Al^{3+} and aluminiumphosphate ($AlPO_4$), 0.2 mg Al^{3+}

Vaccine	Composition
Vaxelis / MCM Vaccine B.V.	
EU/1/15/1079 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis and *Haemophilus* type b vaccine (adsorbed) 0.5 ml	Diphtheria toxoid[1], >20 IU Tetanus toxoid[1], >40 IU *Bordetella pertussis* antigens[1]: Pertussis toxoid, 20 µg Filamentous haemagglutinin, 20 µg Fimbriae type 2 and 3, 5 µg Pertactin, 3 µg Hepatitis B surface antigen[2,3] Inactivated poliovirus[4]: Inactivated type 1 poliovirus, 40 DE Inactivated type 2 poliovirus, 8 DE Inactivated type 3 poliovirus, 32 DE *Haemophilus influenzae* type b polysaccharide (Polyribosylribitol Phosphate), 3 µg Conjugated to meningococcal protein[2], 50 µg [1] adsorbed on aluminiumphosphate, 0.17 mg Al^{3+} [2] adsorbed on amorphous aluminium hydroxyphosphate sulfate, 0.15 mg Al^{3+} [3] produced in yeast (*Saccharomyces cerevisiae*) cells by recombinant DNA technology [4] produced in Vero cells [5] or equivalent antigenic quantity determined by a suitable immunochemical method
REVAXIS / SP	
RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria toxoid[1], >2 IU Purified tetanus toxoid[1], >20 IU Inactivated poliovirus type 1[2], 40 DU Inactivated poliovirus type 2[2], 8 DU Inactivated poliovirus type 3[2], 32 DU [1]adsorbed to aluminium hydroxide, 0.35 mg (as aluminium) [2]produced in Vero cells
Engerix-B Junior / GSK	
RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen recombinant (S protein)[1,2], 10 µg [1] adsorbed to aluminium hydroxide, hydrated, 0,25 mg Al^{3+} [2] produced on genetically engineered yeast cells (*Saccharomyces cerevisiae*)

Vaccine	Composition
Engerix-B / GSK	
RVG17316 Hepatitis B (rDNA) vaccine (adsorbed) 1 ml	Hepatitis B-virus surface antigen[1,2], 20 µg [1] adsorbed on aluminium hydroxide, hydrated, 0.5 mg Al^{3+} [2] produced on yeast cells (*Saccharomyces cerevisiae*) with recombinant DNA technology
Cervarix / GSK	
EU/1/07/419	Human papillomavirus type 16 L1 protein[1,2,3], 20 µg Human papillomavirus type 18 L1 protein[1,2,3], 20 µg [1] adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL)[3], 50 µg [2] absorbed on aluminium hydroxide, hydrated ($Al(OH)_3$), 0.5 mg Al^{3+} in total [3] L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system, which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*
Nimenrix / Pfizer	
EU/1/12/767 Conjugated meningococcal group A, C, W-135 and Y vaccine 0.5 ml	*Neisseria meningitidis*-group A polysaccharide[1], 5 µg *Neisseria meningitidis*-group C polysaccharide[1], 5 µg *Neisseria meningitidis*-group W-135 polysaccharide[1], 5 µg *Neisseria meningitidis*-group Y polysaccharide[1], 5 µg [1] conjugated to tetanus toxoid carrier protein, 44 µg
Synflorix / GSK	
EU/1/09/508 Pneumococcal polysaccharide conjugate vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 1[1,2], 1 µg Pneumococcal polysaccharide serotype 4[1,2], 3 µg Pneumococcal polysaccharide serotype 5[1,2], 1 µg Pneumococcal polysaccharide serotype 6B[1,2], 1 µg Pneumococcal polysaccharide serotype 7F[1,2], 1 µg Pneumococcal polysaccharide serotype 9V[1,2], 1 µg Pneumococcal polysaccharide serotype 14[1,2], 1 µg Pneumococcal polysaccharide serotype 18C[1,3], 3 µg Pneumococcal polysaccharide serotype 19F[1,4], 3 µg Pneumococcal polysaccharide serotype 23F[1,2], 1 µg [1] adsorbed on aluminium phosphate, 0.5 mg Al^{3+} in total [2] conjugated to protein D (derived from non-typeable *Haemophilus influenzae*) carrier protein, 9–16 µg [3] conjugated to tetanus toxoid, 5–10 µg [4] conjugated to diphtheria toxoid, 3–6 µg

More extensive product information can be found at: www.cbg-meb.nl and www.emea.europe.eu.

