



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

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

Surveillance and developments  
in 2020-2021





# The National Immunisation Programme in the Netherlands

Surveillance and developments in 2020-2021

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## Colophon

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## Synopsis

### The National Immunisation Programme in the Netherlands

#### *Surveillance and developments in 2020-2021*

In 2020, 1,026,872 children and pregnant women were vaccinated as part of the National Immunisation programme (NIP). They received a total of 2,205,249 vaccinations. Vaccination coverage in the Netherlands has increased slightly, just as it did in the previous year. This concerns children who received most of their vaccinations before the SARS-CoV-2 outbreak. It appears the measures that were implemented to control the COVID-19 pandemic had little negative effect on the number of children that were vaccinated in 2020. The exact vaccination coverage for these children cannot be calculated until a later date as not all of the necessary data is available at this time.

In 2020, fewer people fell ill due to a disease that is included in the NIP vaccination schedule compared to 2019. This is very likely due to COVID-19 control measures such as social distancing and handwashing. The decrease was observed primarily for pertussis (943), mumps (64), pneumococcal disease (approximately 1,500 cases), and measles (2). There were no notifications of rubella and polio in 2020. There were 3 confirmed cases of diphtheria and 2 confirmed cases of tetanus. The number of notifications for meningococcal disease caused by serotype W (12) decreased further after introduction of the vaccine into the NIP in 2019. Only *Haemophilus influenzae* type b (Hib) occurred more frequently than in 2019. The number of notifications increased from 39 in 2019 to 68 in 2020. The RIVM is currently investigating the cause of this increase.

The number of chronic hepatitis B notifications (825 cases) decreased by about 30 percent compared to 2019. This is probably the result of a decrease in doctors' visits and therefore diagnoses during the COVID-19 pandemic. It takes a long time for hepatitis B to cause noticeable symptoms, which means it is usually discovered by chance.

In June 2021, the Health Council of the Netherlands recommended offering routine rotavirus vaccination to all children. In September 2021, the council recommended inviting more risk groups for flu vaccination, including pregnant women.

The RIVM collects and analyses data on the effectiveness of vaccination. These analyses show that COVID-19 vaccines are effective.

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 2020-2021*

In 2020 zijn 1.026.872 kinderen en zwangere vrouwen gevaccineerd via het Rijksvaccinatieprogramma (RVP). In totaal kregen zij 2.205.249 vaccinaties. De vaccinatiegraad in Nederland is licht gestegen, net als het jaar ervoor. Het betreft kinderen die hun vaccinatie(s) bijna allemaal vóór de uitbraak van het coronavirus SARS-CoV-2 kregen. Het lijkt erop dat de maatregelen om het coronavirus te bestrijden weinig negatieve invloed hebben gehad op het aantal kinderen dat in 2020 is gevaccineerd. De precieze vaccinatiegraad voor deze kinderen kan pas later worden berekend omdat dan pas alle benodigde cijfers bekend zijn.

In 2020 kregen minder mensen dan in 2019 een ziekte waartegen binnen het RVP wordt gevaccineerd. Dit komt heel waarschijnlijk door de coronamaatregelen zoals afstand houden en handen wassen. De daling geldt vooral voor kinkhoest (943), bof (64), pneumokokkenziekte (ongeveer 1.500) en mazelen (2). Er waren geen meldingen van rodehond en polio in 2020. Er zijn 3 patiënten met difterie en 2 met tetanus gemeld. Ook het aantal meldingen van meningokokkenziekte type W (12) is verder gedaald na de invoering van deze vaccinatie in het RVP in 2019. Alleen *Haemophilus influenzae* type b (Hib) kwam vaker voor. Het aantal meldingen steeg van 39 in 2019 naar 68 in 2020. Het RIVM onderzoekt de oorzaak.

Het aantal meldingen van chronische hepatitis B (825) daalde met ongeveer een derde vergeleken met 2019. Dit aantal is waarschijnlijk lager omdat mensen tijdens de coronapandemie minder vaak naar een dokter gingen. Deze ziekte geeft lange tijd weinig klachten, waardoor hij meestal toevallig wordt ontdekt.

De Gezondheidsraad adviseerde in juni 2021 om het vaccin tegen het rotavirus aan alle kinderen aan te bieden. In september 2021 heeft de Gezondheidsraad geadviseerd om meer risicogroepen uit te nodigen voor de griepvaccinatie, onder wie zwangere vrouwen.

Het RIVM verzamelt en onderzoekt gegevens over hoe goed vaccinaties werken. Hieruit blijkt dat coronavaccinaties goed werken.

**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 2020 and the first part of 2021 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, and varicella zoster virus (VZV) infection. In addition, the report presents an overview of vaccines against infectious diseases undergoing clinical trials that are relevant for the Netherlands, including COVID-19 vaccines.

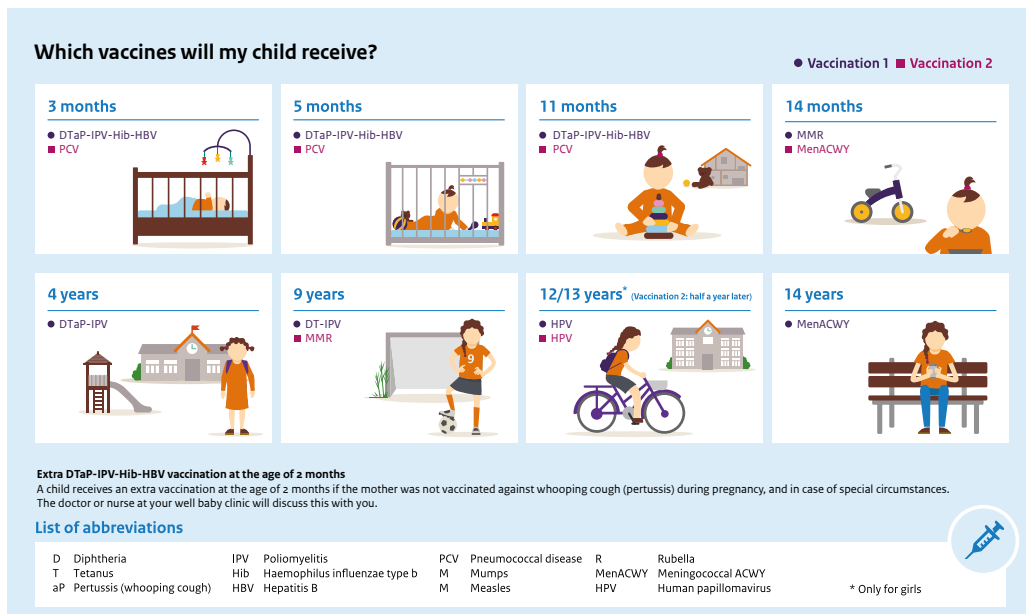
The report is structured as follows:

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 the burden of diseases covered by the NIP. Public acceptance of vaccination and NIP communication 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 is a new addition to the report and discusses COVID-19 epidemiology, Health Council recommendations, the COVID-19 vaccination programme and coverage and its effect on the pandemic, sero-epidemiology and pathogen surveillance, a section on COVID-19 vaccine modelling, 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 1997 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.

# Comprehensive summary

## Current vaccination schedule



**Figure 1** Vaccination schedule for 2020 in the Netherlands.

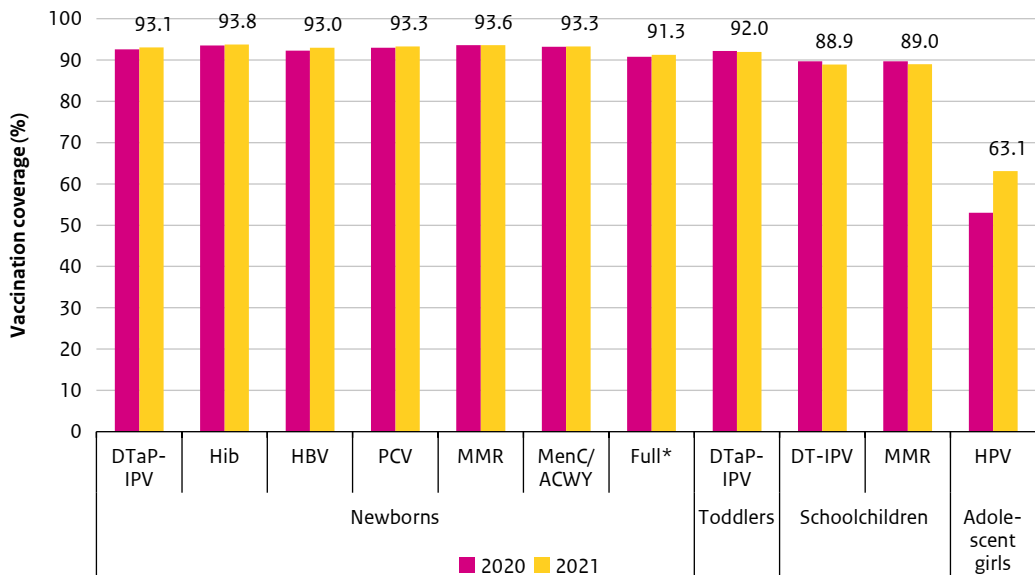
Source: <http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals>.

## Vaccination coverage

For most infant vaccinations in the NIP, national vaccination coverage has risen for the second year in a row. This *coverage* concerns children born in 2018 who had received almost all their vaccination(s) *before* the COVID-19 outbreak. In addition to the small increase for infants (maximum 0.7%), the increase for HPV vaccination from 53% to 63% is particularly striking as HPV vaccination coverage has never been this high. Approximately 70% of pregnant women took part in the 22-week vaccination programme that protects babies against whooping cough from birth.

*Provisional figures* suggest that the measures due to the COVID-19 outbreak have had little negative impact on the number of children vaccinated during the COVID-19 pandemic and resulting lockdown. For example, participation in the first MMR vaccination only lags 1-2% behind compared to a year earlier. The exact *vaccination coverage* for these children cannot be calculated until next year because only then will all relevant data be available.





**Figure 2** Vaccination coverage per vaccine for newborns, toddlers, schoolchildren, and adolescent girls in 2020 and 2021.

\* Full = all NIP vaccinations received according to schedule at 2 years of age.

Source: Præventis.

## Burden of disease

For the year 2020, the estimated total burden of disease caused by vaccine-preventable diseases if the specific strains of the pathogens are included in the vaccines, as expressed in disability-adjusted life years (DALYs), was highest for HPV (based on the burden in 2019 instead of 2020; 19,400 DALYs (75% among women)), invasive pneumococcal disease (6,200 DALYs), invasive *Haemophilus influenzae* disease (1,000 DALYs), invasive meningococcal disease (400 DALYs), pertussis (390 DALYs), and rotavirus infection (390 DALYs). For most vaccine-preventable diseases, the estimated burden in 2020 was considerably lower compared to the estimated burden in 2019, probably due to the implementation of various COVID-19 response measures such as social distancing and handwashing. The burden of invasive *H. influenzae* disease type b was higher in 2020. The reason for this increase is unknown.

The burden of COVID-19 is estimated at 169,000 DALYs for 2020, 99% of which is due to individuals dying at a younger age than they would have in a situation without COVID-19. This is an underestimation of the actual burden since long-term consequences of the disease have not been taken into account.

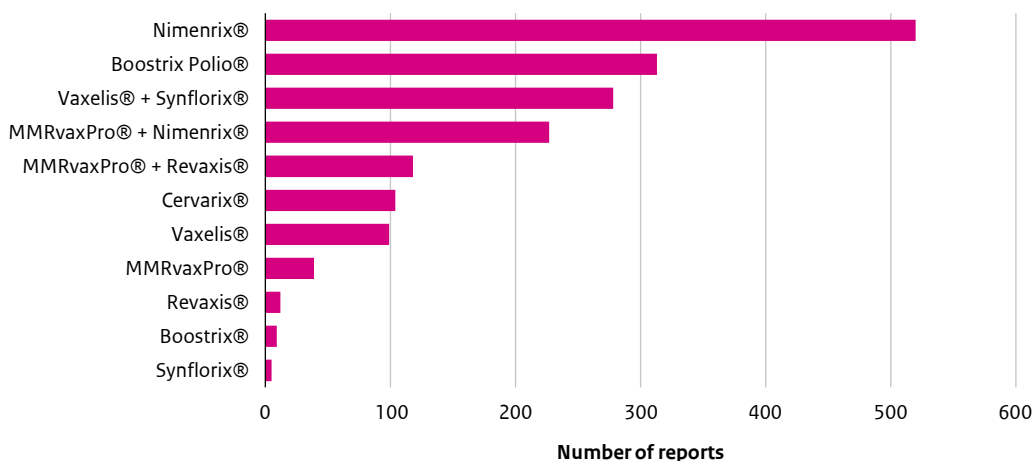
## Acceptance of vaccination

Several studies have shown that (relevant) healthcare professionals influence attitude towards vaccination and through this acceptance of vaccinations. Positive attitudes among healthcare professionals are therefore important. Improving information provision and the way information is presented, for example regarding the maternal pertussis vaccination, could have a positive impact on the attitude of healthcare professionals. Furthermore, social norms (i.e. what family and friends believe regarding vaccination) and vaccine safety play a part in the acceptance of vaccinations. This is also relevant when looking at the various COVID-19 vaccines. Another factor that plays a part in the acceptance of COVID-19 vaccination is the possibility that vaccination may end the pandemic (i.e. the crisis). Techniques to increase vaccine acceptance and minimise disparities between groups might be to send reminders, provide information in native languages, and re-invite people for vaccination. International studies show that transparent, clear and concise information, including pros and cons (such as potential side-effects), could help increase vaccine acceptance.

## Adverse events

In 2020, Lareb received 1,475 notifications representing a total of 4,640 adverse events following immunisation (AEFI) within the NIP. This number of reports is almost equivalent to the number of reports received in 2018 (n=1,519), but lower compared to the number received in 2019 (n=2,009). This is possibly due to the catch-up campaign for MenACWY vaccination in adolescents in 2019. The number of reported AEFIs per report was 3.1, which is slightly lower compared to 2018 and 2019 (3.4 and 3.7 respectively).

No new signals of disturbing adverse events were found.



**Figure 3** Number of adverse event reports per suspected vaccine(s) in 2020.

Source: Lareb.

## Current NIP

### Diphtheria

In 2020, three cases of diphtheria were reported. One of these individuals (with *C. ulcerans*) was fully vaccinated, one (with *C. diphtheria*) was born before introduction of vaccination and one (with *C. ulcerans*) was unvaccinated. In 2021, for the period up to and including March, no cases of diphtheria were reported.

The outbreak of diphtheria that was declared in Yemen in October 2017 is still ongoing and affects almost all governorates. For the period up to and including April 26<sup>th</sup>, 2020, the country reported 5,701 probable cases of diphtheria and 330 related deaths. In addition, five countries in the Region of the Americas reported a total of 80 confirmed diphtheria cases, of which 21 deaths, in 2020. Moreover, due to the COVID-19 pandemic in 2020, postponement of vaccination campaigns occurred in the Region of the Americas.

### Haemophilus influenzae disease

In 2020, the number of invasive *Haemophilus influenzae* type b cases had increased from around 40 cases per year between 2017 and 2019 (incidence approximately 0.25 per 100,000 inhabitants) to 68 (incidence: 0.39 per 100,000). This increase is striking as the country was in a partial lockdown due to control measures for the COVID-19 pandemic, which coincided with a decrease in the incidence of most other respiratory infectious diseases including disease caused by other *H. influenzae* (Hi) types.

The increase was observed in most age groups. Of all Hib cases in 2020, 34 were in vaccine-eligible children, 8 of which were sufficiently vaccinated (i.e. real vaccine failures), resulting in a Hib vaccine effectiveness estimate of 97%, slightly higher compared to previous years (93%).

Invasive disease caused by other Hi types occurred less often than in previous years, likely as a result of COVID-19 control measures. Up to May 2021, there were 20 cases of non-typeable Hi. This is a strong decrease compared to the same period in previous years (77 cases in 2020, 91 cases in 2019).

### Hepatitis B

The reported incidence of acute hepatitis B (n=95) decreased by 9% to 0.5 per 100,000 population in 2020. Sexual contact was the most frequently reported risk factor for acute HBV infection. In 2020, genotype A continued to be the dominant genotype among acute HBV cases with 65% of 40 genotyped cases.

The number of newly diagnosed chronic HBV infections (n=714) decreased by one third compared to 2019 and amounted to 4.1 per 100,000 population. The drop in hepatitis B notifications coincided with the peaks of COVID-19 hospital admissions.

### Human papillomavirus (HPV) infection

The incidence of cervical cancer declined to 8.58 per 100,000 in 2020 (n=796) compared with 9.79 per 100,000 (n=905) in 2019, while the number of deaths caused by cervical cancer remained relatively stable (n=229). The incidence and mortality of other HPV-related cancers remained relatively stable as well.

In a prospective cohort study (HAVANA), high vaccine effectiveness (VE) against HPV16/18 was found for persistent cervicovaginal infections up to ten years post-vaccination after three-times bivalent vaccination. Similarly, high VE against incident HPV16/18 cervicovaginal infections was observed up to five 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 immunogenicity, a high seroprevalence of HPV16/18 antibodies was observed up to 72 months after vaccination in girls vaccinated twice with the bivalent vaccine (HPV-2D study). In a pilot study (EVI) to assess early immune responses to vaccination, HPV16/18-specific antibody levels and memory B and T cell responses were higher in bivalent vaccinees than in nonavalent vaccinees one month after the third vaccination. The opposite was observed for HPV31/45-specific antibodies. In a cross-sectional study (PASSYON), the genital viral load of HPV infections seemed to be associated with the establishment of concurrent genital-anal HPV infection. From 2022 onwards, boys and girls will be invited for HPV vaccination in the year that they turn 10 years old.

### Measles

In 2020, only two measles cases were reported. No cases were reported in the first six months of 2021. The reduction in measles cases is likely related to the COVID-19 pandemic.

### Meningococcal disease

After an increase in invasive meningococcal disease in the years 2015-2018 to 1.2 per 100,000, incidence dropped to 0.39 per 100,000 in 2020 (n=68). All serogroups decreased in incidence. In the first four months of 2021, only 11 cases were observed, mainly serogroup B (menB; n=9). The COVID-19 control measures, including social distancing, likely played a role in the decrease, as well as the introduction of the catch-up campaign for MenACWY vaccination in 2018 and 2019.

In 2020 and 2021 for the period up to and including April, no menA, menC or menY cases occurred among vaccine-eligible age groups and only 2 menW cases were reported in these age groups. Overall, menW incidence decreased by 61% (95% CI: 40–74); 82% (95% CI: 18–96) in children 15–36 months and 14–18 years (vaccine-eligible age groups), and 57% (95% CI: 34–72) in non-eligible age groups, after the introduction of the MenACWY vaccination, including the catch-up campaigns.

## Mumps

The incidence of mumps in 2020 was low (0.4 per 100,000 population; n=64). A sharp decrease was observed from 1 April 2020, which coincided with control measures put in place in response to the COVID-19 pandemic. Most mumps cases in the Netherlands were caused by mumps virus genotype G.

## Pertussis

In 2020, the overall number of notifications and incidence rate (IR) for pertussis amounted to 943 and 5.4 per 100,000 respectively, which is considerably lower compared to 2019 when the overall number of notifications and IR were 6,361 and 36.8 per 100,000 respectively. The drop in the number of infections was probably due to the COVID-19 control measures. Since the IR decreased in all age categories, including infants, it is difficult at this point to detect a potential effect of maternal pertussis vaccination on the IR in 0- to 5-month-olds.

Between April and December 2020, eight pertussis cases in 0- to 3-month-old infants were reported. Of these, three infants had received maternal Tdap vaccination. Using an estimated maternal vaccination coverage of 70%, vaccine effectiveness was estimated at 74% (95% CI: -32 to 96%).

Pertussis seroprevalence was studied in a population-based cross-sectional serosurvey among a representative sample of 7,621 0- to 89-year-old Dutch residents (PIENTER-3 study). Individuals aged  $\geq 7$  years with pertussis toxin concentrations of 100 IU/ml and higher were considered seropositive for recent pertussis infection. Between 1995/1996 and 2006/2007, an increase from 1.0 to 3.5% was found and the current study shows still-increasing seroprevalence from 3.5 to 5.9%. The increased seroprevalence was highest for 12- to 18-year-olds where the percentage more than tripled, towards 11.5% between 2006/2007 and the current study.

In the Immfact study, older adult cases mounted and maintained higher IgA responses to *B. pertussis* than adolescents and younger adult cases, possibly reflecting an altered role for IgA at older adult age as part of immunosenescence processes.

The RIVM recently demonstrated that newly circulating *B. pertussis* strains express a different set of proteins compared to older strains and that they induce distinct immunological pathways in innate immune cells. These findings highlight the importance of considering pathogen adaptation in the design of new generation pertussis vaccines.

### **Pneumococcal disease**

The decrease in invasive pneumococcal disease reported for 2019/2020 persisted in 2020/2021 to 5.6 per 100,000 (about 1,500 cases in total). The decrease was seen across all age groups, but was smallest in <5-year-olds. It is likely the result of COVID-19 measures as the decrease in cases occurred suddenly after control measures were implemented. Since March 2021, the monthly count has increased slightly.

Two vaccine failure cases occurred in the first five months of 2021 in individuals vaccinated with PCV10.

The proportion of cases caused by PCV13 serotypes that are not included in PCV10 (serotypes 3, 6A and 19A), together with the PCV13-associated serotype 6C (cross-protection from 6A), was 39% in 2020/2021. This was higher compared to 2019/2020 (31%) and 2018/2019 (25%). However, the incidence of these serotypes of specific interest was still lower in 2020/2021 than in 2019/2020.

Since the autumn of 2020, the 23-valent pneumococcal polysaccharide vaccine (PPV23) is offered to all 73- to 79-year-olds. Among those invited for vaccination, the percentage of cases with a PPV23 serotype was 60% versus 75% in older adults who were not invited. When corrected for the odds ratio in the previous seasons, the estimated impact of PPV23 on vaccine-type invasive pneumococcal disease was 0.47 (95% CI: 0.27–0.82).

### **Poliomyelitis**

In 2020 and 2021, for the period up to and including April 30<sup>th</sup>, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.

Nigeria, and thus the African region, was declared wildtype polio-free in June 2020. The WHO classified two countries – Afghanistan and Pakistan – as polio-endemic countries in 2020-2021.

The incidence of VDPV2 cases worldwide was almost three times higher in 2020 than in 2019 (1,085 versus 368 respectively). Therefore, demand for monovalent type 2 oral polio vaccine (mOPV2) increased. The WHO advised that all countries should destroy materials containing poliovirus type 2 and provide at least one inactivated polio vaccine (IPV) in their routine vaccination schedule.

### **Rubella**

In 2020 and the first six months of 2021, no rubella cases were notified.

### **Tetanus**

Two tetanus cases were reported in 2020. One occurred in an individual born before introduction of routine vaccination. No *Clostridium tetani* was cultured from the wound. The other patient was an unvaccinated teen. *C. tetani* was cultured from the wound, but no tetanus toxin was found.

## The immunisation programme 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 2020, no vaccine-preventable diseases were reported on Bonaire and Saba. Data for the other islands were not available this year due to the SARS-CoV-2 pandemic.

Findings from the Health Study Caribbean Netherlands (CN) indicate that the circulation of *B. pertussis* in CN is vastly underestimated. Among residents without detectable vaccine-induced humoral immunity, an estimated 8.2% were infected with *B. pertussis* within the previous 12 months, and the highest rates of a recent infection were found in adolescents aged 12-17 (16.1%) and young adults 18-29 years of age (16.7%).

## Potential NIP candidates

### Hepatitis A

In 2020, the number of reported hepatitis A cases (n=51, incidence of 0.3 per 100,000) was the lowest recorded since hepatitis A became notifiable in 1999. Almost two-thirds of the cases reported in 2020 occurred in individuals of 20 years or older. Travel and person-to-person contact are important transmission routes for hepatitis A. Nine cases (18%) contracted the disease abroad, which is lower than observed in previous years (28-59%). The COVID-19 control measures implemented from mid-March 2020 onwards, may explain the deviating, low numbers.

### Respiratory syncytial virus (RSV) infection

During respiratory season 2020/2021 (for the period up to and including week 20 of 2021), the number of Respiratory Syncytial Virus (RSV) detections in the virological laboratory surveillance was extremely low and never exceeded the epidemic threshold of 21 detections. In none of the 414 patients with an acute respiratory infection (ARI) including Influenza-Like Illness (ILI), RSV was detected in nose swabs and throat swabs collected by sentinel GPs during this reporting period. The extremely low circulation was likely the result of the control measures against COVID-19. In week 23 of 2021, after the end of the reporting period for this report, an out-of-season RSV epidemic started in the Netherlands.

### Rotavirus infection

In 2020, 350 rotavirus detections were reported in the virological week reports (note: do not provide nationwide coverage), fewer compared to 2019 (n=1,053). In 2021, for the period up to and including the first week of May, 206 rotavirus detections were reported. Half (11/22) of the typed samples in 2020 were genotype G9P8. The COVID-19 control measures, including social distancing, most likely play a role in the decreased number of detected rotavirus cases. In April 2020, the Ministry of Health, Welfare and Sport (VWS) decided to cease the implementation of rotavirus vaccination for risk infants in the National Immunisation Programme. In June 2020, the Ministry of VWS requested the Health Council to issue a new advice on rotavirus vaccination. In June 2021, the Health Council advised to implement universal rotavirus vaccination in the National Immunisation Programme.

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

VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands was comparable to that in previous years: in 2019, GPs recorded about 52,000 varicella and 95,000 herpes zoster episodes (300 and 550 episodes per 100,000 population, respectively).

### **COVID-19**

The Netherlands has seen four COVID-19 waves, for the period up to and including week 38 of 2021, during which COVID-19 control measures were implemented to prevent further spread of the disease. During the pandemic, testing capacity increased.

The COVID-19 vaccination campaign in the Netherlands started on 6 January 2021 and focused on reducing severe illness and death due to COVID-19 as well as ensuring that the healthcare system would not be overtaxed. Eventually, all persons aged 12 years and older (birth year 2009 and before) were eligible for COVID-19 vaccination. The vaccination schedule was rolled out from old to young, with priority given to risk groups.

While overall vaccination coverage is high, it lags behind for younger age groups compared to older age groups. A few large cities and some municipalities in the so-called Dutch 'Bible Belt' are exceptions to the high national vaccination coverage. Vaccination coverage is lowest in the municipality of Urk.

Two to three months after the vaccination programme started in the Netherlands, it was found to have a significant impact on the COVID-19 burden in the elderly. High vaccine effectiveness (VE) against severe COVID-19 was demonstrated, including in the period during which the Delta variant was dominant. Vaccine effectiveness against transmission to household members was estimated at approximately 70% in the period in which the Alpha variant was dominant.

Data from the PIENTER Corona (PICO) study indicate that young adults have been infected most frequently, especially compared to primary school-aged children. The latest study round (June 2021) showed that over 90% of Dutch inhabitants aged 55 years and over had detectable SARS-CoV-2-specific antibodies, resulting from both natural infection and vaccination.

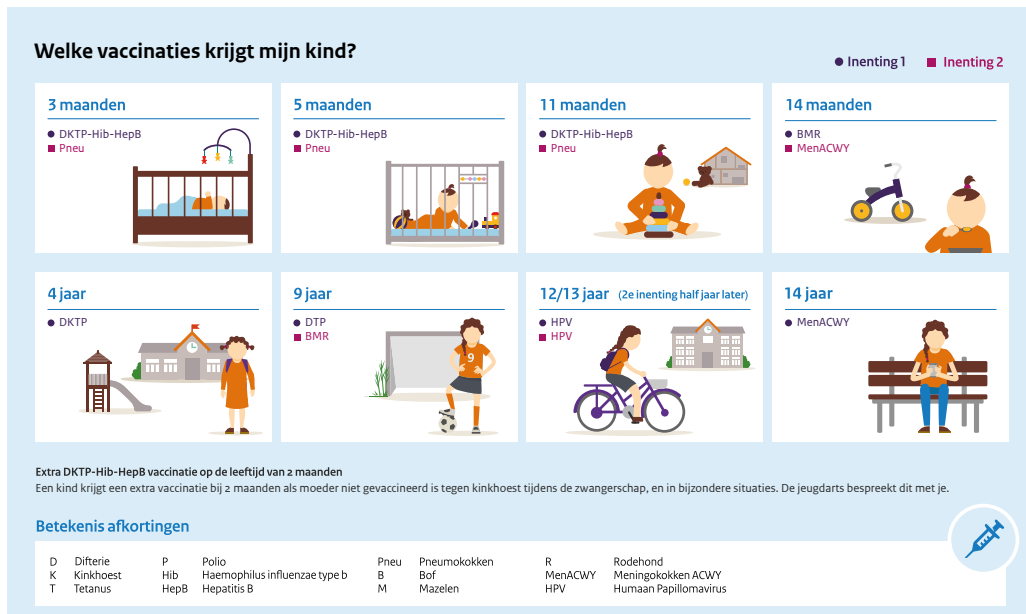
The RIVM sequences randomly selected SARS-CoV-2-positive specimens to monitor the increase or decrease of Variants Of Concern (VOCs). From March up to May 2021, the Alpha variant caused nearly 100% of all infections, while from June 2021 the Delta variant started to spread rapidly, causing almost 100% of infections from August 2021 onwards.

Many studies are ongoing to continuously monitor the SARS-CoV-2 and COVID-19 epidemiological situation in the Netherlands. For recent information, please refer to the [RIVM website](#), and to the [coronadashboard webpage](#) and its related data-specific pages.



# Uitgebreide samenvatting

## Huidig vaccinatieschema



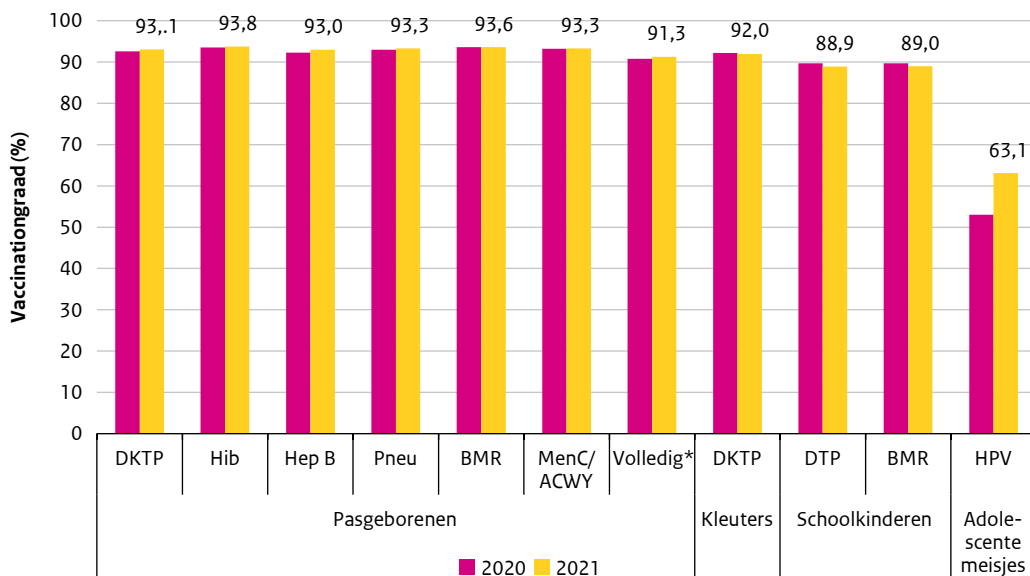
**Figuur 1** Nederlandse vaccinatieschema in 2020.

Bron: RIVM.

## Vaccinatiegraad

De *vaccinatiegraad* betreft kinderen die hun vaccinatie(s) nog bijna allemaal vóór de uitbraak van het coronavirus kregen. Voor de meeste vaccinaties in het RVP is de landelijke vaccinatiegraad opnieuw gestegen. Naast de lichte stijging voor zuigelingen (maximaal 0,7%) is vooral de stijging voor HPV-vaccinatie van 53% naar 63% opvallend; de HPV-vaccinatiegraad was nog nooit zo hoog. Ongeveer 70% van de zwangere vrouwen nam deel aan de 22 wekenprik, die zuigelingen vanaf de geboorte tegen kinkhoest beschermt.

*Voorlopige cijfers* suggereren dat de maatregelen vanwege de uitbraak van het coronavirus weinig negatieve invloed hebben gehad op het aantal kinderen dat in deze periode is gevaccineerd. Zo blijft deelname aan de eerste BMR-vaccinatie slechts 1-2% achter ten opzichte van een jaar eerder. De exacte *vaccinatiegraad* voor deze kinderen kan pas volgend jaar worden berekend omdat dan pas alle cijfers bekend zijn.



**Figuur 2** Vaccinatiegraad per vaccin voor pasgeborenen, kleuters, schoolkinderen en adolescente meisjes in verslagjaar 2020 en 2021.

\* Volledig = alle RVP-vaccinaties volgens schema ontvangen op 2-jarige leeftijd.

Bron: Præventis.

## Acceptatie van vaccinatie

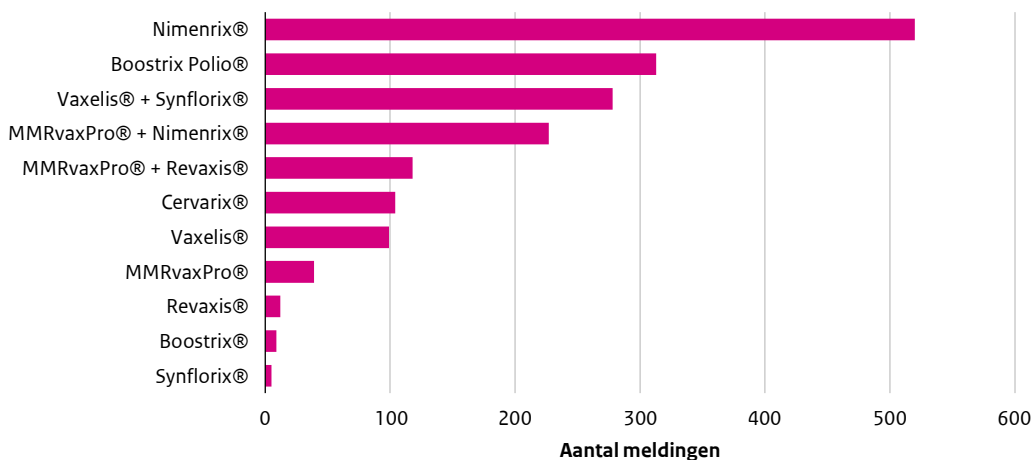
Verschiedende studies hebben aangetoond dat relevante zorgverleners invloed hebben op de attitudes ten opzichte van vaccinaties en daarmee op de acceptatie van vaccinaties. Er voor zorgen dat zorgverleners zo positief mogelijk zijn over vaccinaties is daarom van belang. Het verbeteren van de informatie en de manier waarop deze informatie, bijvoorbeeld over maternale kinkhoestvaccinatie, wordt aangeboden kan de attitude van zorgprofessionals positief beïnvloeden. Overtuigingen met betrekking tot vaccinatiegedrag van familie en vrienden (ook wel sociale norm genoemd), de veiligheid van het vaccin spelen een rol bij de acceptatie van vaccinaties, ook bij de acceptatie van COVID-19 vaccinaties. Een andere factor die invloed heeft op de acceptatie van COVID-19 vaccinaties, is de mogelijkheid van deze vaccinaties om een einde te maken aan de crisis. Technieken om de acceptatie van vaccinatie te verhogen en ongelijkheden tussen bepaalde groepen te verminderen zijn bijvoorbeeld mensen nogmaals uitnodigen of een herinnering sturen en informatie in eigen taal aan te bieden. Uit internationale studies blijkt ook dat transparante informatie waarbij zowel de voordelen als nadelen, zoals bijwerkingen, helder en duidelijk worden benoemd kan helpen bij het verhogen van de acceptatie van vaccinaties.

## Ziekte­last

De geschatte totale ziekte­last veroorzaakt door ziekten die door vaccinatie te voorkomen zijn indien de betreffende stammen van de pathogenen zijn opgenomen in de vaccins, uitgedrukt in disability adjusted life years (DALYs), was in 2020 het hoogst voor HPV (gebaseerd op de ziekte­last in 2019 in plaats van 2020; 19.400 DALYs (75% voor vrouwen)), invasieve pneumo­kokkenziekte (6.200 DALYs), invasieve ziekte veroorzaakt door *H. influenzae* (1.000 DALYs), invasieve meningokokkenziekte (400 DALYs), kinkhoest (390 DALYs) en rotavirusinfectie (390 DALYs). Voor de meeste ziekten die door vaccinatie te voorkomen zijn was de totale geschatte ziekte­last in 2020 aanzienlijk lager dan de geschatte ziekte­last in 2019. Dit is waarschijnlijk toe te schrijven aan de implementatie van verschillende COVID-19 responsemaatregelen zoals afstand houden en handen wassen. De ziekte­last van invasieve *H. influenzae* type b was hoger in 2020, de reden voor deze toename is onbekend.

De ziekte­last van COVID-19 wordt geschat op 169.000 DALYs voor 2020, waarbij 99% van de ziekte­last te wijten is aan mensen die eerder overlijden dan in een situatie zonder COVID-19. Dit is een onderschatting van de werkelijke ziekte­last, aangezien er geen rekening is gehouden met de gevolgen van de ziekte op lange termijn.

## Bijwerkingen



**Figuur 3** Aantal meldingen van mogelijke bijwerkingen per vaccin(s) in 2020.

Bron: Lareb.

In 2020 ontving Bijwerkingencentrum Lareb 1.475 meldingen van in totaal 4.640 mogelijke bijwerkingen van vaccins. Dit aantal meldingen is ongeveer gelijk aan het aantal ontvangen meldingen in 2018 (n=1.519), maar lager ten opzichte van het aantal ontvangen meldingen in 2019 (n=2.009). Dit is mogelijk een gevolg van de inhaalcampagne van de meningokokken ACWY-vaccinatie bij 14-18-jarigen in 2019. Het aantal geregistreerde mogelijke bijwerkingen na vaccinatie per melding was 3.1. Dit is iets lager in vergelijking met 2018 en 2019 met respectievelijk 3.4 en 3.7 mogelijke bijwerkingen na vaccinatie per melding.

Er werden geen nieuwe signalen van verontrustende bijwerkingen gevonden.

## Huidig RVP

### Difterie

In 2020 werden drie gevallen van difterie gemeld. De eerste melding (*Corynebacterium ulcerans*) betrof een patiënt die niet gevaccineerd was. De tweede melding betrof een volledig gevaccineerde, in Nederland geboren patiënt (*C. ulcerans*). De derde patiënt was niet gevaccineerd en geboren in het buitenland (*C. diphtheriae*). In 2021 zijn er tot en met maart geen gevallen van difterie gemeld.

De uitbraak van difterie die in oktober 2017 in Jemen werd erkend, is nog steeds aan de gang en treft bijna alle gouvernementen. Tot en met 26 april 2020 meldde het land 5701 vermoedelijke gevallen van difterie en 330 gerelateerde sterfgevallen. Daarnaast meldden vijf landen in de Amerikaanse regio in totaal 80 bevestigde gevallen van difterie, waarvan 21 doden, in 2020. Bovendien was er vanwege de COVID-19-pandemie in 2020 uitstel van vaccinatiecampagnes in de Amerikaanse regio in vergelijking met 2019.

### *Haemophilus influenzae*-ziekte

In 2020 is invasieve *Haemophilus influenzae* type b (Hib)-ziekte gestegen van ongeveer 40 gevallen per jaar tussen 2017 en 2019 (incidentie ongeveer 0.25 per 100.000 inwoners) tot 68 Hib gevallen (incidentie 0.39 per 100.000). Deze toename tijdens de coronapandemie is opvallend aangezien de coronamaatregelen ook tegen spreiding van Hib werken. Ziektegevallen door andere respiratoire infecties, waaronder ziekte veroorzaakt door andere *H. influenzae* (Hi) typen, daalden wel tijdens de pandemie.

De toename werd gezien in de meeste leeftijdsgroepen. Van alle Hib gevallen in 2020 kwamen er 34 voor bij kinderen die in aanmerking kwamen voor vaccinatie, waarvan er voldoende gevaccineerd waren. Dit betekent dat de effectiviteit van het Hib-vaccin met ongeveer 97% iets hoger ligt dan het gemiddelde van 93% de afgelopen jaren.

Ziekte veroorzaakt door andere Hi typen kwam in 2020 minder voor dan in eerdere jaren, waarschijnlijk vanwege de coronamaatregelen. Tot mei 2021 waren er 20 gevallen bekend van niet-typeerbare Hi. Dit is een sterke afname vergeleken met dezelfde periode in voorgaande jaren (77 gevallen in 2020, 91 in 2019).

## Hepatitis B

De incidentie van acute hepatitis B-meldingen (n=95) daalde met 9% tot 0,4 per 100.000 inwoners. Seksueel contact was de meest gemelde risicofactor voor een acute HBV-infectie. In 2020 bleef genotype A het dominante genotype onder acute HBV-gevallen met 65% van de 40 getypeerde gevallen.

Het aantal nieuw gediagnosticeerde chronische HBV-infecties (n=714) daalde met een derde vergeleken met 2019 en was 4,1 per 100.000 inwoners. De daling in meldingen van chronische hepatitis B viel samen met de pieken in COVID-19 ziekenhuisopnames.

## Humaan papillomavirus (HPV)-infectie

De incidentie van baarmoederhalskanker is in 2020 gedaald naar 8,58 per 100,000 vrouwen (n=796) ten opzichte 9,79 per 100,000 vrouwen (n=905) in 2019. Het aantal overlijdens veroorzaakt door baarmoederhalskanker is stabiel gebleven (n=229). 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 HPV16/18 tot in ieder geval 10 jaar na vaccinatie met een 3-dosis schema van het bivalente vaccin. Ook werd een hoge VE tegen nieuwe vaginale infecties met HPV16/18 gevonden 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. In het HPV-2D onderzoek, werd een hoge seroprevalentie van HPV16/18-specifieke antilichamen gevonden tot 72 maanden na bivalente vaccinatie met een 2-dosis schema. Een pilot onderzoek (EVI) naar de vroege immuunreactie na vaccinatie liet een hogere seroprevalentie van HPV16/18-specifieke antilichamen en een hogere reactie van geheugen-B-cel en T-cel zien bij bivalent gevaccineerden dan bij nonavalent gevaccineerden. Voor HPV31/45-specifieke antilichamen was dit andersom. In een dwarsdoorsnede onderzoek (PASSYON) werd een associatie gevonden tussen de genitale virale lading van HPV-infecties en het hebben van een genitaal-anaal HPV-infectie. Vanaf 2022 zullen jongens en meisjes worden uitgenodigd voor een HPV-vaccinatie in het jaar dat zij 10 worden.

## Mazelen

In 2020 zijn twee gevallen van mazelen gemeld. In de eerste zes maanden van 2021 zijn geen gevallen gemeld. Het lage aantal mazelen gevallen hangt waarschijnlijk samen met de COVID-19 pandemie.

## Meningokokkenziekte

Na een toename in de incidentie van invasieve meningokokkenziekte in de jaren 2015-2018 naar 1,2 per 100.000, nam de incidentie af tot 0,39 per 100.000 in 2020 (n=68). De incidentie van alle serogroepen ging naar beneden. In de eerste 4 maanden van 2021 waren er slechts 11 gevallen van invasieve meningokokkenziekte. Deze werden voornamelijk veroorzaakt door serogroep B (menB; n=9). De afname is waarschijnlijk het gevolg van de preventieve maatregelen die zijn getroffen vanwege de COVID-19 pandemie. Ook de introductie en catch-up campagne van meningokokkenACWY-vaccinatie speelt zeer waarschijnlijk een rol in de afname.

In 2020 en tot en met april 2021 zijn er geen invasieve meningokokken ziektegevallen geweest door serogroepen A, C, of W (menA, menC of menW) in de leeftijdsgroep die voor vaccinatie in aanmerking kwam. Er waren slechts twee gevallen veroorzaakt door menW in deze leeftijdsgroepen. In totaal nam de menW incidentie na de introductie en inhaalcampagne van menACWY vaccinatie af met 61% (95% betrouwbaarheidsinterval: 40-74%). In de betrokken leeftijdsgroepen was de afname 82% (18-96%) en in niet-betrokken leeftijdsgroepen was dit 57% (34-72%).

### **Bof**

De incidentie van bof was laag in 2019 (0,4 per 100.000; n=64). Vanaf 1 april 2020 daalde het aantal meldingen sterk. De daling viel samen met het ingaan van maatregelen om de COVID-19 epidemie te bestrijden. De meeste bofgevallen in Nederland werden veroorzaakt door het bofvirus genotype G.

### **Kinkhoest**

In 2020 werden in totaal 943 kinkhoestmeldingen ontvangen (5,4 per 100.000), hetgeen aanzienlijk lager is dan in 2019, toen het totaal aantal meldingen 6.361 (36,8 per 100.000) bedroeg. Deze daling was waarschijnlijk het gevolg van de maatregelen om de COVID-19-pandemie onder controle te krijgen. Omdat de incidentie in alle leeftijdscategorieën, inclusief de zuigelingen, daalde, is het nog moeilijk om een mogelijk effect van de maternale kinkhoestvaccinatie op de incidentie bij zuigelingen van 0-5 maanden oud te detecteren.

Tussen april en december 2020 werden acht gevallen van kinkhoest bij zuigelingen van 0-3 maanden oud gemeld, waarvan drie zuigelingen de maternale kinkhoestvaccinatie hadden gekregen. Uitgaande van een geschatte maternale vaccinatiegraad van 70%, werd de werkzaamheid van het vaccin geschat op 74% (95%-BI: -32 tot 96%).

In een populatie-gebaseerde cross-sectionele sero-survey onder een representatieve steekproef van 7.621 0-89-jarige Nederlanders (PIENTER-3-onderzoek) is de seroprevalentie van kinkhoest onderzocht. Personen van  $\geq 7$  jaar met pertussistoxineconcentraties van 100 IE/ml en hoger werden als seropositief beschouwd voor een recente kinkhoestinfectie. Tussen 1995/1996 en 2006/2007 werd een stijging gevonden van 1,0 naar 3,5% en het huidige onderzoek laat een nog steeds stijgende seroprevalentie zien van 3,5 naar 5,9%. De stijging van de seroprevalentie was het grootst bij 12-18-jarigen, waar hij sinds 2006/2007 meer dan verdrievoudigde, naar 11,5% in het huidige onderzoek. In het kader van de EUPertstrain-groep is door het RIVM een seroprevalentieonderzoek uitgevoerd in Europese landen voor kinkhoest, difterie en tetanus in de leeftijdsgroep 40-60 jaar, welke gefinancierd werd door het ECDC. Deze cross-sectionele seroprevalentiestudie in 18 Europese landen toonde aan dat de circulatie van *B. pertussis* wijdverbreid is, ondanks vaccinatieprogramma's voor kinderen met een hoge dekkinggraad.

In de Immfact-studie vertoonden en behielden oudere volwassen geïnfecteerden hogere IgA-responsen op *B. pertussis* dan adolescenten en jongere volwassen geïnfecteerden, mogelijk als gevolg van een veranderde rol voor IgA op oudere volwassen leeftijd.

Het RIVM heeft onlangs aangetoond dat nieuw circulerende *B. pertussis*-stammen een andere set eiwitten tot expressie brengen in vergelijking met oudere stammen en dat ze verschillende immunologische routes induceren in aangeboren immuuncellen. Deze bevindingen helpen de hernieuwde opkomst van kinkhoest in gevaccineerde populaties te begrijpen en benadrukken het belang van het overwegen van aanpassing van pathogenen bij het ontwerp van nieuwe generatie kinkhoestvaccins.

### **Pneumokokkenziekte**

De afname in de incidentie van invasieve pneumokokken ziekte die gezien was in 2019/2020 zette verder door in 2020/2021 naar 5,6 per 100.000 (ongeveer 1.500 gevallen in totaal).

De afname werd gezien in alle leeftijdsgroepen maar was het kleinst in kinderen jonger dan 5 jaar. De afname is zeer waarschijnlijk het resultaat van de geïmplementeerde maatregelen om COVID-19 te voorkomen. De afname was plotseling vanaf het moment dat Nederland in lock-down ging. Vanaf maart 2021 neemt het maandelijkse aantal gevallen met invasieve pneumokokkenziekte weer wat toe.

In de eerste vijf maanden van 2021 zijn er twee voldoende met PCV10 gevaccineerde gevallen geweest die geïnfecteerd waren met een vaccine serotype (serotype 19F en 14). Het kindje dat met serotype 14 was geïnfecteerd had geen bekend onderliggend lijden.

Negen-en-dertig procent van alle gevallen was geïnfecteerd met een serotype dat gedekt wordt door PCV13 maar niet door PCV10 (serotype 3, 6A of 19A) of door serotype 6C, een serotype waar PCV13 ook tegen lijkt te werken. In voorgaande jaren was dit percentage iest lager (31% in 2019/2020 en 25% in 2018/2019). De incidentie van deze specifieke serotypen was overigens nog steeds later in 2020/2021 dan in de eerdere jaren.

In de herfst van 2020 hebben alle 73-79-jarigen het 23-valente pneumokokken vaccine (PPV23) aangeboden gekregen. In de uitgenodigde leeftijdsgroep was het percentage van de gevallen dat geïnfecteerd was door een PPV23-serotype 60% terwijl dit 75% was onder niet uitgenodigde ouderen. De voor eerder seizoenen gecontroleerde schatting van het effect van PPV23 op pneumokokken ziekte veroorzaakt door PPV23 serotypen was geschat op 0.47 (95% BI interval 0.27–0.82).

### **Polio**

In 2020 en tot en met 30 april 2021 zijn er geen gevallen van poliomyelitis gemeld in Nederland, ook niet in Caribisch Nederland.

Nigeria, en daarmee de Afrikaanse regio, is in juni 2020 wildtype poliovrij verklaard. Twee landen, namelijk Afghanistan en Pakistan, zijn in 2020-2021 door de WHO geclassificeerd als polio-endemische landen.