Appendix 5 Overview of recent RIVM publications (01/07/2021 to 30/06/2022)

Vaccination coverage

N/a

Acceptance of vaccination

1. de Munter AC, Klooster TMST, van Lier A, Akkermans R, de Melker HE, Ruijs WLM. Determinants of HPV-vaccination uptake and subgroups with a lower uptake in the Netherlands. BMC Public Health. 2021;21(1):1848.
2. Venderbos JR, Eilers R, de Vries H, van Zoonen K. A qualitative study of parental associations and beliefs regarding the HPV vaccination for Dutch boys. BMR Public Health. 2022;22:1188.
3. de Vries M, Çoban FR, Claassen L, te Wierik MJM, Timmermans DRM, Timen A. Information needs during an emerging outbreak of meningococcal W135 disease in the Netherlands: a study among teenagers, their parents and healthcare professionals. BMC Public Health. 2021;21.
4. de Vries M, Claassen L, Te Wierik MJM, Timmermans DRM, Timen A. Dynamics in public perceptions and media coverage during an ongoing outbreak of meningococcal W disease in the Netherlands. BMC Public Health. 2022;22(1):633.

Burden of disease

1. Benincà E, Lagerweij GR, Pijnacker R, Friesema IHM, Kretzschmar M, Franz E, Mughini Gras L. Disease burden of food-related pathogens in the Netherlands, 2020. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2021 (RIVM report 2021-0161).
2. Klous G, van Hout D, Lagerweij G, van Hoek A, Franz E. Staat van infectieziekten in Nederland, 2020 [State of Infectious Diseases in the Netherlands, 2020]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2021. RIVM report 2021-0208.
3. Reukers DFM, van Asten L, Brandsema PS, Dijkstra F, Hendriksen JMT, Hooiveld M, et al. Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2020/2021. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2021. RIVM report 2021-0133.
4. Steens A, Knol MJ, Freudenburg-de Graaf W, de Melker HE, van der Ende A, van Sorge NM. Pathogen- and type-specific changes in invasive bacterial disease epidemiology during the first year of the COVID-19 pandemic in the Netherlands. Microorganisms. 2022;10(5):972.
5. Steens A, Stanoeva KR, Knol MJ, Mariman R, de Melker HE, van Sorge NM. Increase in invasive disease caused by *Haemophilus influenzae* b, the Netherlands, 2020 to 2021. Euro Surveill. 2021;26(42).

Adverse events

N/a

Current NIP

Diphtheria
N/a

Haemophilus influenzae disease caused by type b (Hib) and other serotypes
N/a

Hepatitis B
N/a

Human papillomavirus (HPV)

1. Hoes J, King AJ, Schurink-van 't Klooster TM, Berkhof PJ, Bogaards JA, de Melker HE. Vaccine effectiveness following routine immunization with bivalent HPV vaccine: Protection against incident genital HPV infections from a reduced-dosing schedule. J Infect Dis. 2021.
2. Hoes J, Woestenberg PJ, Bogaards JA, King AJ, de Melker HE, Berkhof J, et al. Population Impact of Girls-Only Human Papillomavirus 16/18 Vaccination in The Netherlands: Cross-Protective and Second-Order Herd Effects. Clin Infect Dis. 2021;72(5):e103-e11.