De incidentie van door vaccin afgeleide gevallen van poliovirus 2 (VDPV2) was in 2020 wereldwijd bijna drie keer hoger dan in 2019 (respectievelijk 1085 versus 368). Daarom is er een grotere vraag naar monovalent type 2 oraal poliovaccin (mOPV2) ontstaan. Deze grote



vraag heeft zelfs de voorraad van dit vaccin bedreigd. De WHO adviseerde alle landen om de materialen die poliovirus type 2 bevatten te vernietigen en ten minste één geïnactiveerd poliovaccin (IPV) in hun routinevaccinatieschema op te nemen.

### Rodehond

In 2020 en in de eerste zes maanden van 2021 werden geen gevallen van rodehond gemeld.

### Tetanus

In 2020 zijn twee gevallen van tetanus gemeld. Eén geval betrof een patiënt geboren voor 1950 en daardoor niet in aanmerking komend voor vaccinatie. Er werd geen *Clostridium tetani* uit de wond gekweekt. De andere melding betrof een niet-gevaccineerde tiener. *C. tetani* werd uit de wond gekweekt, hoewel er geen tetanustoxine werd gevonden.

## Het vaccinatieprogramma in Caribisch Nederland

In het algemeen genomen is de vaccinatiegraad in Caribisch Nederland (CN; Bonaire, St. Eustatius, en Saba) hoog. In 2020 zijn er op Bonaire en Saba geen ziekten gerapporteerd waartegen binnen het RVP gevaccineerd wordt. Data voor de andere eilanden waren dit jaar niet beschikbaar door de COVID-19 pandemie.

Bevindingen van de Gezondheidsstudie Caribisch Nederland geven aan dat de circulatie van *B. pertussis* in CN zwaar onderschat wordt. Onder inwoners zonder detecteerbare vaccin-opgewekte humorale immuniteit, waren een geschatte 8.2% in de laatste 12 maanden geïnfecteerd met *B. pertussis*. De hoogste graad van recente besmettingen werd gevonden in pubers tussen de 12 en 17 jaar oud (16.1%) en jongvolwassenen tussen 18 en 29 jaar oud (16.7%).

## Potentiële RVP-kandidaten

### Hepatitis A

Er werden in 2020 51 hepatitis A gevallen gerapporteerd (incidentie 0.3 per 100,000). Dit is het laagste aantal meldingen sinds de start van de meldingsplicht voor hepatitis A in 1999. Iets minder dan twee derde van de gemelde gevallen in 2020 betrof een volwassene ( $\geq 20$  jaar). Reizen en mens-op-mens contact zijn belangrijke transmissieroutes voor hepatitis A. Negen patiënten (18%) hadden de infectie in het buitenland opgelopen. Dit is lager dan in de voorgaande jaren toen 28-59% van de infecties in het buitenland werd opgelopen. Sinds half maart 2020 gelden er allerlei maatregelen om de coronaviruspandemie onder controle te krijgen. Deze maatregelen zullen hebben bijgedragen aan deze afwijkende, lage aantallen.

### Respiratoir syncytieel virus (RSV)-infectie

Tijdens het respiratoire seizoen 2020/2021 (tot en met week 20/2021) was het aantal respiratoir syncytieel virus (RSV) detecties dat gerapporteerd werd door de laboratoria van de virologische weekstaten extreem laag en kwam niet boven de epidemische drempel van 21 detecties per week uit. In geen van 414 patiënten 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 komt waarschijnlijk door de coronamaatregelen, die ook helpen om de verspreiding van andere virussen te voorkomen. In week 23, na het einde van deze rapportage periode, begon een RSV-epidemie buiten het gebruikelijke seizoen.

### **Rotavirusinfectie**

Er werden in 2020 350 rotavirus detecties gerapporteerd in de virologische weekstaten, wat minder is dan het aantal detecties in 2019 (n=1,053). Tot en met de eerste week van mei 2021 zijn 206 rotavirus detecties geobserveerd. De helft van alle getypeerde monsters in 2020 betrof rotavirus G9P8 (11/22). De COVID-19 maatregelen, waaronder sociale afstand, spelen waarschijnlijk een rol in de daling van het aantal gerapporteerde rotavirus detecties. Het ministerie van Volksgezondheid, Welzijn en Sport (VWS) heeft in april 2020 besloten de implementatie van vaccinatie tegen het rotavirus voor hoog-risico kinderen in het Rijksvaccinatieprogramma stop te zetten. In juni 2020 heeft het Ministerie van VWS de Gezondheidsraad verzocht opnieuw een advies uit te brengen over rotavirus vaccinatie. In juni adviseerde de Gezondheidsraad om algemene rotavirus vaccinatie in het Rijksvaccinatieprogramma op te nemen.

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

De epidemiologie van VZV (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) was vergelijkbaar met voorgaande jaren: in 2019 werden door huisartsen ongeveer 52.000 waterpokken- en 95.000 gordelroosepisodes gerapporteerd (respectievelijk 300 en 550 episodes per 100.000 inwoners).

### **COVID**

In Nederland zijn er tot en met week 38 van 2021 vier coronagolven geweest. In deze periode zijn coronamaatregelen geïmplementeerd om verdere verspreiding te voorkomen.

De COVID-19 vaccinatiecampagne startte in Nederland op 6 januari 2021, en focuste op het verminderen van ernstige ziekte en overlijden door COVID-19, en vermindering van de druk op zorg. Uiteindelijk kwamen alle personen ouder dan 12 jaar (geboren in 2009 en daarvoor) in aanmerking voor vaccinatie, waarbij van oud naar jong werd uitgenodigd en voorrang werd gegeven aan personen uit risicogroepen.

Ook al is de algehele vaccinatiegraad hoog, de vaccinatiegraad voor jongere leeftijdsgroepen blijft achter op die van de oudere groepen. Een aantal grote steden en een aantal gemeenten in de Nederlandse "Bible Belt" zijn uitzondering op de hoge landelijke vaccinatiegraad. De laagste vaccinatiegraad wordt gezien in de gemeente Urk.

In de eerste 2 tot 3 maanden na de start van de vaccinatiecampagne werd bij bejaarden een grote impact op de COVID-19 ziektelast gezien. Hoge vaccin effectiviteit (VE) werd gevonden tegen ernstige ziekte door COVID-19, ook in de periode waarin de Delta variant dominant was. De VE tegen overdracht naar huisgenoten werd geschat op 70% in de periode waarin de Alpha variant dominant was.

De PIENTER Corona (PICO) studie geeft aan dat jongvolwassenen het vaakst geïnfecteerd waren geweest, vooral vergeleken met kinderen van basisschool-leeftijd. Data uit de laatste ronde (juni 2021) liet zien dat meer dan 90% van de Nederlanders van 55 jaar of ouder, detecteerbare SARS-CoV-2 specifieke antilichamen hadden, zowel door natuurlijke infectie en vaccinatie.

Het RIVM bepaalt van willekeurig geselecteerde SARS-CoV-2-positieve monsters de sequenties van het virus. Zo wordt gemonitord welke zorgwekkende varianten (Variants of Concern; VOCs) toenemen of afnemen. Van maart tot mei 2021 werd bijna 100% van de besmettingen veroorzaakt door de Alpha variant, terwijl vanaf juni 2021 de Delta variant snel begon te verspreiden en vanaf augustus 2021 bijna 100% van de besmettingen veroorzaakte.

Veel studies blijven lopen om zo continu de Nederlandse epidemiologische situatie rondom SARS-CoV-2 en COVID-19 te monitoren. Recente informatie is te vinden op de [RIVM-website](#), en op de [coronadashboard pagina](#) en de daaraan verbonden data-specifieke pagina's.



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 administered 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 this typical schedule, DTaP-IPV-Hib-HBV vaccinations are offered at 3, 5, and 11 months. However, if the mother did not receive Tdap vaccination at a sufficiently early stage of pregnancy or the child was born prematurely (before 37 weeks of pregnancy) or has low birth weight, children receive an additional DTaP-IPV-Hib-HBV vaccination at 2 months of age. Additionally, newborns to HBsAg positive mothers are given an HBV vaccination and HBV immunoglobulin, preferably within two hours of 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 good long-term immunity against NIP target diseases. The youth healthcare physician assesses their vaccination status and offers a personalised vaccination schedule, including a hepatitis B vaccination series. Furthermore, all asylum seeker infants are offered an additional MMRo dose at 9 months of age.

### 1.1.1 Recent changes in the vaccination schedule

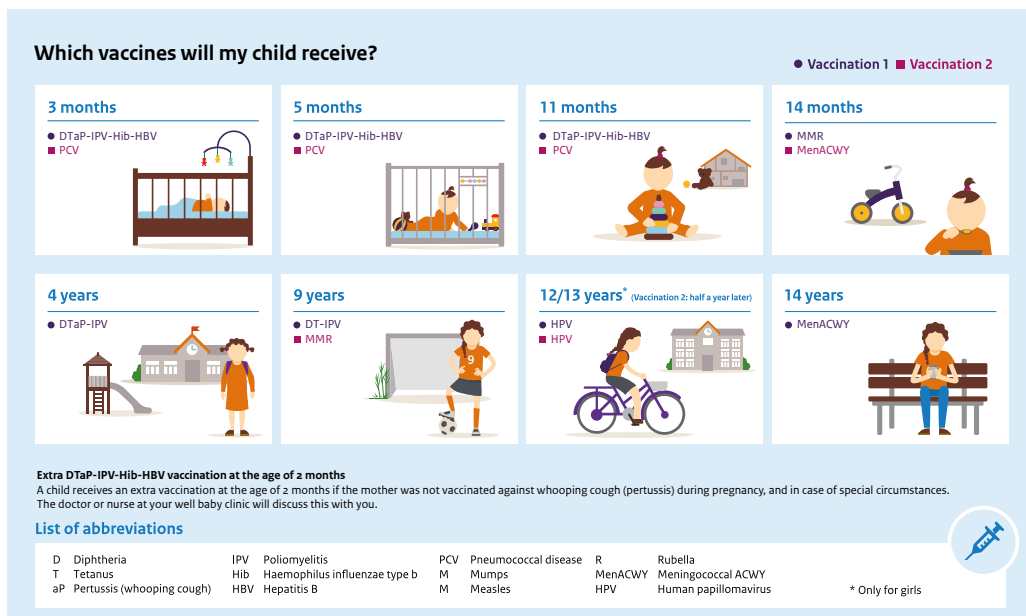
In May 2018, the MenC vaccination at 14 months of age was replaced by MenACWY vaccination to prevent the development of meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W, and Y (MenACWY). Between October 2018 and June 2019, all children born between January 1<sup>st</sup>, 2001, and December 31<sup>st</sup>, 2005 (14- to 18-year-olds) were offered MenACWY vaccination in a catch-up vaccination campaign. Since 2020, MenACWY vaccination is being offered to children in the year they turn 14 years as part of the NIP.

In addition, the maternal pertussis vaccination (MPV) was integrated into the NIP in December 2019, leading to a change in the first series of DTaP-IPV-Hib-HepB from being provided at 2, 3, 4 and 11 months to being offered at 3, 5 and 11 months, as mentioned above.

### 1.1.2 Number of vaccinated children

In 2020, the vaccination schedule consisted of 12 (boys) or 14 (girls) vaccine doses per child. Of these, 7 were given between the ages of 0 and 11 months.

In 2020, 901,889 children and 125,089 pregnant women were immunised under the Dutch NIP. The children received 2,082,537 vaccine doses, whereas the pregnant women received a total of 125,089 vaccine doses; one Tdap vaccine each.



**Figure 1.1** NIP vaccination schedule

Source: <http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals>.

## 1.2 New recommendations and decisions

### 1.2.1 New decisions of the Ministry of Health, Welfare and Sport

In 2020, pneumococcal vaccination (PPV23) was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups. As a result, all 73- to 79-year-olds have been offered PPV23 vaccination in the fall of 2020. In the fall of 2021, persons aged 69 to 73 years will receive an invitation for pneumococcal vaccination from their GP [1].

In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella (VZV) to the NIP in the Caribbean Netherlands, and also recommended that residents of the Caribbean Netherlands who had not yet contracted varicella should be offered a single vaccination against VZV [2]. The State Secretary of Health, Welfare, and Sport has provisionally adopted this advice. The implementation date will depend on availability of the vaccine and availability of the healthcare providers that carry out the NIP in the Netherlands Caribbean.

### 1.2.2 New recommendations from the Health Council of the Netherlands

The Ministry of Health, Welfare and Sport requested a new advice on rotavirus vaccination after cancelling the original implementation of rotavirus vaccination of risk groups.

On June 30<sup>th</sup>, 2021, the Health Council issued their new advice on rotavirus vaccination and recommended introducing universal rotavirus vaccination in the NIP. The Council indicated that the price of the available rotavirus vaccines should be lower if it was to be cost-effective [3].

On September 20<sup>th</sup>, 2021, the Health Council issued a new advice on influenza vaccination. They added a number of risk groups to be invited for vaccination, including pregnant women to protect both the mother during pregnancy and their children in the first 6 months of life.

## 1.3 Vaccination of risk groups

Influenza vaccination is offered to individuals aged 60 years and over and to those with an increased risk of morbidity and mortality following influenza. These vaccinations are offered through the National Influenza Prevention Programme (NPG). Vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries. 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 [4-7].

In addition to including 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 [8].

Information on vaccination of travellers and employees at risk of work-related infections can be found on the website [www.rivm.nl/vaccinaties](http://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 public programmes. Vaccinations registered for infants are those against gastro-enteritis caused by rotavirus infection, VZV, and meningococcal B disease (MenB). For both older children and adults, influenza, MenACWY, and pertussis vaccinations are available, and boys can receive an HPV vaccination. For adults specifically, vaccinations 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 a hepatitis A (HAV) vaccine simultaneously with their HBV vaccine. They will then receive a discount for the HAV component.

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



## 1.5 Literature

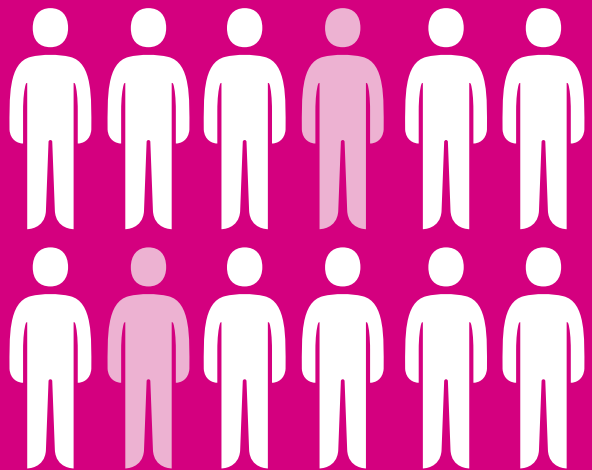
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\* RIVM publication.



2

# Vaccination coverage



## 2.1 Key points

- For most vaccinations in the NIP, national vaccination coverage has risen once more. It must be noted that this relates to children, almost all of whom received their vaccination(s) before the COVID-19 outbreak.
- In addition to the small rise for infants (maximum 0.7%), the increase for HPV vaccination from 53% to 63% is particularly striking; HPV vaccination coverage has never been this high.
- Approximately 70% of pregnant women opted for the maternal pertussis vaccination (22-week vaccination).
- Provisional figures suggest that the measures relating to the COVID-19 pandemic have had little negative impact on the number of children vaccinated during this period. For example, participation in the first MMR vaccination lags just 1-2% behind compared to a year earlier. The exact vaccination coverage for these children cannot be calculated until next year as all the required data will not be available until then.

## 2.2 Tables and figures

**Table 2.1** Vaccination coverage (%) per vaccine for age cohorts of newborns, toddlers, schoolchildren and adolescent girls in 2006-2021 [1].

Reporting year	Newborns*							
	Cohort	DTaP-IPV	Hib	HBV <sup>a</sup>	PCV <sup>**</sup>	MMR	MenC/ACWY	Full <sup>***</sup>
2006	2003	94.3	95.4	15.2	-	95.4	94.8	
2007	2004	94.0	95.0	17.1	-	95.9	95.6	
2008	2005	94.5	95.1	17.9	-	96.0	95.9	
2009	2006	95.2	95.9	18.6	94.4	96.2	96.0	
2010	2007	95.0	95.6	19.3	94.4	96.2	96.1	
2011	2008	95.4	96.0	19.4	94.8	95.9	95.9	
2012	2009	95.4	96.0	19.5	94.8	95.9	95.9	
2013	2010	95.5	96.1	19.7	95.1	96.1	96.0	
2014	2011	95.4	95.9	51.4	95.0	96.0	95.8	
2015	2012	94.8	95.4	94.5	94.4	95.5	95.3	
2016	2013	94.2	94.9	93.8	93.8	94.8	94.6	
2017	2014	93.5	94.2	93.1	93.6	93.8	93.5	91.2
2018	2015	92.6	93.4	92.2	92.8	92.9	92.6	90.2
2019	2016	92.4	93.1	92.0	92.6	92.9	92.6	90.2
2020	2017	92.6	93.5	92.3	93.0	93.6	93.2	90.8
<b>2021</b>	<b>2018</b>	<b>93.1</b>	<b>93.8</b>	<b>93.0</b>	<b>93.3</b>	<b>93.6</b>	<b>93.3</b>	<b>91.3</b>

Table continued on next page.

Reporting year	Toddlers*			Schoolchildren*			Adolescent girls*		
	Cohort	DTaP-IPV <sup>b</sup>	DTaP-IPV <sup>c</sup>	DTaP-IPV <sup>d</sup>	Cohort	DT-IPV	MMR****	Cohort	HPV
2006	2000	92.5	1.4	93.9	1995	93.0	92.9		
2007	2001	92.1	1.6	93.7	1996	92.5	92.5		
2008	2002	91.5	1.6	93.1	1997	92.6	92.5		
2009	2003	91.9	2.0	93.9	1998	93.5	93.0		
2010	2004	91.7	2.6	94.3	1999	93.4	93.1		
2011	2005	92.0	2.6	94.7	2000	92.2	92.1		
2012	2006	92.3	2.1	94.4	2001	93.0	92.6	1997	56.0
2013	2007	92.3	2.4	94.7	2002	93.1	92.9	1998	58.1
2014	2008	92.0	2.4	94.4	2003	92.7	92.4	1999	58.9
2015	2009	91.9	2.2	94.1	2004	92.7	92.7	2000	61.0
2016	2010	91.5	2.1	93.7	2005	92.0	92.0	2001	61.0
2017	2011	91.1	2.1	93.2	2006	90.8	90.9	2002	53.4
2018	2012	90.4	2.3	92.7	2007	90.0	90.1	2003	45.5
2019	2013	90.3	2.2	92.5	2008	89.5	89.5	2004	45.5
2020	2014	89.9	2.4	92.2	2009	89.7	89.7	2005	53.0
<b>2021</b>	<b>2015</b>	<b>89.4</b>	<b>2.6</b>	<b>92.0</b>	<b>2010</b>	<b>88.9</b>	<b>89.0</b>	<b>2006</b>	<b>63.1</b>

\* Vaccination coverage is assessed at the ages of 2 (newborns), 5 (toddlers), 10 (schoolchildren), and 14 years (adolescent girls).

\*\* Only for newborns born on or after April 1<sup>st</sup>, 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).

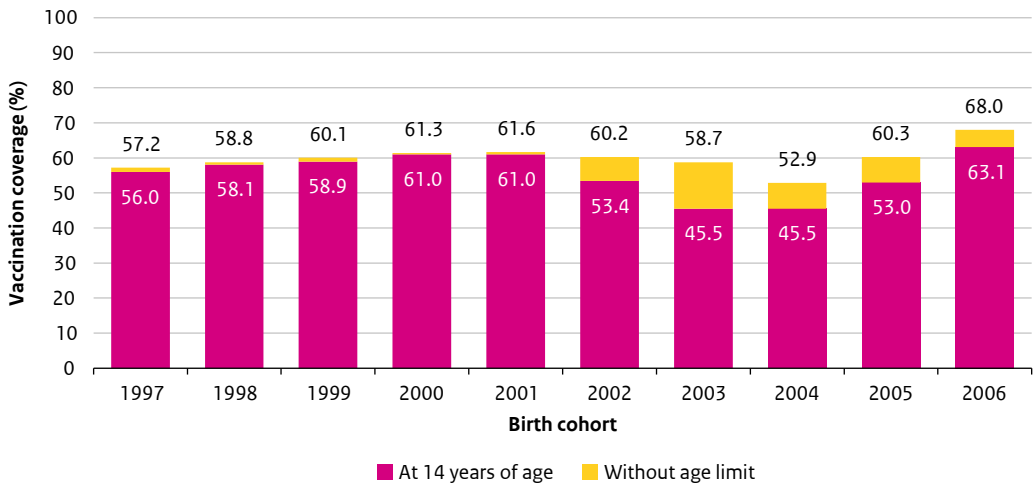
<sup>a</sup> Percentage for the total cohort. Universal hepatitis B vaccination was introduced in 2011; only risk groups were vaccinated previously.

<sup>b</sup> Revaccinated toddlers.

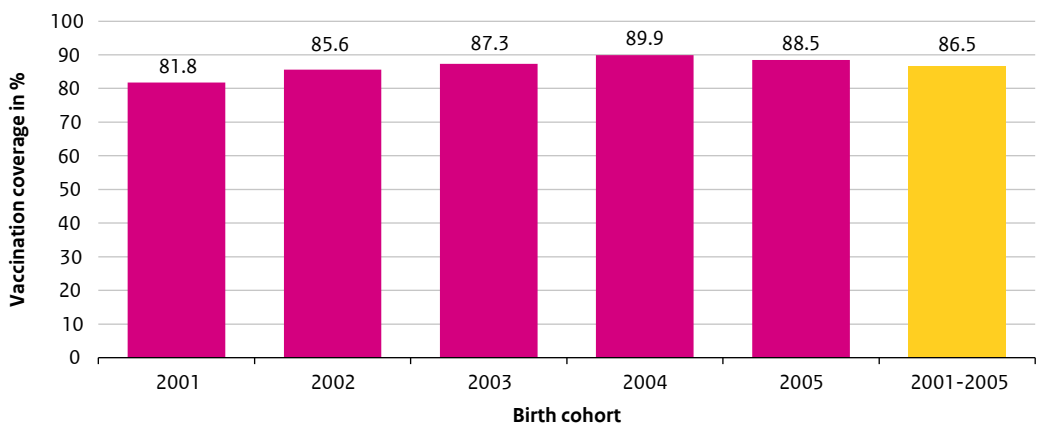
<sup>c</sup> Toddlers that reached basic immunity at 2–5 years of age were not eligible for revaccination at toddler age.

<sup>d</sup> Sufficiently protected toddlers (sum of <sup>b</sup> and <sup>c</sup>).

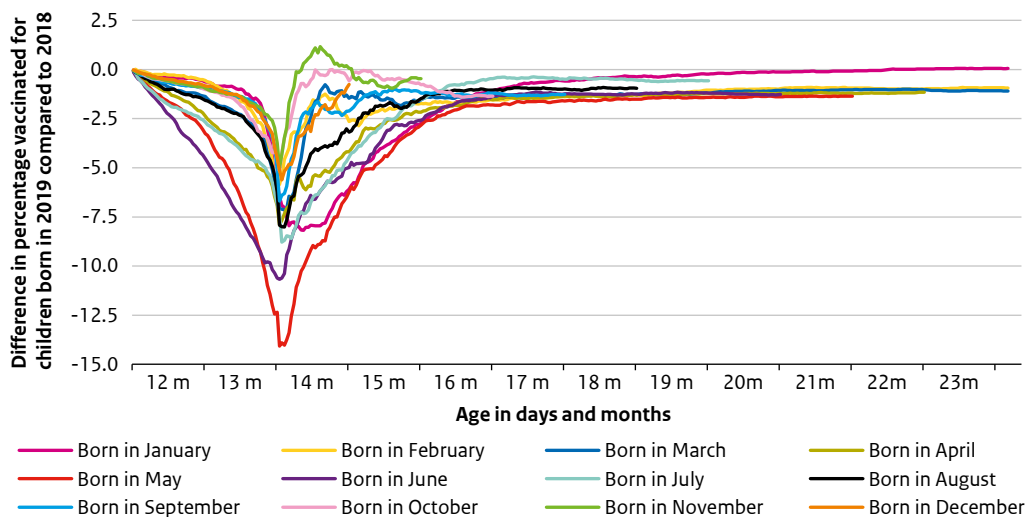
Source: Præventis.



**Figure 2.1** HPV vaccination coverage determined at 14 years of age and without age limit (situation on March 2<sup>nd</sup>, 2021), by birth cohort [1].

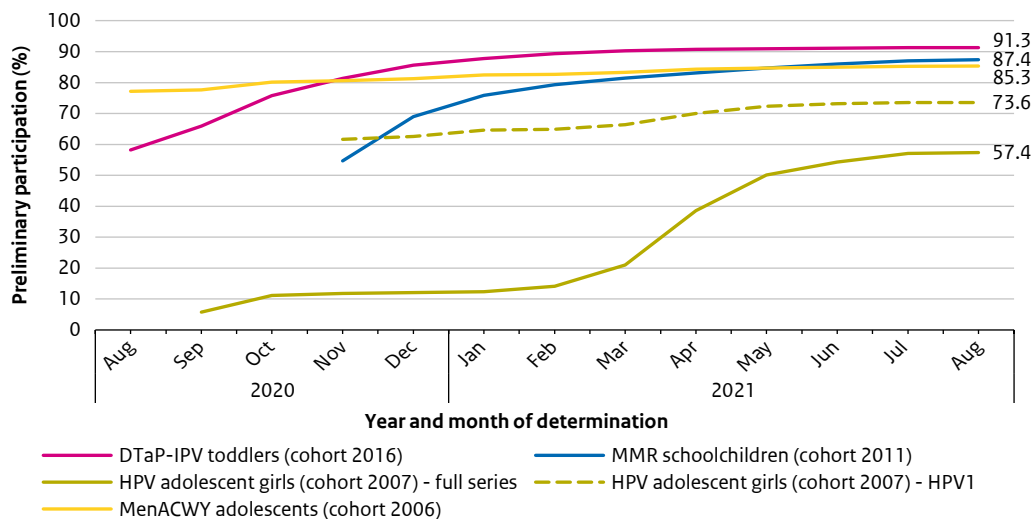


**Figure 2.2** Vaccination coverage for meningococcal ACWY vaccination of adolescents, by birth cohort (situation on March 2<sup>nd</sup>, 2021) [1].



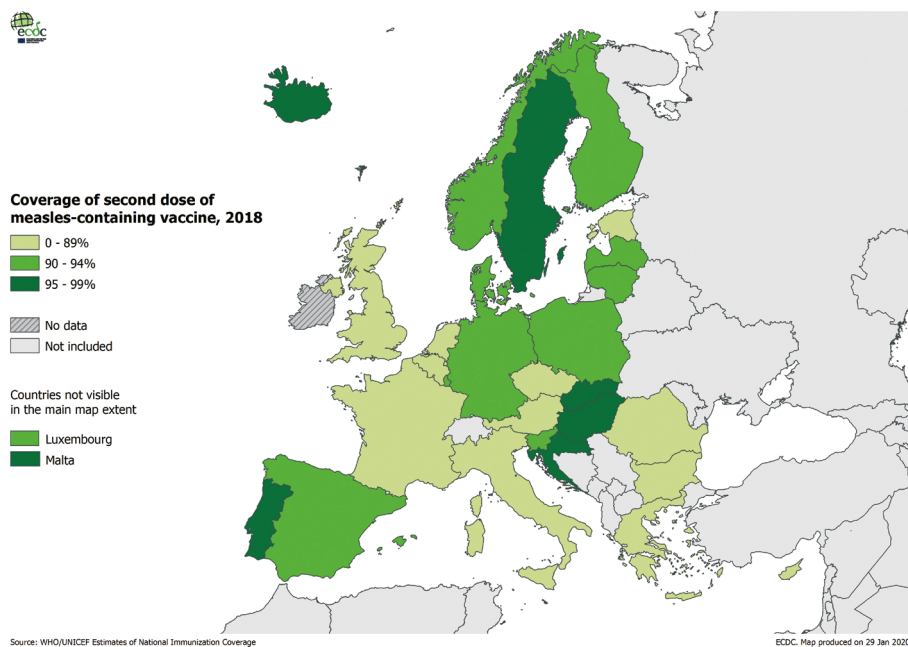
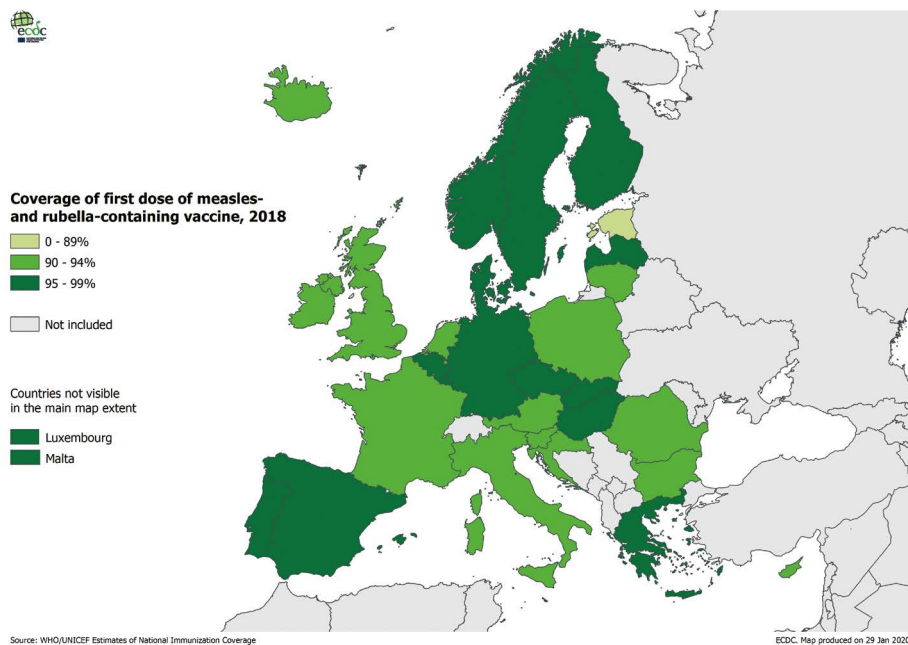
**Figure 2.3** Difference in participation in the first measles/mumps/rubella vaccination (MMR1) for children born in January-December 2019 compared to children born in January-December 2018 [1].

Note: Children are scheduled to be vaccinated at the age of 14 months. Children born in January-December 2019 were scheduled to be vaccinated in March 2020-February 2021. A difference of -8 at 436 days after birth means that the percentage vaccinated for children born in January 2019 (scheduled to be vaccinated in March 2020) at that age was 48% instead of 56% for children born in January 2018.



**Figure 2.4** Development of participation in vaccination over time for children eligible for vaccination in 2020.





**Figure 2.5** Vaccination coverage for first (above) dose of measles- and rubella-containing vaccine, and second (below) dose of measles-containing vaccine, EU/EEA and the UK, 2018 [2].

## 2.3 National developments

Compared to last year, national vaccination coverage has risen once again for most NIP vaccinations (Table 2.2.1). It must be noted that it relates to children, almost all of whom received their vaccination(s) before the COVID-19 outbreak. In addition to the small rise for infants (maximum 0.7%), the increase for HPV vaccination from 53% to 65% is particularly striking; HPV vaccination coverage has never been this high. In addition, the results for HPV also show a catch-up effect (vaccination after the age of 14 years) (Figure 2.2.1) that is higher for younger birth cohorts. This is probably due to additional catch-up vaccination moments because of the introduction of MenACWY vaccination for adolescents. Furthermore, national participation for MenACWY vaccination among adolescents born in the period 2001-2005 was high (86.5%) (Figure 2.2.2). Approximately 70% of pregnant women with a child born in the period April-December 2020 took part in the 22-week vaccination that protects babies against whooping cough from birth [1]. This is the first coverage estimate for the 22-week vaccination since its introduction in 2019.

## 2.4 Future challenges

### 2.4.1 Impact of the COVID-19 pandemic

The vaccination coverage shown in Table 2.2.1 concerns children that were mainly vaccinated before March 2020, i.e. before the coronavirus outbreak. However, the COVID-19 pandemic affected the way the NIP was conducted in 2020. The vaccinations at the child health clinics (0-4-year-olds) and the 22-week vaccination for pregnant women to protect babies against whooping cough from birth continued as much as possible. If necessary, the vaccinations for 4-year-olds (DTaP-IPV) were allowed to be postponed until the autumn of 2020 at the latest. Group vaccinations for 9-year-olds (DT-IPV/MMR) and 13-year-olds (HPV) were postponed until after the summer holidays; these vaccinations were allowed to be given individually and as of July 1<sup>st</sup>, 2020, vaccination of small groups per time slot became possible. The vaccination for 14-year-olds (MenACWY) was converted from group to individual vaccination, which should preferably be completed before July 1<sup>st</sup>, 2020 [1].

Since the start of the COVID-19 pandemic, participation in the first MMR vaccination has been monitored on a monthly basis using data generated by Præventis. Due to the infectious nature of measles, a high participation rate is especially important for the first MMR vaccination. Children born in January-December 2019 would normally have been vaccinated from March 2020 onwards; during the COVID-19 pandemic. In Figure 2.2.3, provisional participation for their first MMR vaccination is compared per month of birth with the participation of children born in January-December 2018. The figure clearly shows that there was some delay in participation, but also that catch-up vaccinations did occur at a later date. However, participation for most birth months still lags behind by 1-2% compared to a year earlier [1]. The first results of this analysis on children born in January-July 2019 were previously published in the journal *Vaccine* [3].

From August 2020 onwards, provisional participation in a number of vaccinations in older age groups has also been monitored on a monthly basis (Figure 2.2.4). In particular, provisional participation in the full series of the HPV vaccination is still lagging behind (grey line). However, it is too early to properly assess participation in the full HPV series since the HPV vaccination was initially postponed until after the summer holidays and a series of two vaccinations with an interval of six months is required. Preliminary figures (dotted grey line) show that almost 74% of girls born in 2007 had already received their first HPV vaccination by August 2021 (Figure 2.2.4), which is considerably higher than in previous years. It is therefore expected that participation for the full HPV series will increase significantly in the coming months [1].

In conclusion, it appears that COVID-19 control measures have had little negative impact on the number of children vaccinated during this period. The exact vaccination coverage for these children cannot be calculated until next year because all the required data will not be available until then. The extent of the impact of the coronavirus outbreak on vaccination coverage will depend on the duration of the crisis and whether people will catch up on missed vaccinations (in a timely manner).

#### **2.4.2 Informed consent**

The informed consent for the NIP is currently being prepared by the Youth Health Care (Jeugdgezondheidszorg; JGZ) in consultation with VWS, the Association of Netherlands Municipalities (VNG), and RIVM, and will be introduced as of January 1<sup>st</sup>, 2022. It will require the parent(s) and/or child to give permission for the exchange/transmission of the child's personalised vaccination data to the RIVM. After introduction of the informed consent, vaccination coverage for children will become an estimate instead of a calculation. The question is whether small changes in vaccination coverage, such as those seen in recent years for infants, and temporary effects such as those caused by the COVID-19 pandemic (section 2.4.1), can then still be detected. The vaccination coverage data is also important for monitoring of side effects and vaccine effectiveness. A clear explanation of the importance of full registration of vaccination data with the RIVM, subject to good privacy safeguards, is crucial to obtain as many permissions as possible. Only then, points for improvement to the NIP programme can still be identified, allowing necessary adjustments to be made in time. This continuous optimisation of the NIP program is imperative for it to keep on functioning properly [1].

## **2.5 International developments**

In 2020, the WHO European Region experienced a 1% decrease in routine immunisation coverage from 95% to 94% for the third dose of DTaP-IPV vaccination. These figures are based on preliminary data reported by 68% of the Member States through the annual WHO/UNICEF Joint Reporting Form. The relatively small decrease in regional coverage, which was smaller than in other regions, reflects intense efforts made by the ministries of health in the Region to continue or catch up on childhood immunisations despite programmatic restrictions due to COVID-19 control measures. However, the decrease masks large variations among countries, larger declines in some countries, and a lack of reported data from some countries where

COVID-19 disruptions have also affected capacity to collect and report routine immunisation coverage data. The WHO reported that among the 36 European Member States for which estimates are available, a significant ( $\geq 5\%$ ) general drop in routine immunisation coverage (across all antigens combined) was reported by Azerbaijan, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan and the Republic of Moldova. While reported measles cases have declined dramatically (from over 104,000 in 2019 to approximately 12,000 in 2020, and only 59 for January to May this year so far), any decrease in vaccination coverage can lead to a rapid accumulation of vulnerable children and potentially fuel large outbreaks in the future [4].

Only five countries (Hungary, Malta, Portugal, Slovakia and Sweden) in the European Union/ European Economic Area (EU/EEA) reported at least 95% vaccination coverage for both the first and second doses of measles- and rubella-containing vaccine in 2018 (see Figure 2.2.5) [2]. These figures are not yet available for 2019 due to the COVID-19 pandemic.

## 2.6 Literature

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\* RIVM publication.

3

# Acceptance of vaccination



### 3.1 Key points

- Studies show that improvements in the provision of information regarding maternal pertussis vaccination (MPV) could promote positive attitudes towards the MPV among healthcare providers.
- Studies on COVID-19 show that beliefs surrounding vaccination behaviour of family and friends (i.e. social norms), the safety, side effects, and the COVID-19 vaccines' ability to end the current crisis predicted COVID-19 vaccine acceptance.
- Qualitative studies show that particular focus should be given to why the HPV vaccine will be offered at the age of 10 years.
- A study on meningococcal uptake shows that recall after first invitation to get vaccinated can diminish immunisation disparities.
- International studies show that tailored information and communication, including both benefits and barriers such as side effects, can help increase vaccination uptake.

### 3.2 Monitoring Acceptance of the NIP

The COVID pandemic and other large-scale outbreaks of vaccine-preventable diseases (VPDs) have highlighted the importance of vaccine acceptance among the general public [1, 2]. Here, 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 European countries, making it important to monitor acceptance continuously [3].

Unfortunately, in this age of the internet and social media, less-than-reputable information sources erode public trust in vaccines and healthcare systems across the board. To safeguard against such erosion and achieve broad public vaccine confidence, consistent, clear risk-benefit communication about vaccination is vital. This could boost confidence not only in the vaccines themselves but also in the systems that deliver them [4, 5].

This chapter covers relevant research regarding vaccine acceptance, improving vaccine communication campaigns, and the decision-making processes driving vaccine acceptance/refusal.

### 3.3 Pregnancy (pre-birth)

#### 3.3.1 Maternal pertussis vaccination (MPV)

A qualitative study conducted among 25 orthodox Protestant women found that the decision-making process for this group of women, who are known vaccine-refusers, involves two stages [6]. In the first stage, the orientation stage, women described they want to fulfil their information needs and discuss the vaccination with others. During the second stage, the deliberation stage,

women weighed the consideration of vaccination against their most important values, namely parental responsibility, religious values, and health. Women want to make a well-considered decision and reported that full support of, and agreement with a spouse was crucial. The decision-making framework developed from using the insights from this study can assist healthcare providers (HCP) in supporting orthodox Protestant women in their decision-making process regarding vaccination.

It is known that pregnant women highly value the opinion of their antenatal HCP when considering whether to accept the MPV [7]. As such, the RIVM examined the (factors that influence) attitudes of antenatal HCPs (e.g. primary-care and clinical midwives, gynaecologists and medical assistants) towards MPV. In the study, attitudes towards MPV were positive and correlated with positive attitudes towards the NIP in general, irrespective of whether an e-learning course about the MPV was completed. Overall positive attitudes toward the MPV also correlated with the HCPs feeling competent in informing pregnant women about MPV. Gynaecologists and resident doctors were more positive compared to primary care and clinical midwives. HCPs should therefore inform all pregnant women about the availability of the pertussis vaccine during pregnancy irrespective of the latter's religious beliefs. Information should be provided at a point in the pregnancy that leaves sufficient time for well-informed and considered decision-making [6]. Obstetric care providers and general practitioners are the primary information source for pregnant women. They could therefore benefit from engagement with MPV-specific online training courses. Improvements in providing such information could promote positive attitudes towards the MPV among HCPs, which in turn could improve attitudes towards and acceptance of the MPV among pregnant women.

## 3.4 Adolescents

### 3.4.1 MenACWY

In 2018 and 2019, a MenACWY vaccination campaign was implemented in the Netherlands, including recall after non-attendance. This campaign targeted adolescents 14–18 years of age. The uptake was 86% among all eligible adolescents, including 5% uptake after recall [8]. The most important predictor of vaccine uptake after the first invitation was the parents' country of birth, with lower uptake when parents were born abroad. For those who were recalled, the most important predictors of uptake were distance to vaccination site and the percentage of votes for the conservative Christian Reformed Party (SGP) in the municipality [8]. The larger the distance to the clinic and the higher the proportion of Christian Reformed Party (SGP) votes, the lower the vaccine uptake. Similar to the initial responders, the parents' country of birth of recalled adolescents was also an important predictor of uptake. However, uptake was higher after recall when parents were born abroad.

### 3.4.2 HPV for boys

The RIVM and Maastricht University conducted a joint qualitative study investigating associations and beliefs regarding the HPV vaccination for boys. The study also explored parental attitudes towards including this vaccination in the NIP for boys in the year they turn 10 years old.

Most parents were unaware of HPV infections in boys and/or the possibility to vaccinate their sons. Instead, HPV and the HPV vaccination were associated with girls and the prevention of cervical cancer. Many parents assumed that the HPV vaccination for boys would therefore offer cross-protection for girls. Furthermore, most parents shared their concerns regarding the age at which the vaccination will be offered to boys and the possible occurrence of unknown adverse effects. The HPV vaccination for boys campaign should present a comprehensive, transparent, and coherent overview of changing vaccination policies. The study indicates that special focus should be given to why the HPV vaccine will be offered at 10 years of age. Furthermore, the campaign could be strengthened by including guidance for parents and caretakers on how to discuss HPV vaccination with their sons and wards.

## 3.5 Adults

### 3.5.1 COVID-19 and Influenza

The Behavioural Insights Unit of the RIVM monitors developments regarding COVID-19. The unit focuses particularly on COVID-19 preventive measures (such as social distancing and vaccines) and general public acceptance of these measures. The unit also investigates factors associated with intentions to receive a COVID-19 vaccination [9].

The most frequently cited reasons for refusing a COVID-19 vaccination mirror the reasons given for refusal of other vaccines, including doubts as to the efficacy of vaccines and concerns about adverse effects [9]. Results until January 2021 showed an increase in the number of Dutch citizens willing to receive a COVID-19 vaccine [9-11]. Beliefs relating to the safety, side effects, and the COVID-19 vaccines' ability to end the current crisis were especially important predictors of vaccine acceptance. COVID-19 vaccine acceptance was also strongly associated with the expectations and beliefs surrounding vaccination behaviour of family and friends (social norms) [9, 11].

Vaccination with the AstraZeneca vaccine was suspended in the Netherlands between March 14<sup>th</sup> and 28<sup>th</sup> due to concerns about adverse effects. The RIVM examined the impact of this pause on vaccine acceptance by sending a follow-up questionnaire (between March 30<sup>th</sup> and April 6<sup>th</sup>) to the respondents of a previous survey regarding COVID-19. The preliminary results show that, compared to overall willingness of respondents to vaccinate against COVID-19, the willingness to receive an AstraZeneca vaccine was much lower. Approximately 25% of all respondents indicated that they did not want to be vaccinated against COVID-19 irrespective of the vaccine brand. Regardless of their willingness to receive a vaccine, 25% of respondents indicated that they think the AstraZeneca vaccine is not safe enough. Of the respondents who were willing to receive a vaccine, 20% reported that they would rather wait until they could receive a different (non-AstraZeneca) vaccine. A further 15% of these respondents indicated they would rather wait until more information about the AstraZeneca vaccine is available.

These findings are supported by other research conducted by the RIVM, which shows that the most important themes mediating the decision-making process regarding COVID-19 vaccination were the risk perception of COVID-19, beliefs about the COVID-19 vaccine, social responsibility, and individual benefits. Social responsibility (protecting others by receiving vaccination) and being part of a risk group for COVID-19 were the most frequently cited



reasons for wanting a COVID-19 vaccine. Possible side effects and the speed at which the vaccines were developed were the most frequently cited reasons for doubting the safety and effectiveness of the vaccine. These were also the most common reasons cited to justify postponing vaccination, along with the desire to wait until more clarity on these issues is available before making a decision.

The same study found that the most important themes for receiving the influenza vaccine were risk perception of influenza, beliefs about the influenza vaccine, social responsibility, and the impact of the COVID-19 pandemic. Therefore, the COVID-19 pandemic may have influenced the decision-making process for influenza vaccination. Similar to the COVID-19 vaccine, being part of a risk group was the most frequently cited reason for receiving the influenza vaccination. Having doubts about the influenza vaccine's effectiveness was the most frequently cited reason for not wanting to receive the vaccine. Several participants also indicated that the presence of COVID-19 prompted them to receive the influenza vaccination for the first time in 2020. Reasons cited included wanting to reduce the risk of co-infection with COVID-19 and influenza and believing that the influenza vaccine might boost the immune system against COVID-19 as well.

### 3.6 Strategies and interventions to increase vaccine uptake

The four largest municipalities in the Netherlands are working to increase vaccine uptake in under-served communities. The programmes use tailored, targeted interventions delivered with the help of key community figures, such as religious leaders and health ambassadors (see <https://nos.nl/artikel/2378368-kinderen-met-migratieachtergrond-minder-vaak-ingeent-tegen-hpv-en-meningokokken.html> and *Kinderen met migratieachtergrond laten zich minder vaak vaccineren tegen baarmoederhalskanker* | Home | AD.nl).

### 3.7 International literature and studies

#### 3.7.1 Vaccination in general

##### 3.7.1.1 Communication about vaccinations

The use of social media platforms such as Facebook, is becoming increasingly common for disseminating vaccine-related information. However, social media and internet use have been linked to changes in the cognitive biases of its users [12]. Cognitive biases subconsciously influence individual perceptions of reality and decision-making processes. Subsequently, these biases have the potential to influence public perception of social media and internet campaigns regarding vaccination, as well as shape ongoing public debate about vaccinations. It is therefore likely that these biases could directly influence vaccine acceptance and uptake. This is supported by a study that demonstrated that cognitive biases (such as reporting bias, recall bias, visibility bias, and selection bias) shaped by social media, directly influence acceptance and uptake of the measles vaccine [12]. For example, people who suffered an unfavourable clinical course of a VPD may be largely in favour of vaccination, while those with mild clinical courses might oppose it (reporting bias). Furthermore, remembrance of the severity of an event that occurred long ago might be incorrect (recall bias), influencing

someone's attitude towards vaccination. Survivorship bias denotes the distorted perception of an exposure, such as a measles episode, when examining only those with a favourable outcome (e.g. survival).

Recent studies demonstrate that public health communications should not only take into account attitudes and behaviours relating to vaccines, but also consider social media use and any potential underlying cognitive biases of target audiences [13, 14]. Educational efforts to promote vaccine uptake, combined with considered message framing, might also increase the acceptability of and intention to receive a vaccine such as the HPV vaccine [15]. Furthermore, emphasising the benefits of vaccination in a broader perspective and leveraging the influence of significant community figures, such as HCPs and religious leaders, could also improve vaccine confidence and acceptance [3, 5]. Improving the transparency of national-level decision-making processes regarding vaccines may also improve acceptance.

As is usual for vaccine campaigns, trusted sources like HCPs have a sizeable influence on the public's acceptance of vaccines. Unfortunately, vaccine acceptance varies widely even among HCPs. Although it has been demonstrated that medical students have a generally positive attitude towards vaccination, vaccine uptake in HCPs remains low [16-18]. Furthermore, levels of vaccine hesitancy among HCPs are comparable to those in the general public [16-18]. Overall, tailoring messages to local needs and values, and providing tailored and appropriate information to professionals seem essential steps in increasing vaccination uptake [15, 17, 19, 20]. However, communication efforts may fall flat if logistical issues hinder the translation of acquired knowledge to action. Clear guidance on staffing requirements and HCP responsibilities within a vaccination programme is critical to maximising vaccine uptake [21].

### 3.7.1.2 Migrants

Among migrant parents, knowledge of HPV-related diseases and awareness of the available HPV vaccine is low. Unfortunately, due to the limited knowledge these parents have, attitudes and perceptions are unfortunately often negative [22]. This highlights the pressing need for well-designed HPV-related health and vaccine educational programmes, covering the importance, safety, and efficacy of HPV vaccination. Furthermore, multi-level interventions specifically targeting migrant parents are required to increase HPV vaccine uptake in these currently low uptake groups [22, 23]. Other studies support these recommendations and suggest that the impact of targeted interventions may be enhanced when accompanied by a physician's recommendation [24, 25].

### 3.7.2 Pregnancy – maternal pertussis (MPV) and influenza vaccinations

Two studies on the acceptance of MPV found that a HCP's recommendation improved MPV uptake [26, 27]. Also, the willingness of women to protect their offspring and themselves positively influenced MPV acceptance. MPV uptake was also strongly associated with acceptance of the maternal influenza vaccine and uptake of the hepatitis B vaccine for new-borns. These results suggest a level of trust in vaccines rather than a relative absence of vaccine hesitancy [26]. Vaccine safety concerns were again found to form a barrier to vaccination for maternal vaccines [27].

Interestingly, another study found that most women were willing to receive recommended vaccinations during pregnancy. Willingness to vaccinate was not mediated by psychosocial factors such as educational level [28]. However, the authors stress that these factors do influence the actual uptake of maternal vaccinations, and should therefore be taken into account when designing interventions and implementation of these vaccinations.

### 3.7.3 Infancy and Childhood – Rota, Measles, and varicella

#### 3.7.3.1 Rota

A non-systematic literature review showed that acceptance of rotavirus vaccination was low due to poor confidence in the vaccine as well as lack of knowledge regarding rotavirus' burden of disease and the possibility of preventing this through vaccination. Even when parents felt distress when facing the possibility of hospitalisation caused by a rotavirus infection, many were still unwilling to immunize their babies against rotavirus [29]. A patient-centred approach to making health decisions (e.g. shared decision making (SDM)), educational level, and rotavirus vaccination of a previous child influenced the acceptance of rotavirus vaccination [30]. SDM assisted by patient-decision aids (PDAs) provides more information and helps understand what parents need, reduces their decisional conflict and increases rotavirus vaccine uptake [30].

#### 3.7.3.2 Varicella

A literature review highlighted the most influential factors for acceptance of the varicella vaccine. It was found that recommendation of varicella vaccination by a physician and the individual's perception of severity of the disease, strongly influenced acceptance of this vaccine [31].

#### 3.7.3.3 Measles

A recent literature review examined the influence of vaccine confidence, complacency, and convenience on mumps, measles and rubella (MMR) vaccine acceptance [32]. Using MacDonald's 3C model of vaccine hesitancy, the review showed that MMR 'acceptors' trusted vaccine safety, effectiveness, and the opinions of experts [33]. Acceptors of the MMR were more likely to be content with the information provided to them, and mostly sourced information from the general media, the internet, HCPs, and other lay information sources [32, 34]. MMR 'rejectors' and vaccine-hesitant parents mostly feared adverse effects from MMR vaccination. These parents were concerned about the combination of vaccines, the young age of children when they receive MMR vaccination, and expressed fears of needles. Importantly, these parents expressed a significant lack of trust in experts and their motivations. This lack of trust was shaped by previous negative experiences and receiving inconsistent and/or unclear information [32, 34].

Perceptions of low-risk infection and low severity of measles were prominent amongst all hesitant parents, but especially in anthroposophical communities. In these communities, parents reported preferring natural development of the immune system or felt natural measures to avoid measles were more important than vaccinations. Acceptors considered

measles to be severe, and also felt a sense of responsibility to protect their child as well as the community [32]. MMR rejectors and hesitant parents also reported feeling pressured to vaccinate by their vaccinated peers. However, peer judgement, feelings of social responsibility, and guilt were also found to encourage vaccine uptake [32]. These findings resemble the outcomes of other reviews on general childhood vaccines in Europe [35, 36].

Another study showed that the last measles outbreak in Europe during 2016-2017 led to overall increased MMR vaccination uptake, but there was no large spill-over effect on other vaccinations [37].

#### 3.7.4 *Adolescence - HPV*

Studies found that the main barriers to acceptance of the HPV vaccine were insufficient knowledge about HPV and HPV vaccination and concerns about vaccine safety [38, 39]. Higher uptake of the HPV vaccine is associated with perceptions and knowledge as well as perceived risk of susceptibility to HPV infection, perceived benefit of vaccination, and sexual experience. Previously having received information regarding sexually transmitted diseases at home was also positively associated with vaccine uptake [40-45].

Overall adolescent intention to vaccinate against HPV is influenced by social norms (i.e. feeling supported by their doctor and/or parents to get vaccinated), and feelings of self-efficacy [39, 46].

Despite the imminent roll-out of the HPV vaccination for boys in the UK, awareness of the programme remained low. More than half of parents (55%) were aware of the HPV vaccination for girls, and only 23% were aware that the programme would be expanded to include boys [47]. After providing information on HPV vaccination to participants, 62% indicated they would vaccinate their child, 10% would not vaccinate their child, and 28% did not know. Parents of girls were more willing to vaccinate than parents of boys [47]. Positive attitudes and awareness were independently associated with acceptance of HPV vaccination.

Based on the findings of these studies, it is clear that public health campaigns should focus on promoting the extension of the HPV vaccination programme to boys. To support undecided parents, campaigns should ensure coverage of vaccine safety and efficacy, as well as any other key topics of concern raised by parents in the studies above [47]. It is recommended again that efforts should be increased to improve knowledge and awareness among stakeholders, such as teachers, physicians, parents, and adolescents themselves. These individuals play a pivotal role in assuaging vaccine hesitancy and mediating social norms. As such, coordinated educational efforts will improve the information flow to relevant populations and may considerably increase HPV vaccine uptake [23, 38, 39, 43, 45, 48-50].

#### 3.7.5 *Communication and policy*

A key theme that arises from the studies described thus far is the importance of improving awareness and knowledge of vaccination in key populations. However, these studies did not investigate the cost-effectiveness of various suggested interventions.

A study conducted in the US prioritised interventions that aimed to increase HPV vaccine uptake based on their cost-effectiveness from a US state perspective [51]. Three interventions

were compared: a system of centralised reminders and recalls for HPV vaccination, a school-based HPV vaccination programme, and an intervention that improved the quality of visits to primary care clinics. By comparing a 'no intervention' situation to a 'one-year implementation' of three intervention styles, the study showed that all three intervention styles were cost-effective relative to 'no intervention', and demonstrated that all three interventions offered substantial health benefits [51]. Another study also showed that school-based programmes achieve higher coverage [52].

### 3.7.6 *Adults and Elderly – Pneumococcal and influenza vaccination*

Between 2011 and 2016, an Australian study showed that pneumococcal vaccine uptake declined in the elderly (>65 years of age). Uptake depended on the patient's age, health status, and regularity of practice visits. Patients with comorbidities, ex-smokers, and patients that frequently visited their primary HCP were more likely to get vaccinated [53].

Another study from the US demonstrated that of those people who did not receive influenza or pneumococcal vaccinations, the majority were unaware that they could get the vaccine. Further, unvaccinated individuals frequently reported that they had not been recommended a vaccination by their doctor [54]. The study participants' central reason for not getting vaccinated against influenza related to concerns about side effects. Individuals might be hesitant about a vaccine for different reasons and a tailored approach by trusted HCPs or the healthcare system is required. How individuals respond to and interact with HCPs is critical in the process of (decision-making regarding) vaccination and hence vaccination coverage. The study highlights the importance of national guidelines that call for all HCPs to ensure adults are fully immunised [54]. This study underscores the importance of tailored communication to target groups, and that these communications should stress the importance of both influenza and pneumococcal vaccines. Furthermore, communication efforts must address potential patient concerns related to vaccine side effects and other key topics that may be a barrier to vaccination.

In Germany, a monitoring system to estimate influenza vaccine uptake and its determinants among German hospital staff was developed (OKaPII) [55]. Influenza vaccine uptake among German hospital staff is low, with higher uptake in physicians compared to nurses. Self-protection was the most commonly stated reason to receive influenza vaccination. As to why they did not receive the vaccination, nurses most commonly reported a lack of confidence in the vaccine, whilst physicians mostly identified constraints [55].

Increased influenza vaccination uptake was associated with older age, male sex, increasing numbers of comorbidities, and previously receiving a pneumococcal vaccination. Furthermore, uptake was positively associated with the expenses annually made for specialist medical care and/or specific medical resources [56]. Finally, influenza vaccine uptake depended on the specific general practitioner responsible for the elderly patient, once again highlighting the influence of HCPs on vaccine uptake [56].

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\* RIVM publication.



# 4 Burden of disease



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## 4.1 Key points

- The estimated total burden of disease caused by (partially) vaccine-preventable diseases expressed in disability adjusted life years (DALYs) for the year 2020 was highest for HPV (19,400 DALYs (75% among women) based on the burden in 2019 instead of 2020), invasive pneumococcal disease (6,200 DALYs), invasive *Haemophilus influenzae* disease (1,000 DALYs), invasive meningococcal disease (400 DALYs), pertussis (390 DALYs), and rotavirus infection (390 DALYs).
- For most vaccine-preventable diseases, the estimated burden in 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 handwashing. The burden of invasive *H. influenzae* disease type b was higher in 2020; the reason behind this increase is unknown.
- The burden of COVID-19 is estimated to be 169,000 DALYs for 2020, where 99% of the burden is due to people dying at a younger age than they would have in a situation without COVID-19. This is an underestimation of the actual burden since long-term consequences of the disease have not been taken into account.

## 4.2 Tables and figures

**Table 4.1** Estimated annual disease burden in DALYs in 2016-2020, and DALYs per 100 infections in 2020 in the Netherlands (with 95% uncertainty intervals) [1-3].

Disease	DALYs (95% uncertainty interval)					DALYs/100 infections
	2016	2017	2018	2019	2020	
Diphtheria	2 (2-3)	4 (3-4)	3 (3-4)	0 (0-0)	0.3 (0.2-0.3)	26 (19-33)
Hepatitis A virus infection	44 (27-73)	200 (120-340)	100 (62-170)	90 (55-150)	28 (17-45)	11 (8-15)
Hepatitis B virus infection (acute)	180 (170-190)	150 (140-160)	130 (120-140)	120 (110-120)	100 (100-110)	23 (21-24)
Human papillomavirus infection <sup>a</sup>						
- Females	13,200 (12,400-14,400)	12,900 (12,100-13,800)	13,800 (13,000-14,700)	14,600 (13,800-15,400)		n/a
- Males	5,300 (4,400-6,400)	5,200 (4,200-6,300)	5,400 (4,400-6,400)	4,800 (4,000-5,800)		n/a
Invasive <i>H. influenzae</i> disease	860 (800-910)	980 (930-1,000)	1,000 (960-1,100)	970 (920-1,000)	1,000 <sup>b</sup> (970-1,100)	450 (420-480)
Invasive meningococcal disease	880 (730-1,000)	1,100 (980-1,300)	1,100 (960-1,300)	890 (740-1,100)	400 <sup>c</sup> (300-510)	560 (490-630)
Invasive pneumococcal disease	9,800 (9,200-10,400)	9,800 (9,200-10,400)	10,800 (10,100-11,400)	9,500 (8,900-10,000)	6,200 <sup>d</sup> (5,800-6,600)	370 (340-390)
Measles	1 (1-1)	3 (2-3)	5 (4-5)	16 (15-18)	0.4 (0.3-0.5)	2 (1-2)
Mumps	0.5 (0.5-0.6)	0.4 (0.3-0.4)	0.6 (0.5-0.6)	1 (1-1)	0.5 (0.5-0.5)	0.4 (0.4-0.4)
Pertussis	1,500 (1,400-1,600)	2,000 (1,900-2,200)	2,000 (1,900-2,100)	2,600 (2,500-2,800)	390 (370-420)	1 (1-1)
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	670 (280-1,300)	1,100 (440-2,200)	1,200 (470-2,400)	1,100 (440-2,300)	390 (160-790)	0.5 (0.3-0.9)
Rubella	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	n/a
Tetanus	2 (2-2)	0.6 (0.5-0.8)	1 (1-1)	0 (0-0)	9 (8-11)	760 (730-790)

DALY = disability adjusted life year.

n/a = not applicable; no cases occurring in 2020 or unknown number of infections (HPV).

For HPV, the burden in 2020 could not be determined yet.

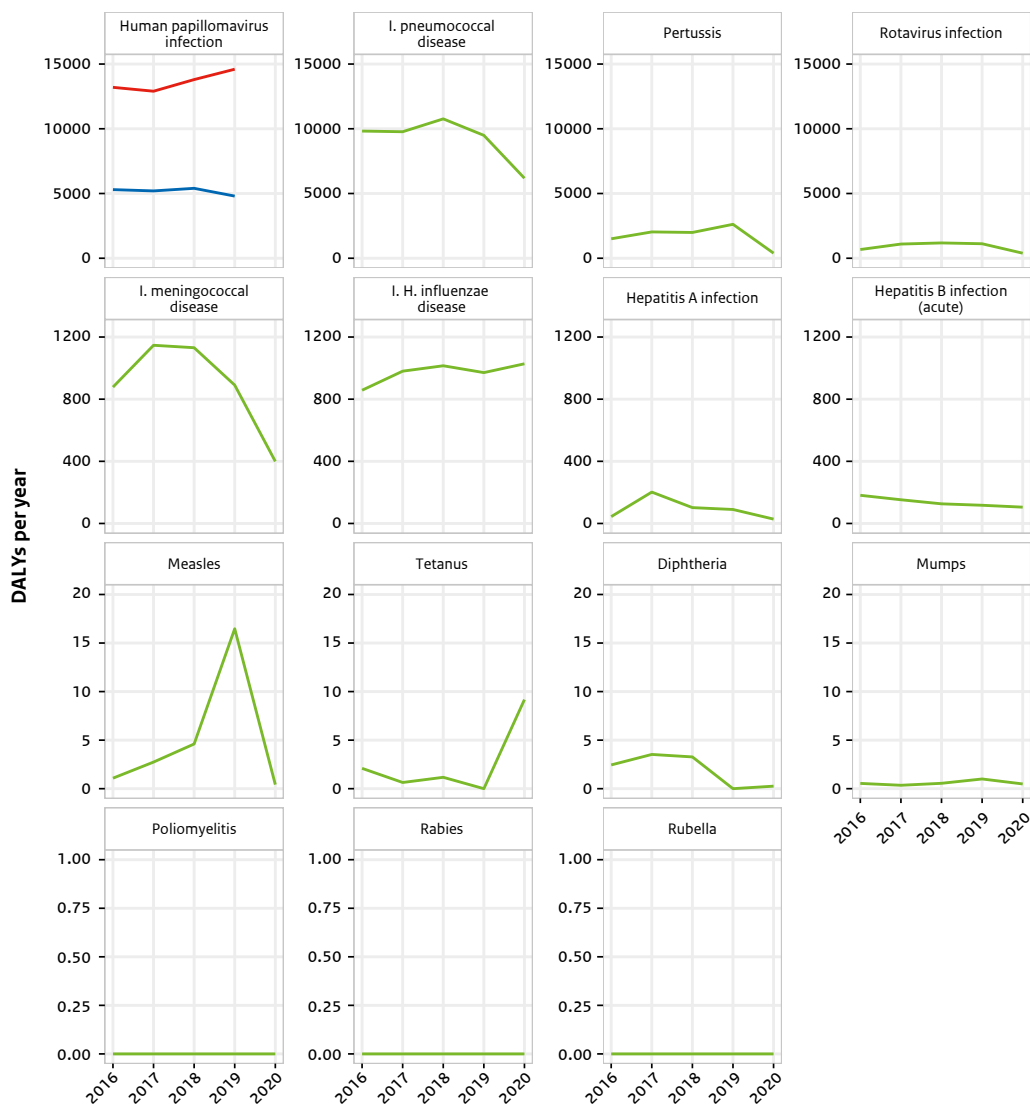
<sup>a</sup> To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. The most recent year of available data on the incidence of anogenital warts and high-grade cervical lesions was 2016 and 2018, respectively. Therefore, the incidence rate of anogenital warts for 2016 was carried forward to 2017–2019 and the incidence rate of high-grade cervical lesions for 2018 was carried forward to 2019.

<sup>b</sup> Proportion caused by vaccine-preventable type b in 2020: 47%.

<sup>c</sup> Proportion caused by vaccine-preventable type C in 2020: 0%; proportion caused by type B in 2020: 69%; proportion caused by type W in 2020: 14%.

<sup>d</sup> Proportion caused by vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F in 2020: 5%.

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 2016-2020 [1-3].

Notes:

1. DALY = disability adjusted life year; for HPV, the burden in 2020 could not be determined yet.
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 ACWY and pneumococcal serotype 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F. 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 expressed in disability adjusted life years (DALYs) of vaccine-preventable diseases in the period 2016–2020. We present the same estimates for 2016–2019 as published previously in the ‘State of infectious diseases in the Netherlands, 2019’, 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, 2020’ [3]. 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 infection, the burden in 2020 could not yet be determined at this point. Note that the calculation method used for HPV is not fully comparable to that for other diseases: instead of using the number of incident infections (which are 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  $\geq 10,000$ , 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 2016–2020 and the DALYs per 100 infections in 2020 (a measure of the disease burden at individual patient level) in the Netherlands, with 95% uncertainty intervals. For poliomyelitis, rabies, and rubella, the estimated disease burden in 2020 was zero because no cases were reported. For diphtheria, measles and mumps, the disease burden in 2020 was estimated to be very low, while the highest burden was estimated for HPV infection (based on the burden in 2019 instead of 2020), followed by invasive pneumococcal disease, invasive *Haemophilus influenzae* disease, invasive meningococcal disease, pertussis, and rotavirus infection.

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 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 handwashing (see also the article by Middeldorp et al. [4]). For the first year since the introduction of vaccination in 2002, no cases of invasive meningococcal C disease were reported in 2020 and therefore the burden was 0 DALYs. The proportion of the burden due to serogroup W in the total burden of invasive meningococcal disease decreased further: from 42% in 2018 to 29% in 2019 and 14% in 2020. The proportion of the burden due to *H. influenzae* disease type b in the total burden of invasive *H. influenzae* disease increased from 28% in 2018/2019 to 47% in 2020, due to an increase of invasive *H. influenzae* disease type b and a decrease of non-typeable invasive *H. influenzae* disease. The latter development is probably due to the COVID-19 control measures. The reason for the increase of invasive *H. influenzae* disease type b is under investigation but as of yet unknown.

It must be noted that the total disease burden for pneumococcal disease, meningococcal disease, and *H. influenzae* disease, is higher than presented here seeing as we limited our analyses to invasive disease. Furthermore, the disease burden of these diseases, as well as

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. Our analyses only reflect the (future) burden of new cases of hepatitis B virus infection in the period 2016–2020, which means that 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, a different method was used that also serves to calculate the disease burden of some food-related infections. This method takes the registered mild and serious illness and deaths due to COVID-19 as direct input for the calculations. The number of serious illnesses and deaths due to COVID-19 is therefore not estimated by using progression probabilities because these are not yet well known for COVID-19.

The disease burden of COVID-19 is estimated to 169,000 DALYs (95% uncertainty interval 166,000-173,000) for the whole of 2020, where 99% of the burden is due to people dying at a younger age than they would have in a situation without COVID-19. The presented burden estimate of COVID-19 is an underestimation of the actual burden since long-term consequences of the disease are not taken into account.

There is insufficient information about the epidemiology and long-term impact of COVID-19 to properly estimate the disease burden in DALYs/100 cases and compare that with the disease burden of other respiratory infections. First, the probabilities of progression from mild to severe disease and death are not yet well established. In addition, due to limited observation time the long-term effects for people with mild COVID-19 as well as for people with a more severe disease course are still unclear. Since there is insufficient data to accurately calculate the (largely unknown) long-term sequelae for COVID-19, the burden estimate of COVID-19 is based on the acute phase of the disease [5].

In partnership with other organisations, the RIVM has developed a guide to calculate the disease burden for COVID-19 [6].



## 4.5 Literature

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\* RIVM publication.



# 5 Adverse events





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## 5.1 Key points

- In 2020, Lareb received 1,475 reports of a total of 4,640 adverse events following immunisation (AEFIs). This number of reports is almost similar to the number of reports received in 2018 (n=1,519) but lower than the number of reports received in 2019 (n=2,009 due to the catch-up campaign of MenACWY vaccination in adolescents). The number of reported AEFIs per report was 3.1, which is slightly lower compared to 2018 and 2019 (3.4 and 3.7, respectively).
- No new signals of disturbing adverse events were found.

## 5.2 Tables and Figures

**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®	99	<b>133</b>	41	24	12	4	1	17	5		6	17	4		1		1
Synflorix®	5	<b>12</b>		6	1			3		1					1		
Vaxelis® + Synflorix®	278	<b>358</b>	12	132	78	2		121	4	3	2	2	1				1
MMRvaxPro®	39	<b>64</b>			1		3		28	15	3	9	5		1		
Nimenrix®	520	<b>60</b>							3	4	1	2		45	4		1
MMRvaxPro® + Nimenrix®	227	<b>173</b>	1						102	60	9						
Boostrix Polio®	313	<b>268</b>			1			1	1			256		2		7	
Revaxis®	12	<b>12</b>											11	1			
MMRvaxPro® + Revaxis®	118	<b>124</b>								1			118	5			
Cervarix®	104	<b>52</b>												32	18		2
Boostrix®	9	<b>189</b>															189
Combination of vaccines not in NIP		<b>16</b>	1	2	1					1	1	3	4	2	1		
Vaccinated within old schedule	245	<b>14</b>	3	1		1	1	1	2	1		3	1				
Other	40																
<b>Total 2020</b>		<b>1,475</b>	<b>58</b>	<b>165</b>	<b>94</b>	<b>7</b>	<b>5</b>	<b>143</b>	<b>145</b>	<b>86</b>	<b>22</b>	<b>292</b>	<b>144</b>	<b>87</b>	<b>26</b>	<b>198</b>	<b>3</b>
Total 2019	2,009		181	192	46			128	236			316	128	75	497	9	201
Total 2018	1,519		187	169				170	263			326	110	65	62		167
Total 2017	1,383		216	167				154	200			387	106	77			76
Total 2016	1,483		174	155				126	171			572	84	146			55
Total 2015	1,494		173	156				142	208			422	88	257			48
Total 2014	982		148	138				101	139			274	108	59			15
Total 2013	1,212		217	193				118	133			335	92	82			42
Total 2012	1,387		250	264				103	138			423	52	104			53
Total 2011	1,103		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
<b>Rash, eczema</b>	<b>5</b>	<b>10</b>	<b>15</b>	<b>1</b>	<b>0</b>	<b>21</b>	<b>71</b>	<b>35</b>	<b>4</b>	<b>14</b>	<b>16</b>	<b>1</b>	<b>2</b>	<b>0</b>	<b>6</b>	<b>201</b>
<b>Respiratory symptoms</b>	<b>6</b>	<b>7</b>	<b>3</b>	<b>0</b>	<b>2</b>	<b>2</b>	<b>1</b>	<b>7</b>	<b>0</b>	<b>5</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>6</b>	<b>41</b>
Apnoea, Dyspnoea, Irregular breathing	5	3	3	0	0	1	1	6	0	5	1	0	1	0	6	32
Breath- holding spells	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	4
Other	1	0	0	0	2	1	0	1	0	0	0	0	0	0	0	5
<b>Neurologic symptoms</b>	<b>19</b>	<b>21</b>	<b>16</b>	<b>0</b>	<b>1</b>	<b>22</b>	<b>16</b>	<b>7</b>	<b>2</b>	<b>12</b>	<b>9</b>	<b>14</b>	<b>1</b>	<b>0</b>	<b>9</b>	<b>149</b>
Ataxia, spasms, tics	1	2	0	0	0	2	3	1	0	1	3	0	0	0	0	13
Cataplexy	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	2
Delirium febrile	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	3
Febrile convulsion, seizures, tonic convulsion	0	2	7	0	0	9	8	3	0	5	1	0	0	0	0	35
Facial paresis/Bell's palsy	0	0	0	0	0	1	0	0	0	0	0	2	0	0	1	4
Hypotonic-hyporesponsive episode	8	7	2	0	0	0	0	0	0	0	0	0	0	0	0	17
Status epilepticus	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
Other	10	9	7	0	1	9	5	3	2	5	4	10	1	0	8	74
<b>Extensive swelling of vaccinated limb</b>	<b>2</b>	<b>2</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>14</b>	<b>3</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>27</b>
<b>Body temperature ≥40.5 - ≤42°C</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>4</b>	<b>3</b>	<b>1</b>	<b>4</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>19</b>
<b>Persistent crying</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Skin discolouration</b>	<b>1</b>	<b>10</b>	<b>7</b>	<b>0</b>	<b>0</b>	<b>4</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>26</b>
<b>Abscess</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>4</b>
Injection site abscess	0	1	1	0	0	0	1	0	0	0	0	0	0	0	0	3
Injection site abscess sterile	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1
<b>Immune mediated disorders</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>8</b>
Acute haemorrhagic oedema of infancy	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	2
Autoimmune haemolytic anaemia	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Guillain-Barré syndrome	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
Immune thrombocytopenia	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
Neuralgic amyotrophy	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1
Type 1 diabetes mellitus	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	2
<b>Dehydration</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>3</b>
<b>Death*</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>1</b>
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
<b>Encephalitis/meningitis</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>

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
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
(Venous) thrombosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic arthritis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Complex regional pain syndrome (CRPS)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<b>Adverse events concerning pregnancy</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>15</b>	<b>15</b>
Amniotic cavity infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Foetal death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Foetal movement disorder	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Normal newborn	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Premature baby	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Premature delivery	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	5
Premature labour	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Preterm premature rupture of membranes	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Uterine contractions during pregnancy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	3

\* 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 managed by Lareb (the Netherlands Pharmacovigilance Centre) receives AEFI reports for all vaccines covered by the NIP. In 2020, Lareb received 1,475 reports with a total of 4,640 AEFIs (Table 5.1) [1]. This number of reports is almost equivalent to the number of reports received in 2018 (n=1,519), but lower compared to the amount received in 2019 (n=2,009; due to the catch-up campaign of MenACWY vaccination in adolescents). Most reported AEFIs were injection site reactions (n=802), fever (n=566), crying (n=179) and vomiting (169). Of the reports, 65 (4.4%) were classified as serious [1]. For most vaccines, the number of reports are mostly within the range of the last years (see Table 5.1). However, in 2020 the number of reports after pertussis vaccinations given to pregnant women increased considerably due to the introduction of maternal pertussis vaccination in mid-December 2019. Following this introduction, the vaccination schedule for children has been adjusted. If a mother receives the maternal pertussis vaccination, then her child will not receive its first vaccination until the age of three months. This may explain the decrease in reports in infants aged two months. For the other vaccines given in the first and second years of life, no remarkable findings were noted.

The decrease in the number of reports after administration of DTP-IPV at the age of four years, which started in 2017, continued in 2020 (n=292), whereas a rising trend is seen after the vaccination at nine years of age. The number of reports after HPV vaccination appears to be stabilising. Lareb received fewer reports following meningococcal ACWY vaccination. This is probably due to the catch-up campaign among adolescents for this vaccine in 2018 and 2019, as a result of which fewer vaccinations were given in 2020.

In earlier years, reports of vaccines that were not given as per the vaccination schedule were classified as an adverse event at another or unknown vaccination moment. This year, adverse events were presented by age categories (see Table 5.1) regardless of timeliness. This explains the drop in the number of reports with an unknown vaccination moment.

The number of reported AEFIs per report was 3.1; slightly lower than 2018 and 2019 (3.4 and 3.7, respectively) [2, 3].

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. The decline in reports of extensive limb swelling among 4-year-olds (n=59 in 2017 and n=21 in 2018) did not continue in 2019 (n=45), but in 2020 another drop was seen (n=12). Furthermore, the increase in notifications of rash after the vaccination at the age of 14 months continued in 2020 (n=95 in 2018, n=115 in 2019, n=201 in 2020).

No reports were received of postural orthostatic tachycardia syndrome (POTS) or chronic fatigue syndrome (CFS) after HPV vaccination.

In 2020, Lareb received 12 reports of serious adverse events following maternal pertussis vaccination (MPV). The notifications mainly concerned (symptoms associated with threatened) preterm birth. Lareb also received one report of intrauterine foetal death. With every pregnancy,

including those without an MPV, there is a 7% risk of premature birth and a 6% risk of a child with a low birth weight. There is also a small (0.5%) risk of intra-uterine foetal death. Based on the reports that were received, Lareb does not see new or worrisome side effects after MPV.

Overall, no new signals of disturbing adverse events were found.

### 5.3.2 Signals/overviews

Two overviews were written in 2020 following a vaccine change within the NIP. The first overview is an update of an earlier report from 2018 comparing 3 different DTP-IPV vaccines over the years. The update confirmed that there was a decrease in the number of reported suspected adverse reactions after replacement of Infanrix IPV® with Boostrix Polio® in 2017 [1]. The second overview was made following the transition of the DTP-IPV-HBV-Hib vaccine Infanrix hexa® to Vaxelis®. A comparison was made between reports on these vaccines. No new or worrying side effects have been found [1].

## 5.4 International Developments

### 5.4.1 Vaccines targeting diseases included in the current NIP

#### 5.4.1.1 MMR/MMRV

MMR, MMRV, and measles-containing vaccines are generally well tolerated [4-6], even in patients with immunosuppressive agents [7], liver transplant recipients [8] and in children with prior severe neurologic diseases who received these vaccines during a measles outbreak [9]. However, one case report was published relating to a case in a new military recruit sensitized to gelatin IgE who suffered anaphylaxis after receiving the MMR vaccine [10]. A systematic review and meta-analysis demonstrated the safety of a rubella-containing vaccine, even in pregnant women [11].

Results from a study in Australia do not provide evidence of an association between routine childhood vaccination (including MMR vaccination) and the incidence of ADEM (Acute Disseminated Encephalomyelitis) [12]. A phase IV study showed that concurrent immunisation with a live attenuated vaccine against Japanese encephalitis is not associated with any unusual safety signals [13].

A third MMR dose was shown to be safe and well-tolerated in young adults [14, 15].

#### 5.4.1.2 Pneumococcal vaccine

No safety concerns were found for PCV7, PCV10 and PCV13 in infants [16-18], and for PCV13 in immunocompromised patients [19] and women of childbearing age [20]. PPV23 was shown to be safe among people aged 60 years and over, and in patients with coronary artery disease with simultaneous inoculation with trivalent influenza vaccine [21, 22]. In addition, PPV23 has a low reported AEFI rate, which is a little higher for children than for the elderly [23]. A systematic review found no safety issues for pneumococcal vaccination in dialysis patients [24].

No differences in adverse effects were found between PPV23 and PCV13 among solid organ transplant recipients [25] and in individuals with chronic kidney disease [26]. PCV10 and PPV23 proved equally safe in pregnant women with HIV.

Evidence for PCV10/PCV13 interchangeability regarding safety in children is limited but growing [27-29].

Several studies were conducted to assess the safety of novel pneumococcal vaccines. A novel ten-valent PCV (SIIP-PCV) as well as novel PCV12 and PCV15 vaccines administered in children were well-tolerated with no identified safety concerns [30-32]. A phase 2 study showed the safety of a PCV20 vaccine in adults [33, 34]. Administration of cPCV7 (which contains 7 non-PCV13 serotypes) in adults was well tolerated [34, 35].

#### 5.4.1.3 *Meningococcal ACWY vaccine*

Findings from a comprehensive review of reports to VAERS (Vaccine Adverse Event Reporting System) provide reassurance on the safety of MenACWY-DT [36]. In addition, no safety issues were identified for MenACWY-DT as a two-dose series in infants and as a single dose in individuals 2-55 years of age [37] or as a two-dose series in adults [38].

MenACWY-TT vaccine was well-tolerated in children [39-41], even when co-administration with other paediatric vaccines [42] or given as a booster dose 6-10 years of age after primary vaccination [43-45]. No safety concerns were identified in adolescents and adults either [46, 47]. In China, no safety issues were found for a domestic MenACWY vaccine after administration to three-month-old infants [48].

A systematic review of real-world evidence regarding the safety of MenACWY vaccines in the U.S. provided an updated safety assessment of these vaccines, particularly among high-risk infants, toddlers, and children 2-10 years [49]. While early reports detected safety concerns regarding GBS and syncope in adolescent and young adult vaccine recipients, only Bell's palsy was subsequently detected as a potential safety concern when MenACWY-CRM was received concomitantly with other vaccines. However, two later studies (one on MenACWY-DT and one on MenACWY-CRM) did not find increased risks of Bell's palsy following MenACWY vaccination regardless of co-administration with other vaccines.

#### 5.4.1.4 *DTaP-IPV-HBV-Hib*

Several studies showed the safety of infant pentavalent and hexavalent vaccines [50-55], even in co-administration of other vaccines in infants [56, 57] or in HIV-exposed infected and uninfected infants [58]. Hexavalent vaccines also showed an acceptable safety profile in premature infants [59, 60] and in adult recipients of allogeneic hematopoietic stem cell transplantation [61]. The incidence of adverse reactions after DTaP-Hib vaccination in infants was low [62, 63], regardless of the site of inoculation [62]. Prophylactic paracetamol administration mitigated systemic reactions after DTaP-IPV-HBV/Hib + pneumococcal conjugate or meningococcal serogroup B vaccination [57].

Several study results provided reassuring evidence of the safety of maternal pertussis vaccination with no increased risk of adverse pregnancy and birth outcomes [64-67]. The reactogenicity and safety profiles of the DTaP-IPV-HVB-Hib and PCV13 booster doses in toddlers did not change depending on exposure/non-exposure to Tdap during pregnancy. Solicited and unsolicited AE rates were similar between groups, no vaccination-related SAEs were reported and no differences were observed in terms of neurodevelopment and congenital anomalies.[68]. Another study showed that prenatal Tdap vaccination was not associated with ADHD risk in offspring [69].

DTaP as well as Tdap are generally well tolerated across all age groups [70, 71]. Recombinant pertussis vaccines aPgen and TdaPgen are safe in adolescents and adults, including pregnant women vaccinated in the second or third trimester of pregnancy [72].

#### 5.4.1.5 HPV vaccines

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

Several studies did not reveal new or unexpected safety issues for 2vHPV in healthy individuals [73-75] and in women living with HIV [76, 77]. Also for 4vHPV vaccines, no safety concerns were found in healthy women [75, 78-82] and in patients with juvenile dermatomyositis [83], SLE patients [84, 85], women after hematopoietic allogeneic stem cell transplant [86] and women living with HIV [76, 77, 87]. Furthermore, no positive associations were detected between inadvertent exposure to 4vHPV during pregnancy and any adverse pregnancy or infant outcomes [88]. The 9vHPV vaccine was also generally well-tolerated [89-92], even in HIV-infected persons and solid organ transplant recipients [93]. A review in VAERS demonstrated the safety profile of HPV vaccines in the male population, although limitations due to spontaneous reporting should be considered [94]. However, most of the AEs were already reported in premarketing clinical trials and acknowledged for the corresponding vaccines.

Comparing AEs between the 2vHPV and 4vHPV vaccines showed that both local reactions and systemic AEs were somewhat more frequent with the 2vHPV vaccine than with the 4vHPV vaccine. This might be caused by an immune response induced by adjuvant contained with the vaccines [95].

Using data-mining methods, disproportionate reports of premature ovarian insufficiency (POI)-related events following 4vHPV vaccination were detected from VAERS. No signal was detected for 2vHPV and a non-stable signal was found for 9vHPV. However, these results only represent statistical associations between HPV vaccine and POI-related events, so further research and causality investigation between HPV vaccine and POI are suggested [96].

The discussion about the association between HPV vaccination with POTS/CFS/CRPS is still ongoing. Gotzsche et al. outlined that they found a significantly higher number of serious neurological harms in HPV vaccine groups than in the comparator groups in a systematic review based on clinical study reports in EMA's possession [97]. They believe that the basis for EMA's decision was flawed and that the EMA dismissed compelling evidence from independent researchers. On the other hand, a population-based self-controlled case series in Denmark did not support a causal association between 4vHPV vaccination and chronic fatigue syndrome, complex regional pain syndrome, or postural orthostatic tachycardia syndrome [98]. Another Danish study used absence data from school records to address safety concerns without relying on medical diagnosis [99]. They concluded that HPV vaccination does not increase the risk of morbidity in any matter that manifests as absence from school due to illness. Another Danish study tested the hypothesis whether symptoms reported by some females may be caused by long-lasting symptoms after Epstein-Barr virus (EBV) infection. EBV infection is associated with symptoms of long-lasting tiredness and may therefore being misinterpreted as adverse events caused by HPV vaccines. However, results from this study showed that this finding is more likely explained by protopathic bias, i.e. the fact that a larger proportion of females suspecting adverse events are tested for EBV [100].

#### 5.4.1.5.2 *New vaccines*

Oral administration of live *Salmonella typhi* Ty21a expressing major capsid proteins (L1) of HPV 16 and 18 is a potential choice for immunisation in adolescent girls under low resource settings. The results from a nonclinical safety evaluation in mice, rats and rabbits suggests ‘no observable adverse effects’ of this vaccine even at higher dosages [101].

In a double-blind phase III trial, a novel *Escherichia coli*-produced HPV-16/18 bivalent vaccine showed an acceptable safety profile [102].

### 5.4.2 **Other potential future target diseases**

#### 5.4.2.1 *Meningococcal B*

A comprehensive review concluded that the safety profile of 4CMenB administered in real-world settings was consistent with pre-licensure clinical data [103]. Three clinical studies confirm this conclusion in infants [104] as well as in adolescents [105, 106]. In addition, no evidence was found for an increased risk of nephrotic syndrome [107] or Kawasaki disease [108] following 4CMenB vaccination. For MenB-FHbp, no new safety issues were identified either [109].

#### 5.4.2.2 *Varicella*

Several studies showed the safety of live attenuated varicella vaccines [110, 111], even in patients with Cartilage-Hair Hypoplasia [112] and in immunosuppressed children [113], although more systemic AEs after VZV vaccination were found in HIV-exposed uninfected than in HIV-unexposed children [114]. Vaccination of children and adults with varicella zoster immune globulin did not raise any safety concern [115]. A new live attenuated MAV/06 strain varicella vaccine showed a similar safety profile compared to the licensed live attenuated vaccine Varivax [116].

#### 5.4.2.3 *Herpes Zoster*

A systematic review and meta-analysis showed that herpes zoster vaccines (live attenuated or adjuvant recombinant subunit vaccines) did not increase the risk of adverse events in patients with renal disease [117]. The live attenuated herpes zoster vaccine also showed a good safety profile in healthy adults, in patients on the waiting list for lung transplantation, and in hematopoietic stem-cell transplant patients [118-121].

No safety concerns were identified for adjuvanted recombinant zoster vaccine in healthy adults [122-126] and in several immunocompromised populations [127-132]. Another study showed that the percentage of participants reporting solicited adverse events after vaccination with recombinant zoster vaccine tended to decrease with increasing frailty [133]. A case study showed that, although post-vaccination VZV infection or reactivation appears to be rare, clinicians should be aware of this potential complication of the recombinant subunit vaccine [134].

#### 5.4.2.4 Hepatitis A

A case report described anaphylaxis following simultaneous administration of inactivated hepatitis A vaccine and purified chick embryo-cell rabies vaccine after multiple doses [135], but other studies demonstrated the safety of inactivated hepatitis A vaccine in adolescents and adults [136] as well as in HIV-exposed uninfected children [114]. Inactivated hepatitis A vaccine administered subcutaneously was even safer than the intramuscular route (Nakasone). Data from a seroprevalence study in China showed evidence of a good safety profile for both inactivated and live attenuated hepatitis A vaccine [137]. Data on live attenuated hepatitis A vaccine in India established this tolerability [138]. A review did not indicate any concerning pattern of adverse pregnancy outcomes following exposure to hepatitis A vaccination during pregnancy [139].

#### 5.4.2.5 Hepatitis B

Hepatitis B vaccination has shown to be safe and well-tolerated in patients on long-term dialysis, people with diabetes, immunocompromised individuals, children after completion of chemotherapy and (or) hematopoietic stem-cell transplantation, and patients with cirrhosis [140-144]. Furthermore, no correlation has been found between vaccination against hepatitis B and the risk of MS [145]. Data from VAERS show that myopericarditis remains rarely reported after administration of licensed vaccines, including hepatitis B vaccination [146]. The safety of a tri-antigenic hepatitis B vaccine was shown in healthy adults [147-149] and in those with stable and controlled chronic conditions [147]. A good safety profile was also found for a hepatitis B vaccine containing CpG adjuvant, including in patients with chronic diseases [150-152], although its long-term safety has yet to be established [153]. Healthy non-responders could safely be revaccinated with a hepatitis B vaccine adjuvanted with ASo4 [154] or with a HBAI2o vaccine containing a new AI2o adjuvant [155]. A review did not indicate any concerning pattern of adverse pregnancy outcomes following exposure to hepatitis B vaccination during pregnancy [139].

#### 5.4.2.6 Rotavirus

Several studies did not identify serious adverse events for both Rotarix and Rotateq [156-160], even in premature children when administered in NICU-hospitalised infants [161]. However, a pharmacovigilance analysis on American and European data showed some new potential safety signals [162]. So, although most of the reported AEFIs were listed in the SPCs, the need to investigate potential safety signals remains in order to complete the descriptions of AEFIs for licensed rotavirus vaccines.

A good safety profile was also demonstrated for several new rotavirus vaccines like Rotavac [163-167] and for Rotasiil and Rotavin-M1 [164].

New vaccines, such as a porcine circovirus-free rotavirus vaccine [168, 169], a trivalent live human-lamb reassortant rotavirus vaccine [170] and a hexavalent rotavirus vaccine [171], were shown to be well-tolerated.

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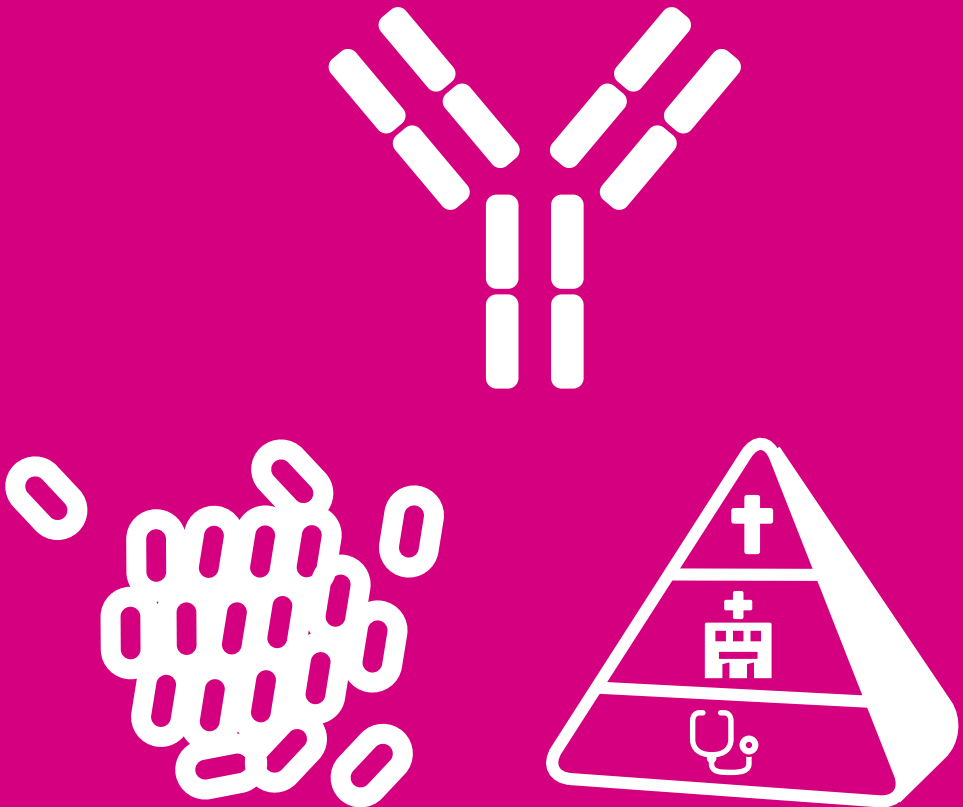
\* RIVM publication.

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6

# Current National Immunisation Programme



## 6.1 Diphtheria

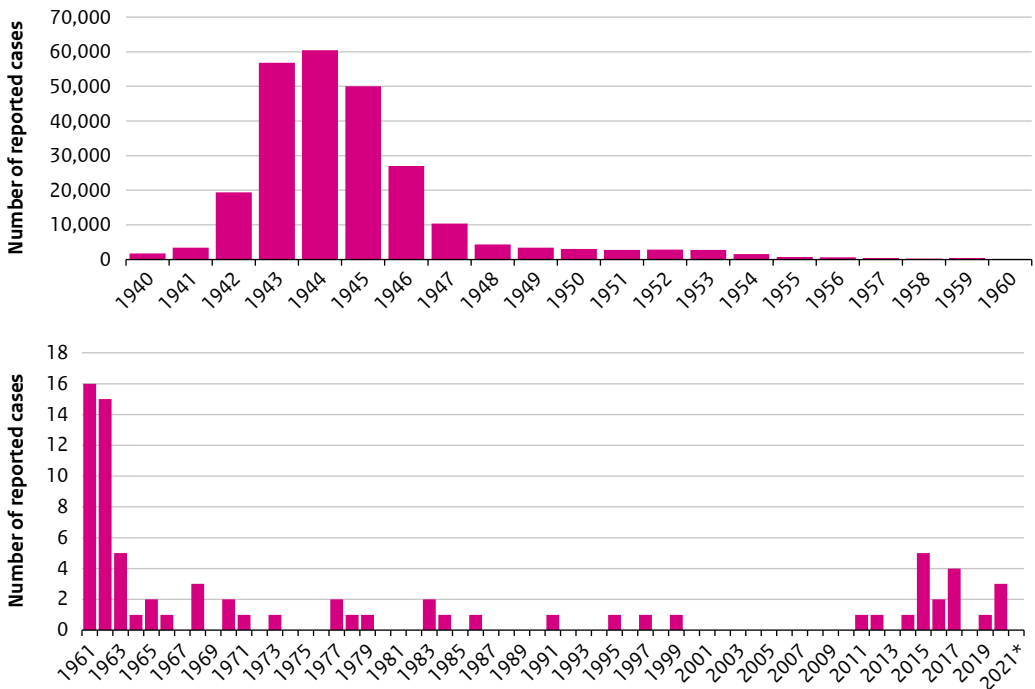


D.L. van Meijeren, F.A.G. Reubsaet, D.W. Notermans, H.E. de Melker, N.A.T. van der Maas

### 6.1.1 Key points

- In 2020, three diphtheria cases were reported, two of which were probably infected in the Netherlands and one in Central Europe.
- In 2021, for the period up to and including March, no cases of diphtheria were notified.
- The outbreak of diphtheria that was declared in Yemen in October 2017 is still ongoing and affects almost all governorates. For the period up to and including April 26<sup>th</sup>, 2020, the country reported 5,701 probable cases of diphtheria and 330 related deaths.
- Five countries in the Region of the Americas reported a total of 80 confirmed diphtheria cases, of which 21 deaths, in 2020.
- Due to the COVID-19 pandemic in 2020, postponement of vaccination campaigns was seen in the Region of the Americas compared with 2019.

### 6.1.2 Tables and figures



**Figure 6.1.1** Diphtheria notifications per year for 1940-1960 (above) and 1961-2021\* (below).

\* Notifications for the period up to and including March 2021 are included.

**Table 6.1.1** Laboratory results of confirmation testing for *Corynebacterium diphtheriae* and *Corynebacterium ulcerans* at RIVM for 2016-2021\*. Date of delivery to the laboratory is used for year of classification.

	<i>Corynebacterium diphtheriae</i>				<i>Corynebacterium ulcerans</i>			
	PCR		Elek		PCR		Elek	
	Negative	Positive	Positive	Non-conclusive	Negative	Positive	Positive	Non-conclusive
2016	12	1	1	n/a	2	1	n/a	1
2017	9	1	0	0	0	2	n/a	2
2018	7	0	0	0	1	2	1	1
2019	7	0	n/a	n/a	8	0	n/a	n/a
2020	3	1	n/a	1	5	1	n/a	1
2021*	0	0	0	0	0	0	0	0

\* For the period up to and including April 22<sup>nd</sup>, 2021.

### 6.1.3 Epidemiology

In 2020, three cases of diphtheria were reported (Figure 6.1.1). The first case concerned a man born in the Netherlands before 1940 and therefore not eligible for vaccination, with clinical signs of a diabetic foot, after which *Corynebacterium ulcerans* was cultured out of the wound. The patient was most likely infected in the Netherlands, possibly by his dog or one of his donkeys. The second case concerned a woman in her early 20s, born in the Netherlands, with clinical signs of cutaneous diphtheria after which *C. ulcerans* was cultured out of the wound by a laboratory in France. The woman was probably infected in the Netherlands by her parents' dog or the neighbour's cat. She was fully vaccinated against diphtheria. The third patient concerned an unvaccinated woman, born in the early 80s in Slovakia, with clinical signs of cutaneous diphtheria after which *Corynebacterium diphtheriae* was cultured out of the wound. The woman had probably been infected in Slovakia. In 2021, for the period up to and including March, no cases of diphtheria were notified.

### 6.1.4 Pathogen

In 2020, the RIVM received ten *C. diphtheriae* or *C. ulcerans* strains isolated from wounds or ulcers. In 2021, for the period up to and including April 22<sup>th</sup>, the RIVM received no *C. diphtheriae* or *C. ulcerans* strains. Out of the ten strains in 2020, one positive test result regarding *C. diphtheriae* and one positive test result regarding *C. ulcerans* were found. These positive test results refer to two of the three cases reported in 2020. Regarding the third case, *C. ulcerans* was cultured out of the wound by a laboratory in France. See Table 6.1.1 for details on laboratory results for the respective strains.

### 6.1.5 International developments

Five countries in the Region of the Americas reported a total of 80 confirmed diphtheria cases, of which 21 deaths, in 2020. Brazil reported 2 cases, the Dominican Republic 3 cases and 2 deaths, Haiti 66 cases and 16 deaths, Peru 4 cases and 1 death, and the Bolivian Republic of Venezuela 5 cases and 2 deaths. Among others, non-compliance with vaccination coverage has contributed to the occurrence of diphtheria outbreaks in the Region of the Americas. Due to the COVID-19 pandemic in 2020, postponement of vaccination campaigns was seen in the region compared with 2019. Moreover a decrease in the demand for the first and third doses of the diphtheria, tetanus and pertussis vaccine (DTP<sub>1</sub> and DTP<sub>3</sub>) was reported comparing January, February and March 2019 with the same months in 2020 [1].

The outbreak of diphtheria that was declared in Yemen in October 2017 is ongoing and affects almost all governorates. For the period up to and including April 26<sup>th</sup> 2020, the country reported 5,701 probable cases of diphtheria and 330 related deaths. After a vaccination campaign that started in November 2018 targeting 300,000 children, the proportion of cases aged 0-4 years old was reduced from 19% to 14% [2].