Measles
N/a

Meningococcal disease

1. de Greeff SC, Schoffelen AF, Verduin CM. NethMap 2021. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands in 2020 / MARAN 2021. Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2020. 2021.
2. Kemmeren JM, van Balveren L, Kant A, de Melker H. Tolerability of MenACWY-TT vaccination in adolescents in the Netherlands; a cross-sectional study. BMC Public Health. 2021;21(1):1752.
3. Miellet WR, Mariman R, Pluister G, de Jong LJ, Grift I, Wijkstra S, et al. Detection of *Neisseria meningitidis* in Saliva and Oropharyngeal Samples from College Students. Sci Rep. 2021.
4. Ohm M, Boef AGC, Stoof SP, van Ravenhorst MB, van der Klis FRM, Berbers GAM, et al. Sex-Related Differences in the Immune Response to Meningococcal Vaccinations During Adolescence. Front Public Health. 2022;10:871670.
5. Ohm M, Knol MJ, Vos ERA, Bogaard MJM, van Rooijen DM, Sanders EAM, de Melker HE, van der Klis FRM, Berbers GAM. Seroprevalence of meningococcal ACWY antibodies across the population in the Netherlands: Two consecutive surveys in 2016/17 and 2020. Vaccine. 2022;40(1):59-66.
6. Steens A. Meningococcal disease serogroup B. Updated information for the Dutch Health Council. 2022. Report No.: 2022-0046.

Mumps

1. Kaaijk P, Emmelot ME, Meiring HD, van Els C, de Wit J. Novel mumps virus epitopes reveal robust cytotoxic T cell responses after natural infection but not after vaccination. Sci Rep. 2021;11(1):13664.
2. Kaaijk P, Wijmenga-Monsuur AJ, Ten Hulscher HI, Kerkhof J, Smits G, Nicolaie MA, et al. Antibody Levels at 3-Years Follow-Up of a Third Dose of Measles-Mumps-Rubella Vaccine in Young Adults. Vaccines (Basel). 2022;10(1).
3. Lanfermeijer J, Nuhn MM, Emmelot ME, Poelen MCM, van Els C, Borghans JAM, et al. Longitudinal Characterization of the Mumps-Specific HLA-A2 Restricted T-Cell Response after Mumps Virus Infection. Vaccines (Basel). 2021;9(12).

Pertussis

1. Abu-Raya B, Maertens K, Munoz FM, Zimmermann P, Curtis N, Halperin SA, et al. Factors affecting antibody responses to immunizations in infants born to women immunized against pertussis in pregnancy and unimmunized women: Individual-Participant Data Meta-analysis. Vaccine. 2021;39(44):6545-52.
2. Abu-Raya B, Maertens K, Munoz FM, Zimmermann P, Curtis N, Halperin SA, et al. The effect of tetanus-diphtheria-acellular-pertussis immunization during pregnancy on infant antibody responses: individual-participant data meta-analysis. Front Immunol. 2021;12.
3. Diks AM, Versteegen P, Teodosio C, Groenland RJ, de Mooij B, Buisman AM, et al. Age and Primary Vaccination Background Influence the Plasma Cell Response to Pertussis Booster Vaccination. Vaccines. 2022;10(2):136.
4. Gillard J, Blok BA, Garza DR, Venkatasubramanian PB, Berbers GASM, van Gageldonk PGM, et al. BCG-induced trained immunity enhances acellular pertussis vaccination responses in an explorative randomized clinical trial. NPJ Vaccines. 2022;7(1).
5. Knuutila A, Versteegen P, Barkoff AM, van Gageldonk P, Mertsola J, Berbers G, et al. Pertussis toxin neutralizing antibody response after an acellular booster vaccination in Dutch and Finnish participants of different age groups. Emerg Microbes Infect. 2022;11(1):956-63.
6. Kroes MM, Miranda-Bedate A, Hovingh ES, Jacobi R, Schot C, Pupo E, et al. Naturally circulating pertactin-deficient *Bordetella pertussis* strains induce distinct gene expression and inflammatory signatures in human dendritic cells. Emerg Microbes Infect. 2021;10(1):1358-68.
7. Kroes MM, Van Vliet LC, Jacobi RHJ, Kuipers B, Pieren DKJ, Miranda-Bedate A, et al. Long Lasting Antibodies From Convalescent Pertussis Patients Induce ROS Production and Bacterial Killing by Human Neutrophils. Front Cell Infect Microbiol. 2022;12(888412).
8. Lambert EE, Van Twillert I, Beckers L, Poelen MCM, Han WGH, Pieren DKJ, et al. Reduced *Bordetella pertussis*-specific CD4+ T-Cell Responses at Older Age. Frontiers in Aging. 2022.
9. Versteegen P, Barkoff AM, Valente Pinto M, Van de Kasteele J, Knuutila A, Bibi S, et al. Memory B Cell Activation Induced by Pertussis Booster Vaccination in Four Age Groups of Three Countries. Frontiers in Immunology. 2022;13(864674).
10. Versteegen P, Berbers GAM, Smits G, Sanders EAM, van der Klis FRM, de Melker HE, et al. More than 10 years after introduction of an acellular pertussis vaccine in infancy: a cross-sectional serosurvey of pertussis in the Netherlands. The Lancet Regional Health – Europe. 2021;10(100196).