### 6.1.6 Literature

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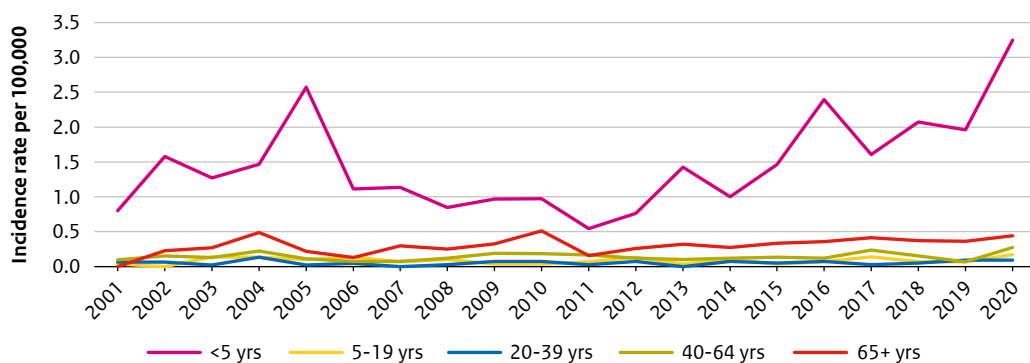
## 6.2 Haemophilus influenzae disease

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### 6.2.1 Key points

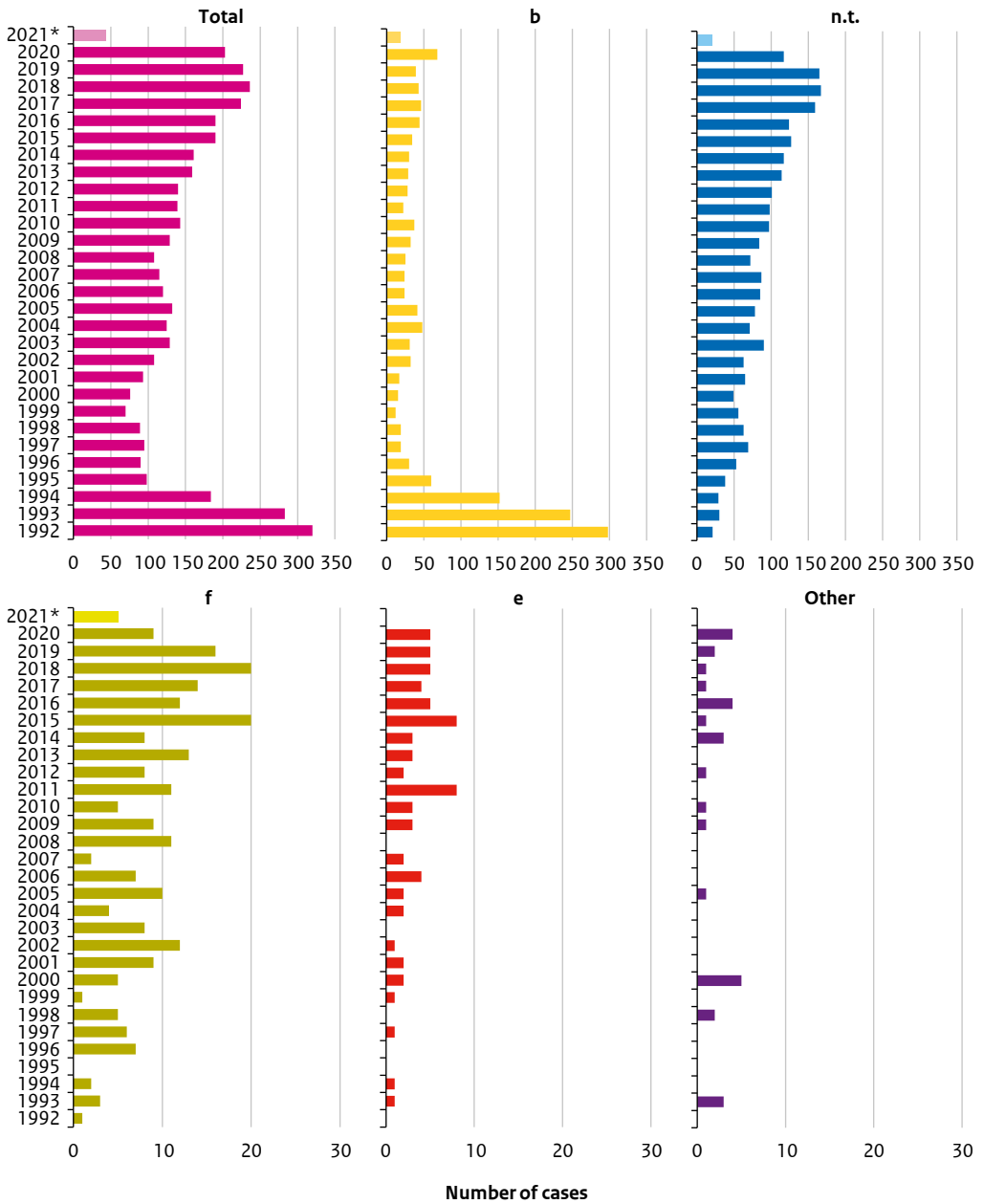
- The incidence of invasive disease caused by *Haemophilus influenzae* type B (Hib) increased from around 0.25 per 100,000 in 2017-2019 to 0.39 per 100,000 in 2020 (68 cases in total), predominantly due to infections among unvaccinated cases. The rise is striking as it occurred while control measures for the COVID-19 pandemic were in place.
- Vaccine effectiveness against Hib was stable over time (97% (95% CI: 94-99) in 2020).
- The incidence of invasive disease caused by other *H. influenzae* types decreased, likely as a result of the control measures for the COVID-19 pandemic.
- For the period up to and including April 2021, only 20 cases with non-typeable Hi disease were reported compared to 77 and 91 in the same period in 2020 and 2019, respectively.

### 6.2.2 Figures



**Figure 6.2.1** Age-specific incidence rate of *Haemophilus influenzae* type b (Hib) invasive disease, 2001-2020.

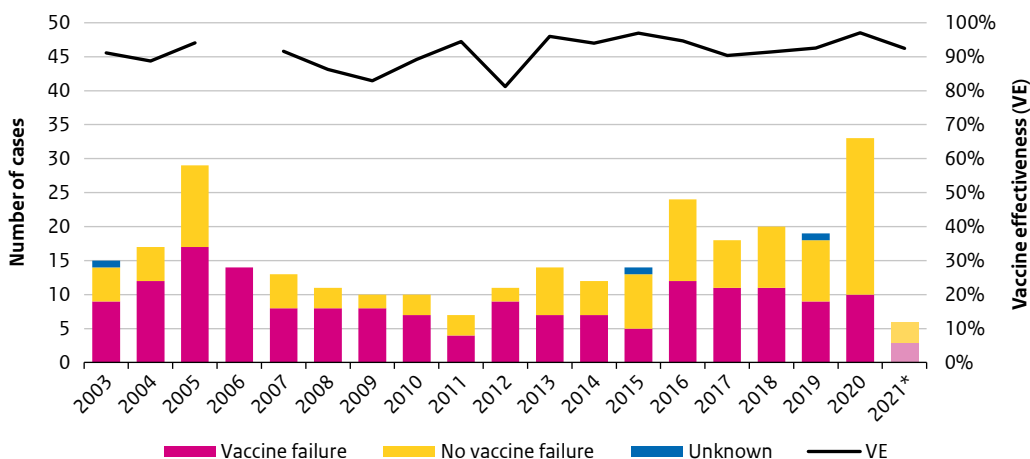




**Figure 6.2.2** Number of *Haemophilus influenzae* invasive disease cases per serotype, 1992-2021\*.

Note: The category 'Other' includes serotypes a and d.

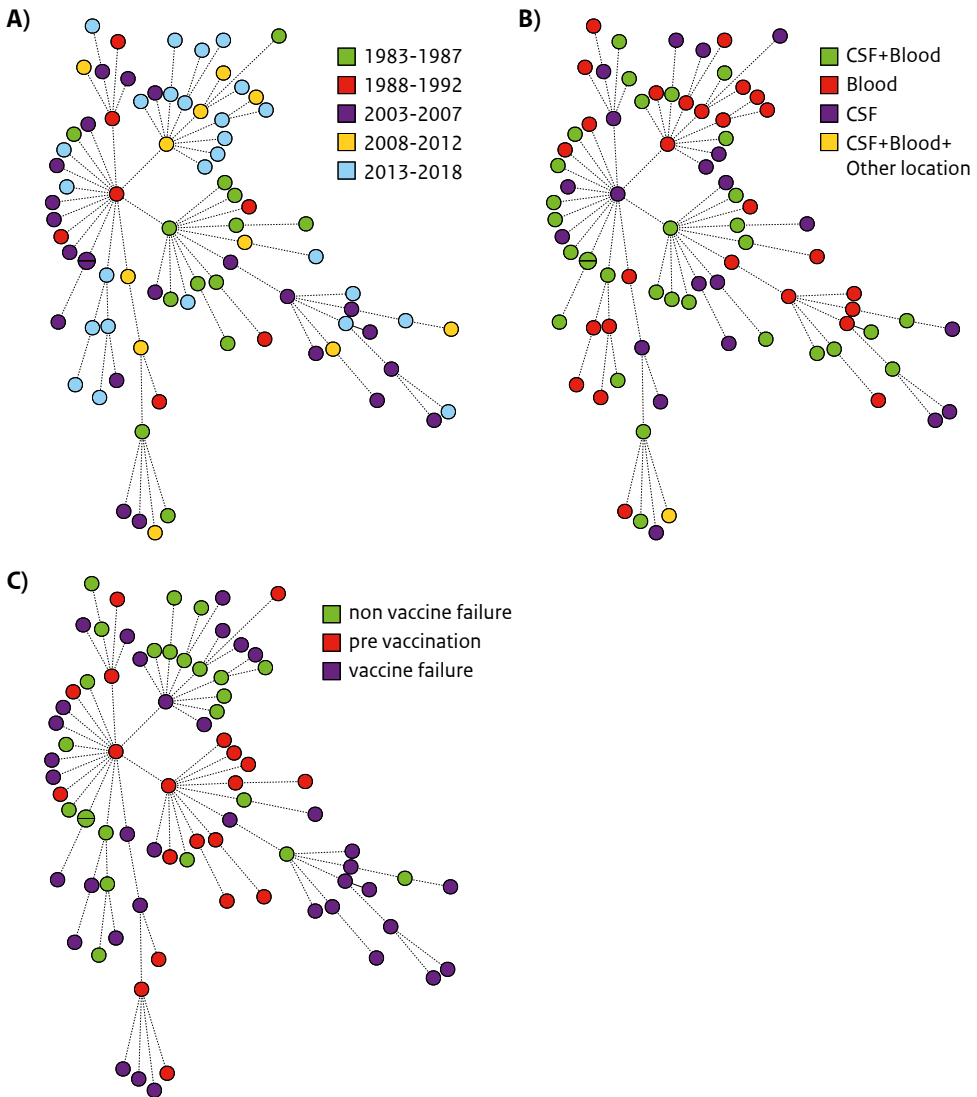
\* Up to and including April.



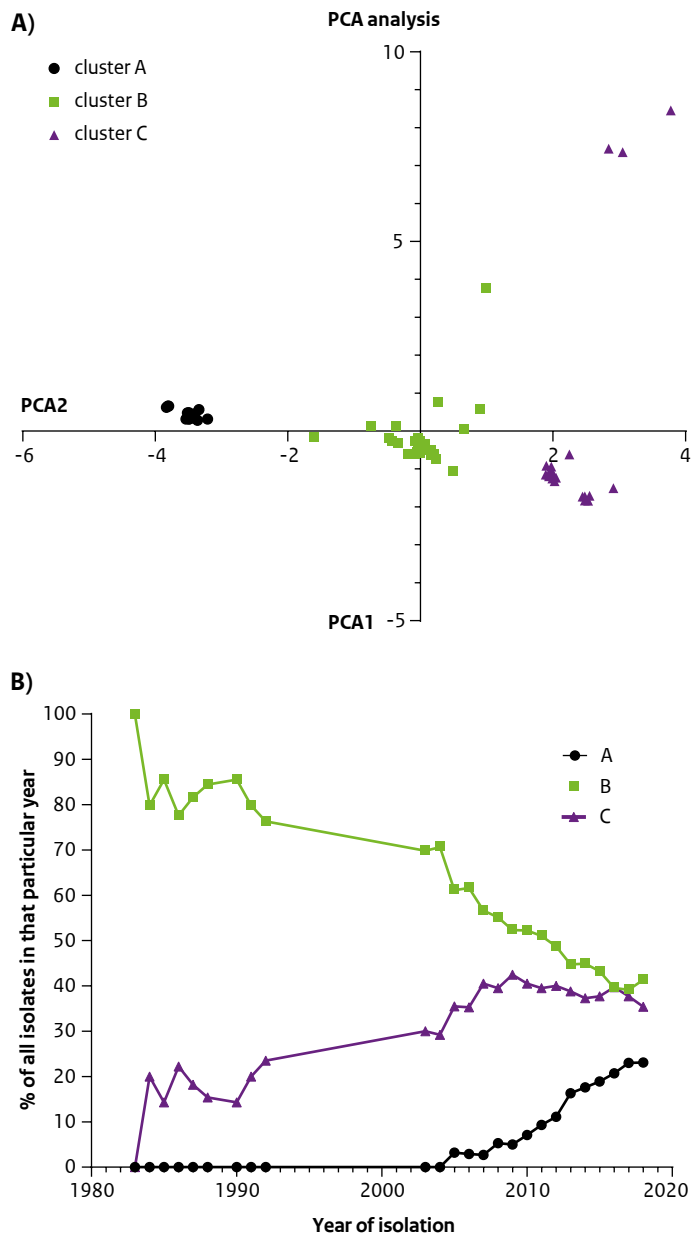
**Figure 6.2.3** Number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after April 1<sup>st</sup>, 1993) by vaccination status and estimated vaccine effectiveness, 2003-2021\*.

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

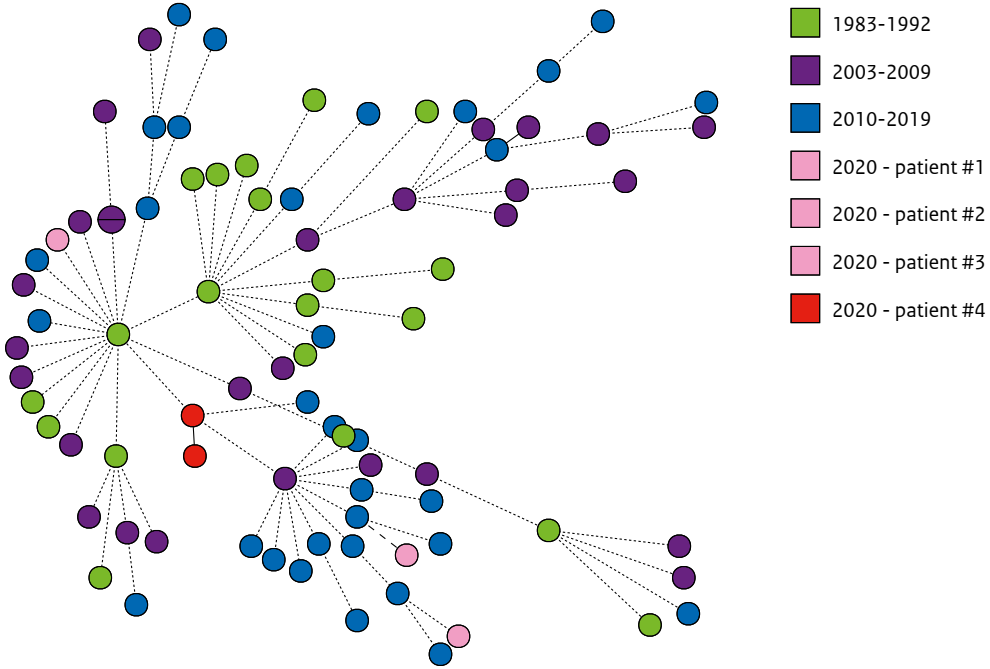
\* Up to and including April.



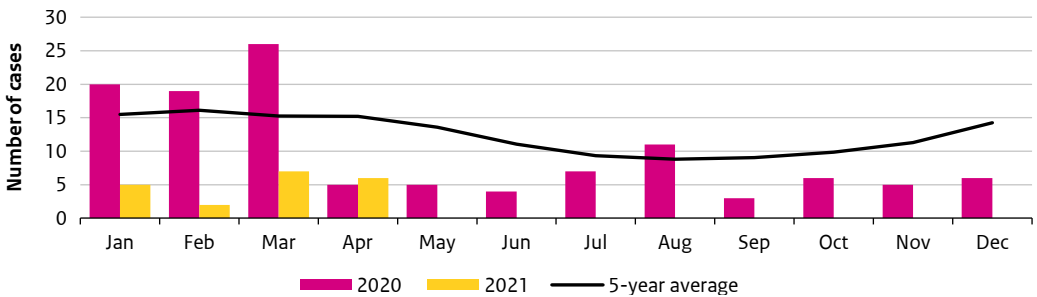
**Figure 6.2.4** Genetic relationship between 80 clinical isolates based on cgMLST. Each node of the minimum spanning tree based on cgMLST represents a single Hib isolate. The length of the lines between isolates represents the number of different genes. No clustering of strains can be observed by year of isolation (A), source of isolation (B), or vaccination status (C).



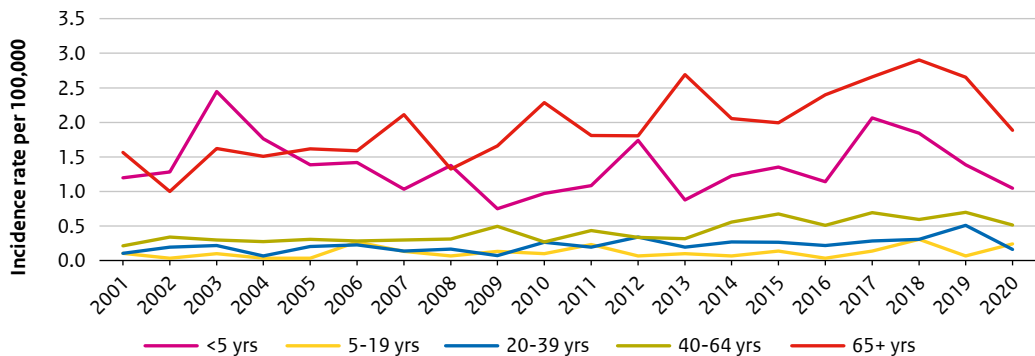
**Figure 6.2.5** (A) Unsupervised principal component analysis (PCA) on the total cgMLST (1,738 genes) of 65 isolates with the dominant Sequence Type 6, revealed 3 clusters along components 1 and 2. (B) Relative contribution of each cluster to the total number of isolates analysed in a particular year.



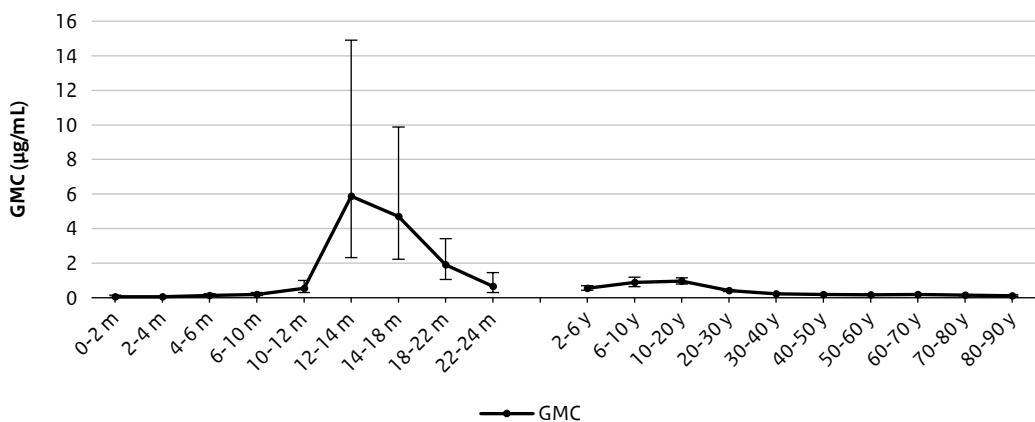
**Figure 6.2.6** Genetic relationship between 85 clinical isolates based on cgMLST. Each node of the minimum spanning tree based on cgMLST represents a single Hib isolate. The length of the lines between isolates represents the number of different genes. The red and pink nodes represent invasive isolates from four unvaccinated children that clustered in place and time (July and August 2020). Note that for patient #4, two isolates were analysed that had one SNP difference, thereby showing technical replication of the results.



**Figure 6.2.7** Number of non-typeable *Haemophilus influenzae* cases in 2020 (violet) and January-April 2021 (yellow) by month compared with the pre-COVID 5-year moving average (2015-2019). Note that the Netherlands went into lockdown in mid-March 2020.



**Figure 6.2.8** Age-specific incidence rate of non-typeable *Haemophilus influenzae* disease, 2001-2020.



**Figure 6.2.9** Geometric mean concentration (GMC) and corresponding 95% confidence interval of anti-Hib IgG antibodies by age group (in months – left, or years – right) in individuals included in the national sample of the PIENTER-III study.

## 6.2.3 Epidemiology

### 6.2.3.1 Hib disease

#### 6.2.3.1.1 Incidence

The number of Hib cases increased from 22 in 2011 to 44 in 2016 and subsequently stabilised at around 40 cases per year between 2017 and 2019 (incidence around 0.25 per 100,000 inhabitants). However, 68 Hib cases were observed in 2020 (incidence: 0.39 per 100,000) (Figure 6.2.1). This rise is striking as the country was in partial lockdown due to control measures for the COVID-19 pandemic, which coincided with a decrease in the incidence of most other respiratory infectious diseases including disease caused by other *Haemophilus influenzae* types (see sections 4.3 and 6.2.3.3). The incidence rose in all age groups except for those aged 20-39 years (Figure 6.2.2). The rise as well as absolute incidence were highest in children <5 years old (3.3 per 100,000 compared to 2 per 100,000 in the years 2018-2019 and a maximum incidence of 2.4 per 100,000 in the previous 5 years). Whether the rise will continue needs to be established, as the number of Hib cases in the first 4 months of 2021 was similar to that in the same period in 2020 (n=18) and 2018 (n=17) but higher than that in the same period in 2019 (n=10).

The disease outcome is known for 66 cases in 2020 and 13 cases in 2021. Of these, 4 patients died in 2020 and none in 2021. One of the 4 fatal cases was <5 years old; the others were all over 70 years old. Vaccination status was known for only 2 of the fatal cases, including the child, and these were unvaccinated.

#### 6.2.3.1.2 Vaccinated cases

In 2020 and 2021 (up to and including April), 34 and 8 Hib cases, respectively, were reported among cohorts eligible for vaccination (born from 1 April 1993 onwards; Figure 6.2.3). Of the 38 cases with a known number of vaccine doses, 24 (63%) were unvaccinated (22 in 2020, 2 in 2021), 2 cases were insufficiently vaccinated (in 2020), while 12 (32%) were sufficiently vaccinated (i.e. received at least 2 vaccinations with at least 2 weeks between the second vaccination and date of diagnosis; 8 in 2020 and 3 in 2021). This proportion and absolute number of unvaccinated cases were higher than in previous years (<50% in the previous 5 years) while the absolute number of vaccinated cases was similar to previous years (11 or 12 in previous 5 years). 14 out of 17 unvaccinated cases with information (82%) reported to be Reformed orthodox (n=10) or critical to vaccination (n=4). The unvaccinated children were between 0 and 9 years old. Most vaccinated cases (8 in 2020 and 3 in 2021) were younger than 5 years old and 3 (8%) had a known immune disorder.

#### 6.2.3.1.3 Vaccine effectiveness

The estimated vaccine effectiveness (VE) of Hib vaccination using the 'screening method' (see Appendix 1) was 97% (95% CI: 94-99) in 2020 (Figure 6.2.3). The overall VE for 2003-2021 was 93% (95% CI: 91-94).

### 6.2.3.2 Genetic relationship of Hib isolates

We aimed to elucidate thus far unexplained changes in epidemiology of invasive Hib in the Netherlands by genotypic characterisation of clinical isolates found in 2003-2018 (Figure 6.2.4 and Figure 6.2.5) as well as 4 isolates from 2020 (Figure 6.2.6). For the first analysis, a total of 80 Hib strains isolated from children aged <5 years were obtained from the collection of the Nederlandse Referentie Laboratorium voor Bacteriële Meningitis (NRLBM, Netherlands Reference Laboratory for Bacterial Meningitis). The researchers randomly selected 20 strains from the pre-vaccine era (1986-1992) and 60 strains from both vaccinated and unvaccinated children represented the vaccine era (2003-2018). Overall, no clear genetic clustering of Hib isolates was observed by analysing whole genome sequencing data (WGS) (Figure 6.2.4). A minimum spanning tree based on core genome Multilocus Sequence Typing (cgMLST) showed substantial genetic variation within the Dutch Hib population with an average distance of 35 genes between two neighbouring isolates (range 1-148 genes). However, in-depth analysis of the dominant sequencing type 6 by applying principal component analysis (PCA) revealed three distinct clusters of isolates (Figure 6.2.5). Cluster A, which appeared after the introduction of the vaccine, is gradually increasing and now comprises one-third of all clinical isolates, suggesting that the recent increment in cases might be caused by expansion of a more successful genotypical Hib cluster. Otherwise, data from 2020 was applied to give context to four Hib strains that were isolated from unvaccinated children in a region with low-vaccination coverage in July and August 2020. As shown in Figure 6.2.6, we found substantial genetic variation between the strains, indicating that there was no common source of these cases.

### 6.2.3.3 Non-typeable Hi (NTHi) disease

In 2020, 117 cases of NTHi were reported. This was ~30% lower than the two preceding years (165 in 2019 and 167 in 2018; Figure 6.2.1). The decrease occurred suddenly from April 2020 onwards (Figure 6.2.7), likely because the Netherlands went into lockdown due of COVID-19 from mid-March up to June 2020 and continued with social-distancing measures and increased hygiene. Except for August, the case number per month has been below the 5-year average since. For the period up to and including April 2021, 20 cases were reported compared to 77 in 2020 and 91 in 2019. In 2020, the incidence was still highest among persons aged 65 and over (1.9 per 100,000; n=64) and children aged under five years (1.0 per 100,000; n=9) (Figure 6.2.8).

### 6.2.3.4 Disease due to other Hi serotypes

In 2020, five Hi cases with serotype e (Hie) were reported, similar to previous years (Figure 6.2.1). For the period up to and including April 2021, no Hie cases were reported. In 2020, 9 cases of Hif were reported throughout the year, which was fewer than in previous years (2018: n=20, 2019: n=16; Figure 6.2.1). For the period up to and including April 2021, five Hif cases were reported. In 2020, 4 cases caused by other Hi types were observed. So far, no other Hi cases have been observed in 2021.

## 6.2.4 Pathogen

There are no indications that the pathogenicity of Hib has changed.



### 6.2.5 Current/ongoing research at RIVM

Monitoring of the seroprevalence of NIP-targeted disease occurs periodically via serosurveys in Netherlands (PIENTER-I [1], PIENTER-II [2], PIENTER-III [3]). The most recent survey, PIENTER-III, was conducted in 2016/2017. A national sample was drawn from residents aged 0-89 years and a sample of persons living in areas with low vaccination coverage. Anti-Hib IgG antibody concentrations were quantified in serum samples using a fluorescent-bead-based multiplex immunoassay (MIA). Geometric mean concentrations (GMC) were calculated by age group. Preliminary results show a peak in GMC for the national sample in individuals aged 12-14 months following the booster Hib vaccination with the hexavalent vaccine (DTPa-HBV-IPV/Hib) around the age of 11 months (Figure 6.2.9). The GMC is decreasing in the age groups 14-16 months up to 2-6 years. Persons in the age groups 6-10 and 10-20 years received a pentavalent vaccine (DTPa-IPV/Hib or DTPw-IPV/Hib) or PRP-T. A slightly higher GMC is observed in these age groups compared with the age group of 2-6 years. The GMC in persons aged 20-89 years seems similar across age groups. These GMCs reflect natural immunity since the majority of these persons were not eligible for Hib vaccination within the NIP. A similar pattern in GMCs was observed for all age groups in areas with low vaccination coverage (data not shown). Even so, the GMCs were lower compared to the national sample due to lower vaccination coverage.

As shown above, the incidence of Hib increased in 2020, while Hi caused by other types as well as the incidence of several other respiratory diseases decreased [4]. This rise was striking as it coincided with the COVID-19-related control measures. The VE was stable over time. We performed a more in-depth descriptive analysis to investigate the increased incidence, comparing incidence among vaccine-eligible cases (born after 1993 and >3 months old) against previous years (2015-2019), stratified by municipalities with low vaccination coverage ('Bible belt') and other municipalities. For 19 unvaccinated eligible cases, the reason for not vaccinating was reported as being related to Reformed orthodoxy (n=9), critical towards vaccination (n=3) and unknown (n=7). In 2020, the incidence among unvaccinated but vaccine-eligible and non-eligible cases was significantly higher in the Bible belt (0.69 vs. 0.07/100,000 and 0.49 vs. 0.18/100,000 respectively), while the incidence among vaccinated eligible cases did not differ in the Bible Belt versus the rest of the Netherlands. An explanation for this difference is currently under investigation.

### 6.2.6 International developments

Overall, the recent relevant studies published internationally report findings similar to what we have seen in the Netherlands in the past 10 years, i.e. a decrease in Hib incidence for both the vaccinated and unvaccinated groups but an increase in NTHi (as well as Hia, mainly in the Americas [5]).

The impact of conjugate vaccines on the incidence of bacterial meningitis in the Netherlands was published based on the nationwide surveillance data of all cerebrospinal fluid isolates received from 1988 to 2019 [6]. *H. influenzae* and meningococcal meningitis were seen predominantly in pre-school children (1,560 of 1,970 *H. influenzae* [79.2%]). The absolute decrease in Hib incidence was largest in preschool children, in whom incidence decreased from 22.94 to 0.46 episodes per 100,000 per year. The relative reduction in Hib incidence was similar for the non-vaccinated age groups (IRR 0.02 [95% CI: 0.02-0.04]).

Data from the Invasive Respiratory Infection Surveillance (IRIS) Initiative on pneumococci, *H. influenzae*, and meningococci was used to determine the incidence of invasive disease due to these pathogens during the early months of the COVID-19 pandemic [7]. They compared weekly numbers of cases in 2020 with corresponding data for 2018 and 2019. The stringency of COVID-19 containment measures was quantified using the Oxford COVID-19 Government Response Tracker (OxCGRT [8]) and population movements were assessed using Google COVID-19 Community Mobility Reports. The analysis included data generated by 24 laboratories from 24 countries (n= 7796). They showed that all countries had experienced a significant and sustained reduction in invasive Hi disease coinciding with the introduction of COVID-19 containment measures in each country.

While only a small and partly temporary decrease was observed in vaccine uptake during the COVID-19 pandemic in the Netherlands (preliminary results: [9]), this did occur in some other countries. A Japanese modelling study estimated the incremental burden of invasive Hib disease due to a decline of childhood vaccination during the COVID-19 pandemic [10]. They concluded that the decrease in vaccine coverage for Hib-including vaccines causes an incremental disease burden irrespective of the possible decrease of Hib transmission rate by COVID-19 mitigation measures.

In Germany, nationwide surveillance confirmed a large drop in Hib infections after vaccination [11]. It should be noted that only 59% of cases could be linked with the isolates. Overall, 4,036 reported *H. influenzae* cases, of which 1,902 were matched, were included in the analysis. Information on vaccination status was available for 29/35 (83%) Hib cases aged <27 years (i.e. those eligible for Hib vaccination). Three out of 29 (10%) were fully vaccinated and were therefore vaccine failures, which is lower than we have seen in the Netherlands (see 6.2.3.1.2).

In Italy, surveillance data of children ≤15 years showed a vaccine effectiveness of 83% (95% CI: 45-95) and dominance of sequence type (ST) 6 [12], which is also the dominant type in the Netherlands. Most cases in children ≤2 years occurred in unvaccinated subjects, and overall, 14 cases of vaccine failure were observed. No host predisposing factors could explain the vaccine failures and vaccine failure was not associated with specific genotypes or amplification status of the *capB* locus.

### 6.2.7 Literature

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\* RIVM publication.

### 6.2.8 Other RIVM publications

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## 6.3 Hepatitis B

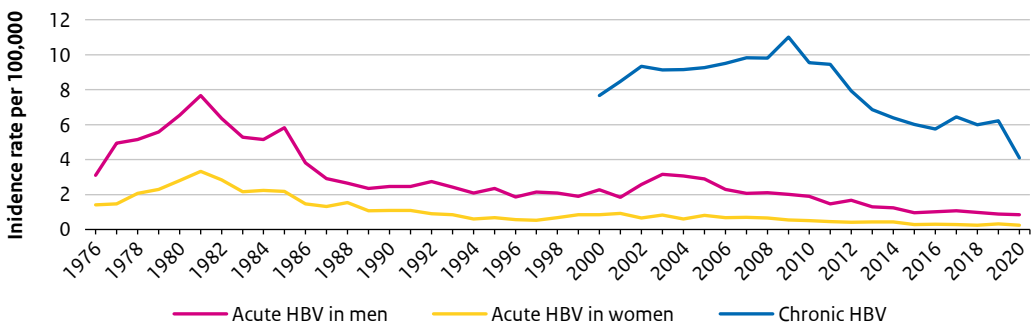


I.K. Veldhuijzen, K.S.M. Benschop, F. van Heiningen, A. Meiberg, J. Cremer, A.J. King, H.E. de Melker, E. Op de Coul

### 6.3.1 Key points

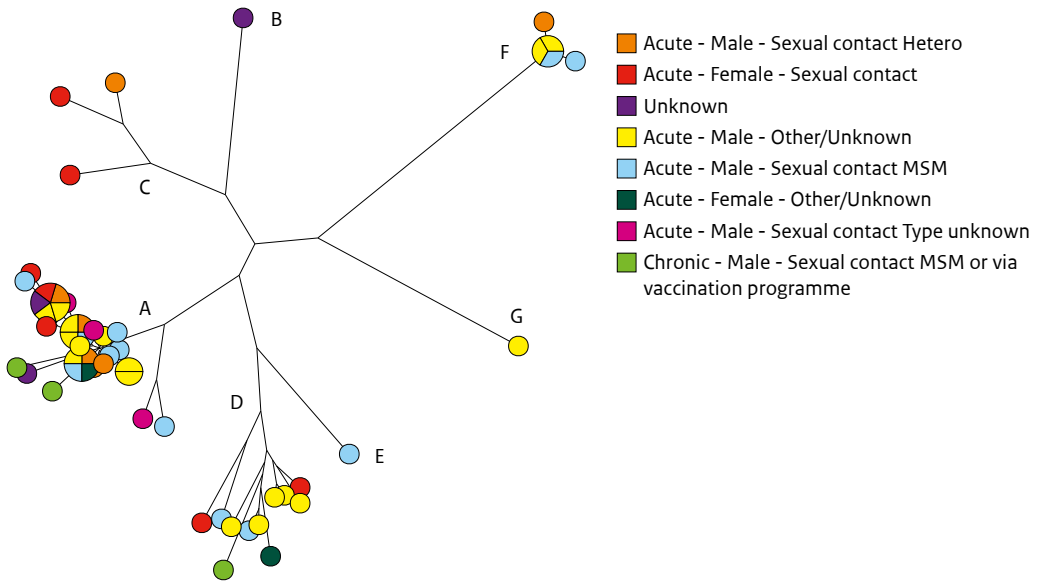
- Of the total number of 825 reported hepatitis B cases, 12% had an acute infection and 88% a chronic infection.
- The incidence of acute hepatitis B notifications decreased by 9% in 2020 compared to 2019, and was 0.5 per 100,000 population.
- The number of newly diagnosed chronic HBV infections decreased by one third compared to 2019, and was 4.1 per 100,000 population.
- The drop in hepatitis B notifications coincided with the peaks of COVID-19 hospital admissions.
- Among both men and women, sexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2020, genotype A continued to be the dominant genotype among acute HBV cases with 65% of 40 genotyped cases, followed by genotype D (18%).
- Genotype F increased among acute HBV cases in 2019. A molecular subcluster of genotype F1b was identified that also included cases diagnosed in 2020 and 2021.

### 6.3.2 Tables and figures

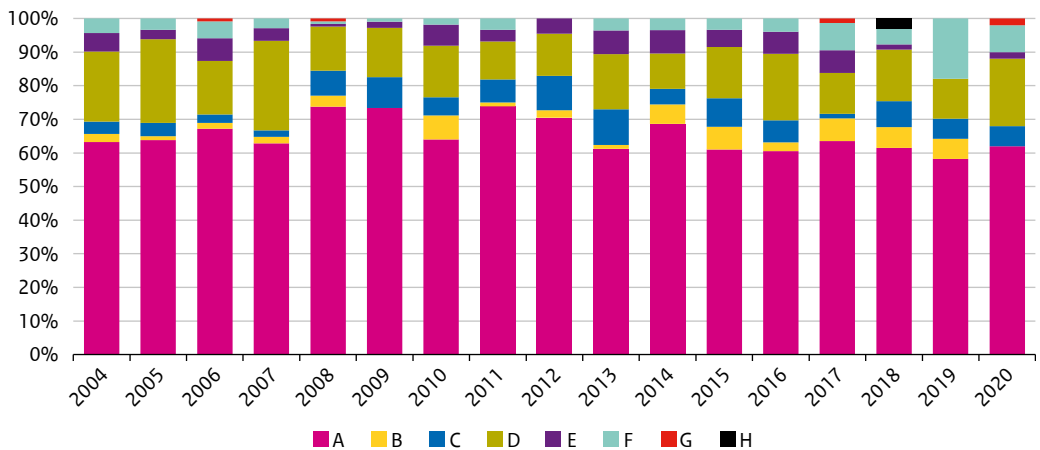


**Figure 6.3.1** Incidence rate of acute HBV infections in men and women in the Netherlands from 1976 onwards and chronic HBV infections from 2000 onwards.

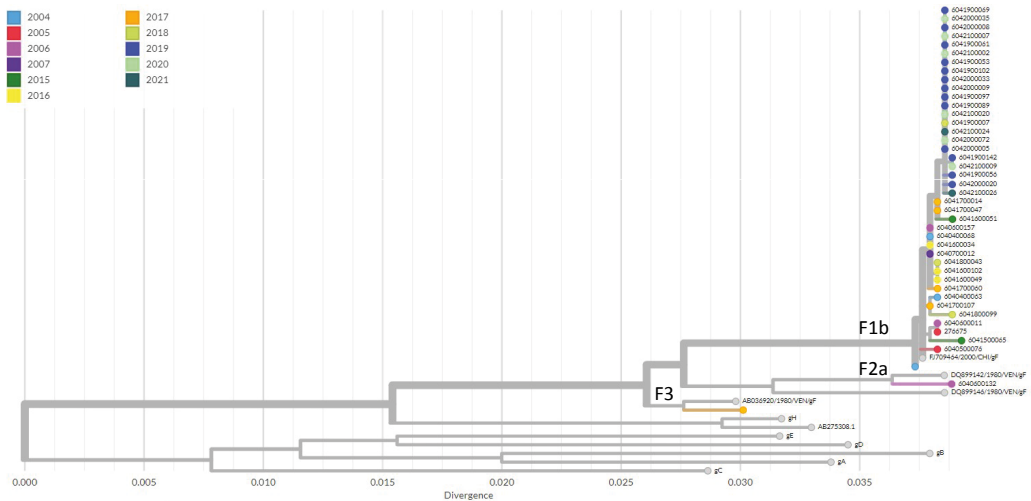
Source: Osiris.



**Figure 6.3.2** Optimised maximum parsimony tree based on the full-length sequence of HBV cases in the Netherlands in 2020 by reported type of infection, gender and transmission route (n=55). Genotype G is under investigation to identify whether genotype is a single or double infection (with gA). gX = genotype.

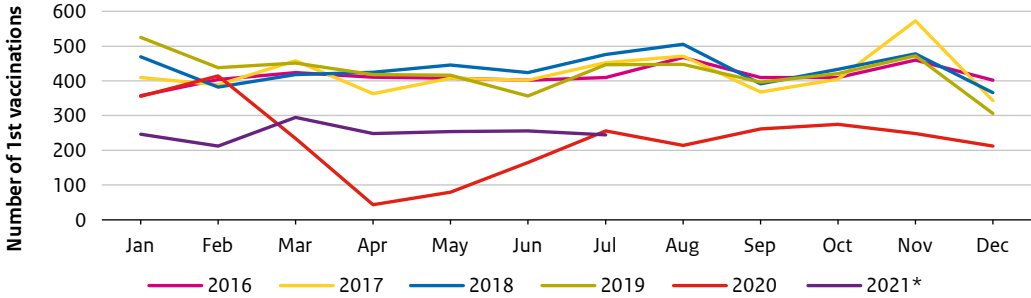


**Figure 6.3.3** Genotype distribution of acute HBV cases in the Netherlands from 2004 to 2020.



**Figure 6.3.4** Phylogenetic tree of genotype F (2004-2021) based on complete genome (2.7kb/3.2 kb) data collected as of June 2021.

\* Chronic cases.



**Figure 6.3.5** Number of first vaccinations per month from 2016, for the period up to and including July 2021 in the programme for behavioural risk groups.

### 6.3.3 Epidemiology

In 2020, 825 cases of hepatitis B virus (HBV) infection were notified. Of these, 714 (88%) were chronic infections and 95 (12%) were acute infections (16 cases with unknown status).

#### 6.3.3.1 Acute HBV epidemiology

The number of notified acute HBV infections was 95 in 2020, a 9% decrease compared to 2019 when 105 cases were notified. In the first half of 2021, 30 cases of acute HBV were reported. The incidence of acute HBV notifications in 2020 was 0.5 per 100,000 population, 0.9/100,000 among men and 0.2/100,000 among women. HBV incidence over time is shown in Figure 6.3.1. The mean age of patients with acute HBV infection was 42.2 years and is higher in men (43.7) than in women (36.7). No cases of acute hepatitis B were reported among children; the youngest patient was 19 years old.

Twenty-four (26%) patients with acute hepatitis B were admitted to the hospital in 2020. One patient died after a fulminant acute HBV infection.

In 2020, most cases of acute HBV infection (58%) were acquired through sexual contact. For 34% of the reports of acute HBV infection, the most likely route of transmission remained unknown despite source tracing. The proportion with unknown transmission route is higher for men (41%) than women (10%). Among men (74 cases), sexual contacts between MSM accounted for 27% of acute infections and heterosexual transmission for 20%. Among women (21 cases), heterosexual contact accounted for 71% of cases. The majority of patients with acute hepatitis B were born in the Netherlands (71%).

#### 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 decreased in 2020 to 714 cases (incidence 4.1 per 100,000) (Figure 6.3.2). Since chronic hepatitis B is largely asymptomatic, the number of new diagnoses is strongly influenced by testing practices. The number of people tested for HBV infection annually is unknown but the lower number in 2020 is likely related to the COVID-19 pandemic (see 6.3.5.1).

In 2020, 91% of chronic HBV patients for whom the country of birth was known, were born abroad. The number of newly diagnosed chronic HBV infections in individuals born abroad is about 60 times higher than that in people born in the Netherlands (43 compared to 0.8 per 100,000 population). The number of notifications per country of birth fluctuates over time. In 2020, the most frequently reported countries of birth were Turkey (n=67, 10%), China (n=65, 9%), and Syria (n=36, 5%). Around 30 cases each were born in Suriname, Poland, Ghana, and Eritrea. Around half of the cases (49%) acquired chronic HBV infection through vertical transmission. In around one third (35%) of the reports of chronic HBV infection, the most likely route of transmission was unknown. Sexual contact was the source of infection for 2%, while for the remaining 9%, transmission may have occurred via other routes such as nosocomial transmission, needle stick injuries, or via injecting drug use (IDU).

Since 2003 serological evaluation of children from mothers with chronic HBV infection is recommended. In 2020, no chronic HBV infections were reported in children born in the Netherlands after 2003.

#### 6.3.4 Pathogen

Samples for genotyping are collected from all acute HBV infections, from chronic infections in MSM and individuals detected through the vaccination programme for behavioural risk groups. In 2020, samples of 51 acute HBV cases (54%) and 14 chronic HBV cases (2%) were available for molecular typing. In the preceding 5 years a sample was available from around 60 to 70% of acute HBV cases. The lower proportion in 2020 might be related to the increased workload in laboratories due to COVID-19. Polymerase Chain Reaction (PCR) amplification and sequencing gave results for 55 samples of HBV infections for the full-length genome. An optimised maximum parsimony tree of these sequences by most likely transmission route is shown in Figure 6.3.2. In 2020, 7 different genotypes were found (Genotype A-G). The largest cluster of cases continues to present among genotype A cases, the most common genotype for acute HBV in the Netherlands. Of acute cases with genotype information, 62% were genotype A. Genotype D was the second most commonly detected genotype among acute cases, (n=10, 20%). Genotype A was also most common among chronic cases in risk groups (6/9; 67%).

Since 2004, molecular HBV surveillance provides an impression of the different genotypes occurring in the Netherlands. The distribution of genotypes found in acute HBV cases in the period 2004-2020 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 10-27%). In addition, genotypes B, C, E and F are found in 3-6% of the samples. Genotype G and H are found sporadically (range 0-2 samples/patients (0-3%)). In 2019, a remarkable rise of genotype F was observed. The proportion of genotype F was 0-8% in the period 2004 to 2018, and 18% in 2019. 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. For part of the samples, it was possible to perform a complete genome analysis to identify subtypes and molecular clusters. In the past 17 years, 42 samples (40 acute hepatitis B and 2 chronic hepatitis B (2005 and 2019)) have been classified as genotype F (subtyping F1b n=40, F2a n=1, F3 n=1) by means of complete genome analysis. A 100% identical (n=17) or nearly identical (99.95%, n=5) subcluster was observed in 22 of the 40 F1b samples since December 2018. In 2018, 2019 and 2020, 1 of the 3, all 13 and all 6 subtype F1b classified as subtype F1b, respectively, belong to the same subcluster (Figure 6.3.4). Twelve of the 22 patients with viruses within the subcluster were reported in the province of North Holland, the other 10 cases were spread over 6 Municipal Health Services (Gemeentelijke Gezondheidsdiensten; GGD) regions in the provinces of South Holland, Gelderland, Brabant and Drenthe. Of the 21 acute hepatitis B cases, sexual risk (n=14) was most commonly cited as the most likely transmission route for 6 women, 4 men who had sex with men (MSM) and 4 heterosexual men. Seven subjects had an unknown risk.



## 6.3.5 Research

### 6.3.5.1 *Hepatitis diagnoses during the COVID-19 pandemic*

New chronic HBV and HCV diagnoses in 2020 were 40% lower than in 2019 and the weekly relative reduction mirrored weekly COVID-19 hospital admissions. Chronic viral hepatitis is mostly asymptomatic and often identified as part of the evaluation of non-specific symptoms. The decrease in chronic viral hepatitis diagnoses likely reflects missed opportunities for diagnosis due to a reduction in health-seeking behaviour during the COVID-19 pandemic [1].

### 6.3.5.2 *HBV vaccination programme for risk groups during the COVID-19 pandemic*

The number of first vaccinations administered 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 6.3.5 shows the monthly numbers of first vaccinations from 2016 up to July 2021. In February and March 2020, the number of first vaccinations among sex workers and MSM dropped sharply from around 400 to 50. In the three following months, the number rose again and it has been fluctuating between 200 to 300 vaccinations per month since then. The decrease in vaccinations was likely related to the COVID-19 pandemic.

### 6.3.5.3 *Mathematical modelling of HBV transmission among MSM*

Risk-group HBV vaccination for men who have sex with men (MSM) was introduced in the Netherlands in 2002, followed by universal infant vaccination in 2011. This will enable termination of risk-group vaccination over time. A mathematical model for HBV transmission among MSM was developed to investigate the impact of the transition from risk-group to universal HBV vaccination, accounting for improvements in HBV testing and treatment, as well as the introduction of pre-exposure prophylaxis (PrEP). Universal vaccination resulted in a 24% reduction in the total number of estimated HBV infections among MSM to occur between 2020 and 2070. In the model with universal vaccination, ending risk-group vaccination in 2030 or 2040 resulted in 30% or 10% more HBV infections over 2020-2070, respectively, compared to continuation of risk-group vaccination until 2070. With PrEP and continued risk-group vaccination, the total number of HBV infections over 2020-2070 was reduced by 13% [2]. Although universal HBV vaccination can lead to a major reduction in HBV incidence among MSM, efforts to maintain high levels of HBV vaccination, testing and treatment need to be continued in the next decade in order to eliminate HBV in this population.

### 6.3.5.4 *Evaluation of HBV vaccination programme for medical students*

The vaccination programme for medical students at Erasmus MC was evaluated in almost 3,000 students over a period of 7 years (2012-2019). Vaccination with Engerix-B at 0, 1 and 6 months was effective (surpassing the protection limit of 10 IU/L) in 98.8 percent of students (95% CI: (98.4-99.2)). In an additional cohort of students who completed a primary HBV vaccination series in the past, the strategy of administration of a booster vaccination prior to anti-HBs titre determination was compared with a new policy of a titre check at first presentation. As 80% of the students were still sufficiently protected and did not need a booster dose, the new policy turned out to be more efficient than the previous policy [3].

### 6.3.5.5 Characterisation of HBV

Analysis of HBV based on the complete genome is essential for public health surveillance, as it provides higher genetic resolution to conduct accurate characterisation and phylogenetic analysis of circulating strains and identify possible recombinants. Currently two separate assays are used for HBV surveillance; the S-gene for typing and the C-gene to gain insight in transmission patterns due to the higher genetic variation. Unfortunately, the C-gene does not enable accurate typing.

The Centre for Infectious Diseases Research, Diagnostics and Screening at RIVM developed a complete genome-sequencing assay to generate complete genomes of HBV and evaluated the assay for characterisation and analysis of HBV strains for HBV surveillance using samples collected from January 2017 to January 2020. The samples were obtained from acute and chronic cases with year of diagnosis 2017-2019 reported to OSIRIS. Analysis of the complete genome showed a high genetic resolution to enable both typing and transmission analysis. These analyses also enabled complete characterisation of a recombinant gC/gD strain not previously identified in the Netherlands [4].

### 6.3.6 Literature

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- 4.\* Benschop KSM, Cremer J, van Heiningen F, Veldhuijzen IK. Characterization of Hepatitis B virus based complete genome analysis improves accuracy and identifies a recombinant C/D strain. 23<sup>rd</sup> Annual Conference of the European Society for Clinical Virology; online 2021.

\* RIVM publication.

## 6.4 Human papillomavirus (HPV)

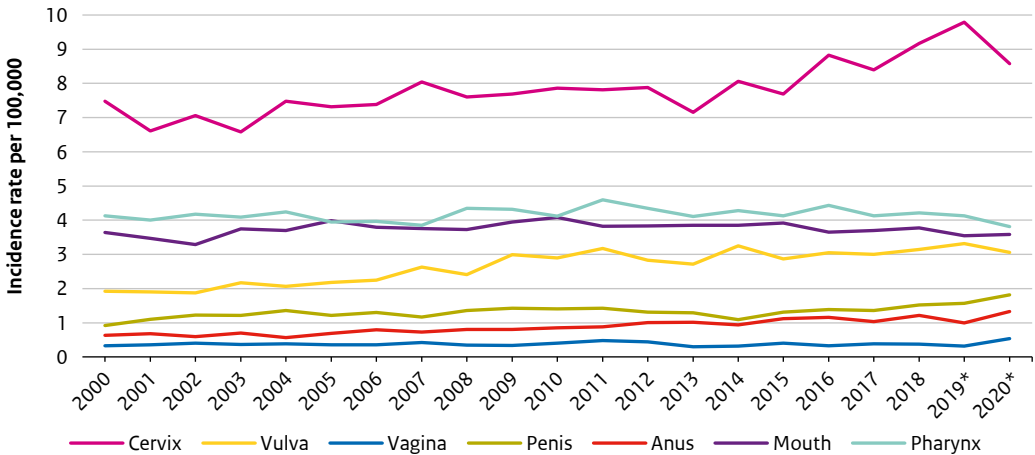


J.G.M. Brouwer, J. Hoes, K. van Eer, S. Mooij, A. Buisman, A.J. King, H.E. de Melker

### 6.4.1 Key points

- Vaccine effectiveness of the bivalent HPV vaccine against persistent vaccine type (HPV16/18) infections and persistent cross-protective type infections (HPV31/33/45) remained high at ten years after a three-dose vaccination schedule.
- Vaccine effectiveness of the bivalent HPV vaccine against incident vaccine type infections following a two-dose schedule was high up to five years after vaccination.
- A high seroprevalence and high antibody levels against vaccine-types HPV16/18 were observed up to 72 months following vaccination with the bivalent HPV vaccine with a two-dose schedule.

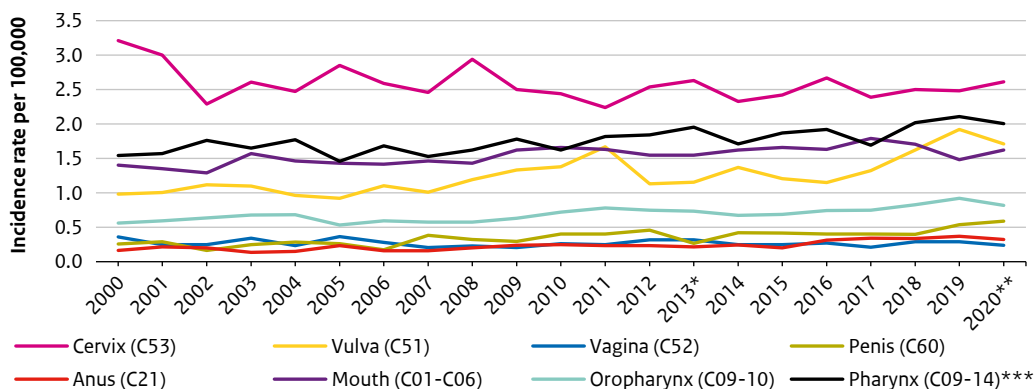
### 6.4.2 Tables and figures



**Figure 6.4.1** Incidence rates\*\* (per 100,000, standardised by European standardised rates) of cervical-, vulvar-, and vaginal cancer for women, penile cancer for men, and anal-, mouth/oral- and pharyngeal cancer for men and women in the Netherlands, 2000-2020.

\* Preliminary incidence rates.

\*\* Incidence rates were obtained from the Netherlands Cancer Registry, IKNL ([iknl.nl/nkr-cijfers](http://iknl.nl/nkr-cijfers), accessed April 20<sup>th</sup>, 2021).

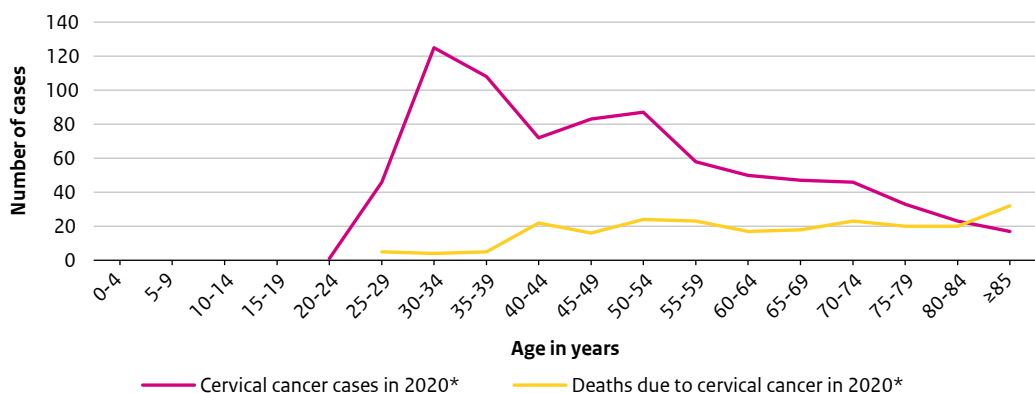


**Figure 6.4.2** Incidence rates per 100,000 of deaths related to cervical-, vulvar- and vaginal cancer for women, penile cancer for men, and anal-, mouth-, oropharyngeal- and pharyngeal cancer for men and women in the Netherlands, 2000-2020.

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

\*\* Preliminary incidence rates.

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



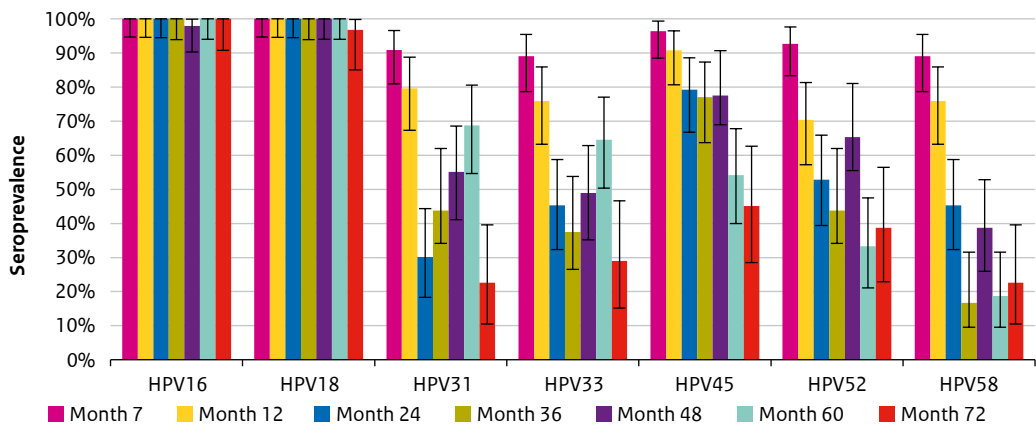
**Figure 6.4.3** Absolute number of newly diagnosed cervical cancer cases and absolute number of deaths due to cervical cancer in 2020\*.

\* Preliminary data.

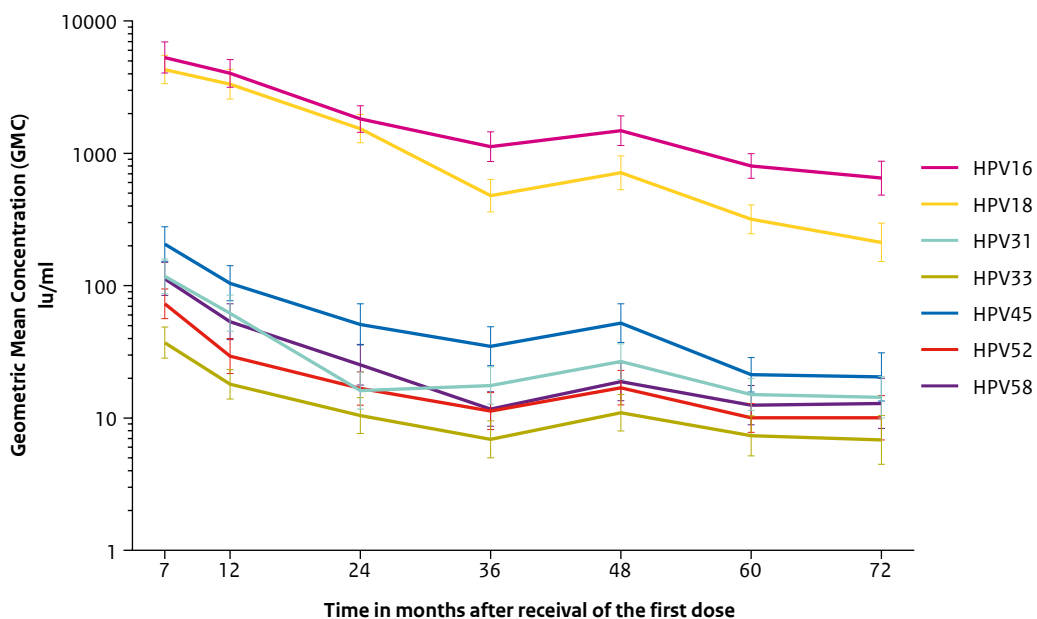
**Table 6.4.1** Vaccine effectiveness against incident and persistent HPV infections (12 months) in young women in the HAVANA study up to ten years post vaccination.

	Adjusted* VE (95% CI)	
	Incident infections	Persistent infections
Vaccine types (16/18)	78.8% (69.1-85.5%)	95.8% (86.6-98.7%)
Cross-protective types (31/33/45)	49.6% (31.6-62.8%)	64.7% (37.8-79.9%)
hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59)	9.3% (-1.8-19.3%)	21.7% (5.2-35.4%)
hrHPV types 9-valent vaccine (16/18/31/33/45/52/58)	32.3% (20.4-42.5%)	51.6% (35.8-63.6%)

\* VE adjusted for age, urbanisation degree, ever smoked, ever had sexual intercourse and ever used contraception.  
 CI: confidence interval.



**Figure 6.4.4** Seroprevalence among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36, 48, 60 and 72 months after the first dose.



**Figure 6.4.5** Geometric Mean Concentrations (GMC; IU/ml) among HPV2D participants of HPV types 16/18/31/33/45/52/58 following a two-dose schedule (0, 6 months) at 7, 12, 24, 36, 48, 60 and 72 months after the first dose.

### 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 (genital) HPV infections is asymptomatic and cleared or suppressed within 2 years after exposure [3-6], a persistent infection with a hrHPV can lead to the development of (pre)cancerous lesions in the anogenital and oropharyngeal areas. The most common cancer caused by persistent HPV infection is cervical cancer, for which a HPV infection is a necessary cause [7]. In 2020, cervical cancer was diagnosed in over 600,000 women and caused death in over 340,000 women globally [8]. 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 2020 ranged between 0.54 to 8.58 per 100,000 individuals, with the highest incidence rate of 8.58 per 100,000 women for cervical cancer and the lowest of 0.54 per 100,000 women for vaginal cancer (preliminary data, Figure 6.4.1). Mortality rates of cervical cancer reached 2.61 per 100,000 women in 2020 and 0.24 per 100,000 women for vaginal cancer (preliminary data, Figure 6.4.2). In absolute numbers, preliminary data in the Netherlands show that 2,159 women and 1,541 men were diagnosed with HPV-related cancers in 2020 [9] while 654 women and 484 men died of HPV-related cancers (CBS).

The non-oncogenic low-risk HPV types 6 and 11 can cause genital warts (GWs). In 2020, 882 sexual health clinic visitors in the Netherlands were diagnosed with GWs after a GW indication (positivity rate of 0.8% of all visits) [10]. Those warts were diagnosed in 314 women (0.7% of the visits by women), 378 heterosexual men (2.1% of the visits by heterosexual men) and 190 men who have sex with men (MSM; 0.4% of the visits by MSM). The absolute number of diagnosed GWs was lower compared with 2019 while the positivity rate was higher. At general practices, the number of GW episodes increased in 2019 to 46,871 with 2.3 and 3.1 episodes per 1,000 population in women and men, respectively.

#### 6.4.4 Current/ongoing research

##### 6.4.4.1 *The effect of viral load on the establishment of concurrent genital-anal HPV infections.*

HPV is the causative agent of about 90% of anal cancer cases. Women with a history of HPV-related genital lesions in particular are at increased risk of developing anal cancer. These women more frequently experience a concurrent HPV infection (i.e. the detection of an identical HPV type) in the genital and anal sites compared to lesion-free women. Therefore, a concurrent genital-anal HPV infection may impose an increased risk of developing anal cancer. We investigated the potential effect of viral load in the establishment of concurrent genital-anal infections with 14 HPV types, including 11 hrHPV types, with data of the PASSYON study. We also analysed the effect of the bivalent vaccine on the prevalence of concurrent genital-anal infections with the vaccine types (HPV16/18) and cross-protective types (HPV31/35/45). Our data show that the genital viral load of HPV types in concurrent genital-anal infections was often significantly higher than the viral load in genital-only infections. On the other hand, the anal viral load of HPV types in concurrent genital-anal infections was similar to the viral load in anal-only infections. Interestingly, the majority of anal HPV infections was concurrently present in the genital area. Moreover, nearly all concurrent genital-anal HPV types had significantly higher genital copy numbers than anal copy numbers. Therefore, our data indicate that the genital viral load is associated with establishment of concurrent genital-anal HPV infection. The impact of vaccination was most profound against concurrent genital-anal infections with HPV16/18 (vaccine types) and HPV31/35/45 (cross-protective types) compared to genital-only and anal-only infections with these types.

##### 6.4.4.2 *HPV amongst 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. The bivalent vaccine showed a statistically significant high VE against both incident and 12-month persisting vaccine-type infections (HPV16/18) up to ten years post-vaccination (79% and 96%, respectively). A high VE against cross-protective types (HPV31/33/45) was observed as well (50% and 65%, respectively). VE estimates up to ten years post-vaccination against incident and persistent infections are shown in Table 6.4.1.

Type-specific statistically significant VE up to ten years post-vaccination against 12-month persistent infection was found for HPV16 (95.2%, 95% CI: 84.5-98.5%), HPV18 (100%, model did not converge due to absence of infections among vaccinated), and HPV31 (75.0%, 95% CI: 47.5-88.1%). Statistically significant VE estimates against incident infections were found for the same HPV types with the addition of HPV45.

#### 6.4.4.3 HAVANA2

In 2016, a second prospective cohort study (HAVANA2) was started among vaccinated and unvaccinated girls (birth cohort 2001). These girls were the first eligible for the two-dose HPV vaccination schedule, which was initiated in 2014. Follow-up of this cohort is performed annually for at least five years, where the girls are asked to fill out a questionnaire and hand in a vaginal self-swab. Although the absolute number of HPV infections is still low, vaccine effectiveness against incident infections could be estimated using the first four years of data collection, i.e. until five years after vaccination. This resulted in a VE of 89.5% against incident HPV16/18 infections and 66.6% against HPV31/33/45 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 five years post-vaccination. These results are in line with findings from the three-dose schedule.

#### 6.4.4.4 Monitoring the immunogenicity of the two-dose schedule (HPV-2D)

To monitor the quality and quantity of the immune response generated following a two-dose vaccination schedule, a cohort study among the first birth cohort that was eligible for vaccination with a two-dose schedule, i.e. birth cohort 2001, started in 2014. Annually, girls donate a blood sample and fill in a questionnaire. To date, results were available up to the seventh round. These results showed high seroprevalence against vaccine types HPV16/18 up to 72 months of follow-up (91% for HPV16 and 85% for HPV18) (Figure 6.4.4). In the first 36 months after vaccination, a decrease in geometric mean concentrations (GMC) of HPV16/18 antibody levels was observed (Figure 6.4.5). Thereafter, HPV 16/18 antibody levels stabilised until 48 months after vaccination followed by a decrease up to 72 months after vaccination. HPV16/18 antibody levels were still high 72 months after vaccination with a GMC of 650 IU/ml and 213 IU/ml, respectively. Seroprevalences were considerably lower for HPV types 31, 33, 45, 52, 58 and, similar to HPV types 16/18, some waning of antibody levels for those HPV types was observed (Figure 6.4.4 and Figure 6.4.5).

#### 6.4.4.5 Characterisation of the early immune responses to vaccination in the EVI study

Early cellular immune reactions after HPV vaccination with either the bivalent or the nonavalent HPV vaccine was assessed in a pilot study (EVI study). Kinetics of circulating cells were related to the induction of long-term antibody and cellular memory responses upon vaccination. The numbers of plasma cells expanded in the first week after both primary and tertiary vaccination in both bivalent and nonavalent HPV vaccinees. HPV16 and 18-specific antibody levels and memory B and T cell responses were higher in the bivalent cohort than in the nonavalent vaccinees at one month after the third vaccination. For HPV31- and HPV45-specific antibody levels, this response was higher in the nonavalent vaccinees. The numbers of monocytes showed clear expansion at one day after vaccination in both cohorts but were



significantly higher in the bivalent vaccine cohort. A large heterogeneity in responses of the other cell subsets was observed between donors. This pilot study showed a consistent response of monocytes and plasma cells after vaccination and a large variation in other circulating immune cells in both types of HPV vaccines [11].

#### 6.4.4.6 *Implementation of gender-neutral vaccination*

The HPV vaccine for boys will be included in the NIP in 2022. This means that all children, boys and girls, will receive an invitation to get the HPV vaccination in the calendar year in which they turn 10. Furthermore, there will be a catch-up campaign in 2022 and 2023 targeting adolescents up to the age of 18 years to receive the HPV vaccine free of charge.

### 6.4.5 International developments

#### 6.4.5.1 *Global Strategy for the elimination of cervical cancer as a public health problem*

In August 2020, the World Health Assembly adopted the Global Strategy to accelerate the elimination of cervical cancer as a public health problem [12]. To eliminate cervical cancer as a public health problem, all countries must work towards a cervical cancer incidence rate below 4 per 100,000 women. To achieve this, the 90-70-90 targets should be met by 2030 and maintained thereafter for each country:

- 90% of the girls should be fully vaccinated by the age of 15 years;
- 70% of women should be screened twice-lifetime using a high-performance test;
- 90% of women with pre-cancerous lesions should be treated and 90% of women with invasive cancer should be managed.

#### 6.4.5.2 *Impact of HPV vaccination*

Real-world data regarding the impact of HPV vaccination on (pre-cancerous lesions of) cervical cancer is increasing. For instance, in the context of an organised cervical cancer screening programme in Italy, catch-up HPV vaccination almost halved the risk of cytological abnormalities [13].

Also in Denmark, the real-world effectiveness of HPV vaccination against cervical cancer was determined. Using nationwide registries, information on HPV vaccination and cervical cancer diagnoses were retrieved. The cohort comprised 867,689 women. At baseline, 36.3% were vaccinated at  $\leq 16$  years, and during follow-up, 19.3% and 2.3% were vaccinated between 17–19 and 20–30 years, respectively. For women vaccinated at  $\leq 16$  or between 17–19 years, the incidence rate ratios (IRRs) of cervical cancer were 0.14 (95% CI: 0.04, 0.53) and 0.32 (95% CI: 0.08, 1.28), respectively, compared to unvaccinated women. In women 20–30 years at vaccination, the IRR was 1.19 (95% CI: 0.80, 1.79) compared with unvaccinated women. This indicates HPV vaccine effectiveness against cervical cancer at the population level is high among girls vaccinated before age 20 years. The lack of immediate effect in women vaccinated at age 20–30 years points to the importance of early age at vaccination [14].

Pooled data from the Costa Rica Vaccine Trial and Papilloma Trial Against Cancer in Young Adults showed that efficacy of the 2vHPV vaccine against different clinical outcomes increased

with severity (irrespective of HPV type); ranging from 27.7% to 58.7% for cytologic outcomes (low-grade squamous intraepithelial neoplasia lesion or greater, and high-grade squamous intraepithelial neoplasia lesion or greater, respectively) and 66.0% to 87.8% for histologic outcomes (CIN2+ and CIN3+, respectively). High efficacy of the 2vHPV vaccine is presumably due to cross-protection against several nonvaccine HPV types [15].

The effectiveness of 1, 2 or 3 doses of (predominantly quadrivalent) HPV vaccine against HPV16/18-positive cervical intraepithelial neoplasia (CIN) grades 2+ was assessed in the US HPV Vaccine Impact Monitoring Project (HPV-IMPACT; 2008–2014) with a test-negative design. Among 3,300 women with CIN2+, 1,561 (47%) were HPV16/18-positive, 136 (4%) received 1 dose of HPV vaccine, 108 (3%) received 2 doses, and 325 (10%) received 3 doses. Adjusted odds ratios for vaccination with 1, 2, and 3 doses were 0.53 (VE = 47%), 0.45 (VE = 55%), and 0.26 (VE = 74%), respectively. This indicates a significant real-world VE against HPV16/18-positive CIN2+ after 3 doses of HPV vaccine and lower but significant VE with 1 or 2 doses [16].

Projections of the residual risk for cervical abnormalities after HPV vaccination are important in light of the integration of HPV vaccination and cervical cancer screening programmes. The lifetime (screen-detected) CIN3+ risk under five-yearly primary HPV screening between age 30 and 60 years was estimated, using data of women participating in a screening trial with two HPV-based screening rounds. The lifetime CIN3+ risk was 4.1% and decreased by 53.5% and 70.5% after bivalent vaccination without and with cross-protection, respectively, translating into a residual lifetime CIN3+ risk of 1.9% and 1.2%. The CIN3+ risk decreased by 88.5% after nonavalent vaccination, translating into a residual lifetime CIN3+ risk of 0.5%. This indicates that HPV vaccination will lead to a strong decrease in the lifetime CIN3+ risk and the remaining absolute CIN3+ risk will be very low. It also shows the importance of thoroughly evaluating the integration of vaccination and screening, especially in high vaccine uptake settings where de-intensification of screening could be considered [17].

#### 6.4.5.3 Nonavalent HPV vaccine

Long-term follow-up data on the nonavalent HPV vaccine (9vHPV) is becoming increasingly available. For example, a long-term study in young Scandinavian women aged 16–26 years was initiated to evaluate if vaccine effectiveness remained above 90%. Vaccine effectiveness was measured as percent reduction in the incidence of HPV16/18/31/33/45/52/58-related high-grade cervical dysplasia in the cohort relative to expected incidence in a similar unvaccinated cohort. No new cases of HPV16/18/31/33/45/52/58-related high-grade cervical dysplasia were observed during the study period over 4,084.2 person-years (up to 8 years post-vaccination). Thus, there were no signals indicative of vaccine effectiveness waning below 90%. These observations show that the 9vHPV vaccine provides continued statistically significant protection through at least 6 years, with indications of continued effectiveness through 8 years [18].

The pivotal 36-month Phase III immunogenicity study of 9vHPV vaccine in 9- to 15-year-old girls and boys was extended to assess long-term immunogenicity and effectiveness with data up to approximately 8 years of follow-up after vaccination. Seropositivity rates remained >90% through month 90 for each of the 9vHPV vaccine types. No cases of

HPV6/11/16/18/31/33/45/52/58-related high-grade intraepithelial neoplasia or genital warts were observed based on a maximum follow-up of 8.2 years after dose 3 of the vaccine. Incidence rates of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection in females and males were 49.2 and 37.3 per 10,000 person-years, respectively, which were within ranges expected in vaccinated cohorts. This indicates that, up to 8 years after vaccination with the 9vHPV vaccine, sustained immunogenicity and durable effectiveness is observed among both vaccinated girls and boys aged 9-15 years [19].

#### 6.4.5.4 Cost-effectiveness

Cost-effectiveness of a vaccine is one criteria in the decision-making process of funding health interventions [20].

##### 6.4.5.4.1 Gender-neutral vaccination

In the European response to the WHO call to reduce the cervical cancer incidence to less than 4 per 100,000 women, it is suggested that all European countries should achieve population-based HPV vaccination of girls, and also vaccination of boys if cost-effective [21].

In France, researchers evaluated the cost-effectiveness of a gender-neutral vaccination (GNV) compared with a girls-only vaccination (GOV) programme of the 9vHPV [22]. For cervical diseases, GNV was estimated to cost €24,763 and €40,401 per quality-adjusted life year (QALY) gained compared to GOV with a coverage rate of 26.2% and 60%, respectively. It is concluded that, based on the WHO recommended cost-effectiveness threshold of below 3 times the Gross Domestic Product (GDP) per capita, which is €113,979 for France, GNV is considered cost-effective in France.

##### 6.4.5.4.2 Extending (catch-up) age of vaccination

Apart from the discussion regarding GNV's cost-effectiveness, the cost-effectiveness of extending the (catch-up) age of vaccination was also evaluated in the United States (US). Chesson et al. [23] assessed the incremental costs and benefits of introducing the 9vHPV for those aged 27 to 45 years in the US. In the current vaccination programme, 9vHPV is a routine vaccination for adolescents aged 11 or 12 years and catch-up vaccinations are recommended for women and men through the age of 26 and 21 years, respectively. The cost-effectiveness of vaccinating individuals aged 12 through 45 years with 9vHPV (i.e. mid-adult vaccination) was compared with the cost-effectiveness of vaccinating women aged 12 through 26 years and men aged 12 through 21 years (i.e. comparison strategy). Mid-adult vaccination was estimated to cost \$653,300 per additional QALY gained compared to the comparison strategy. The incremental cost per QALY gained increased as the upper age cut-off for mid-adult vaccination increased. It was concluded that mid-adult vaccination is much less cost-effective than HPV vaccination of adolescents and young adults.

The cost-effectiveness of expanding the catch-up recommendations to 13-45 years instead of 13 through 26 years for women and 13 through 21 years for men was investigated in another US study by Daniels et al.[24]. The cost-effectiveness of the 9vHPV vaccine in an expanded catch-up programme that included vaccinating men and women aged 13-45 years (expanded catch-up) compared with vaccinating women aged 13-26 years and men aged 13-21 years (status quo). The incremental costs per QALY gained with the expanded catch-up was estimated to be

\$141,000. The incremental cost effectiveness ratio was \$117,000 per QALY for expanding the vaccination through age 34 years. It was concluded that the results support catch-up vaccination through the age of 34 years and shared clinical decision making through age 45 years.

Kim et al. [25] evaluated the cost-effectiveness of extending the upper age limit of 9vHPV vaccination in US men and women to the age of 30, 35, 40 or 45 years. Strategies to extend the age to 30, 35 or 40 years were less cost-effective than vaccinating up to 45 years. The incremental cost effectiveness ratio of extending the upper range to 45 years ranged from \$315,000 to \$440,600 per QALY, which exceeds the recommended threshold of \$50,000 to \$200,000 per QALY gained in the US. It was concluded that extending the vaccination strategy up to 45 years was unfavourable in the US context.

#### 6.4.5.4.3 Other

In Norway, a country with 89–90% HPV vaccination coverage among girls and boys, a modelling study was conducted to assess how the HPV vaccination and cervical cancer screening policy decisions have influenced the timing of cervical cancer elimination [26]. Additionally, the cost-effectiveness of the potential future policy of switching from the bivalent HPV vaccine (2vHPV) to 9vHPV was evaluated. With introduction of routine vaccination for 12-year-old girls using 4vHPV in 2009, it was predicted that the elimination goal would be reached by 2056. Subsequent changes in the vaccination strategy (i.e. temporary catch-up of women aged up to 26 years with 2vHPV; switching to 2vHPV and adding 12-year old boys to the routine vaccination programme) accelerated the time to elimination to 2048. Elimination was predicted to be reached in 2039 after switching from cytology to primary HPV-based cervical cancer screening. Switching from the use of 2vHPV to 9vHPV was estimated to cost \$174,500 per QALY gained. It was concluded that the cervical cancer policies implemented in the past may have accelerated the timeframe to elimination by more than 17 years. A potential switch to 9vHPV may not be cost-effective.

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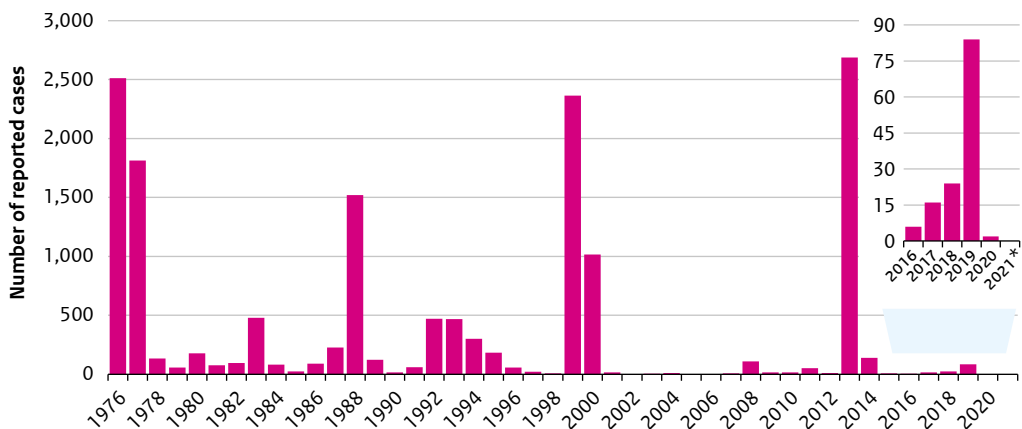
## 6.5 Measles

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 2020, only 2 measles cases were reported. No cases were reported in the first six months of 2021.
- The reduction in measles incidence is likely related to the COVID-19 pandemic.
- Genotype D8 was the only genotype detected.

### 6.5.2 Tables and figures



**Figure 6.5.1** Annual reported measles cases since the introduction of measles in the Dutch vaccination programme.

\* Up to and including June.

### 6.5.3 Epidemiology

After the outbreak of 2013/2014, the number of reported measles cases was less than 10 in 2015 and 2016, around 20 in 2017 and 2018, and relatively high with 84 in 2019. In 2020, only 2 cases were reported, with dates of onset in January and February (see Figure 6.5.1). The first patient had an unknown vaccination status and was infected with the measles virus in Romania. The second patient was an unvaccinated 3-year-old who was admitted to the hospital. The source of infection remained unknown for this patient. In the first half of 2021, no cases were reported.

The reduction in measles cases after the start of the COVID-19 pandemic is likely related to reduced travel and social-distancing measures [1].

#### 6.5.4 Pathogen

Measles virus genotype D8 was detected in both reported cases in 2020.

#### 6.5.5 Research

##### 6.5.5.1 *Molecular surveillance of measles virus*

Molecular surveillance of measles virus is an essential tool to demonstrate whether cascades of infections in a certain region or country are the result of endemic spread or repeated introduction of the virus. A study combining epidemiological data and sequence results of measles virus from 77 cases reported in the Netherlands in 2018 and 2019 describes a novel sequencing approach. The study shows that the current worldwide approach of sequencing a limited region of the genome does not provide enough resolution, but that sequencing additional regions is an efficient way to distinguish transmission chains and can improve molecular surveillance of measles virus [2].

#### 6.5.6 International developments

The number of reported measles cases in EU/EEA countries including the UK declined from over 13,000 in 2019 to around 2,000 in 2020. Of the cases reported in 2020, 94% occurred in the first four months of 2020 [3].

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\* RIVM publication.



## 6.6 Meningococcal disease

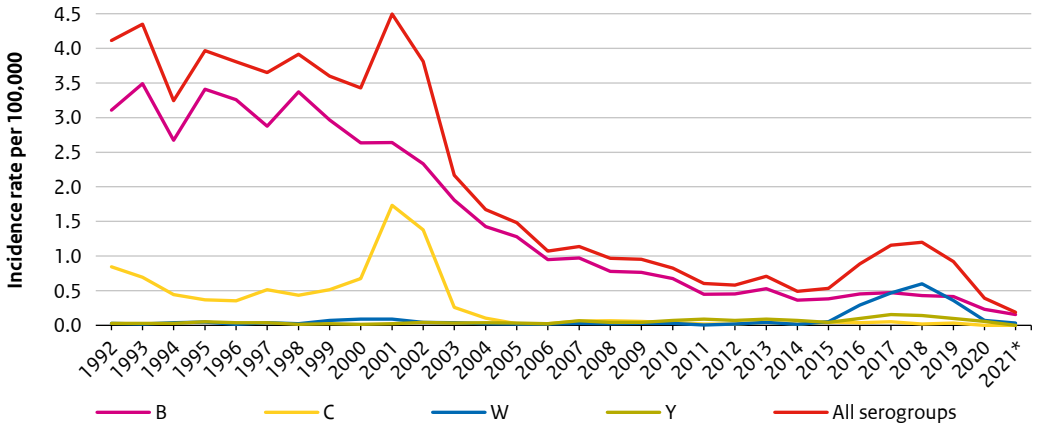


A. Steens, M.J. Knol, W. Freudenburg-De Graaf, G. den Hartog, M. Ohm, K Trzciński, W. Miellet, C. van Els, H.E. de Melker, N.M. van Sorge

### 6.6.1 Key points

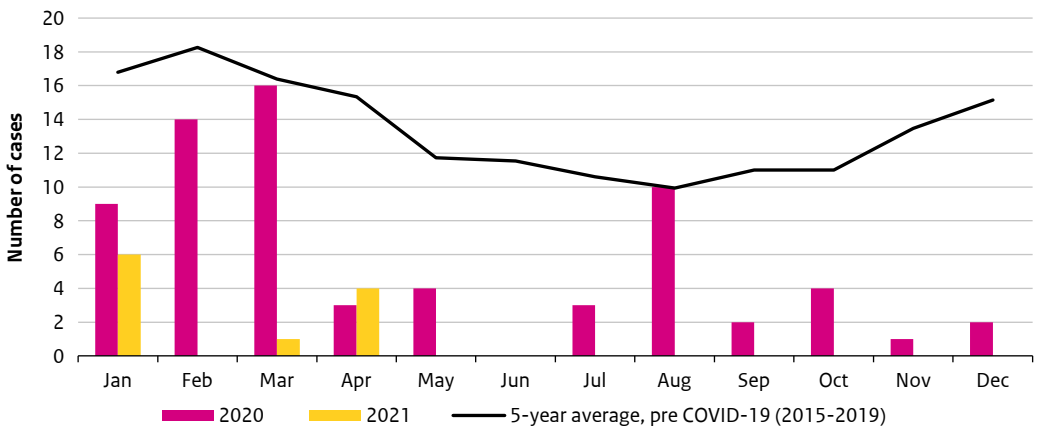
- After an increase in invasive meningococcal disease in the years 2015-2018 to 1.2 per 100,000, the incidence decreased to 0.39 per 100,000 in 2020 (n=68). In the first four months of 2021, only 11 cases were observed. In addition to MenACWY vaccination, COVID-19 control measures including social distancing likely play a role in this decline.
- While for the period up to and including 2018 meningococcal serogroup W disease (MenW) incidence increased, it has since decreased to 0.07 per 100,000 in 2020. In 2021, 2 cases occurred up to and including April compared to 8 cases in 2020 in that period.
- In 2020, incidence of invasive meningococcal disease caused by serogroup B (MenB) declined from about 0.5 per 100,000 to 0.23 per 100,000. Overall, MenB represented 59% of all meningococcal cases. While in 2016-2019, an increase was observed in the number of MenB cases with finetype P1.22,14:F5-1, no MenB cases with this finetype were reported in 2020-2021.
- In 2020 and in the first four months of 2021, no invasive meningococcal disease caused by serogroup C (MenC) cases were observed.
- Since May 2018 and January 2020, MenACWY vaccination at 14 months of age and in the year children turn 14 years of age, respectively, is included in the national immunisation programme (NIP). Furthermore, between October 2018 and June 2019, a catch-up campaign was organised for 14- to 18-year-olds. Overall MenW incidence dropped by 61% (95% CI: 40-74) after the campaign (July 1<sup>st</sup>, 2019 to March 31<sup>st</sup>, 2020) compared to the pre-campaign incidence (July 1<sup>st</sup>, 2017 to March 31<sup>st</sup>, 2018). The incidence decreased with 82% (95% CI: 18-96) in children 15-36 months and 14-18 years (vaccine-eligible age groups), and by 57% (95% CI: 34-72) in non-eligible age groups.

### 6.6.2 Figures

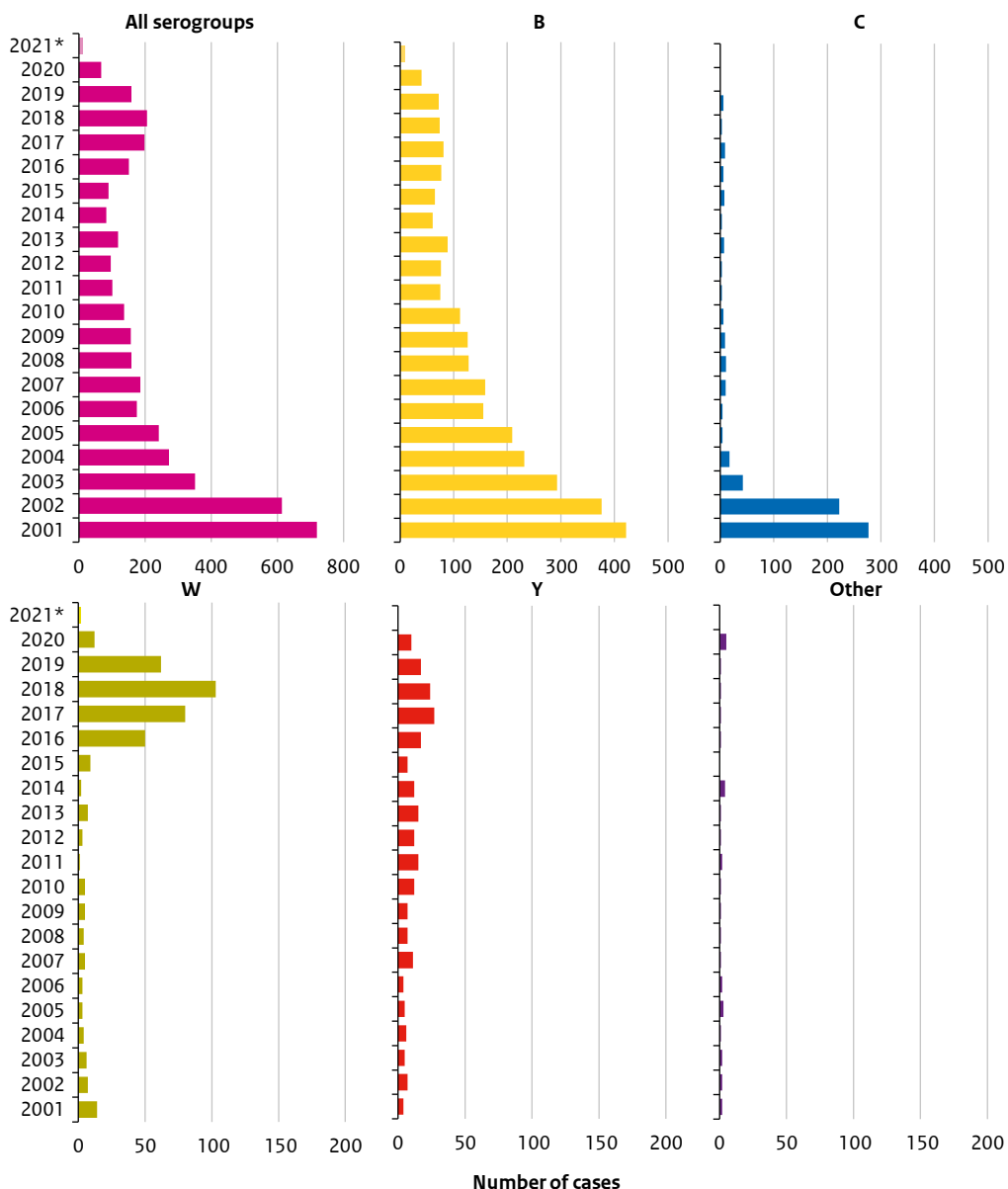


**Figure 6.6.1** Incidence of meningococcal disease by serogroup, 1992-2021\*.

\* Note that the incidence for 2021 is extrapolated based on data up to and including April.

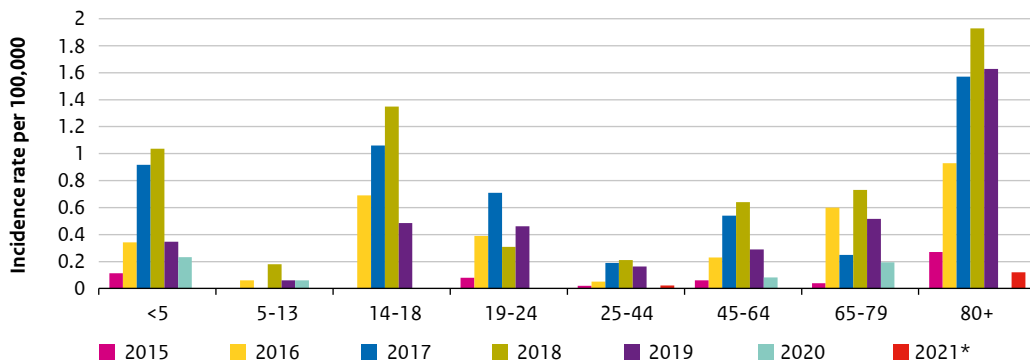


**Figure 6.6.2** Number of Men cases per month in 2020 (violet bars) and in the first four months of 2021 (yellow bars), as well as the pre-COVID 5-year average (2015-2019; black line).

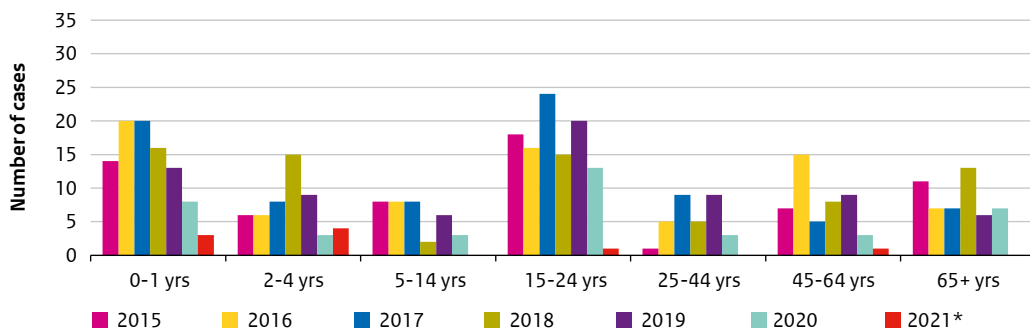


**Figure 6.6.3** Number of cases of meningococcal disease by serogroup, 2002-2021\*. Note the different scale in the graphs.

\* Up to and including April.



**Figure 6.6.4** Age-specific incidence of meningococcal serogroup W disease by year, 2015-2021\*. Due to the low numbers (overall n=2 in 2021), the incidence is not extrapolated to the full year. \* Up to and including April.



**Figure 6.6.5** Number of cases of meningococcal serogroup B disease by age group, 2011-2021\*. \* Up to and including April.

### 6.6.3 Epidemiology

#### 6.6.3.1 Meningococcal disease

The incidence of meningococcal disease declined from 4.5 per 100,000 in 2001 to 0.49 per 100,000 in 2014, after which it again to 1.2 per 100,000 in 2018. In 2020, the incidence decreased once again to 0.39 per 100,000 (see Figure 6.6.1). Except for August 2020, there were fewer meningococcal cases in all months compared to the previous 5-year average (see Figure 6.6.2). Although a clear decrease was observed in cases caused by meningococcal serogroup W (MenW), other serogroups also decreased (see Figure 6.6.3). COVID-19 control measures, including school closures, reduced social contacts, social distancing and increased hand hygiene, are a likely explanation for the observed decrease in meningococcal disease [1], as well as the introduction of MenACWY vaccination in the NIP. In the first four months of 2021 only 11 cases have been observed, which is 75% and 85% lower than in the same period in the two preceding years, respectively (n=70 in 2019 and n=42 in 2020; Figure 6.6.2).

#### 6.6.3.2 Meningococcal serogroup C

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 MenC disease cases decreased significantly from 277 in 2001 to an average of 6 cases per year from 2005 onwards (see Figure 6.6.3). The incidence decreased in all age groups due to herd protection and has remained below 0.1 per 100,000 since 2005 (see Figure 6.6.1). In 2020 and in the first four months of 2021, no MenC cases were observed.

Since the introduction of MenC vaccination, 16 MenC cases in age groups that were eligible for vaccination according to their date of birth (either for the 14-month programme or the catch-up campaign in 2002) were observed. Of these cases, seven were unvaccinated, five were vaccinated and for four cases the vaccination status was unknown. The five vaccinated cases were between 16 and 26 years old at diagnosis. Two of the patients had an underlying immune deficiency.

Since 2015, one patient with MenC disease has died, resulting in a case fatality rate of 3% (1/32).

#### 6.6.3.3 Meningococcal serogroup W

Since May 2018, MenACWY vaccination at 14 months of age is part of the NIP. Between October 2018 and June 2019, all children born between January 1<sup>st</sup>, 2001 and December 31<sup>st</sup>, 2005 (14- to 18-year-olds) were offered MenACWY vaccination in response to the increasing MenW incidence. Vaccination uptake during the vaccination campaign was 84% and an additional 2% of the population had been vaccinated prior to the campaign [2]. From 2020 onwards, MenACWY vaccination is offered to children in the year they turn 14 years of age as part of the NIP.

The incidence of MenW disease increased between 2015 and 2018, with a peak incidence of 0.60 per 100,000 in 2018 (n=103; Figures 6.6.1 and 6.6.3). In 2019, the incidence decreased to 0.39 per 100,000 (n=62); the decrease was seen in all age-groups (Figure 6.6.4). In 2020 and 2021, the incidence decreased further: in 2020 only 12 MenW cases occurred, resulting in an

incidence of 0.07; in 2021, 2 cases occurred in the period up to and including April compared to 8 cases in 2020 in that same period. Of the meningococcal cases in 2020/2021, 18% (n/N=14/79) were caused by serogroup W compared to 39% in 2019. This further decrease in 2020 and 2021 coincided with COVID-19 control measures in addition to the assumed effect of vaccination. Of the 14 MenW cases in 2020/2021, only two were eligible for vaccination.

The impact of the introduction of MenACWY vaccination on MenW disease was investigated by determining age group-specific incidence rate ratios (IRR) using the incidence before (July 1<sup>st</sup>, 2017 to March 31<sup>st</sup>, 2018) and after (July 1<sup>st</sup>, 2019 to March 31<sup>st</sup>, 2020) the campaign [3]. Overall, MenW incidence decreased by 61% (95% CI: 40–74). It declined by 82% (95% CI: 18–96) in children 15–36 months and 14–18 years (vaccine-eligible age groups), and by 57% (95% CI: 34–72) in non-eligible age groups. The MenW incidence reduction in non-eligible age groups may be caused by herd protection resulting from the vaccination programme. However, other factors may also have played a role as MenW incidence in non-eligible age groups was already in decline during the vaccination campaign and MenY incidence did not decrease in the same period in non-eligible age groups. Implementation of the COVID-19 control measures limited the follow-up period after MenACWY vaccination introduction as these measures probably also affected the number of cases as a result of reduced transmission.

Among children eligible for MenACWY vaccination at 14 months, there have been two MenW cases since the transition from MenC vaccination (both were two years old), of which one was vaccinated and one was unvaccinated. None of these cases occurred in 2020 or 2021. Vaccine effectiveness (VE) against MenW disease in this population was estimated using the screening method (see Appendix 1). VE was 92% (95% CI: -20–99.5) in 14-month-olds. Among adolescents who were eligible for MenACWY vaccination in 2018–2021, there have been no MenW cases. We can therefore conclude that the MenACWY vaccination programme was effective in preventing MenW in the target population.

Since 2015, 50 out of 311 (16%) MenW cases have died, with no deaths reported in 2020. Deaths occurred in nearly all age groups, with the highest case fatality rate in 14- to 24-year-olds (16/61=26%). One of the two MenW cases that were reported in the first four months of 2021 died.

#### 6.6.3.4 Meningococcal serogroup B

The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties and has stabilised at 0.5 per 100,000 since 2011 (see Figure 6.6.1). In 2020, MenB incidence declined further to 0.23 per 100,000 (n=40; Figure 6.6.3), which represents 59% of all meningococcal cases. In the period up to and including April 2021, 9 MenB cases were reported, compared to 21 in 2020 and 30 in 2019. This decrease in 2020–2021 is likely related to the COVID-19 control measures, resulting in reduced transmission. As in previous years the incidence of MenB disease in 2020 was highest in children under five years (1.3 per 100,000, n=11), followed by 15- to 24-year-olds with an incidence of 0.6 per 100,000 (n=13) (see Figure 6.6.5).

Since 2016, 17 out of the 347 (5%) MenB cases have died. There was one death among MenB cases in 2020-21 (2%), which is similar to before: in the last five years, 1-2 children under five years of age died of MenB disease annually. Case fatality rates did not differ between age groups (5% overall in the last five years).