11. Versteegen P, Bonačić Marinović AA, Van Gageldonk PGM, Van der Lee S, Hendrikx LH, Sanders EAM, et al. Long-Term Immunogenicity upon Pertussis Booster Vaccination in Young Adults and Children in Relation to Priming Vaccinations in Infancy. Vaccines. 2022;10(5):693.

Pneumococcal disease

1. Arends DW, Miellet WR, Langereis JD, Ederveen THA, van der Gaast-de Jongh CE, van Scherpenzeel M, et al. Examining the Distribution and Impact of Single-Nucleotide Polymorphisms in the Capsular Locus of Streptococcus pneumoniae Serotype 19A. Infect Immun. 2021;89(11):e0024621.
2. Asogwa OA, de Hoog MLA, Bruijning-Verhagen P. Impact of 7-valent versus 10-valent pneumococcal conjugate vaccines on primary care consultations across various age groups in the Netherlands, 5 years after the switch: A time-series analysis. Vaccine. 2022;40(2):334-43.
3. Garcia Garrido HM, Vollaard A, D'Haens GR, Spuls PI, Bemelman FJ, Tanck MW, et al. Immunogenicity of the 13-Valent Pneumococcal Conjugate Vaccine (PCV13) Followed by the 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23) in Adults with and without Immunosuppressive Therapy. Vaccines (Basel). 2022;10(5).
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Poliomyelitis

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2. Mbaeyi C, Moran T, Wadood Z, Ather F, Sykes E, Nikulin J, et al. Stopping a polio outbreak in the midst of war: Lessons from Syria. Vaccine. 2021;39(28):3717-23

Rubella

N/a

Tetanus

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Potential NIP target diseases

Hepatitis A

1. Severi E, Georgalis L, Pijnacker R, Veneti L, Turiac IA, Chiesa F, et al. Severity of the clinical presentation of hepatitis A in five European countries from 1995 to 2014. Int J Infect Dis 118: 34-43.

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Rotavirus

N/a

Varicella zoster virus (VZV) infection

N/a

COVID-19

COVID-19 epidemiology in the Netherlands

N/a

Recommendations from the Health Council of the Netherlands

N/a

COVID-19 vaccination pathogen

N/a

COVID-19 vaccination coverage

N/a

Effects of vaccination

1. de Gier B, Andeweg S, Backer JA, Hahné SJ, van den Hof S, de Melker HE, et al. Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), the Netherlands, August to September 2021. Euro Surveill. 2021;26(44).
2. de Gier B, Andeweg S, Joosten R, Ter Schegget R, Smorenburg N, van de Kassteele J, et al. Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021. Euro Surveill. 2021;26(31).