Vaccination against MenB is available but not included in the Dutch NIP. To determine its potential to prevent MenB cases, the strain coverage is important. Strain coverage is determined based on whole genome sequencing and includes the match of the four vaccine antigens: Neisseria adhesin A (NadA), Neisserial Heparin-Binding Antigen (NHBA), fHbp, and porin A protein (PorA) of the outer membrane vesicles (OMV). Data from Dutch surveillance during the epidemiological years 2017-2019 showed that 39% (n=122) of meningococcal cases were caused by serogroup B, and 73% (95% CI: 64-80%) of these were covered by 4CMenB based on whole genome sequencing [4]. Strain coverage varied between age groups as the distribution of the different clonal complexes varied by age group. For 0- to 4-year-olds, 58% (95% CI: 43-72%) of isolates were covered, for the 15- to 24-year-olds this was 86% (95% CI: 68-96).

#### 6.6.3.5 Meningococcal serogroup Y

While the incidence of meningococcal serogroup Y (MenY) disease increased in the years 2015-2017 to an incidence of 0.16 per 100,000, the incidence decreased in the past two years to 0.06 per 100,000 in 2020 (n=10; Figure 6.6.1 and Figure 6.6.3). In 2020, 15% of all meningococcal cases were serogroup Y. As described above, it is likely that the COVID-19 control measures play a (possibly important) role in the decrease of MenY disease in 2020 and 2021. As in earlier years, most cases were adults aged 45 years or older (8/10 in 2020); no MenY cases occurred among children or adolescents who were eligible for MenACWY vaccination. In 2021 (up to and including April), no MenY cases have yet occurred, while in 2019 and 2020, 8 cases each had occurred in the same time period. Since 2017, 7 out of 90 (8%) MenY cases have caused the person to die.

#### 6.6.3.6 Other meningococcal serogroups

In 2020, one case due to meningococcal serogroup E (MenE), one case due to meningococcal serogroup X (MenX) and two cases of meningococcal disease due to non-groupable meningococci were reported. No serogroup A disease was observed. In the first four months of 2021, no meningococcal disease cases due to these serogroups were reported. Meningococcal disease due to serogroups X and E are rare in the Netherlands with eight and nine reported cases, respectively in the period 2001-2021. These serogroups are also sporadic in other European countries. Also meningococcal disease due to a non-groupable meningococcus is rare with 10 reported cases between 2001 and 2021 and occurs mainly in individuals with immune disorders, which was also true for one of the two cases in 2020.

#### 6.6.4 Pathogen

Within serogroups, the finetype is routinely determined based on the antigen sequence type of two variable regions of PorA and one variable region of the FetA protein. Furthermore, core genome multilocus sequence typing (cgMLST) is routinely conducted to study the

phylogeny of meningococcal strains and to sequence type (ST) meningococcal strains for seven housekeeping genes, which can be used to identify the genetic lineage (clonal complexes; cc) of a strain. CC is an identification that can be shared between different serogroups. In the period 2015–2020, almost all serogroup W strains had the same finetype P1.5,2:F1–1 (271/300; 90%) and belonged to clonal complex 11 (cc11; 262/276; 95%). When focussing on serogroup W cc11, the isolates in 2016 and 2017 seemed to cluster, while in later years (data from 2018 and 2019; due to the lower number of cases no data for 2020–2021 was included), there was no clear clustering anymore.

In 2016–2019, an increase was observed in the number of MenB cases with finetype P1.22,14:F5-1, which caused three MenB cases in 2016, twelve in 2017, seven in 2018 and 11 in 2019. In 2020 and 2021 for the period up to and including April, no MenB cases with this finetype were reported.

From 2017 to 2019, whole genome sequences were obtained of 337 meningococcal isolates. As described above, the vast majority of serogroup W isolates belonged to cc11 (95%). Among serogroup Y, cc23 was the dominant clonal complex (76%). Serogroup B isolates consisted of 11 different clonal complexes, with 84% of assigned isolates belonging to cc32 (32%), cc41/44 (21%), cc269 (15%), or cc213 (16%).

#### 6.6.4.1 Current/ongoing research at RIVM

Since teenagers and young adults are at an elevated risk of invasive meningococcal disease and are also considered to be the main reservoir of meningococci in the population, we investigated meningococcal carriage in college students in Utrecht in the fall of 2018 [5]. The objective was to assess vaccine-type genogroup carriage prevalence among teenagers and young adults at the time of MenACWY vaccine introduction in the Netherlands. Genogroups resemble serogroups but are determined by whole genome sequencing instead of serological tests. We also tested the feasibility of saliva sampling in studies on carriage. To this end, we applied conventional diagnostic culture and qPCR-based molecular methods to detect meningococci in paired saliva and oropharyngeal samples collected from 299 students at the University of Applied Sciences (Hogeschool) Utrecht. Altogether, 74 students (24% of 299) were identified as carriers of meningococci. The prevalence of genogroups A, B, C, W, and Y were 0%, 9%, 1%, 1% and 6%, respectively. Overall, 8% of students carried MenACWY vaccine-type genogroupable *N. meningitidis*. Meningococci were cultured significantly more often from oropharyngeal swabs (n=70 positives or 23%) than from saliva (n=54 positives or 18%; McNemar's test,  $p < 0.001$ ). The number of positive samples detected through qPCR was not significantly different between the two different samples: n=59 or 20% positive oropharyngeal swabs and n=52 or 17% positive saliva samples (McNemar's test,  $p = 0.07$ ). Although detection through qPCR was overall slightly lower compared to detection through culturing, the prevalence of meningococcal carriage detected with qPCR did not differ significantly between the different samples (oropharyngeal and saliva) and showed near-perfect agreement (96%; Cohen's  $\kappa = 0.88$ ). Easy-to-collect saliva combined with molecular detection of the pathogen can therefore be considered for meningococcal carriage studies.



Serosurveillance studies provide valuable knowledge on population immunity and support optimising national vaccination policies. Meningococcal serological status in the Netherlands was assessed in serum from the third cross-sectional population-based biobank collected in 2016-17 [6], 15 years after introduction of the MenC conjugate vaccination in the childhood immunisation programme alongside a large mass campaign for all children 1-18 years of age. A national sample (including oversampling of non-Western migrants) was drawn by sampling via a two-stage cluster technique, with age-stratified random sampling within each included municipality. Participants were 0-89 years of age at inclusion. Serum samples (n=5,552) were tested for MenA-, MenC-, MenW-, and MenY-polysaccharide-specific serum IgG concentrations, using a fluorescent-bead-based multiplex immunoassay (MIA). Functional MenC antibodies were determined for a large subset of serum samples (n=1,041) by using the serum bactericidal antibody (SBA) assay. Both MenC geometric mean IgG concentrations and prevalence of protective titres MenC bactericidal antibodies were low, except in recently vaccinated 14- to 23-month-olds and in young adults who were vaccinated at adolescent age in the MenC mass campaign in 2002. MenAWY IgG concentrations were low across all age groups. These findings show the lack of MenAWY immunity across the population in 2016-2017, but also the lack of MenC immunity in most age groups when only young children are vaccinated. It underlines the importance of the teenage MenACWY-TT booster vaccination that was implemented in 2018, which possibly provides long-term protection into adulthood.

MenC and MenACWY vaccination campaigns were launched after the MenC cc11 outbreak in 2002 and the cc11 MenW outbreak in 2018. The vaccination campaigns resulted in successful control of the outbreaks. Multiple clinical isolates of the MenC and MenW types of various cc/ST (amongst others ST8, ST11, ST22, ST167, ST865) and clinical background were collected from the NRLBM and tested in an SBA assay. In this assay, serum samples of 1 month after vaccination were used to test the ability of vaccine-induced antibodies to initiate complement-mediated killing of the invasive meningococcal bacteria. The vaccine-induced antibodies showed similar killing between the different isolates, and also compared with the default MenC and MenW isolates routinely used in the assay by various laboratories. These data confirm that the vaccine-induced antibodies mediate protection against the variety of genetically distinct isolates.

## 6.6.5 (Inter)national developments

### 6.6.5.1 Meningococcal carriage

Two different reviews that include the effect of meningococcal vaccination on MenB carriage were published last year: I, a systematic review of McMillan et al. including three studies on the effect of the 4-component recombinant MenB vaccine (4CmenB), two studies on the recombinant factor H-binding protein (fHbp) MenB vaccine (MenB-FHbp), and three studies on MenB outer membrane vesicle (OMV) vaccines [7], and II, a non-systematic summary of studies of routine 4CmenB use in Quebec, South Australia, the UK, Italy and Portugal [9]. Both included cross-sectional and cohort studies. The reviews came to the same conclusion, i.e. that none of the MenB vaccines protect against MenB carriage. McMillan et al. calculated a relative risk of group B carriage for 4CmenB of 1.12 (95%CI 0.90-1.40) and for MenB OMV vaccination of 0.98 (95% CI: 0.53-1.79).

Furthermore, the McMillan et al. review [7] also determined the protection of MenACWY vaccines to vaccine-group carriage compared to monovalent MenC vaccination. Eight MenACWY studies and two MenC studies were included; this included cross-sectional studies, a cohort study and an RCT. Note that the risk of bias due to confounding, misclassification of the intervention and missing data was serious. The researchers did not find an effect of MenACWY vaccination on vaccine-type carriage (relative risk 0.88 [95% CI: 0.66-1.18]) in contradiction to the monovalent MenC vaccines: relative risk for MenC carriage 0.50 (95% CI: 0.26-0.97). The lack of effect of MenACWY vaccines was still present when the analysis was restricted to the three studies that focused systematically on vaccine-type carriage (relative risk 0.87 [95% CI: 0.63-1.19]).

#### 6.6.5.2 Meningococcal disease

While meningococcal conjugate vaccinations induce functional protective antibodies, seroprotection wanes over time. Because meningococcal disease can develop very rapidly, the presence of antibodies (over immunological memory) is important. Functional antibody titres obtained in two phase-IV trials in the Netherlands were analysed five years after administration of a single-dose MenACWY-TT vaccine in adolescents and adults aged 50-65 years at time of vaccination [9]. The adolescents (10-15 years) had been primed with MenC-TT at 14 months and 3 years of age. The adults (50-65 years) were naïve to meningococcal vaccination. Based on the SBA assay, sufficient protection for MenC, MenW, and MenY was achieved in 94-96% of the adolescents five years postvaccination, but only for 32% for MenC, 65% for MenW and 71% for MenY in adults. The calculated duration of protection was 4, 14 and 21 years for MenC, W and Y for adults and 32, 98 and 33 years for the adolescents.

The systematic review and meta-analysis of McMillan et al. [7] determined the impact of meningococcal vaccines at reducing confirmed invasive meningococcal disease. The review included five studies on monovalent MenC vaccination, two on 4CMenB, five on OMV MenB vaccines and one on MenACWY (case-control studies, cross-sectional studies, interrupted timeseries and RCTs). The overall risk of bias due to confounding, misclassification of the intervention and missing data was considered serious. The estimated odds ratio for protection resulting from monovalent MenC vaccination against disease caused by MenC was 0.13 (95% CI: 0.07-0.23), from MenACWY vaccines against disease caused by MenACWY was 0.31 (95% CI: 0.20-0.49), and from OMV MenB vaccines against disease caused by MenB was 0.35 (95% CI: 0.25-0.48), thereby confirming that these vaccines protect against confirmed meningococcal disease.

#### 6.6.5.3 MenW disease

The epidemiology of invasive meningococcal disease caused by MenW in Denmark was analysed for the period 1980-2018 [10]. The study included 5,825 meningococcal disease cases. Overall, the incidence of meningococcal disease had decreased over the period, but the incidence of disease caused by MenW had increased since 2015. Age <20 years and ≥60 years was associated with more disease caused by MenW compared to the reference age group 20-39 years. Furthermore, W and Y had a higher case fatality rate than other serogroups, however, after adjustment for age, sex, and manifestation, they found that the 30-day mortality was similar for serogroups.

#### 6.6.5.4 MenB disease

4CMenB has been used in the NIP in several countries, among which the UK, Italy, Austria and South Australia, as well as privately at relatively good coverages in Spain and Portugal (roughly 30-50% [8]). An analysis of surveillance data of the UK showed a decrease in MenB disease among vaccine-eligible age groups for three consecutive years [11], and the trend continued in year 4 [12]. In Portugal, the use of 4CMenB in children younger than 18 years was examined in a matched case-control study with an incidence density design [13]. The aim of the study was to determine the association between receipt of 4CMenB and invasive MenB disease. They used ascertained vaccine status with 2-4 doses, depending on the age of the child, as exposure and confirmed MenB disease as outcome. They included 69 MenB cases and 142 controls. Five of the cases (7%) and 33 of 142 controls (23.1%) were fully vaccinated (OR: 0.21 [95% CI: 0.08-0.55]), corresponding to a vaccine effectiveness of 79%  $((1-OR)*100)$ . For all serogroup meningococcal disease, 6 of 85 cases (7%) and 39 of 175 controls (22%) were fully vaccinated (OR: 0.22 [95% CI: 0.09-0.53]; VE=78%). For group B disease, 8 of 82 cases (10%) and 50 of 168 controls (30%) received at least 1 vaccine dose (OR, 0.18 [95% CI, 0.08-0.44]; VE 82%) and for all serogroup disease, 11 of 98 cases (11%) and 61 of 201 controls (30%) received at least 1 vaccine dose (OR: 0.23 [95% CI, 0.11-0.49]; VE 77%). The study therefore concluded that vaccination with 4CMenB was less likely among children who developed invasive meningococcal disease compared with matched controls without invasive meningococcal disease.

In Italy, the recommendation for use of 4CMenB varies between regions. This allowed for an analysis of the impact of different vaccination schedules. Azzari et al. compared lab-confirmed invasive meningococcal disease in Tuscany (vaccination since 2014 at 2, 4, 6, 12 months) with invasive meningococcal disease in Veneto (since 2015, at 7, 9, 15 months) in an observational study [14]. Data and samples collected as part of routine clinical activity were evaluated retrospectively. The researchers evaluated the vaccine's impact by comparing the incidence rate ratios after versus before vaccine introduction in the regions. In Tuscany, 31 MenB cases before and 4 cases post-vaccination occurred among 0- to 5-year-olds, in Veneto this was 34 versus 7 cases. The study showed a larger overall impact of the programme in Tuscany (68% reduction (95% CI: 10-89)) taking into account both vaccinated and unvaccinated children, compared to 31% (95% CI: -56-69) in Veneto). VE was estimated using the screening method, yielding a VE of 93.6% (95% CI: 55.4-99.1) in Tuscany and of 91.0% (95% CI: 59.9-97.9) in Veneto. The study's results therefore indicate that 4CMenB has had a very high effectiveness in Italy. Although the point estimate was even higher than seen in other countries, the 95% CI: overlaps with those studies [11, 13]. The authors concluded that the impact of vaccination appeared greater where the immunisation program was started at younger age.

#### 6.6.6 Effect of COVID on meningococcal disease

Similar to the Netherlands [1], French surveillance data were analysed for the effect of SARS-CoV-2 on other (respiratory) diseases [15]. The researchers used data from the French National Reference Centre for meningococci and *Haemophilus influenzae* for the periods January up to and including May 15<sup>th</sup>, for the years 2018, 2019 and 2020. As in the Netherlands, they observed fewer cases during the lockdown period (n=23) compared to the same period in preceding years (2018: n=73, 2019: n=68). The decrease was especially noticeable among

the hyperinvasive isolates; serogroups B, C and W, but not Y and other serogroups or non-groupable isolates. However, the researchers also found that IMD cases that were associated with respiratory presentations (pneumonia or bronchopneumonia) significantly increased in 2020 (n=18) compared to 2018 (n=13; p=0.029) and 2019 (n=7; p=0.002). This increase involved elderly and was due to unusual isolates.

The Invasive Respiratory Infection Surveillance (IRIS) Initiative on pneumococci, *H. influenzae*, and meningococci was used to determine the incidence of invasive disease due to these pathogens during the early months of the COVID-19 pandemic [16]. The study compared the weekly number of cases in 2020 with corresponding data for 2018 and 2019 and used the Oxford COVID-19 Government Response Tracker [17] for information on the stringency of COVID-19 control measures. For meningococcal disease, the analysis included data of 5,877 cases from 21 countries. As described for pneumococci and *H. influenzae*, all countries experienced a clear reduction in IMD coinciding with the introduction of COVID-19 control measures in each country.

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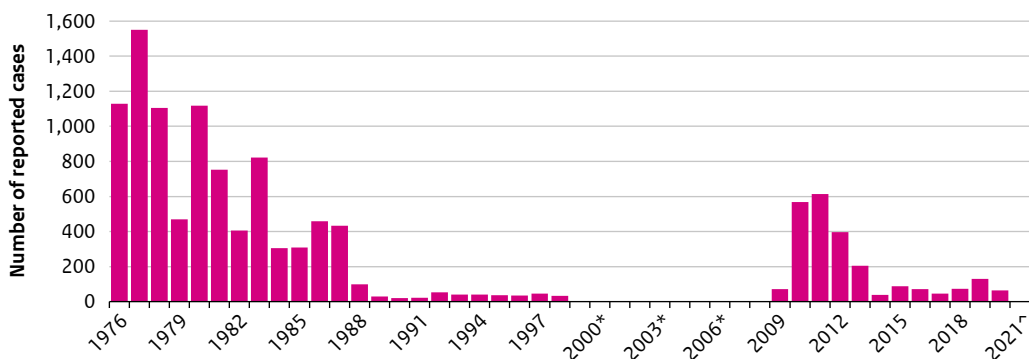
## 6.7 Mumps

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### 6.7.1 Key points

- The incidence of mumps in 2020 was low (0.4 per 100,000, 64 cases in total). A sharp decrease was seen from 1 April 2020, which coincided with control measures that were put in place in response to the COVID-19 pandemic.
- Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

### 6.7.2 Tables and figures



**Figure 6.7.1** Number of notified mumps cases in the period 1976–2021.

\* In the period 1999–2008, mumps was not a notifiable disease.

^ Cases for the period up to and including June.

Source: Osiris.

### 6.7.3 Epidemiology

Following the introduction of mumps vaccination in the NIP in 1987, a substantial decline was observed 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) [1]. Since 2012, the number of reported mumps cases among students has declined in the Netherlands.

In 2020, 64 cases of mumps were reported (Figure 6.7.1). The year started off with a higher number of cases per month compared to Q1 2019 (n=30), and reached a total of 61 cases in Q1 2020. In early March 2020, nationwide control measures were put in place in response to the COVID-19 pandemic and from 1 April 2020, a decrease in the number of mumps notifications was observed. As the average incubation period for mumps is between 16 and

18 days, this shows that the decrease coincided with the implementation of the control measures. Samples from suspected mumps cases were still submitted for laboratory diagnostics after March 2020, indicating a possible decrease in health-seeking behaviour might have contributed only partly to the decrease in mumps cases. In 2021, for the period up to and including June, no cases of mumps were reported.

In 2020, more cases were male (59%), and the mean age was 27 years (range 2-70). Eighteen students (31%) were reported with mumps. Forty-five cases (73%) were vaccinated; 7 (16%) with one dose, 35 (78%) with two or more doses of vaccine, and 3 (7%) were vaccinated with an unknown number of doses. The vaccination status was not known for the two remaining cases. Four cases reported orchitis, all were vaccinated and two were hospitalised.

Twenty-three percent of the cases (n=15) acquired the infection abroad and country of infection is unknown for three persons. In 2020, eight clusters including 21 patients in total were identified. The clusters consisted of two to four individuals. Three of the eight clusters included one or more persons who travelled abroad and were most likely imported cases.

#### 6.7.4 Pathogen

In the past decade, most mumps cases in the Netherlands were caused by infection with genotype G mumps viruses. In 2020, a genotype was obtained from mumps viruses detected in 40 cases. All but one of these cases were genotype G, the other case was genotype C. The case with genotype C was likely infected in Suriname.

#### 6.7.5 Research

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

##### 6.7.5.1 Molecular surveillance

Improved molecular surveillance using sequence data with a higher resolution on mumps genotype G viruses revealed that two major genetic lineages were present in 2017-2019 [2]. This indicates that mumps genotype G viruses continued to circulate in the Netherlands and surrounding countries in these years. Comparison of phylogenetic trees prepared by analysis of SH+NCRs and near complete genomes indicated that the topologies of both trees were similar, while branches lengths were different. Therefore, analysis of SH+NCRs sequences is a useful approach for molecular surveillance. However, to study exact transmissions trees, preferably complete genomes are analysed. This can be helpful to support epidemiological data or show transmission links that cannot be identified by epidemiological data. From October 1<sup>st</sup>, 2019 to March 31<sup>st</sup>, 2020, 14 epidemiological clusters (including 46 cases) were identified where two or more cases met the mumps notification criteria and had an epidemiological link to a confirmed case with a date of symptom onset between this period. Twelve molecular groups could be distinguished, of which the two largest groups included cases from respectively 3 and 4 epidemiological clusters. Overall, 21 of 71 (30%) epidemiologically and/or molecularly-associated cases were identified solely through epidemiological information, 25 (35%) were identified solely from molecular surveillance, and 25 (35%) were identified using both [3].

### 6.7.6 International developments

An outbreak among adolescents and young adults (median age 20 years) was described in Ireland in 2019 and the first quarter of 2020 [4]. Vaccination status was known for 32% of the cases and of those, 72% received two doses of MMR vaccine. In addition to factors such as shared housing and crowded social environments, the authors mention the historical low uptake of MMR vaccine in the early 2000s (70-75%) as an explanation for the outbreak. Similar to the Netherlands, the outbreak declined in early April 2020 as a result of COVID-19 control measures.

A study from the US using molecular analysis showed how repeated introductions fuelled an outbreak in the Marshallese community in Washington [5].

### 6.7.7 Literature

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\* RIVM publication.



## 6.8 Pertussis

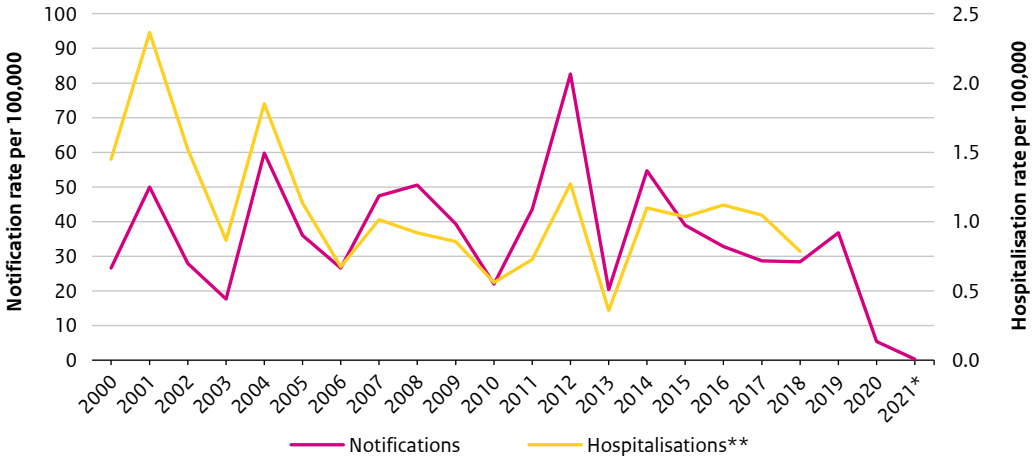
D.L. van Meijeren, A. Buisman, N. Rots, P. Versteegen, C.A.C.M van Els, R. Mariman, E. Pinelli Ortiz, H.E. de Melker, N.A.T. van der Maas



### 6.8.1 Key points

- In 2020, the overall number of pertussis notifications and the incidence rate (IR) were 943 and 5.4 per 100,000, respectively. This is considerably lower than in 2019, when the overall number of notifications and the IR were 6,361 and 36.8 per 100,000. The lower number of notifications was probably due to COVID-19 control measures.
- Since the IR decreased in all age categories, including in infants, it is difficult to detect a potential impact of the maternal pertussis vaccination on the IR in 0- to 5-month-olds at this time.
- In 2021, for the period up to and including April 30<sup>th</sup>, only 17 cases of pertussis were notified. This low number was probably also due to COVID-19 control measures.
- Between April and December 2020, eight pertussis cases in 0- to 3-month-olds were reported. Of these, three infants had received maternal Tdap vaccination. Using an estimated maternal vaccination coverage of 70%, vaccine effectiveness was estimated at 74% (95% CI: -32 to 96%).
- Among Dutch individuals aged  $\geq 7$  years, seroprevalence of IgG antibody levels above 100 IU/ml, indicating a recent pertussis infection, as measured in the PIENTER 1- and PIENTER 2 study, increased from 1.0% in 1995/1996 to 3.5% in 2006/2007. The PIENTER-3 study in 2016/2017 showed that the seroprevalence of IgG antibody levels  $>100$  IU/ml increased to 5.9%.
- A seroprevalence study in 18 European countries among 40- to 60-year-olds conducted by the RIVM showed that circulation of *B. pertussis* is widespread.
- In-depth analysis of the natural humoral immune response to *B. pertussis* suggests an altered role for IgA at older adult age.
- Recent RIVM data shows that newly circulating *B. pertussis* strains express a different set of proteins compared to older strains and that they induce distinct immunological pathways in innate immune cells.

### 6.8.2 Tables and figures

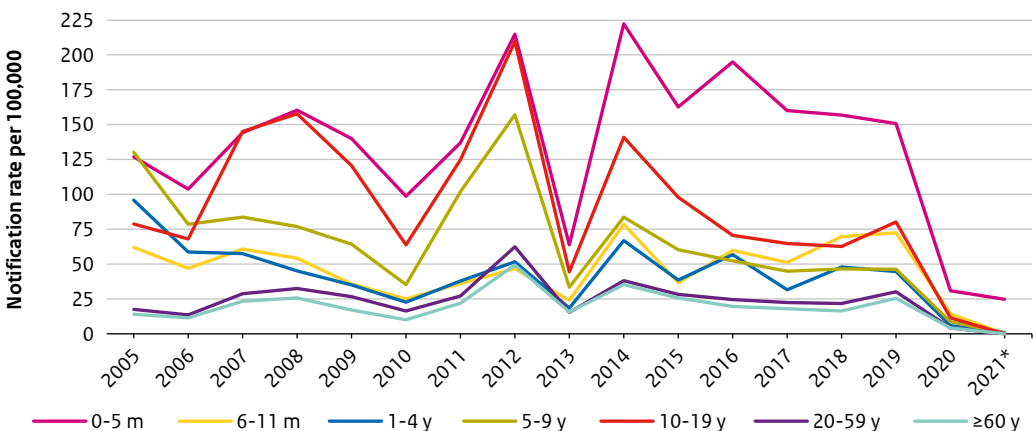


**Figure 6.8.1** Pertussis notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 2000–2021\*.

\* For 2021, notifications are depicted for the period up to and including April 30<sup>th</sup>, extrapolated to numbers for a whole year.

\*\* No hospitalisation data from 2018 onwards are available yet.

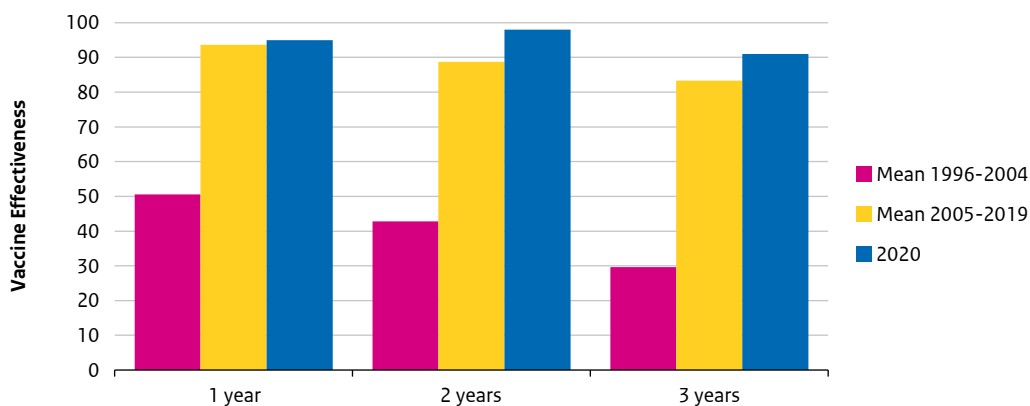
Source: Osiris, Statistics Netherlands.



**Figure 6.8.2** Pertussis notifications per 100,000 per age category for 2005–2021\*.

\* For 2021, notifications are depicted for the period up to and including April 30<sup>th</sup>, extrapolated to numbers for a whole year.

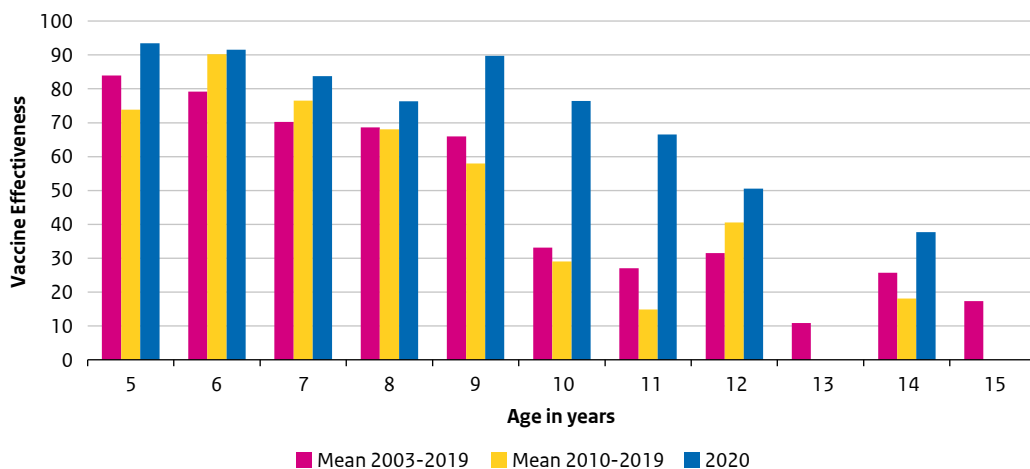
Source: Osiris.



**Figure 6.8.3** Vaccine effectiveness of the 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 separately).

\* A population coverage of 94% was used for 2017, and 93% for 2018, 2019 and 2020. For all other years, a population coverage of 96% was used.

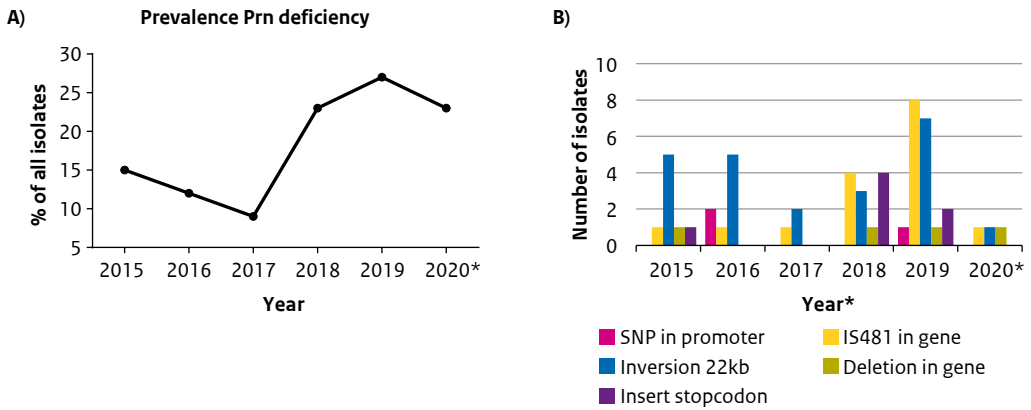
Source: Osiris, National vaccination coverage report [1].



**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 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.

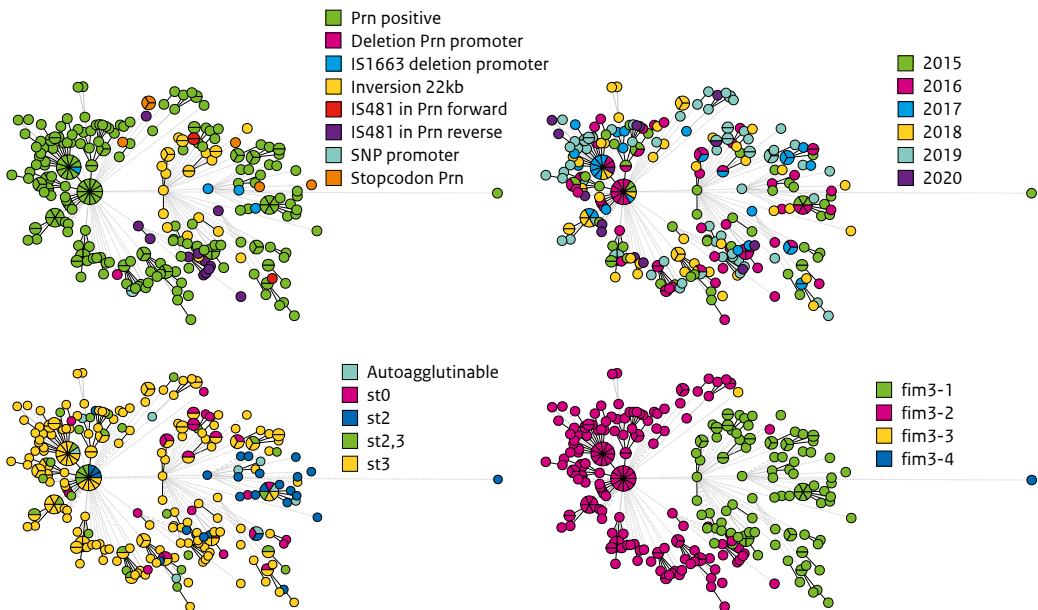
Source: Osiris, National vaccination coverage report [1].



**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.



**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, up to and including May, no isolates were sequenced.

### 6.8.3 Epidemiology

#### 6.8.3.1 Disease

In 2020, the overall number of pertussis notifications and the incidence rate (IR) were 943 and 5.4 per 100,000, respectively. These amounts are considerably lower than in 2019, when the overall number of notifications was 6,361 and the IR 36.8 per 100,000 respectively (Figure 6.8.1). The drop in the number of notifications was probably due to COVID-19 control measures.

In all age categories, the IR dropped by at least 80% compared with 2019. The IR was lowest in persons aged 60 years and older at 4 per 100,000. The IR remained highest in 0- to 5-month-old infants (30.7 per 100,000) (Figure 6.8.2).

In 2021, for the period up to and including April 30<sup>th</sup>, 17 cases of pertussis were notified, six of which in infants. For all six infants, *B. paraptussis* was the reported pathogen. From November 2020 up to and including April 30<sup>th</sup>, 2021, we received a remarkably high number (8) of notifications from one particular area concerning infants or children aged <2 years where *B. paraptussis* was reported as the pathogen. Most of these children were either admitted to one particular hospital, were born there, and/or had been hospitalised there since birth. Screening of parents and hospital staff to identify the source revealed an abnormally large number of positive results, after which the liquids in the tubes and the associated e-swabs were tested. From these unused swabs, 2 out of 7 lot numbers tested positive, indicating contamination. Cultures of the swabs remained negative, which is not unexpected since the swabs are supplied sterile for use. However, this does not mean that residual DNA cannot be present. From 8 notifications related to this area/hospital, 3 notifications in infants were withdrawn due to a proven false-positive result. For the other 5 infants and young children in this area, it is unclear which proportion was truly infected with *B. paraptussis*. From another area, we received 3 notifications between November 2020 and April 30<sup>th</sup>, 2021, concerning infants or young children where *B. paraptussis* was reported as the pathogen. The remaining notifications came from different areas in the Netherlands.

#### 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. Therefore, from April 2020, infants of 0-3 months were eligible for maternal vaccination. Between April and December 2020, eight 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% [1], VE was estimated at 74% (95% CI: -32 to 96%).

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 separately). Since the switch from whole-cell pertussis vaccine to an infant combination vaccine with an acellular pertussis component in 2005, the VE estimate has been consistently high up to the booster vaccination given at 4 years of age.

Following the booster dose at 4 years, the VE estimate shows a decrease after ~5 years, i.e. when children reach the age of 10 years (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 (Figure 6.8.2). In 2020, the vaccine effectiveness estimates for 9-, 10- and 11-year-olds were higher than the mean estimates in 2010–2019. It should be noticed that the number of notifications in 2020 was relatively low, probably as result of COVID-19 control measures relating to the COVID-19 pandemic.

The VE estimates described above have been calculated with the ‘screening method’. This is a rather crude method to estimate VE and is merely used here to study trends in VE estimations. See Appendix 1 on surveillance methodology for details of the screening method.

#### 6.8.4 Pathogen

To study possible adaptations of the bacteria, Dutch medical microbiology laboratories are asked to submit their *B. pertussis*-suspected samples to the RIVM. The strain surveillance focuses on changes in the genotype and phenotype of the *B. pertussis* family in the Netherlands. Confirmed *B. pertussis* strains are whole genome sequenced (WGS) and an antigen expression validation assay is performed for the pertussis antigens; pertussis toxin (Ptx), pertactin (Prn), and filamentous hemagglutinin (FHA).

After week 16 of 2020, COVID-19-related restrictions in society resulted in a sudden and dramatic drop of pertussis notifications reported after diagnostic confirmation. We therefore received just a minor fraction (n=9) of the expected *B. pertussis* isolates in our surveillance programme. In 2021, for the period up to and including June 13th, no strains were received for strain surveillance. We expect an increase in the number of isolates due to the easing of COVID-19 control measures in the second half of 2021.

In the Netherlands, the NIP makes use of an acellular pertussis vaccine consisting of three pertussis antigens, i.e. Ptx, FHA and Prn. The re-emergence of pertussis has been attributed to several factors, including bacterial strain adaptation due to vaccine pressure [2]. Therefore, careful monitoring of the expression of vaccine targets, in particular Prn, by the bacteria is essential. A high frequency of Prn- or FHA-deficient *B. pertussis* isolates could be prognostic for vaccine evasion, leading to an increase in pertussis cases.

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 rise 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 (n=23) cause of Prn deficiency, 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 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 in view 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 Research

### 6.8.5.1 Immunology

#### 6.8.5.1.1 Maternal pertussis vaccination

In the MIKI study, a group of pregnant women received Tdap at 30-32w GA and was compared with a control group of unvaccinated pregnant women. Memory B and T-cells were determined in the infants of both groups pre and post booster vaccination at 11 months of age. Numbers of antigen-specific B-cell and T-cells were detectable one month post booster and were not affected by the maternal vaccination [3]. The pertussis booster vaccination at 4 years of age resulted in a significant IgG antibody response against pertussis antigen Pertussis Toxin (PTx) that was comparable between the maternal vaccination and the control group. The PTx IgG geometric mean concentration (GMC) at 4 years for the maternal group was, however, still lower than for the control group (Barug et al., manuscript in preparation).

#### 6.8.5.1.2 Humoral immunity

In a population-based cross-sectional serosurvey (PIENTER study), pertussis seroprevalence was studied in a representative sample of 7,621 Dutch residents (0-89 years). Individuals  $\geq 7$  years of age with pertussis toxin concentrations of 100 IU/ml and higher are considered seropositive for a recent pertussis infection. Between 1995/1996 and 2006/2007, an increase from 1.0 to 3.5% seropositivity was found, and the current study shows a further increase in seroprevalence from 3.5 to 5.9%. More than a threefold increase, towards 11.5% in the current study, was observed since 2006/2007 among 12- to 18-year-olds. The increase in this specific age cohort might be related to the last two pertussis epidemics in 2012 and 2014. An increase in 7- to 11-year-olds was also observed. This increase might be caused by their acellular vaccination background compared to a whole cell vaccination background in older individuals. To prolong vaccine-induced protection in this age cohort, the preschool booster, currently given at the age of 4, might be delayed to induce longer protection. Individuals 50-64 years of age showed an increase in seropositivity as well, but the proportion is still smaller compared to 7- to 18-year-olds [4].

In a natural infection study, Immfact, humoral immune responses to *B. pertussis* antigens in serum and saliva samples, collected from 3 months up to 3 years post-diagnosis, were compared between older pertussis cases and cases from younger age groups. Notably, while early as well as long-term IgG levels did not differ between older adults and younger adults and adolescents, older adults had significantly higher IgA levels at all time points. This likely reflects repetitive exposure during life, but also indicates that IgA responses to *B. pertussis* may play an altered role at older age.

In another study performed by the RIVM (BERT-study) in collaboration with Oxford and Turku, vaccine antigen-specific IgG and IgA antibody responses were compared between school-aged children, adolescents, young and older adults before, 28 days after and 1 year after the booster

vaccination. IgG responses in older adults were not inferior compared to the other groups and IgA responses were superior [5].

#### 6.8.5.1.3 *Innate and adaptive immunity to B. pertussis*

Despite vaccination, 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 mechanisms explaining why both natural infection and the previous whole cell pertussis vaccine (wP) induce a far more effective and durable immune response than the current acellular vaccine, are being studied in detail in a PhD project. Priming of IFN $\gamma$  and IL-17-type cellular immunity and avoidance of IL-4/IL-13 type cellular immunity seems to be crucial in durable protection to pertussis, and therefore an important hallmark for future improved pertussis vaccines, as recently reviewed [6]. Insight was gained into how *B. pertussis* can interact with local innate immune cells and epithelium cells to modulate subsequent cellular immunity. In order to get a better understanding of the mechanisms underlying innate immunity to *B. pertussis*, we developed in vitro culture systems using, among others, human airway epithelial cells and neutrophils. These tools allow us to investigate host-pathogen interactions and cellular communication in response to *B. pertussis* during the early events of infection. By using a multi-omics approach including transcriptomics and proteomics, we recently demonstrated that newly circulating *B. pertussis* strains express a different set of proteins compared to older strains and that they induce distinct immunological pathways in innate immune cells [7]. These findings help understand the re-emergence of pertussis in vaccinated populations and highlights the importance of considering pathogen adaptation in the design of new-generation pertussis vaccines.

#### 6.8.6 International developments

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria, and tetanus in the age groups 40-60 years was funded by ECDC and conducted by the RIVM. Eighteen countries participated and collected the requested sera (around 500 samples). Measurement of antibody levels against pertussis toxin (PT), diphtheria toxoid (DT), and tetanus toxin (TT) with the Multiplex Immunisation Assay (MIA) was completed, resulting in a final database of around 30,000 values. The percentages of sera per country with a level for IgG-PT  $\geq 100$  IU/mL, indicative of a recent pertussis infection, varied between 1.8% (Finland) and 9.4% (Norway) with 13 out of 18 countries showing a level between 4.0% and 6.4%. Of the samples from the Netherlands, based on the PIENTER-3 serosurvey, 5.4% had IgG-PT concentrations  $\geq 100$  IU/ml. In addition, the GMCs of IgG-PT antibodies varied between 7-15 IU/mL in all countries, suggesting that the epidemiological situation for pertussis across the EU/EEA is broadly similar. This cross-sectional retrospective seroprevalence study among middle-aged adults in 18 European countries showed that the circulation of *B. pertussis* is widespread despite highly implemented childhood vaccination programmes [8].



The Periscope consortium, consisting of pertussis experts from two vaccine companies, four national institutes including the RIVM, and sixteen European universities, 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 acellular pertussis vaccines, the whole-cell pertussis vaccines, and natural infection, and to characterise new biomarkers for protective immunity to *B. pertussis*. The role of the 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. An assay for the measurement of specific memory and plasma B cells was standardised and applied to show that colonisation is an immunising event in a novel human experimental infection model based on the well-characterised RIVM-originating *B. pertussis* isolate BP1917 [9]. Additionally, the consortium developed a highly standardised platform technique to monitor CD4 T-cell dynamics in whole blood after vaccination or infections [10].

Kandeil et al. [11] conducted a systematic review to study the effectiveness of maternal Tdap vaccination for the prevention of pertussis in 0- to 2-month-olds and 0- to 3-month-olds, and the impact of introducing national maternal Tdap immunisation programmes on the epidemiology of pertussis in infants <1 year old. Most included studies were performed in the US and the UK. PCR-confirmed pertussis was the most studied outcome but a few of these studies also investigated hospitalisation due to pertussis. The adjusted VE estimates for preventing PCR-confirmed pertussis varied between 78% and 93% in 0- to 2-month-olds and between 69% and 91% in 0- to 3-month-olds. The adjusted VE estimates for prevention of hospitalisations due to pertussis ranged between 58% and 91% in 0- to 2-month-olds. Only one study, conducted in the UK, investigated pertussis-related death as their outcome and found a 95% VE.

Three studies, of which two from the UK and one from Argentina, were included to study the impact of introducing national maternal Tdap immunisation programmes on the incidence of pertussis in infants <1 year old. In Argentina, the incidence between areas with low coverage were compared to areas with high coverage were compared. They found a relative reduction in pertussis incidence of 51% between high- and low-coverage areas. In the UK, country-wide surveillance data was used to study the incidence before, during and after implementation of the maternal Tdap immunisation programme. Among infants <3 months old, incidence decreased most. In accordance with a cyclical upsurge, an increase in pertussis incidence was seen in all age groups in 2015. However, the incidence among the 0- to 6-month-olds remained lower compared with the incidences seen before implementation of the programme. In 2018, the incidence of PCR confirmed pertussis among 0- to 3-month-olds in the UK was 30 per 100,000. In 2012, the incidence in this age group was 234 per 100,000 [12, 13].

### 6.8.7 Literature

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\* RIVM publication.

## 6.9 Pneumococcal disease

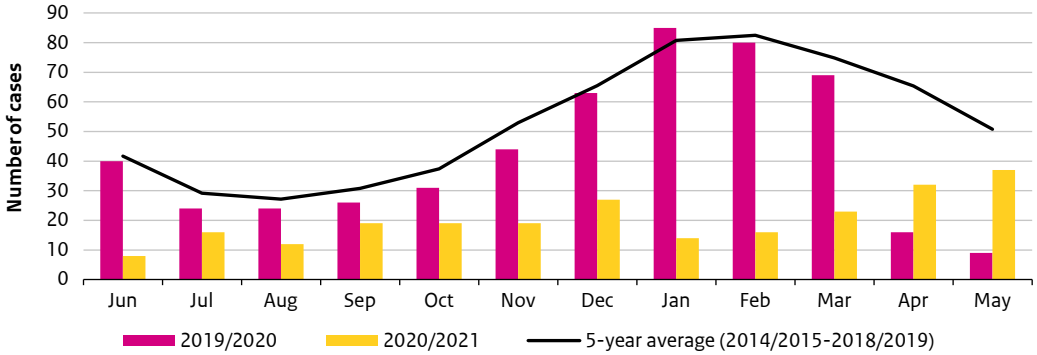


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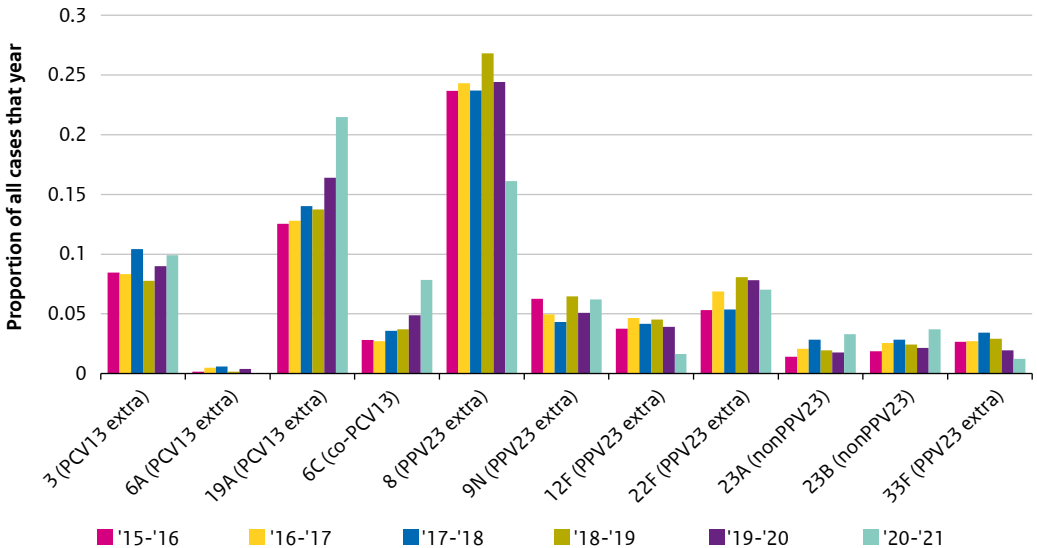
### 6.9.1 Key points

- The decrease in the incidence of invasive pneumococcal disease (IPD) from 14.4 per 100,000 in 2018/2019 to 11.8 per 100,000 in 2019/2020 continued this year to an overall incidence of 5.6 per 100,000 (about 1,500 cases), likely as a result of the COVID-19 control measures. The decrease was observed across all age groups but was smallest in <5-year-olds.
- The number of cases was below the pre-COVID 5-year moving average for all months since the start of the COVID-19 pandemic. In April 2020, the number of cases dropped suddenly after COVID-19 control measures were implemented. The monthly count remained low throughout the year but has been increasing again since March 2021. The increase coincides with opening of primary schools in February and a gradual opening of society in May 2021.
- In the first five months of 2021, two vaccine failures occurred, of which one child without known underlying medical risk conditions.
- The PCV13 serotypes that are not included in PCV10 (serotypes 3, 6A and 19A) together with PCV13-associated serotype 6C (cross-protection from 6A) covered 39% of all cases in 2020/2021. This was higher compared to 2019/2020 (31%) and 2018/2019 (25%). For those aged <5 years, the percentages were 33% for 2020/2021 versus 47% in 2019/2020 and 30% in 2019/2018. Note, however, that for all these serotypes of specific interest, the incidence in 2020/2021 was still lower than in 2019/2020, with the exception of 6C among the <5-year-olds (four cases in both years).
- Since the autumn of 2020, the 23-valent pneumococcal polysaccharide vaccine (PPV23) is offered to all 73- to 79-year-olds. Among those invited for vaccination, the percentage of cases with a PPV23 serotype was 60% versus 75% in older adults not invited for vaccination. When corrected for the odds ratio in the previous seasons, the estimated impact of PPV23 on vaccine-type IPD was 0.47 (95% CI: 0.27–0.82).