Seroepidemiology and immunogenicity of SARS-CoV-2 in the Netherlands

1. Haggenburg S, Lissenberg-Witte BI, van Binnendijk RS, den Hartog G, Bhoekhan MS, Haverkate NJE, et al. Quantitative analysis of mRNA-1273 COVID-19 vaccination response in immunocompromised adult hematology patients. Blood Adv. 2022;6(5):1537-46.
2. den Hartog G, Vos ERA, van den Hoogen LL, van Boven M, Schepp RM, Smits G, et al. Persistence of antibodies to SARS-CoV-2 in relation to symptoms in a nationwide prospective study. Clinical Infectious Diseases. 2021.
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Pathogen surveillance

1. Andeweg SP, de Gier B, Eggink D, van den Ende C, van Maarseveen N, Ali L, et al. Protection of COVID-19 vaccination and previous infection against Omicron BA.1, BA.2 and Delta SARS-CoV-2 infections. medRxiv. 2022:2022.02.06.22270457.
2. Eggink D, Andeweg SP, Vennema H, van Maarseveen N, Vermaas K, Vlaemynck B, et al. Increased risk of infection with SARS-CoV-2 Omicron BA.1 compared with Delta in vaccinated and previously infected individuals, the Netherlands, 22 November 2021 to 19 January 2022. Euro Surveill. 2022;27(4).

Safety of COVID-19 vaccines

N/a

Appendix 6 Overview of relevant websites

General information for NIP professionals

NIP website for professionals:
https://rijksvaccinatieprogramma.nl/professionals

Dienst Vaccinvoorziening en Preventieprogramma's
(DVP, Department for Vaccine Supply and Prevention Programmes):
http://www.rivm.nl/RIVM/Organisatie/Centra/Dienst_Vaccinvoorziening_en_Preventieprogramma_s

Meldingsplicht infectieziekten
(Mandatory notification of infectious diseases in the Netherlands):
http://www.rivm.nl/Onderwerpen/M/Meldingsplicht_infectieziekten

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker_voor_professionals

Surveillance Atlas of Infectious Diseases:
https://www.ecdc.europa.eu/en/surveillance-atlas-infectious-diseases

General information for the public

RIVM websites for the public:
https://rijksvaccinatieprogramma.nl/

Available vaccines that are not (yet) part of a public vaccination programme:
www.rivm.nl/vaccinaties

Volksgezondheidenzorg.info:
https://www.volksgezondheidenzorg.info/

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker

Vaccines Today:
https://www.vaccinestoday.eu/about-us/who-we-are/

Other NIP-related RIVM reports

Immunisation Coverage and Annual Report for the National Immunisation Programme in the Netherlands 2021:
https://www.rivm.nl/bibliotheek/rapporten/2022-0017.pdf

Adverse events in the Netherlands Vaccination Programme, reports in 2010 and review 1994–2010:
http://www.rivm.nl/bibliotheek/rapporten/205051004.pdf

Adverse events in the Netherlands Vaccination Programme. Report 2021:
https://rijksvaccinatieprogramma.nl/documenten/meldingen-van-bijwerkingen-rijksvaccinatieprogramma-2021

Product information

NIP product information and package leaflets:
https://rijksvaccinatieprogramma.nl/professionals/productinformatie-vaccinaties

National organisations

General
Ministry of Health, Welfare and Sport:
http://www.rijksoverheid.nl/onderwerpen/vaccinaties

Gezondheidsraad (Health Council of the Netherlands):
http://www.gezondheidsraad.nl/

GGD GHOR:
http://www.ggdghorkennisnet.nl/

Vaccine safety
Netherlands Pharmacovigilance Centre Lareb:
http://www.lareb.nl/

College ter Beoordeling van Geneesmiddelen (CBG, Netherlands Medicines Evaluation Board):
https://www.cbg-meb.nl/

Data sources

Statistics Netherlands (CBS):
http://www.cbs.nl/

Dutch Hospital Data (DHD):
https://www.dhd.nl/

Nederlands instituut voor onderzoek van de gezondheidszorg
(NIVEL, Netherlands Institute for Health Services Research):
http://www.nivel.nl/