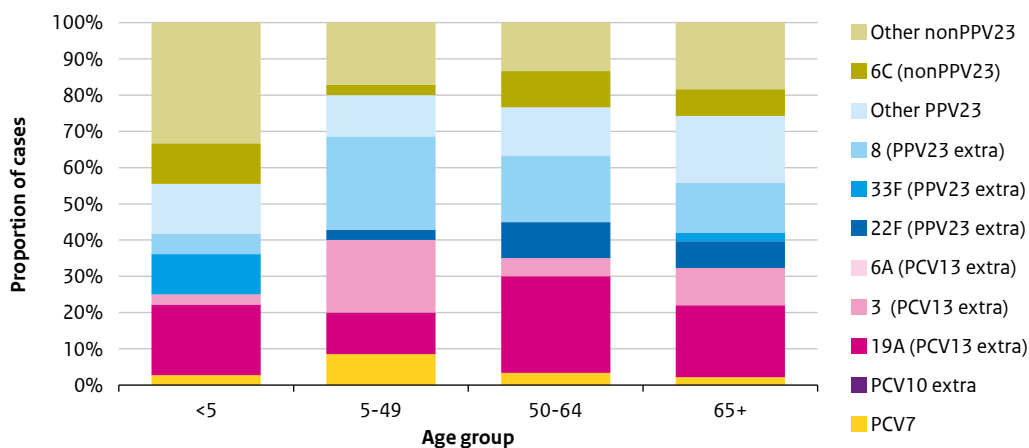
### 6.9.2 Tables and figures



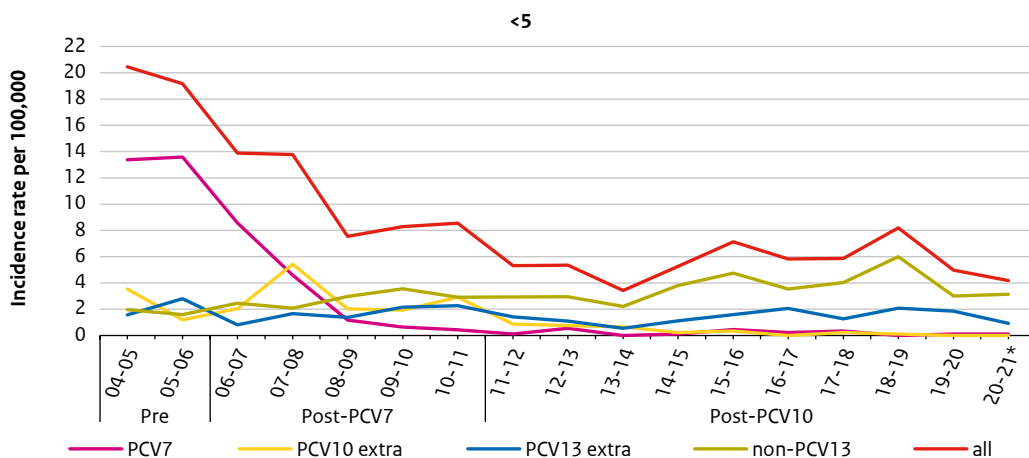
**Figure 6.9.1** Number of cases of invasive pneumococcal disease (IPD) from June 2019 up to and including May 2020 (violet) and June 2020 up to and including May 2021 (yellow) reported by nine sentinel labs (covering ~25% of the Dutch population) by month compared with the pre-COVID 5-year moving average (2014/2015-2018/2019).



**Figure 6.9.2** The proportion of cases in all age groups caused by disease-causing serotypes of special interest in the period 2015-2021. The serotypes were selected based on their coverage by PCV13 (serotype 3, 6A and 19A) or relatedness to a serotype within PCV13 (6C cross-protection from 6A), because they have been described internationally as a serotype of concern (serotype 8, 9N, 12F) and/or based on their incidence (22F, 23A, 23B, 33F). Sentinel surveillance data have been used. The epidemiological year ranges from June to May.

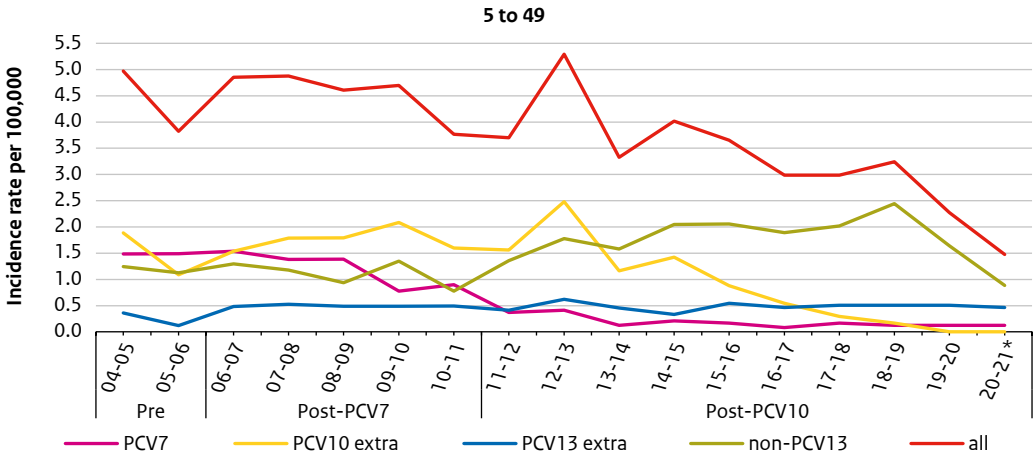


**Figure 6.9.3** Distribution by age group of serotypes causing IPD in epidemiological year 2020/2021. Note that no PCV10-extra serotypes nor 6A were observed in this time period. For children <5 years, data of the national surveillance system have been used. For other age groups, sentinel surveillance data have been used.

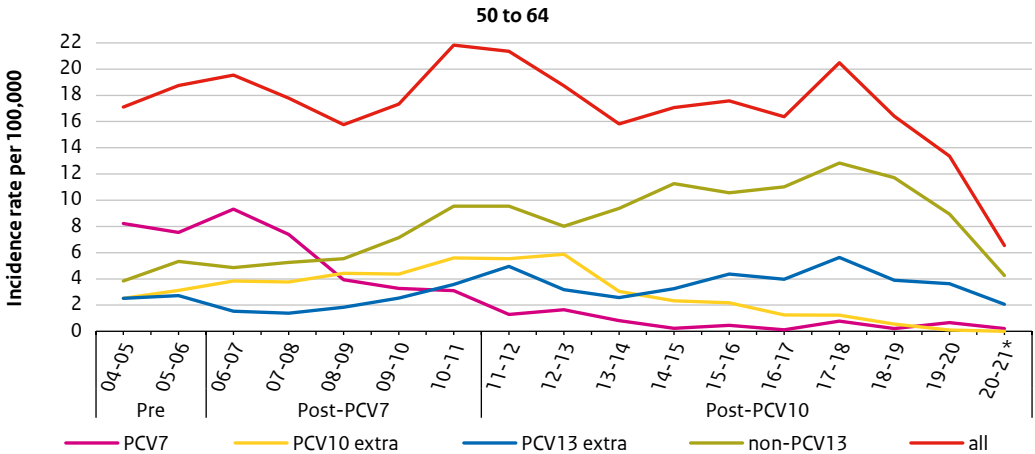


**Figure 6.9.4** Incidence of IPD in children <5 years of age by vaccine serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes and non-PCV13 serotypes) as well as all IPD serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). PCV7 was introduced in June 2006 and PCV10 in May 2011. From 2004-2005 to 2007-2008, sentinel surveillance data have been used and extrapolated to the Dutch population. From 2008-2009 to 2020-2021, data from national surveillance have been used.

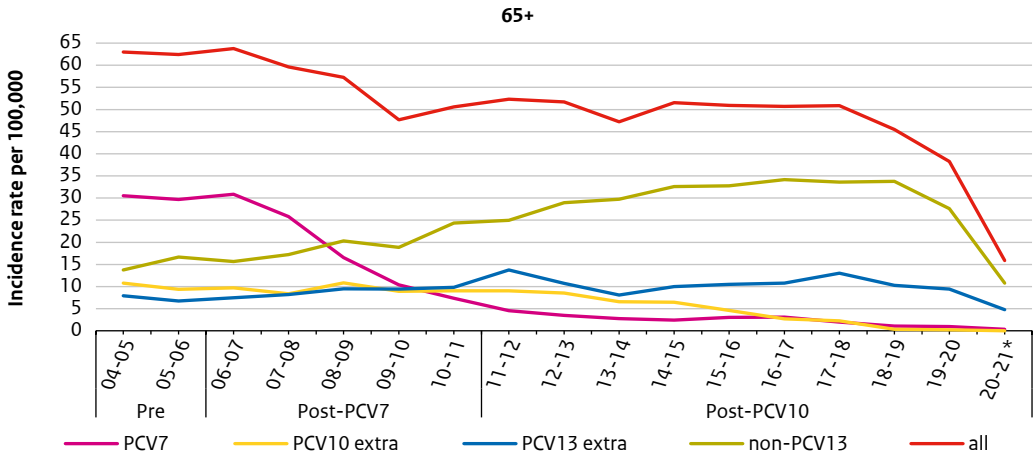
\* Data are affected by the COVID-19 control measures.



**Figure 6.9.5** Incidence of IPD in persons 5-49 years of age by vaccine serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes and non-PCV13 serotypes as well as all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.  
 \* Data are affected by the COVID-19 control measures.



**Figure 6.9.6** Incidence of IPD in persons 50-64 years of age by vaccine serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes and non-PCV13 serotypes as well as all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.  
 \* Data are affected by the COVID-19 control measures.



**Figure 6.9.7** Incidence of IPD in persons aged 65 years or more by vaccine serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes and non-PCV13 serotypes as well as all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.

\* Data are affected by the COVID-19 control measures.

**Table 6.9.1** Serotypes included in the different pneumococcal vaccines.

Serotype	Vaccine					
	PCV7 <sup>#</sup>	PCV10	PCV13	PPV23	PCV15*	20vPnC*
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
3			X	X	X	X
6A			X		X	X
19A			X	X	X	X
2				X		
8				X		X
9N				X		
10A				X		X
11A				X		X
12F				X		X
15B				X		X
17F				X		
20				X		
22F				X	X	X
33F				X	X	X

# Note that PCV7 is no longer in use.

\* Note that PCV15 and 20vPnC are not yet registered in Europe.



**Table 6.9.2** Children eligible for vaccination (born since June 2006) with vaccine-type invasive pneumococcal disease (IPD) who received at least two vaccinations (with at least two weeks between the second dose and diagnosis) based on nationwide surveillance data using data from the period up to and including May 2021.

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

Source: NRLBM, Praeventis, Osiris.

### 6.9.3 Epidemiology

#### 6.9.3.1 Overall

While the overall IPD incidence has been quite stable over time since 2004/2005 with an average incidence of 15.2 per 100,000 per year (range: 13.4 to 16.7 per 100,000 per year), the incidence in the epidemiological year 2019/2020 (June to May) decreased to 11.8 per 100,000 and the decrease continued in 2020/2021 down to 5.7 per 100,000. This is most likely related to the COVID-19 control measures (e.g. social distancing and school closures [1]). The number of cases per month was below the pre-COVID 5-year moving average for all months since the start of the COVID-19 pandemic (Figure 6.9.1). In April 2020, the number of cases dropped suddenly after COVID-19 control measures were implemented. The monthly count has been low since then, but has been increasing since March 2021. The increase coincides with opening of primary schools in February 2021 and a gradual reopening of society in May 2021. This decrease in cases was seen across all age groups and affects the age-specific time trends described below.

The distribution of IPD-causing serotypes has been changing since PCV7 introduction and has continued after the switch to PCV10 in May 2011 (Figure 6.9.2). 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 [2]), PPV23 serotypes 22F and 9N and non-PPV23 serotypes 23A and 23B. Overall, the most common serotypes in 20/21 were serotype 19A (21% of all cases), 8 (16%), 3 (10%) and 6C (8%) (Figure 6.9.2, data shown from 2015 onwards), which was the case for all age groups (Figure 6.9.3). Together with 6C, the PCV13 serotypes that are not in PCV10 (Table 6.9.1) covered 39% of all cases in 2020/2021 compared to 31% and 25% in 2019/2020 and 2018/2019, respectively. Note, however, that for all these serotypes of specific interest, the incidence in 2020/2021 was still lower than in 2019/2020.

#### 6.9.3.2 Children <5 years of age (Figure 6.9.4)

In the epidemiological year 2020/2021, 36 IPD cases were reported in children <5 years of age, resulting in an incidence of 4.2 per 100,000 per year. The incidence decreased substantially after the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2006, up to 80% in 2013/2014. However, after 2013/2014, the incidence started rising again slightly. This has again changed to a decrease over the past two years (Figure 6.9.4), likely related to the COVID-19 control measures (see section 6.9.3.1). This decrease in incidence has not been as large as for other age groups (see below) and was not observed in the incidence of non-PCV13 serotypes (incidence 3.1 per 100,000 in 2020/2021 versus 3.1 per 100,000 in 2019/2020). In 2020/2021, there was only one IPD case caused by a serotype included in PCV10; the case had received three doses of PCV10 (see Table 6.9.2). Eight of the 36 cases (22%) were caused by PCV13 serotypes that are not in PCV10 (see Table 6.9.1); seven of these cases were caused by serotype 19A. Serotype 19A was also the most common serotype seen in 2020/2021 overall (Figure 6.9.2) as well as in this age group. Other common serotypes in this age group were serotype 23B (non-PPV23 type; 5 cases), serotype 6C (4 cases) and serotype 33F (PPV23 type; 4 cases) (Figure 6.9.3). Overall, 33% of cases were caused by a PCV13 or PCV13-associated serotype in 2020/2021 versus 47% in 2019/2020 and 30% in 2019/2018.

### 6.9.3.3 Persons aged 5-49 years (Figure 6.9.5)

In the epidemiological year 2020/2021, 35 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 5-49 years, resulting in an incidence of 1.5 per 100,000 per year. The incidence in this age group has decreased slightly over time since the introduction of PCV7. However, the decrease has been much more substantial in 2019/2020 and continued in 2020/2021 (Figure 6.9.5), presumably as a result of COVID-19 control measures (see section 4.3).

IPD incidence due to serotypes included in PCV10 in 2020/2021 was similar to 2019/2020 at 0.1 per 100,000, which is substantially lower compared to the incidence before introduction of PCV7 in 2006 (3.0 per 100,000). While the serotypes not included in PCV10 have been rising since vaccine introduction from 1.5 to 2.1 per 100,000 per year in 2019/2020, the non-PCV10 incidence was 1.4 per 100,000 in 2020/2021. In 2020/2021, the most common serotypes were 8 (PPV23 serotype; 9 cases), serotype 3 (PCV13 serotype; 7 cases) and 19A (PCV13 serotype; 4 cases) causing 57% of all cases in this age group (Figure 6.9.3).

### 6.9.3.4 Persons aged 50-64 years (Figure 6.9.6)

In the epidemiological year 2020/2021, 60 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 50-64 years, resulting in an incidence of 6.5 per 100,000 per year, which was half of that reported in 2019/2020. Although the incidence in this age group had been quite stable over time, fluctuating around ~18 per 100,000 per year, the incidence has decreased in the last two years, presumably largely caused by COVID-19 control measures (see section 6.9.3.1).

IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV7 in 2006 and its subsequent switch to PCV10 in 2011, from 10.7 to 0.2 per 100,000 per year in 2020/2021. And while a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10 (Figure 6.9.6) in 2018/2019, the incidence of nonPCV10 IPD was 6.4 per 100,000 in 2020/2021. In 2020/2019, the most common serotypes were 19A (PCV13 serotype; 16 cases) and 8 (PPV23 serotype; 11 cases) causing 32% of all cases in this age group (Figure 6.9.3).

### 6.9.3.5 Persons aged 65 years or more (Figure 6.9.7)

In the epidemiological year 2020/2021, the 9 sentinel laboratories (covering 25% of the Dutch population) reported 136 IPD cases in persons aged 65 years or more, resulting in an incidence of 15.9 per 100,000 per year. The incidence in this age group decreased in the first years after PCV7 introduction and has remained stable at around 20 per 100,000 cases per year since the switch to PCV10. However, the incidence has decreased in the last two years, presumably as a result of COVID-19 control measures (see section 6.9.3.1). The further decrease in 2020/2021 was observed in PCV10 IPD (incidence 0.4 per 100,000 in 2021 compared to 1.2 per 100,000 in 2019/2020) as well as nonPCV10 disease (15.6 per 100,000 compared to 37.1 per 100,000; Figure 6.9.7). In 2020/2021, the most common serotypes were 19A (PCV13 serotype; 27 cases), 8 (PPV23 serotype; 19 cases), and 3 (PCV13 serotype; 14 cases) causing 44% of all cases in this age group (Figure 6.9.3).

Since the autumn of 2020, PPV23 vaccination is offered to all 73- to 79-year-olds; from 2021 onwards, those aged 70-73 will be invited. Of all IPD cases in 2020/2021 in persons aged 65+, 74% were caused by a serotype included in PPV23. This was slightly lower compared to earlier years (80% in 2019/2020, 80% in 2018/2019 and 81% in 2017/2018). A (preliminary) estimation of the impact of the vaccination programme was performed on surveillance data from October 2020 up to and including May 2021. The odds ratio was calculated for having PPV23-type IPD in those invited for vaccination compared to older adults not invited (>60 years of age). This was compared with an OR for the same months during the four previous respiratory seasons (2016/2017–2019/2020). For older adults invited for vaccination, the percentage of cases with a PPV23 serotype was in 2020/2021 60%, versus 75% in older adults not invited for vaccination, resulting in an OR of 0.49 (95% CI: 0.30–0.84). The OR for having PPV23-IPD during the same period within the previous four seasons (n=3753) was 1.06 (95% CI: 0.88–1.29). Corrected for the OR in the previous seasons, the impact of vaccination was 0.47 (95% CI: 0.27–0.82). Vaccine effectiveness could not yet be determined since vaccination status of individuals was not available for national surveillance during this season.

#### 6.9.3.6 Vaccine failure

Since the introduction of PCV7, 46 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. Of these, 23 children (50%) were vaccinated with at least two doses (with the second dose given at least two weeks before diagnosis), and therefore were considered vaccine failures (Table 6.9.2). Serotype 19F was the most common serotype among vaccine failure cases (n=8, 35%), a serotype that has also been described in relation to vaccine failure in other settings [3]. There were two vaccine failure cases in the first five months of 2021 in individuals vaccinated with PCV10, one of which was infected with serotype 19F and one with serotype 14. The latter did not have a known underlying medical risk condition.

#### 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 VT cases is compared to the odds of vaccination in non-VT cases. The population included all reported IPD cases for the period up to and including May 2021 that were eligible for PCV10 vaccination and aged 2 months or over, and with known serotype and vaccination status.

Eleven of the 21 (52%) vaccine type IPD cases were vaccinated with at least two doses, as were 288 of the 321 (90%) non-VT IPD cases. This resulted in a VE of 87% (95% CI: 68–95%) for at least two doses of PCV10 compared with no vaccination. The VE against serotype 19A (not covered by PCV10) was 49% (95% CI: -15 to 73%). From these results, cross-protection of PCV10 against vaccine-related IPD including serotype 19A cannot be confirmed.

### 6.9.3.8 IPD mortality among children <5 years

From 2014 up to and including May 2021, 383 IPD cases among children aged under five were reported nationally. For 286 cases (75%), the mortality status was known. Seventeen of the 286 cases (6%) died. These 17 cases all had non-VT IPD (serotypes 8 (n=4), 3 (n=2), 12F (n=2), 6C (n=2), 22F, 10A, 15C, 19A, 23A, 24F, 31). Fifteen cases were <2 years of age and four had known comorbidities.

### 6.9.4 Current/ongoing research at RIVM

In older adults, pneumococcal disease is strongly associated with respiratory viral infections, but the impact of viruses on pneumococcal carriage prevalence and load remains poorly understood. Miellet et al. [4] investigated the effects of influenza-like illness (ILI) on pneumococcal carriage in community-dwelling older adults by quantifying pneumococcal DNA with PCR in saliva samples collected in the 2014/2015 influenza season from 232 individuals with ILI and 194 asymptomatic controls. The prevalence of pneumococcus-positive samples was highest at onset of ILI (18%; 42/232) and lowest among controls (11%; 22/194) although these differences were not significant. However, ILI was associated with significantly elevated pneumococcal abundance in older adults. The impact of ILI persisted for two months and was highest for individuals with acquisition of pneumococcal carriage after the onset of ILI. The study also shows that the true prevalence of pneumococcal carriage is likely to be higher among older adults than commonly reported with culture-based methods. Furthermore, pneumococcal carriage was associated with exposure to young children and rhinovirus infection. These findings are significant as older adults are the age group with the highest burden of disease for both ILI and pneumococcal disease, and the study links viral respiratory disease to altered dynamics of pneumococcal carriage in older adults. This could explain the previously reported higher risk of pneumococcal disease after viral respiratory infection.

To determine the risk of IPD in adult cancer patients and assess herd effects of childhood pneumococcal vaccination, a Dutch population-based cohort study was performed among 7,167 IPD cases of which 1,453 were in patients with malignancies [5]. Adult IPD cases reported to the Netherlands reference laboratory for bacterial meningitis (NRLBM) were linked with data from the Netherlands Cancer Registration. IPD incidences were calculated for each subtype of malignancy, age group and capsular serotype group. They showed that IPD incidence among patients with haematological malignancies was 482/100,000 and among patients with solid organ malignancies, the incidence was 79/100,000. This was much higher than the incidence in persons without malignancies (15/100,000).

## 6.9.5 (Inter)national developments

### 6.9.5.1 Carriage

A Spanish study investigated carriage in 1,821 healthy children aged 1 to 4 years, five years after the introduction of PCV13 [6]. Of these children, 20% carried pneumococci, 14% of which were PCV13-type. The main carried serotypes were non-PCV serotypes 23B, 11A, 10A, 35B/F, and 23A and there was a high rate of resistance to penicillin, erythromycin, and trimethoprim sulfamethoxazole.

Using Israeli age-specific carriage and diseases data, Wyllie et al. showed that adult disease was correlated with carriage patterns in older children [7]. Furthermore, the relative frequency of serotypes causing IPD differed between adults and children, and also differed between older and younger adults and between adults with and without comorbidities. Serotypes over-represented as causes of IPD in adults were more commonly carried in older children (24–59 months of age) as compared to younger children (<24 months old).

#### 6.9.5.2 IPD

A large world-wide study (The Pneumococcal Serotype Replacement and Distribution Estimation project; PSERENADE) conducted in countries that have used PCV13 or PCV10 with a coverage of at least 70% over a period of 5 to 7 years (including the Netherlands) described the effects of the two PCVs on the serotype distribution [8]. In PCV10-countries, the top serotypes were PCV13 serotypes 19A and 3, as well as PCV13-associated serotype 6C, which together caused 42% of the pneumococcal-meningitis cases in <5-year-olds and 37% of cases in ≥5-year-olds. In PCV13 countries, PCV13 types caused 14% in <5-year-olds and 26% in ≥5-year-olds. Of these cases, 4% and 13%, respectively, were caused by PCV13 serotype 3. Overall, compared to the pre-PCV era, the proportion of meningitis cases caused by vaccine-serotypes was lower (<26%) than before PCV introduction (≥70%).

There has long been discussion about the difference in overall impact and serotype replacement after PCV introduction in Europe and North America. A recent study showed that, after stratification by hospitalisation status, the impact and replacement of the vaccination programmes have been similar [9].

#### 6.9.5.3 PCV10

An update of the Cochrane systematic review on the effect of PCV use on the prevention of acute otitis media in children included 15 publications on 11 trials; compared to the previous update, this included one additional publication of a previously included trial [10]. The authors concluded that administration of PCV7 and PCV10 during early infancy was associated with large relative risk reductions in pneumococcal acute otitis media. However, the effects of these vaccines on all-cause acute otitis media were far more uncertain based on low- to moderate-certainty evidence.

A Dutch study analysed episodes of community-acquired pneumococcal meningitis in adults (≥16 years) in the Netherlands to investigate factors for unfavourable outcomes [11]. Cases were identified by the NRLBM and treating physicians between October 1998 and April 2002 and between January 2006 and July 2018. Incidence, pneumococcal serotypes and clinical features including the Glasgow Outcome Scale score were studied and multivariable logistic regression was used to determine unfavourable outcome (Glasgow Outcome Scale 1-4). The data included 1,816 episodes in 1,783 patients. As seen in Dutch surveillance (see above), the incidence of PCV10 type disease decreased and non-PCV10 type disease increased. Over time, adjunctive treatment with dexamethasone increased. Adjunctive dexamethasone therapy was associated with favourable outcome (adjusted OR for unfavourable outcome: 0.58 [95% CI: 0.46 - 0.74]), individual pneumococcal serotypes were not. The study concluded that the implementation of PCV7 and PCV10 and adjunctive dexamethasone therapy have changed the incidence and outcome of pneumococcal meningitis in adults over time.

#### 6.9.5.4 PCV13

The influence of regional vaccine uptake differences on the changing epidemiology of IPD was investigated in Switzerland [12]. They obtained data on vaccine coverage from a nationwide survey according to east and west regions for the periods 2005–2010 and 2011–2019 (early, mid and late) PCV13 eras. Reported incidence rate ratios (IRRs) were compared for successive periods and regions using nationwide IPD surveillance data. PCV uptake rates in Swiss children were slightly higher in the west than the east ( $p < 0.001$ ), and were accompanied by lower IPD incidences across all age groups in the west (9.3/100,000 in the late PCV13 period) compared to the east (12/100,000 in the east) while incidences in the early PCV7 years were similar (13.6/100,000 in west and 13.3/100,000 in east).

Surveillance data from Portugal were used to analyse serotype-specific incidences and antimicrobial susceptibility patterns for the post-PCV13 period 2015–2018 [13]. They included 2,172 isolates of adult IPD cases. Serotypes 8 (19%), 3 (15%), 22F (7%), 14 (6%), and 19A (5%) were the most common serotypes. Overall, 13% of isolates were PCV13-serotypes. The distribution of serotypes differed by age group, with serotype 8 and 4 being relatively more common among those 18–49 years old, and serotypes 3, 22F, 6C, 14, and 31 being more common for the 65+ group. Of all isolates, 15% were penicillin non-susceptible and 15% were Erythromycin resistant (8% of all isolates were both). Penicillin non-susceptibility was most common among serotypes 14, 19A, 15A, 6C, and 11A (together covering 74%), and Erythromycin resistance was most common among serotypes 14, 19A, 6C, 19F, and 15A (together covering 65%).

Pfizer, the producer of serotype 3-containing PCV13, conducted a review on the impact on serotype 3 of PCV13 combined with an analysis by dynamic transmission modelling [14]. To estimate the impact on serotype 3, the researchers compared the incidence of IPD caused by serotype 3 in countries with PCV10 (no serotype 3) with countries where PCV13 is used in the national immunisation programme. The study includes incidence data from the Netherlands for 2016–2018, as well as data from, among others, the UK, US and Israel. They directly compared incidence data but also used published transmission dynamic modelling to ascertain whether PCV13 provides direct or indirect protection. The incidence rate ratios (IRRs) among children <5 years increased non-significantly for both PCV13 countries as well as PCV10 countries, but the annual point estimates were larger for PCV10 countries. For those aged 65+, a slight decrease was observed in PCV13 countries, while a non-significant increase was observed in PCV10 countries. They therefore concluded that PCV13 provides a certain degree of direct and indirect protection against serotype 3 disease.

A Norwegian study including surveillance data of 10,239 IPD cases in the period 2004–2016 found that antimicrobial resistance was rare (maximally 7%, depending on the antimicrobial) and that erythromycin and trimethoprim/sulfamethoxazole-resistant IPD had decreased since the introduction of PCV7 and PCV13, mainly due to the decrease in resistant PCV-serotypes [15]. However, in recent years, they found a small increase in antimicrobial non-susceptibility. This increase was clonal, and mainly due to non-vaccine serotypes 15A-sequence type (ST)63 (multidrug resistant), 24F-ST162 (trimethoprim/sulfamethoxazole-resistant), 23B-ST2372 (penicillin non-susceptible and trimethoprim/sulfamethoxazole-resistant) and 33F

(erythromycin- and clindamycin-resistant). The current PCVs have therefore not fully limited antimicrobial resistance.

The use of antimicrobials after PCV13 introduction among <5 year olds was investigated in Israel using interrupted time-series analysis on more than 1 million prescriptions [16]. They analysed monthly dispensed antibiotic prescription rate trends, adjusted for age, ethnicity and season and calculated incidence rate ratios by comparing late PCV13 period vs. 4 years pre-PCV. They showed that post-PCV7/PCV13 implementation, the dispensed antibiotic prescription rates declined abruptly and significantly, reaching a plateau within 5 years. This was largely driven by amoxicillin/amoxicillin-clavulanate (75% of prescriptions). The overall reduction was estimated at 345 [95% CI: 371-358]/1,000.

#### 6.9.5.5 *Pneumococcal pneumonia*

An Israeli study investigated the protection conferred by PCVs against paediatric pneumonia attributable to vaccine-serotype pneumococci [17]. Nasopharyngeal samples obtained from 12- to 35-month-olds (1,032 community acquired pneumonia cases and 7,743 healthy controls) in 2009-2018 were tested for pneumococcal carriage. PCV7 and PCV13-type carriage among the cases was interpreted as pneumonia being attributable to PCV13-serotype pneumococci. Based on PCV13 vaccination history and pneumonia status (case/control), the researchers could determine overall PCV-conferred protection against PCV13-type pneumonia. VE of the 2+1 PCV13 schedule against PCV13 pneumonia was estimated at 87.2% (95% CI: 8.1-100.0%), and was higher for those aged 4-11 months compared to those aged 36-59 months.

A systematic review on the effectiveness of PCV13 and PPV23 to prevent IPD and pneumonia in older adults (50+ years; an update of previous reviews) was performed and included 15 studies (9 on PCV13 and 6 on PPV23). The outcomes in the included studies ranged from all-cause pneumonia to VT-IPD. Most studies combined bacteraemic and non-bacteraemic pneumonias, and only one study analysed non-bacteraemic pneumonias. The low number of new publications did not allow for meta-analyses stratified by vaccine, study design and outcome. VE in observational studies on PCV13 ranged from negative VE (adjusted VE -69%) against all-cause pneumonia to high protective VE of 71% against VT-CAP. The VE of PPV23 ranged from 3% to 16% against all-cause pneumonia and from 2% to 71% against VT-CAP. Several studies indicate that the effectiveness of PPV23 is highest in younger age groups and that it decreases over time. After five years, PPV23 was still found to be protective by two of the studies included in the review. The authors concluded that both PPV23 and PCV13 prevent vaccine-type pneumonia [18].

#### 6.9.5.6 *Pneumococcal vaccines in development / future PCVs*

MSD is developing a 15-valent PCV (V114) including serotypes 22F and 33F in addition to the serotypes included in PCV13 (Table 6.9.1). A phase II trial comparing V114 with PCV13 in 1,050 healthy infants who were vaccinated at 2, 4, 6 and 12-15 months of age already showed non-inferiority for all 13 shared serotypes [19].



Recently, results of two adult phase III trials that compared V114 directly with PCV13 followed by PPV23 were published. In PNEU-PATH (n=1,205), healthy adults aged 50 years received V114 or PCV13 followed by PPV23 one year later. In PNEU-DAY (n=1,514), immunocompetent adults age 18-49 years with underlying medical conditions received V114 or PCV13 followed by PPV23 six months later. Both studies showed a strong immune response measured by opsonophagocytic activity for all 15 serotypes included; immune responses were similar 30 days after vaccination with PCV13 or V114 for the 13 shared serotypes and higher for the V114-unique serotypes 22F and 33F [20]. PNEUMO-DAY showed superior immune responses for serotype 3 for V114 compared to PCV13. V114 was generally well tolerated, with a safety profile comparable to PCV13. Note that, in the period 2016-2020, 37-45% of all IPD cases in the Netherlands were caused by a serotype included in PCV15.

Pfizer is developing a 20-valent PCV (20vPnC), which has now been tested in children (phase 2) and adults (Phase 3) [21]. In the US, 20vPnC has just been approved by the US FDA for use in adults 18 years and older [22]. 20vPnC was tested in 902 adults aged 18 or older with no history of pneumococcal vaccination. For adults 60+, immune responses were compared between those receiving 20vPnC with those receiving PCV13 or PPV23, and results showed non-inferiority to all the serotypes in common with PCV13 and six of the seven additional serotypes when compared to PPV23 [21]. In the phase II trial for infants, 460 infants aged 42 to 98 days were included, which received either PCV13 or 20vPnC at 2, 3, 4 and 12 months. The safety profile of 20vPnC was reported to be consistent with PCV13. PCV20 elicited immune responses to all 20 serotypes one month after Dose 3 (serotype-specific IgG concentrations and IgG GMCs). Furthermore, booster responses were observed for all serotypes after Dose 4 and immunological memory seemed to be developed (comparing IgG 1 month after dose 3 and after dose 4) [21]. Pfizer submitted a marketing authorisation application for adults to the European Medicines Agency early 2021, which is now being evaluated by the EMA. Note that, in the period 2016-2020, between 72% and 76% of all IPD cases in the Netherlands were caused by a serotype included in 20vPnC.

In addition to PCV15 and 20vPnC, a 24-valent PCV is under development, which has not yet been tested in people but results in mice look promising [23].

Population-based multifaceted surveillance in Israel was performed and included carriage isolates from healthy children, those with lower respiratory tract infections or other illness requiring chest radiography as well as clinical isolates [24]. They found that after PCV13 introduction, serotypes included in the 20vPnC but not in PCV13 (VT20-13) increased more in clinical-related samples than in carriage from healthy children. They concluded that the disproportionate increase of VT20-13 in respiratory infections and IPD suggests a higher disease potential for these serotypes compared to all other non-20vPnC serotypes.

#### 6.9.5.7 Effect of COVID-19 on IPD and carriage

A study performed on 829 paediatric patients who were tested for SARS-CoV-2 (115 positives) in Turkey showed that pneumococcal carriage was higher in patients with COVID-19 compared to non-infected children, however this did not affect the course of COVID-19 disease.

Several studies, including one performed by the RIVM [1], showed a decrease in the IPD incidence during the COVID-19 pandemic. In the UK [25], researchers analysed data on 40 cases with a co-infection of COVID-19 and IPD (out of 160,886 COVID-19 cases and 1,137 IPD cases). They showed that the case fatality rate was almost 8x higher (7.8, 95% CI: 3.8-15.8) among those with a coinfection and about 4x higher (3.9, 95% CI: 1.4-10.7) among those who developed COVID-19 3 to 27 days after IPD compared with patients with IPD only.

Data of the Invasive Respiratory Infection Surveillance (IRIS) Initiative on pneumococci, *Haemophilus influenzae*, and meningococci was used to determine the incidence of invasive disease due to these pathogens during the early months of the COVID-19 pandemic [26].

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## 6.10 Poliomyelitis

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### 6.10.1 Key points

- In 2020 and 2021, for the period up to and including April 30<sup>th</sup>, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.
- Two poliovirus detections were reported in 2020 and 2021 from the environmental surveillance at Utrecht Science Park, location Bilthoven, during standard sampling. In July 2020 this concerned a wild-type 3 poliovirus (WPV3) detection, most likely shed by an infected employee of the vaccine production facility. In February 2021 this concerned a Sabin 3 strain that was either released from a facility or excreted by a recently oral polio vaccine (OPV) vaccinated employee or visitor of the premises. Following the poliovirus detection in July 2020, the frequency of standard sampling at the facilities was doubled to once every three weeks for 2021.
- Almost nationwide coverage of enterovirus surveillance was obtained in 2020, as complete data from 31/35 virological diagnostic laboratories were received. In 95.0% (7,518/7,911) of the stools analysed, poliovirus was shown to be absent. The percentage of EV-positive stools in which poliovirus could be excluded was 29.7% (144/485). Nonetheless, no poliovirus was found in any sequenced sample. The low poliovirus exclusion percentage in EV-positive stools in 2020 compared to previous years is most likely due to the fact that less sequencing was performed on the EV-positive samples compared to previous years.
- In 2020, the incidence of vaccine-derived poliovirus 2 (VDPV<sub>2</sub>) cases worldwide was almost three times higher than in 2019 (1,085 versus 368, respectively). The incidence was particularly high in African countries.
- In 2020-2021, poliovirus remained endemic in two countries; Afghanistan and Pakistan.
- Nigeria, and thus the African region, was declared wildtype polio-free in June 2020.

6.10.2 Tables and figures

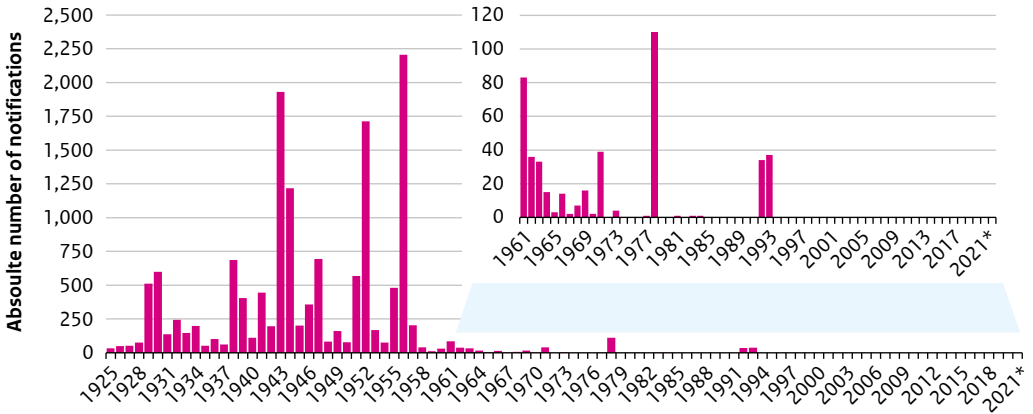


Figure 6.10.1 Notifications of poliomyelitis in the Netherlands from 1924-2021\* and zoomed in on 1957-2021\* (right part).

\* For 2021, reports for the period up to and including April 30<sup>th</sup> are included.

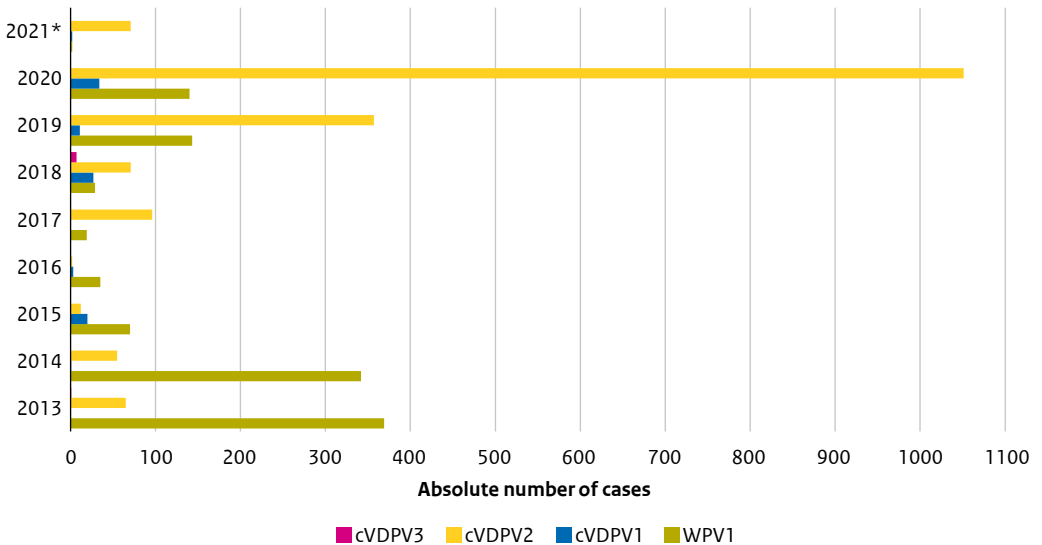


Figure 6.10.2 Total number of global polio cases 2013-2021\* as reported to WHO HQ.

\* For 2021, data for the period up to and including April 26<sup>th</sup> are included.

**Table 6.10.1** Enterovirus + Parechovirus detection rate in The Netherlands in 2020.

		EV			PEV		
		<15 yrs	≥15 yrs	Total	<15 yrs	≥15 yrs	Total
<b>All samples</b>	n tested	6,468	26,566	33,034	3,604	11,019	14,623
	n (%) positive	1,072 (16.6)	1,032 (3.9)	2,104 (6.4)	133 (3.7)	103 (0.9)	236 (1.6)
<b>Faeces</b>	n tested	2,139	5,772	7,911	1,866	5,451	7,317
	n (%) positive	175 (8.2)	310 (5.4)	485 (6.1)	90 (4.8)	46 (0.8)	136 (1.9)

### 6.10.3 Epidemiology & pathogen

#### 6.10.3.1 Epidemiology

In 2020 and 2021, for the period up to and including April 30<sup>th</sup>, 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, the strategy to prevent the import of WPV and maintain polio-free status focuses on two major components: establishing and/or maintaining high vaccination coverage and performing high-sensitive surveillance of polio cases. For countries with a strong healthcare system, high levels of sanitation, and a long period of non-endemicity, including the Netherlands, other surveillance strategies, among which enterovirus and environmental surveillance, are also approved.

#### 6.10.3.3 Enterovirus surveillance

For the year 2020, almost nationwide coverage of enterovirus (EV) surveillance was obtained as complete data from 31/35 virological diagnostic laboratories were received. In total, 33,034 samples, of which 7,911 stool samples, were tested for the presence of EV and were reported including sufficient sample information to allow for analysis (Table 6.10.1). According to the Global Polio Laboratory Network, an effective enterovirus surveillance system detects between 5 and 25% enteroviruses in all samples tested annually [2]. An EV was detected in 2104 samples, resulting in an average EV positivity rate of 6.4%. Stool sampling yielded 485 EV positives, resulting in an average EV positivity rate of 6.1%. In addition to EV detection, laboratories tested samples for parechovirus (PEV). In total, 14,623 samples were tested and 236 were found positive for PEV (1.6%). Out of 7,317 stool samples, 136 were found positive, yielding a detection rate of 1.9% [3]. Of the stool samples tested for EV, 27.0% (2139/7911) came from individuals younger than 15 years of age. Nonetheless, the percentage of EV-positive stools was higher in individuals younger than 15 years compared with persons older than 15 years (8.2% versus 5.4%) [3].

Exclusion of poliovirus presence based on enterovirus surveillance can be defined at two levels: the percentage of stool specimens 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. It is highly recommended but not mandatory to send in EV-positive samples in non-AFP cases for sequencing. In 95.0% (7,518/7,911) of the total stools analysed in 2020, poliovirus was shown to be absent. The percentage of poliovirus excluded in EV-positive stools was 29.7% (144/485). For the years 2015-2019, poliovirus was excluded in 40-50% of EV-positive stools. The lower percentage in 2020 is most likely due to the fact that less sequencing was performed on the EV-positive samples compared to previous years. Nonetheless, no poliovirus was found in any sequenced sample in 2020 [3].

#### 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 2020 underline this statement, as no polioviruses (wild, vaccine, vaccine-derived) were detected during regular sampling at 15 locations in the Bible belt. 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 2020 have again documented the absence of poliovirus circulation in the country in combination with the system for EV surveillance.

Both in July 2020 and February 2021, a poliovirus detection was reported from environmental surveillance at Utrecht Science Park, where the RIVM and two vaccine manufacturers are located. Research showed that an employee of the Science Park was infected with the wild type 3 poliovirus (WPV3) in July 2020. Most likely this employee was the source of the virus in the sewage system in July 2020. Because the employee was vaccinated, he or she did not become ill. This incident did not lead to poliovirus introduction into the Dutch population. At the end of February 2021, a poliovirus Sabin type 3 strain was isolated from a sewer sample. Sabin 3 strains are part of the oral (live) polio vaccine (bivalent OPV with Sabin 1 and 3 strains) that is widely used internationally. bOPV is widely used in Morocco, Turkey and India, for example. The vaccine manufacturer indicates that during the week of sampling, they worked with Sabin 3 in a building that discharges into the sampled well. The Sabin 3 strain found has no mutations relative to the Sabin 3 reference strain. This could mean the strain originates from the vaccine manufacturer or a very recent vaccination of an employee, visitor (or housemate) of one of the on-site businesses. As part of the bOPV, Sabin 3 is not a pathogenic strain. Following the poliovirus detection in July 2020, the frequency of standard sampling at the facilities was doubled to once every three weeks for 2021 [4].



#### 6.10.4 Research

The National Polio Laboratory (NPL), also called the Global Specialised Laboratory (GSL), at the RIVM 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.

In cooperation with the immune-surveillance department at the RIVM, the NPL is developing new serological assays that can be used outside of GAPIII containment. Additionally, the NPL RIVM participates in the validation of new poliovirus strains (S19 strains), including type 2, that can be used outside of GAPIII containment for use in the poliovirus neutralisation assay. The NPL RIVM co-developed the optimised algorithm for environmental surveillance for countries that will use novel type 2 oral polio vaccine (nOPV2). Environmental surveillance as supplemental surveillance in addition to AFP surveillance is mandatory for countries that will be using nOPV2 under the current Emergency Use Listing (EUL). The genetically engineered nOPV2 strains are harder to isolate from sewage samples than WPV, Sabin or current vaccine-derived poliovirus (VDPV) strains, which might hamper detection of these strains. The optimised algorithm is implemented in countries using nOPV2 and will also be employed by NPL RIVM on the sewage samples we will be receiving from Tajikistan for analysis.

#### 6.10.5 International developments

In 2020-2021, the WHO classified two countries – Afghanistan and Pakistan – as polio-endemic countries [5]. Importation of polio into non-endemic countries was not observed. From 2016 onwards, no WPV cases were notified in Nigeria. As a result, Nigeria was declared wild-type polio-free in June 2020 [6], which means that the African region is the fifth wild-type polio-free region, out of all six WHO regions.

In Afghanistan and Pakistan, a combined total of 140 wild-type 1 poliovirus (WPV1) cases were notified in 2020, and 2 WPV1 cases in 2021 for the period up to and including April 26<sup>th</sup>. In environmental surveillance, no WPV1 was detected in countries other than Afghanistan or Pakistan in 2020 and in 2021 for the period up to and including April 26<sup>th</sup> [7].

The global number of circulating vaccine-derived poliovirus 2 (cVDPV2) cases increased from 71 cVDPV2 cases in 2018 to 368 cases in 2019. In 2020, the number of worldwide cVDPV2 cases increased further, particularly in African countries. Globally, there were nearly three times more cVDPV2 cases in 2020 (1,085) compared to 2019 (Figure 6.10.2) [8]. As a result, there has been higher demand for monovalent type 2 oral polio vaccine (mOPV2), a WHO vaccine with the same operational characteristics as bivalent oral polio vaccine (bOPV). This high demand has even threatened stocks of this vaccine. The WHO advised that all countries should destroy the materials containing poliovirus type 2, and provide at least one inactivated polio vaccine (IPV) in their routine vaccination schedule. In May 2019, the WHO announced that all countries worldwide had introduced at least one IPV dose. Polio eradication progress has been hampered by the COVID-19 pandemic.

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 [9]. The first use in a supplementary immunisation activity (SIA) started in Nigeria on March 13th, 2021, followed by roll-out in Liberia and Benin. The introduction of cVDPV2 from Afghanistan into Tajikistan in 2020 [8] introduced cVDPV2 into the WHO EUR region. In response, the use of nOPV2 in Tajikistan is scheduled to start mid-May 2021.

In 2020, 84 and 56 patients with acute flaccid palsy (AFP) due to WPV1 were reported in the last two endemic countries of Pakistan and Afghanistan, respectively [7, 10]. This represented a decrease in Pakistan (n = 147 in 2019) but an increase in Afghanistan (n = 29 in 2019). Both countries also report circulating vaccine-derived poliovirus type 2 (cVDPV2) for 2020 with 135 (Pakistan) and 308 (Afghanistan) AFP cases [8]. cVDPV2 outbreaks also caused enormous problems in Africa in 2020. The number of AFP cases due to VDPVs increased from 366 to 1,059 in 2020, with the first polio cases reported in 5 years in various countries (including Sudan and South Sudan, Guinea, Ivory Coast, Cameroon, Mali). At present, ongoing outbreaks of cVDPV appear to be limited to type 2 in African countries and Afghanistan/Pakistan [8]. cVDPV2 outbreaks are mainly the result of the use of mOPV2 in areas where >80% of the target group cannot be reached and insufficient implementation of vaccination by injection (IPV). As a result, there is insufficient anti-PV2 immunity at the population level.

Due to the COVID-19 pandemic, 62 polio vaccination supplementary immunisation activities (SIAs) were suspended in 28 countries from March to May 2020, and the implementation of IPV in national campaigns was delayed in 14 countries. In addition to the direct impact on vaccinations, there was also a decrease in surveillance. The number of reported AFP cases decreased by 28% from 2019 to 2020, the transport time of samples to the lab increased from an average of 8 to 12 days (and the quality of the samples therefore deteriorated). In addition, polio staff was deployed for COVID-19 response, diagnostics and surveillance in many countries.

At the end of September, cVDPV2 outbreak response was restarted in 14 countries by means of mOPV2 vaccinations. Bivalent OPV SIAs have been carried out in Pakistan and Afghanistan to combat WPV1 transmission. At the end of November, the third nationwide polio vaccination campaign in Pakistan started and 39 million children under the age of 5 were given a polio vaccine in 2020.

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 10<sup>th</sup>, 2021 [11].

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### 6.10.7 Other RIVM publications

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.