Nederlands Referentielaboratorium voor Bacteriële Meningitis
(NRLBM, Netherlands Reference Laboratory for Bacterial Meningitis):
https://www.amc.nl/web/specialismen/medische-microbiologie/medische-microbiologie/het-nederlands-referentielaboratorium-voor-bacteriele-meningitis.htm

Integrated Primary Care Information (IPCI):
http://www.ipci.nl/

The Netherlands Cancer Registry (NKR):
http://www.cijfersoverkanker.nl/

Nederlandse Werkgroep Klinische Virologie
(NWKV, Netherlands Working Group Clinical Virology):
http://www.nvmm.nl/vereniging/commissies-en-werkgroepen/nederlandse-werkgroep-klinische-virologie/

International organisations

World Health Organization (WHO):
http://www.who.int/en/

World Health Organization (WHO) Europe:
http://www.euro.who.int/en/home

European Centre for Disease Prevention and Control (ECDC):
http://ecdc.europa.eu/en/

Centers for Disease Control and Prevention (CDC):
http://www.cdc.gov/
https://www.cdc.gov/vaccines/growing/

ClinicalTrials.gov:
https://clinicaltrials.gov/

Advisory Committees

Joint Committee on Vaccination and Immunisation (JCVI):
https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation

Advisory Committee on Immunization Practices (ACIP):
http://www.cdc.gov/vaccines/acip/

Standing Committee on Vaccination (STIKO):
http://www.rki.de/EN/Content/infections/Vaccination/Vaccination_node.html

Safety of vaccines

European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/

U.S. Food and Drug Administration (FDA):
http://www.fda.gov/

International vaccine schedules

European Centre for Disease Prevention and Control (ECDC):
http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

World Health Organization (WHO):
http://apps.who.int/immunization_monitoring/globalsummary

International networks

EUVAC-Net:
http://ecdc.europa.eu/en/healthtopics/vaccine-preventable-diseases/euvac/Pages/index.aspx

HAVNET:
http://www.rivm.nl/en/Topics/H/HAVNET

National Immunization Technical Advisory Groups (NITAGs):
http://www.nitag-resource.org/

National Respiratory and Enteric Virus Surveillance System (NREVSS):
https://www.cdc.gov/surveillance/nrevss/

The *Streptococcus pneumoniae* Invasive Disease network (SpIDnet):
https://sites.google.com/a/epiconcept.fr/ipd-surveillance/home-2

WHO Global Polio Laboratory Network (GPLN):
https://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/activities/polio-laboratory-network

Respiratory syncytial virus consortium in Europe (RESCEU):
http://resc-eu.org/

Preparing for RSV Immunisation and Surveillance in Europe (PROMISE):
https://imi-promise.eu/

Communication platforms

Epidemic Intelligence Information System (EPIS):
https://ecdc.europa.eu/en/publications-data/epidemic-intelligence-information-system-epis

Vaccination of risk groups

Influenza vaccination

RIVM website on Influenza vaccination:
http://www.rivm.nl/Onderwerpen/G/Griep/Griepprik

Stichting Nationaal Programma Grieppreventie
(SNPG, Foundation for the National Influenza Prevention Programme):
http://www.snpg.nl/

Scientific Institute for Quality of Healthcare:
http://www.iqhealthcare.nl/nl/

Annual Report on Surveillance of Covid-19, Influenza and Other Respiratory Infections in the Netherlands:
https://www.rivm.nl/publicaties/annual-report-surveillance-of-covid-19-influenza-and-other-respiratory-infections-in-0

Tuberculosis

KNCV Tuberculosis foundation:
http://www.kncvtbc.nl/

Annual Report on Surveillance of Influenza and Other Respiratory Infections in the Netherlands:
https://www.rivm.nl/bibliotheek/rapporten/2019-0079.pdf

National Tuberculosis Control Plan 2016-2020:
http://www.rivm.nl/bibliotheek/rapporten/2016-0028.pdf

Traveller vaccinations

Landelijk Coördinatiecentrum Reizigersadvisering
(National Coordination Centre for Information for Travellers):
https://www.lcr.nl/Index.htm

A.J.M. Pluijmaekers, H.E. de Melker

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