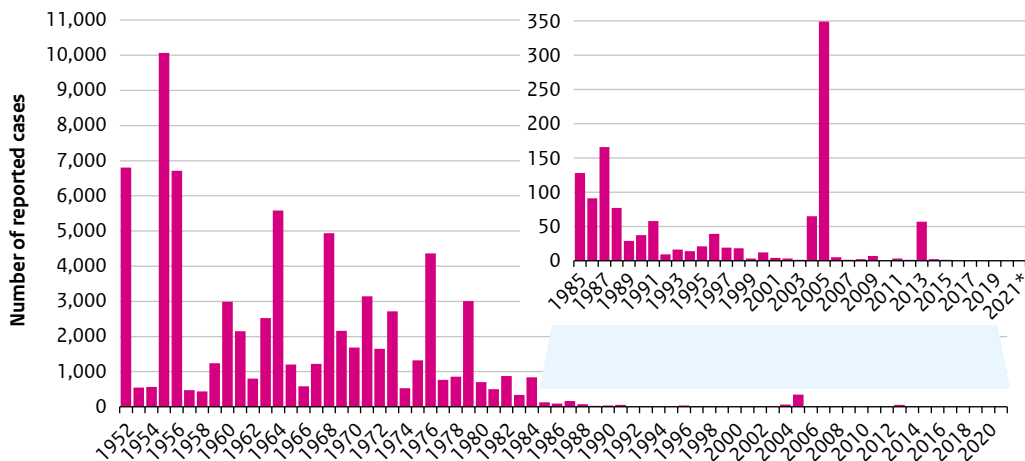
## 6.11 Rubella

I.K. Veldhuijzen, R. Bodewes, W.L.M. Ruijs, N. Rots, R. van Binnendijk

### 6.11.1 Key points

- In 2020 and the first six months of 2021, no rubella cases were reported.
- Across Europe, the number of rubella cases continues to decline in 2020.

### 6.11.2 Tables and figures



**Figure 6.11.1** Reported rubella cases per year since 1952.

\* Up to and including June.

### 6.11.3 Epidemiology

In 2020 and the first six months of 2021, no rubella cases were reported. The last case of rubella in the Netherlands was reported in 2015 (see Figure 6.11.1).

### 6.11.4 Research

A systematic literature review and meta-analysis performed by RIVM as input for the WHO Position Paper on rubella vaccines showed that seroconversion after one dose of rubella containing vaccine (RCV) in children was 99%, based on 26 studies. Data from seven studies demonstrated 88-100% seropositivity after 1 to 20 years of follow-up after one of two doses of RCV [1].

### 6.11.5 International developments

After 2013 when almost 39,000 rubella cases were reported in the EU/EEA, the annual number declined rapidly and since 2017, fewer than 1,000 rubella cases per year are reported. In 2020, only 138 rubella cases were reported by 9 EU/EEA Member States. Nineteen countries reported no cases. The highest numbers of cases were reported by Poland (96), Germany (18) and Italy (15) [2]. The data from Poland should be interpreted with caution as rubella is reported based on clinical symptoms and only 1% of reported cases was laboratory confirmed in 2019 [3].

A study from France supports the Dutch policy to only offer pregnant women screening for rubella antibodies when they are not vaccinated or when their vaccination status is unknown. Serum samples from over 4,000 pregnant women with initial results suggesting possible infection with rubella virus (RV) were further evaluated at the French National Reference Laboratory. Maternal rubella primary-infection was only confirmed in 46/4,104 (1.1%) cases. The positive predictive value of positive RV-IgM was only 1.4% [4]. Especially in the context of elimination and low rubella virus circulation, clinicians should be aware that positive RV-IgM is most often not indicative of a primary infection.

### 6.11.6 Literature

- 1.\* van den Boogaard J, et al., Immunogenicity, duration of protection, effectiveness and safety of rubella containing vaccines: A systematic literature review and meta-analysis. *Vaccine*, 2021. 39(6): p. 889-900.
2. European Centre for Disease Prevention and Control. Reported rubella cases in 2020, Surveillance atlas of infectious diseases. 2020 [cited 2021 19-5-2021]; Available from: <http://atlas.ecdc.europa.eu/public/index.aspx>.
3. European Centre for Disease Prevention and Control, Monthly Measles and Rubella monitoring report – February 2020. 2019, ECDC: Stockholm.
4. Bouthry E, et al., Positive predictive value of seroconversion or positive rubella IgM in diagnosis of maternal rubella infection: Seven-years review of French National Reference Laboratory for Rubella. *J Clin Virol*, 2021. 134: p. 104708.

\* RIVM publication.

## 6.12 Tetanus

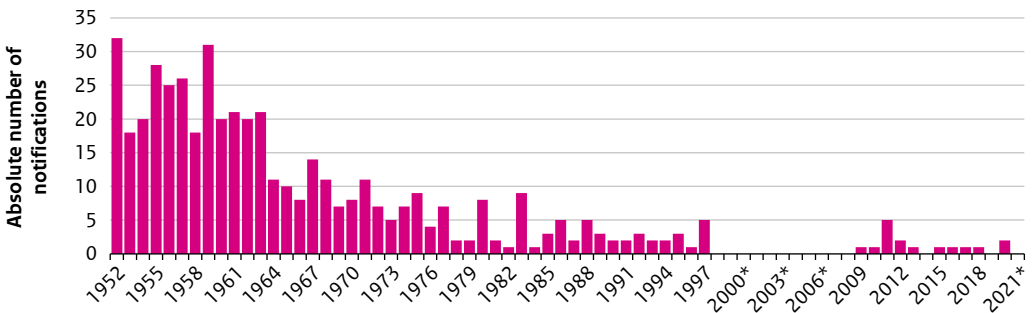


D.L. van Meijeren, D.W. Notermans, N.A.T. van der Maas, H.E. de Melker

### 6.12.1 Key points

- In 2020, two tetanus cases were reported, one elderly woman who was not eligible for routine vaccination and one unvaccinated teenager.
- In 2021, for the period up to and including May, no cases were reported.
- When the Maternal and Neonatal Tetanus (MNT) Elimination Initiative was launched in 1999, MNT was a public health problem in 59 countries worldwide. By December 2020, 47 out of these 59 countries achieved the MNTE status.

### 6.12.2 Tables and figures



**Figure 6.12.1** Reported cases of tetanus in the Netherlands by year, 1952-2021<sup>^</sup>.

\* Between 1999 and 2009, tetanus was not notifiable.

<sup>^</sup> For 2021, notifications for the period up to and including May were included.

### 6.12.3 Epidemiology

In 2020, two tetanus cases were reported. One case concerned a woman born before 1950 and therefore not eligible for the NIP. She contracted a wound after falling outdoors and developed clinical signs of tetanus. She was admitted to the hospital, where she recovered. For post-exposure prophylaxis, she received tetanus toxoid but no tetanus immunoglobulins, although the latter is recommended. No *Clostridium tetani* was cultured from the wound.

The second case concerned an unvaccinated teenager who contracted a headwound due to a slap with a branch. Within several days he developed clear signs of tetanus: neck stiffness, cramps of the facial muscles including lockjaw, and of the chest musculature. He was hospitalised and transferred to the intensive care unit due to breathing difficulties. He recovered after several weeks of severe illness. *Clostridium tetani* was cultured from the wound, although no tetanus toxin was found.

In 2021, for the period up to and including May, no tetanus cases were reported.

#### **6.12.4 International developments**

By December 2020, 12 countries worldwide had not yet reached Maternal and Neonatal Tetanus Elimination (MNTE) status, which is defined as having less than one case of neonatal tetanus per 1,000 live births in every country's district. The MNTE Initiative was launched in 1999 when 59 countries in the African, Eastern Mediterranean, Western Pacific, and South-East Asian Region had not yet achieved MNT elimination. The 12 countries in which MNT is still a public health problem are Afghanistan, Angola, the Central African Republic, Guinea, Mali, Nigeria, Pakistan, Papua New Guinea, Somalia, Sudan, South Sudan, and Yemen. In 2020, 7 countries implemented Td Supplementary Immunisation Activities in high-risk areas: the Central African Republic, Guinea Conakry, Mali, Nigeria, South Sudan, Pakistan, and Yemen [1, 2].

#### **6.12.5 Literature**

1. World Health Organization (WHO). Maternal and Neonatal Tetanus Elimination 2020 [cited 2021 June 25]. Available from: [https://www.who.int/initiatives/maternal-and-neonatal-tetanus-elimination-\(mnte\)](https://www.who.int/initiatives/maternal-and-neonatal-tetanus-elimination-(mnte)).
2. World Health Organization (WHO). Maternal and Neonatal Tetanus Elimination Programmatic Update 2020 [cited 2021 June 25 ]. Available from: [https://www.who.int/initiatives/maternal-and-neonatal-tetanus-elimination-\(mnte\)/programmatic-update](https://www.who.int/initiatives/maternal-and-neonatal-tetanus-elimination-(mnte)/programmatic-update).

#### **6.12.6 RIVM publications**

Berbers G, van Gageldonk P, van de Kasstele J, Wiedermann U, Desombere I, Dalby T, et al. Widespread circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. *Nature Communications*. 2021;12.

7

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





## 7.1 Key points

- In general, vaccination coverage in the Dutch overseas territories, including the Caribbean Netherlands (Bonaire, St Eustatius and Saba), is high.
- In 2020, no vaccine-preventable diseases were reported on Bonaire and Saba. Data for the other islands were not available this year due to the SARS-CoV-2 pandemic.
- Findings from the Health Study Caribbean Netherlands (CN) indicate that the circulation of *B. pertussis* in CN is vastly underestimated. Among residents without detectable vaccine-induced humoral immunity, an estimated 8.2% were infected with *Bordetella pertussis* within the previous twelve months, and the highest rates of a recent infection were found in adolescents aged 12-17 years (16.1%) and young adults 18-29 years of age (16.7%). Furthermore, participants living on Bonaire and those of Dutch Caribbean or Surinamese origin were more likely to be recently infected with *B. pertussis* (9.7% and 10.7%, respectively).

## 7.1.1 Tables and figures

**Table 7.1** Vaccination coverage<sup>a,b</sup> in the Caribbean Netherlands.

		Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
<b>Newborns (2 years)</b>							
<i>Number in cohort 2018</i>							
		*	*	*	16	37	*
DTaP-IPV-Hib-HBV	Number	*	*	*	16	30	*
	%	*	*	*	100%	81.1%	*
HBV	Number	*	n/a	n/a	n/a	n/a	*
	%	*	n/a	n/a	n/a	n/a	*
Polio	Number	n/a	n/a	*	n/a	n/a	n/a
	%	n/a	n/a	*	n/a	n/a	n/a
Pneu	Number	*	*	*	16	30	*
	%	*	*	*	100%	81.1%	*
MMR1	Number	*	*	*	16	29	*
	%	*	*	*	100%	78.4%	*
MMR2	Number	n/a	n/a	*	n/a	n/a	n/a
	%	n/a	n/a	*	n/a	n/a	n/a
MenACWY	Number	n/a	*	n/a	15	29	n/a
	%	n/a	*	n/a	93.8%	78.4%	n/a
<b>Toddlers (5 years)</b>							
<i>Number in cohort 2015</i>							
		*	*	*	23	37	*
DTaP-IPV	Number	*	*	*	22	24	*
	%	*	*	*	95.7%	64.9%	*
MMR2	Number	*	n/a	n/a	23	24	*
	%	*	n/a	n/a	100%	64.9%	*
<b>Schoolchildren (10 years)</b>							
<i>Number in cohort 2010</i>							
		*	*	*	25	51	*
DT-IPV	Number	*	*	*	20	39	*
	%	*	*	*	° 80.0%	76.5%	*
MMR2	Number	*	*	n/a	21	n/a	*
	%	*	*	n/a	° 84.0%	n/a	*
<b>Girls (10 years)</b>							
<i>Number in cohort 2010</i>							
		*	*	*	15	19	*
HPV	Number	*	*	*	13	14	*
	%	*	*	*	° 86.7%	73.7%	*
<b>Adolescents</b>							
<i>Number in cohort 2016</i>							
		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

\* Unknown due to research-technical issues or not yet available due to special circumstances relating to the COVID-19 pandemic.

<sup>a</sup> 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 are linked ad hoc to the population administration.

<sup>b</sup> Vaccination status at 2 years of age: DTaP-IPV/MMR = basic immunity, Hib/HBV/PCV/MenC = completely closed; at 5 years of age: DT(aP)-IPV = re-vaccinated; at 10 years of age: DTaP/MMR/HPV = full participation.

<sup>c</sup> Interim vaccination coverage: the vaccination is linked to school year not birth year; vaccination will be offered in 2020 for part of these children.

**Table 7.2** Number of reports of NIP diseases in the Caribbean Netherlands, 2017-2020.

	Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
<i>Diphtheria</i>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<i>Haemophilus influenzae type b</i>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<i>Measles</i>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<i>Meningococcal disease</i>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<i>Mumps</i>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<i>Pertussis</i>						
No. of reports in 2017	*	2	*	0	*	*
No. of reports in 2018	*	1	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<i>Pneumococcal disease</i>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*

	Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
<b>Poliomyelitis</b>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<b>Rubella</b>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*
<b>Tetanus</b>						
No. of reports in 2017	*	0	*	0	*	*
No. of reports in 2018	*	0	*	0	*	*
No. of reports in 2019	*	0	*	0	*	*
No. of reports in 2020	*	0	*	0	*	*

\* Not yet available due to special circumstances relating to the COVID-19 pandemic.

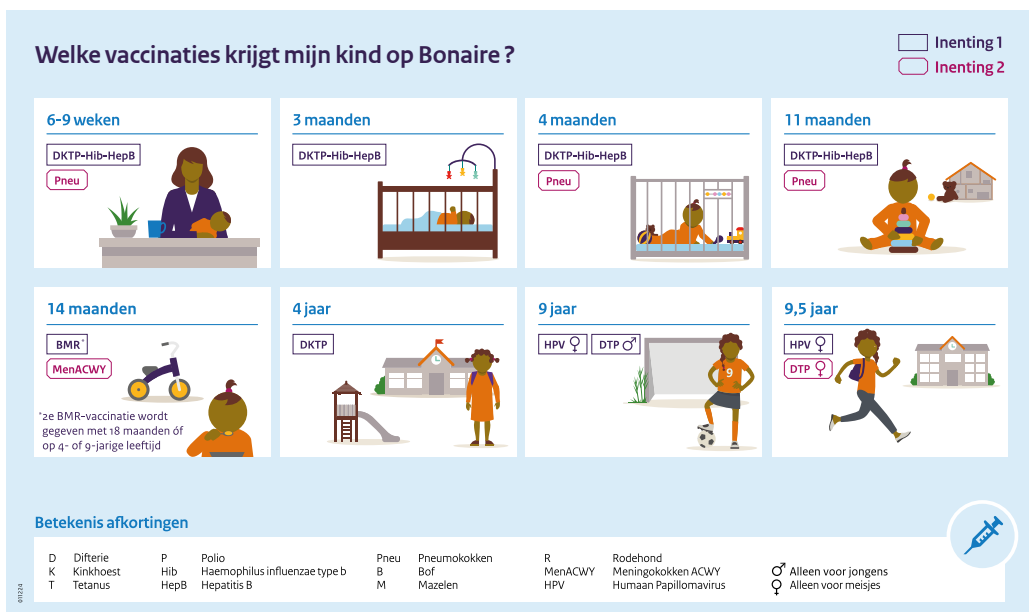


Figure 7.1 Immunisation schedule for Bonaire (in Dutch).

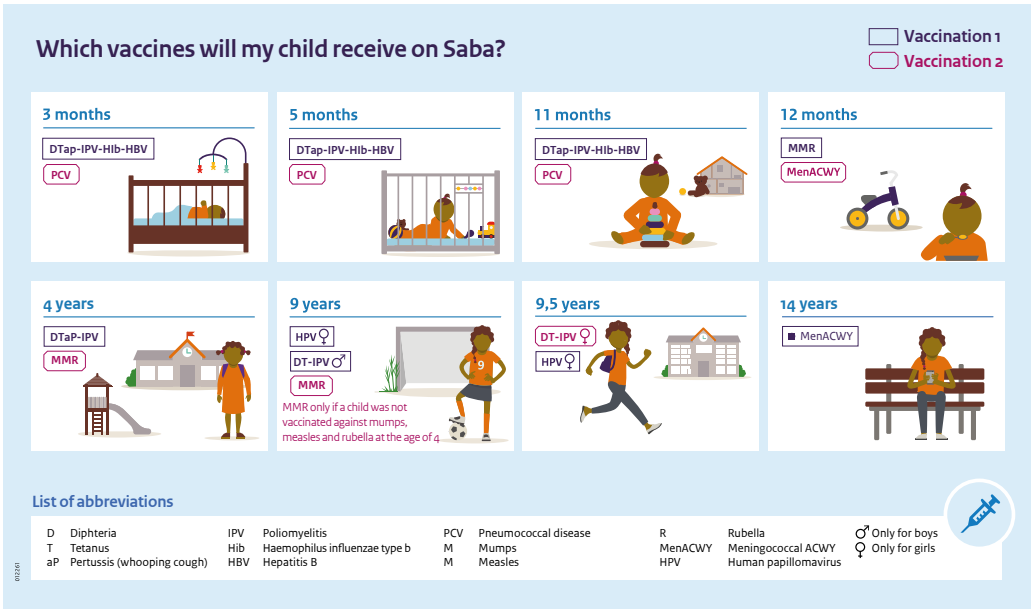


Figure 7.2 Immunisation schedule for Saba.

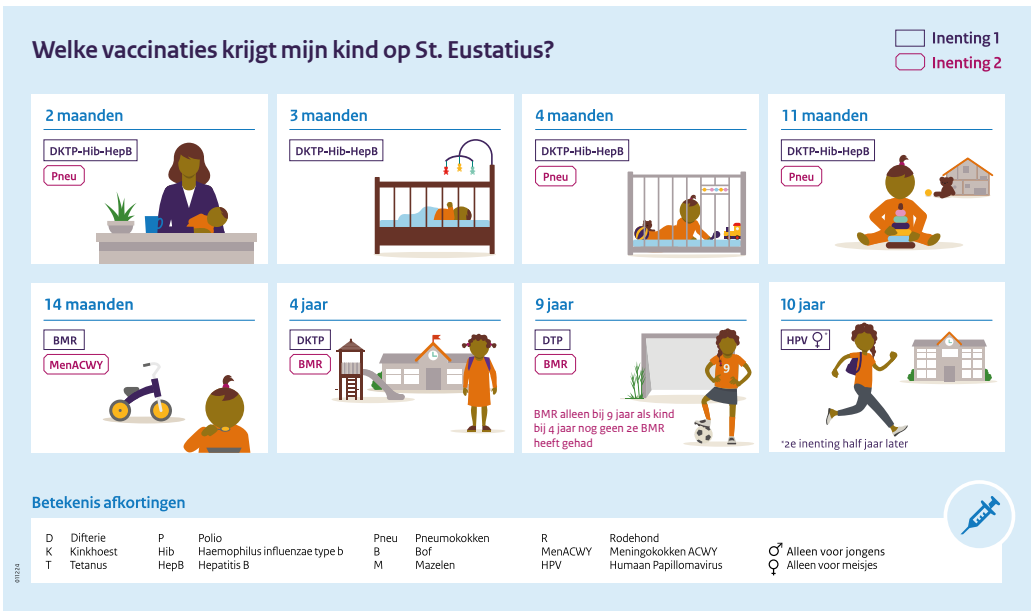


Figure 7.3 Immunisation schedule for St. Eustatius (in Dutch).

**Table 7.3** Immunisation schedule for Curaçao.

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

**Table 7.4** Immunisation schedule for Aruba.

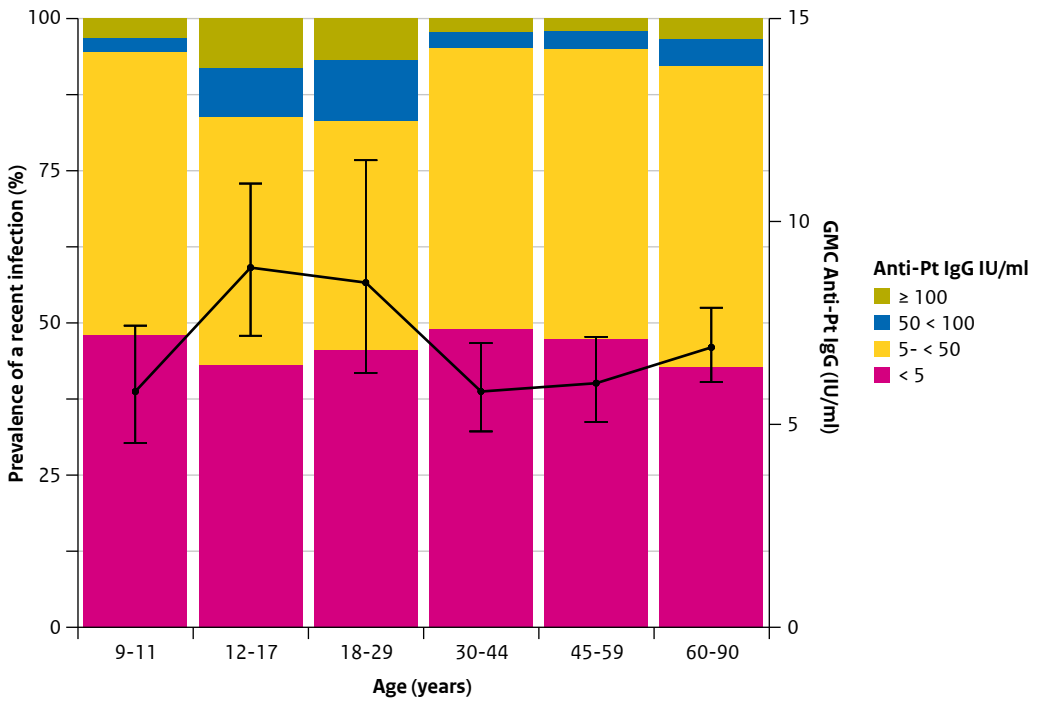
Age or school year	Vaccination 1	Vaccination 2
1 month	HepB 1	
2 months	DTaP-IPV-Hib 1	Pneu 1
3 months	HepB 2	
4 months	DTaP-IPV-Hib 2	Pneu 2
6 months	DTaP-IPV-Hib 3	
9 months	HepB 3	
12 months	MMR 1	Pneu 3
15 months	DTaP-IPV-Hib 4	
4 years	MMR 2	DKTP
5 <sup>th</sup> year (10/11 years)	DKTP	
6 <sup>th</sup> year (11/12 years)	HPV*	

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

**Table 7.5** Immunisation schedule for St. Maarten.

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

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



**Figure 7.4** Weighted age-specific prevalence of recent infection and geometric mean concentrations (GMCs). The prevalence of recent infection was divided into three categories: no recent infection ( $<50$  international units (IU)/mL), infection in the last 6 to 12 months ( $50 < 100$  IU/mL), and infection in the previous 6 months ( $\geq 100$  IU/mL). The black line represents the geometric mean concentration (GMC) with corresponding 95% CI: per age group.

## 7.2 Immunisation schedules

The immunisation schedules for the Caribbean Netherlands are presented in Figures 7.1.1, 7.1.2, and 7.1.3, and Tables 7.3, 7.4, and 7.5.

Saba offers the MenACWY vaccination to 14-year-olds since 2 December 2<sup>nd</sup>, 2019. Pregnant women on Saba are offered the maternal pertussis vaccine since May 22<sup>nd</sup>, 2020. This last addition resulted in a schedule change for the DTaP-IPV-Hib-HepB vaccination, from 4 vaccinations offered at 6-9 weeks and 3, 4, and 11 months, to 3 vaccinations offered at 3, 5, and 11 months.

From October 2021 onwards, the Youth Healthcare on Bonaire offers pregnant women the Maternal Pertussis Vaccination (Tdap) starting at 22 weeks gestation. As a result, Bonaire's DTaP-IPV-Hib-HepB basic series vaccination schedule will change to 3, 5, and 11 months, accompanied by a shift of the first dose of the pneumococcal vaccination series from 6-9 weeks to 3 months. Bonaire is working on the implementation of two more vaccinations in the near future. From the end of 2021, the MenACWY vaccine will be offered to adolescents aged 14 years. Starting on March 1<sup>st</sup>, 2022, Bonaire will offer VZV vaccines to all children aged 14 months (born on or after January 1<sup>st</sup>, 2021), by replacing the MMR vaccine they currently give at 14 months with the MMRV vaccine.

## 7.3 Vaccination coverage

Table 8.1 presents the vaccination coverage in the Caribbean part of the Netherlands. Due to the special circumstances relating to the COVID-19 pandemic, it was impossible to obtain timely data on vaccination coverage for the islands of Bonaire, Curaçao, Aruba and St. Maarten.

In general, vaccination coverage in the Caribbean part of the Netherlands is high. However, due to differences in target groups and vaccination schedules, data on vaccination coverage are not always easy to compare. The method for determining vaccination coverage as used in this chapter often results in an underestimation for schoolchildren in this area, 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.

## 7.4 Epidemiology of diseases included in the NIP

Table 8.2 shows the number of notifications of NIP diseases in the Caribbean Netherlands from 2017 to 2020.

### 7.4.1 Epidemiology in Bonaire

A few cases of pertussis were reported on Bonaire in 2017 and 2018. In 2019 and again in 2020, no cases of pertussis were reported. Also, no cases of diseases included in the NIP were reported in 2020.



#### 7.4.2 Epidemiology in Saba

In 2019 and in 2020, no cases of diseases included in the NIP were reported on Saba.

### 7.5 Research

#### 7.5.1 Seroepidemiology of pertussis in the Caribbean Netherlands

In 2017, the RIVM partnered with the local Municipal Health Services and Statistics Netherlands to conduct the Health Study Caribbean Netherlands. In line with the European Netherlands, registration of clinical pertussis cases is mandatory for disease surveillance in the Caribbean Netherlands. Few cases are reported each year, however due to a lack of laboratory facilities this number is thought to be underestimated. In this seroepidemiological study, our aim was to gain knowledge about the circulation of *Bordetella pertussis* by tracing the frequency of recent infections on the islands of CN. Furthermore, we aimed to investigate what risk factors contribute to the risk of contracting *B. pertussis*.

The results indicate that the circulation of *B. pertussis* in CN is vastly underestimated. Among residents without detectable vaccine-induced humoral immunity, an estimated 8.2% were infected with *B. pertussis* within the previous twelve months, and the highest rates of recent infections were found in adolescents aged 12-17 years (16.1%) and young adults aged 18-29 years (16.7%) (Figure 7.1.4). Furthermore, participants living on Bonaire and those of Dutch Caribbean or Surinamese origin were more likely to be recently infected with *B. pertussis* (9.7% and 10.7%, respectively). These factors should be taken into account in the evaluation of transmission to vulnerable individuals and optimisation of the vaccination programme. We suggest that such seroepidemiological data should be updated regularly for a better understanding of *B. pertussis* circulation [1].

### 7.5 Literature

- 1.\* Immink MM, Vos ERA, Janga-Jansen AVA, Baboe-Kalpoë S, Hulshof K, van Vliet J, et al. Circulation of *Bordetella pertussis* in the Caribbean Netherlands: a population-based seroepidemiological study. *Int J Infect Dis.* 2021;111:21-7.

\* RIVM publication.

8

# Potential NIP target diseases



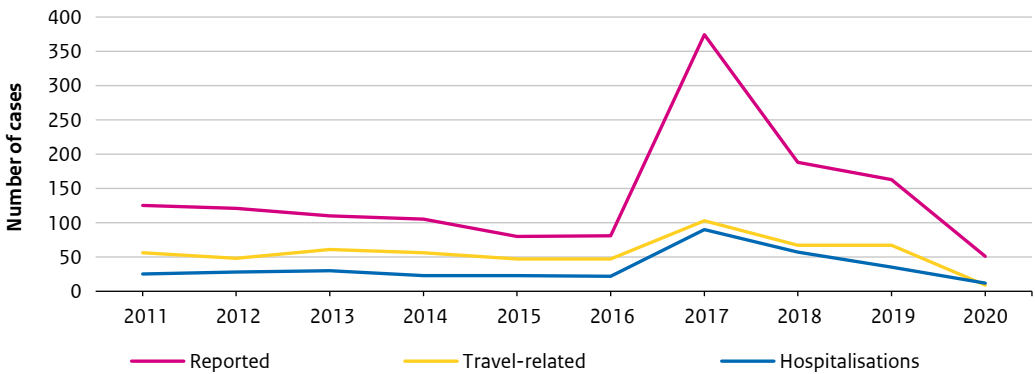
## 8.1 Hepatitis A

I.H.M. Friesema, H. Vennema

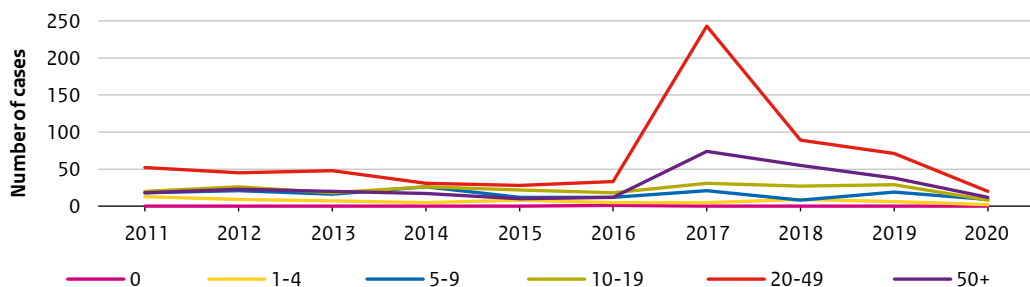
### 8.1.1 Key points

- In 2020, 51 hepatitis A-cases were reported, which is the lowest number since hepatitis A became notifiable in 1999.
- Almost two-thirds of the cases in 2020 were 20 years or older.
- Only nine cases (18%) were reported to be travel-related, compared to 41% (28-59%) in previous years (2011-2019).
- Travel and person-to-person contact are important transmission routes for hepatitis A. The measures taken since mid-March 2020 to control COVID-19 could, therefore, explain the deviant, low numbers.

### 8.1.2 Tables and figures



**Figure 8.1.1** Number of reported, hospitalised and travel-related cases of hepatitis A, 2011-2020. Source: Osiris.



**Figure 8.1.2** Age distribution of hepatitis A cases, 2011-2020.

Source: Osiris.

### 8.1.3 Epidemiology

A large-scale international hepatitis A outbreak occurred in 2017, 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 nationally and internationally [2]. In 2019, the total number of cases remained relatively high compared to 2011-2016 (Figure 8.1.1/Appendix 2). In 2020, only 51 hepatitis A cases were notified, corresponding to 0.3 cases per 100,000, which is the lowest incidence since hepatitis A became notifiable in 1999. This low number is likely the result of the COVID-19 control-measures. No mortality due to hepatitis A was reported in 2020. The age distribution for the years 2011-2020 is shown in Figure 8.1.2. Infections occur primarily in 20- to 49-year-olds. Adults (>19 years) account for 61% of cases. In total, 12 patients were hospitalised (24%), which is comparable to the hospitalisation rates observed in previous years (2011-2019: 20-30%; mean: 25%).

In 2020, only 18% of the cases was travel-related whereas the percentage of travel-related cases varied between 28% (2017) and 59% (2015) in previous years (2011-2019; mean: 41%). The nine travel-related cases in 2020 reported to have contracted the infection in Egypt (n=2), Spain (n=2), Bonaire, Kenya, Mozambique, South Sudan, and Tanzania.

Based on notifications, four epidemiologically linked clusters could be deduced, two of which started in 2019: one cluster with two cases in 2019, of which the first was infected in Morocco and the second occurred in January 2020, and a second cluster with three cases in 2019 and fourteen cases up to the beginning of March 2020, where a school was the main transmission route. The two other clusters consisted of one household (two cases) and a travel-related case. The latter indirectly infected a sewage worker who worked in the drains of the municipality in which the first case was a resident. All but the household cluster were molecularly confirmed.

The low number of cases, travel-related cases and clusters 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 COVID-19 control measures taken from mid-March 2020 onward.

#### 8.1.4 Pathogen

Hepatitis A virus (HAV)-specific IgM-positive samples can be sent to the RIVM IDS for typing as part of the molecular surveillance of this virus. In 2020, samples of 38 of 51 reported cases (75%) were submitted for virus typing. Samples from the remaining cases were not submitted for various reasons, sometimes because the Municipal Health Service had 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 188 serum and faecal samples of 174 unique persons were tested at the RIVM. HAV RNA was detected in 41 samples (22%) and 36 of the reported cases could be typed, which resulted in 17 unique sequences. A total of 25 cases could be assigned to clusters of 2 or more cases. These concerned 6 molecular clusters varying between 2 and 14 cases. In 2020, there were no major foodborne hepatitis A clusters in the Netherlands. A single case and a cluster of 2 cases probably belonged to small clusters seen in other European countries, which were most likely foodborne. All clusters were contained by contact tracing and vaccination. At the end of 2019, a cluster was detected with 3 cases that continued in 2020 with another 14 cases. Transmission occurred within households and a school.

Progress has been made towards whole genome sequence (WGS) analysis for HAV. The biggest advantage is increased resolution, which makes it possible to examine transmission chains in outbreaks and 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 allow WGS for samples with a relatively low titre as well.

#### 8.1.5 Research

The international outbreak of hepatitis A in 2016-2018 and the smaller outbreaks in the Netherlands in 2019 show susceptibility to the virus in adults, and especially in MSM. An analysis is ongoing to determine whether vaccination of MSM could be cost-effective, but has been delayed as time and resources are now focussed on the COVID-19 pandemic.

#### 8.1.6 International developments

Originally, most inactivated HAV vaccines were given using a three-dose schedule. Andani et al. [3] conducted a systematic review on the impact of one-dose and two-dose vaccination of children with these vaccines. In total, 33 peer-reviewed articles and one conference abstract were included, of which 28 studies were conducted in real-world settings and six reported results of clinical trials. More data, especially longer follow-up periods, are available for two-dose than for one-dose vaccinations. Persistence of declines in incidence was reported for at least 14 years and 6 years, respectively; antibody persistence after two-dose and one-dose vaccination was seen for up to 15 years ( $\geq 90\%$ ) and 10 years ( $\geq 74\%$ ), respectively.

Agrawal et al. [4] compared the immune response as reported in one study in children with 15 years of follow-up after two doses of Twinrix® with four studies in adults (one study with three doses of Twinrix® and three studies with two doses of Havrix®) with up to 20 years of follow-up. In part of the adult studies, mathematical modelling predictions of immunogenicity was also available. The geometric mean concentrations (GMCs) followed a comparable trend and remained over the protective threshold level of 20 enzyme-linked immunosorbent assay units of anti-hepatitis A antibodies per ml until the end of the follow-up period across all five studies. It is therefore likely that the GMCs in children will follow the same kinetics after 15 years as seen in the adult studies. A further extrapolation based on the mathematical modelling of the adult data to predict longer-term persistence was done, in which >85% of the vaccinated children would remain protected after 50 years.

A study in Panama compared the antibody persistence approximately 8 (Y8: 7-<10 years) and 10 years (Y10: 10-<13 years) after vaccination with one or two doses of Havrix® in children [5]. In total, 1199 children participated in the two repeated independent cross-sectional serological surveys: 600 at Y8 (300 children per group) and 599 at Y10 (299 in the 1-dose group and 300 in the 2-dose group); 42 children participated in both Y8 and Y10 surveys. At Y8, 74.3% (95% CI: 69.0-79.2%) of children in the 1-dose group and 97.7% (95.3-99.1%) in the 2-dose group had anti-HAV antibody concentrations  $\geq$  15 mIU/mL. At Y10, this was 71.9% (66.4-76.9%) and 96.3% (93.5-98.2%), respectively. At both Y8 and Y10, the anti-HAV antibody GMCs were lower in participants who had received 1 dose compared to those who had received 2 doses with a between-group GMC ratio of 0.32 (95% CI: Y8: 0.27-0.39; Y10: 0.27-0.38).

Within five years after introduction of single dose vaccination with Havrix® for children aged over three years in the immunisation schedule of the Republic of Tuva, no more cases of hepatitis A were reported [6]. A coverage of 87.4% in children aged 3-8 years was reached in the first months of vaccination (August-December 2012). In 2013, hepatitis A incidence dropped with 96.7% to 3.2 per 100,000 in the total population, further declining to zero cases in 2016-2019. Protective anti-HAV antibody concentrations ( $\geq$ 10 mIU/mL) were detected in 98.0% (95% CI: 96.2-99.0% (n=451)) of children tested one month after vaccination, in 93.5% (91.0-95.4% (n=510)) and in 91.1% (88.2-93.4% (n=463)) of children one year and five years after vaccination, respectively.

Vaqa® was incorporated as a one-dose vaccination in the Brazilian national immunisation programme in July 2014, targeting the 1- to 4-year-olds [7]. The effect of this vaccination programme on hepatitis A incidence was examined by conducting an interrupted time-series analysis comparing 2010-2013 with 2015-2018. The mean vaccination coverage in the period 2014-2018 was 78.0%. The overall incidence rate of hepatitis A decreased significantly after the vaccine programme was implemented, ranging from 3.18/100,000 in 2010 to 0.87/100,000 in 2018. A downtrend in incidence of hepatitis A was already seen prior to the start of the universal HAV vaccination with a yearly reduction of 3.9%, which continued in the post-vaccination period with a yearly reduction of 13.4%. A large extra effect of 67.1% reduction in incidence rate in the entire population was noticed immediately following vaccine introduction.

Alaska started universal hepatitis A vaccination for all children in 1996 [8]. A group of children aged 6-24 months from a randomised study set up in 1997 has been followed since then. These infants had received two doses of Havrix® after randomly being assigned to one of three vaccination schedules: aged 6 and 12 months (group 1), aged 12 and 18 months (group 2), or aged 15 and 21 months (group 3). After 20-years of follow-up, 75 of the original 183 participants (41%) were available for analyses of which 50 remained seropositive (68%). Those who were lost to follow-up at this time-point had significantly lower baseline GMCs at the 1-month post-second dose time point compared to those who participated (1,964 mIU/mL vs. 2,248 mIU/mL). The GMC across the three groups was 29.9 mIU/mL (95% CI: 22.4-39.7). A significant difference in GMC was seen compared to the 15-year time-point, but not compared to the 18-year time-point. Furthermore, GMC was significantly lower in infants whose mothers had anti-HAV titres present during pregnancy, and marginally significantly associated with dose group (highest GMC in group 3).

In another study in Alaska, a cohort of Alaska Native children aged 3-6 years in 1991 and followed up for 25 years, 43 of the original 144 participants (30%) were available for analyses of which 35 remained seropositive (81%) [9]. Using data from all persons and all time points, a survival analysis estimated 78.7% of participants had protective levels of anti-HAV at 25 years. The children had received three doses of Havrix® at schedules of 0, 1, 2 months (group A), 0, 1, 6 months (group B), or 0, 1, 12 months (group C). GMC was statistically significantly lower in group A (42.9 mIU/mL) compared to group B (100.6 mIU/mL) and C (176.5 mIU/mL).

Normally, a hepatitis A vaccine is given intramuscularly. However, patients with bleeding disorders should avoid intramuscular injections as it may result in bleeding and bruising of muscles, requiring treatment. Nakasone et al. [10] describe a randomised clinical study in which intramuscular injection (IM group) is compared with subcutaneous injection (SC group) of hepatitis A vaccine. The Havrix® or Vaqta® vaccines were used and given twice with a six-month interval. Out of 78 patients, 38 had serology performed after the first dose. There was no statistically significant difference in seroconversion rates between the SC group (83.3%) and IM group (90.0%). All 40 persons in the SC group and 38 persons in the IM group measured after the second dose reached seroconversion. In a median of nine years after the second dose, antibody titres appeared slightly, but not significantly, higher in the SC group compared to the IM group.

In Thailand, a prospective study was performed to examine the possible effect of obesity on the immunogenicity of live attenuated HAV vaccine (MEVAC™-A) in subjects aged 7 to 25 years [11]. A total of 212 of initial 236 subjects were seronegative at the start of the study and could be followed up until the end of the study. Of this group, 117 (55%) belonged to the non-obese group and 95 (45%) belonged to the obese group. Anti-HAV titre measurement at a mean of eight weeks after vaccination revealed seroprotection for all subjects, with a GMC of 446.11 (95% CI: 421.64-472.01). No differences were seen between the obese and non-obese group. Within the obese group, truncal obesity was associated with a higher postvaccination titre compared to the subjects without truncal obesity.

Wang et al. [12] screened faecal samples from participants vaccinated with live attenuated hepatitis A vaccine. HAV antigen was detected in 11.36% (31/273; day 0), 11.44% (31/271; day 7), 9.70% (26/268; day 14), 8.47% (21/248; day 21) and 9.70% (23/237; day 28) of the faecal samples. All of the 77 randomly selected and isolated HAV strains from the faecal samples were classified into genotypes 1B. Phylogenetic analysis showed that VP1/2A from all isolated strains belonged to or was close to the cluster of the sequence of the attenuated strain. Overall, approximately 25% of the participants tested were positive for HAV antigen in faecal samples within 28 days after vaccination. Therefore, secondary infection and the possibility of mutational shifts of the live vaccine virus cannot be neglected.

### 8.1.7 Literature

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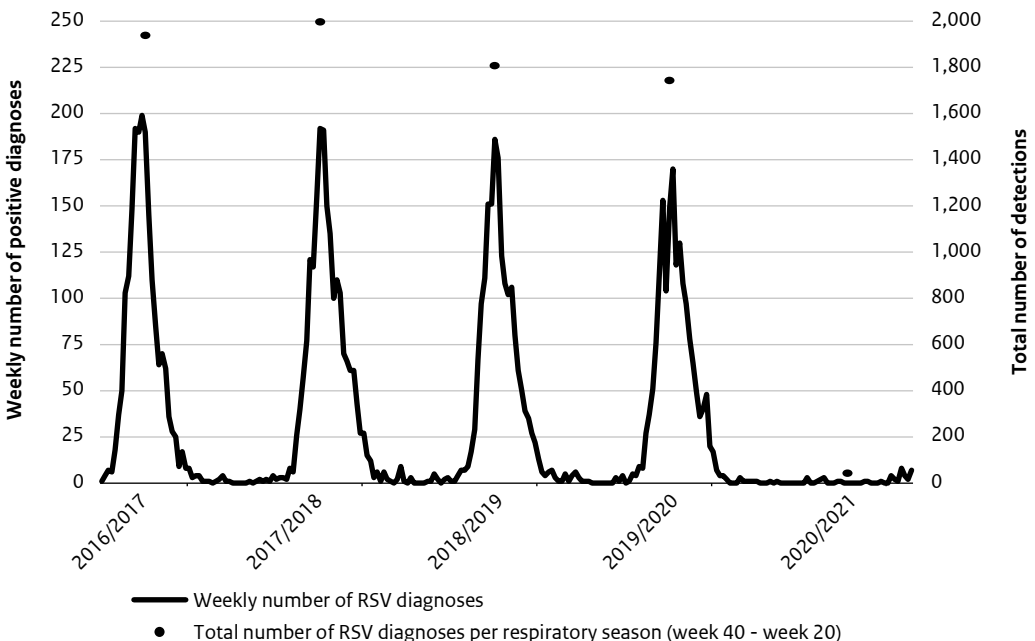
## 8.2 Respiratory Syncytial Virus

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

### 8.2.1 Key points

- During respiratory season 2020/2021, for the period up to and including week 20 of 2021, the number of Respiratory Syncytial Virus (RSV) detections in the virological laboratory surveillance was extremely low and never exceeded the epidemic threshold of 21 detections. This was likely the result of the control measures against COVID-19.
- During this 2020/2021 respiratory season, in none of the 414 patients with an acute respiratory infection (ARI) including Influenza-Like Illness (ILI), RSV was detected in nose swabs and throat swabs, collected by the Nivel sentinel GPs.
- In week 23 2021, after the end of the reporting period of this report, an out-of-season RSV epidemic started in the Netherlands.

### 8.2.2 Tables and figures



**Figure 8.2.1** Number of weekly reported RSV diagnoses (black line) and total number of RSV diagnoses in the respiratory season (blue dot) in the virological laboratory surveillance for the period 2016/2017-2020/2021, for the period up to and including week 20.

Source: virological laboratory surveillance, NWKV.

### 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 into RSV-A and RSV-B based mainly on the variation in the attachment protein, the G-protein.

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 the National Influenza Centre (NIC) at the RIVM for influenza viruses, RSV, rhinoviruses, enteroviruses, SARS-CoV-2 since February 2020, and parainfluenza viruses types 1-3, human metapneumovirus and human seasonal coronaviruses since January 2021. RSV detections in virological laboratory surveillance mainly represent RSV laboratory analysis from hospitalised paediatric patients that are tested for clinical purposes [5, 6].

During the 2020/2021 respiratory season, RSV was detected in none of the 414 patients with an acute respiratory infection (ARI) including Influenza-Like Illness (ILI), in nose swabs and throat swabs collected by sentinel GPs. The total number of diagnoses in the virological laboratory surveillance from week 40 of 2020 up to and including week 20 of 2021 amounted to 42, fluctuating between 0 and 8 with only 7 detections in week 20/2021, and did not exceed the epidemic threshold of 21 detections (determined by the Moving Epidemic method (MEM) [7]) during this period. This indicates an extremely low circulation of RSV, most likely due to the COVID-19 pandemic and accompanying non-pharmaceutical interventions. In week 23 of 2021, shortly after the end of the reporting period for this report, an out-of-season RSV epidemic started in the Netherlands. In that week, the number of detections in the virological laboratory surveillance exceeded the epidemic threshold and the numbers continued to increase until the moment of writing (last update July 21<sup>st</sup>, 2021; 164 detections in week 28). This increased RSV circulation was also observed in many other countries.

For more information on epidemiology in the Netherlands, please refer to the annual report 'Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2020/2021' ([link](#)), and the [RIVM website on RSV surveillance](#) (only available in Dutch).

### 8.2.4 Research

The RIVM is a partner in [the RESCEU project](#), funded by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement 116019, receiving support from the European Union's Horizon 2020 Research and Innovation Programme and the European Federation of Pharmaceutical Industries and Associations. This project aims to explore the clinical, economic and social burden of RSV and strengthen European collaboration through the many different disciplines working on RSV. The aim is to create a sound epidemiological and virological baseline before introduction of a vaccine to identify appropriate target groups for vaccination. As part of the RESCEU project, the RIVM therefore combines data from several sources, such as hospitals, general practitioners and the national perinatal registry, to achieve a better understanding of the burden of RSV in the Netherlands [8, 9]. Further, analyses using data from

the PIENTER serological studies [10] revealed that the majority of children in the Netherlands experience an RSV infection before the age of 2 years, and that age and birth date are strong predictors of early RSV infection. Specifically, at the age of 1 year children born in summer have substantially higher estimated probability of prior infection than those born in winter (0.56 (95% CI: 0.45-0.66) vs. 0.32 (0.21-0.45)). In addition, having young siblings in the household (0-4 years) and attending day-care are also found to significantly increase the probability of prior RSV infection [11].

European collaboration on surveillance of RSV and better harmonisation in both epidemiological and virological aspects of surveillance are important to strengthen RSV surveillance at the national and European level. The RIVM plays an important part in European initiatives on RSV surveillance and works closely with the ECDC and other public health institutes, specifically SSI (Denmark). This has led to the collective formulation of recommendations that can be applied to establish or improve epidemiological and virological RSV surveillance at the national level and for the European region [12].

In addition to epidemiological data, a thorough understanding of the immunological mechanisms underlying (protection from) severe RSV disease is essential for advising on the implementation of novel vaccines. Although RSV is increasingly recognised for causing severe morbidity and mortality in older adults, there are few studies on the RSV-induced immune response in this population. Information on the immunological processes at play during RSV infection in specific risk groups is essential for the targeted design of vaccination strategies. For this reason, we have assessed the antibody and local cytokine response to RSV infection in community-dwelling adults  $\geq 60$  years of age [13]. A statistically significant increase in serum neutralisation titres and IgG concentrations was observed in RSV-infected participants compared to controls. In addition, during acute RSV infection, a statistically significant local upregulation of several cytokines was observed. This study provides novel insights into the basic immune response to RSV infection in an important and understudied risk population.

### 8.2.5 International developments

The past year has witnessed a number of interesting changes in the RSV vaccine development landscape; for a complete overview of the current situation see [link](#). After disappointing results of two phase 3 trials in older adults (NCT02608502) and pregnant women (NCT02624947), Novavax has discontinued the development of their nanoparticle RSV F vaccine. Both GSK (NCT04605159 and NCT04732871) and Pfizer (NCT04424316) have moved their recombinant RSV F subunit vaccines into phase 3 trials in older adults (GSK) and pregnant women (GSK and Pfizer). Moderna has moved their RSV F mRNA vaccine into phase 1 in (older) adults and children (NCT04528719). Finally, promising results were published by MedImmune/Astra Zeneca concerning a phase 2b trial (NCT02878330) of an improved anti-F monoclonal antibody (Nirsevimab) in preterm infants [13]. A phase 3 trial of this prophylactic therapeutic, which requires only a single dose due to its longer half-life, in term infants is currently underway (NCT03979313).

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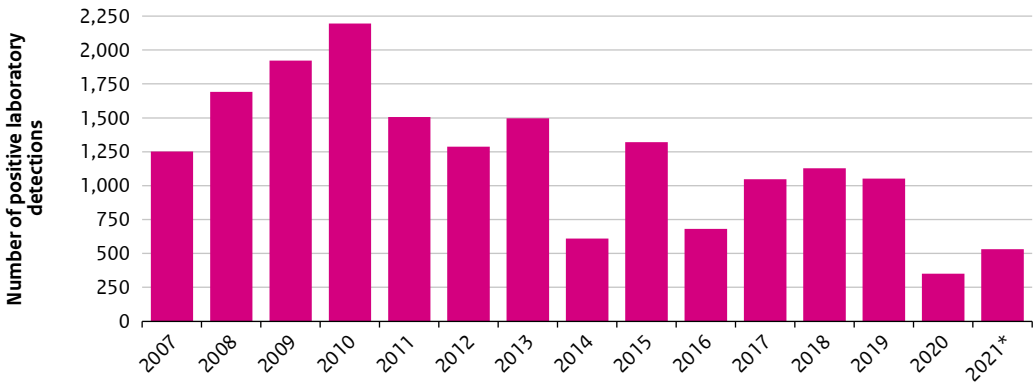
## 8.3 Rotavirus

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### 8.3.1 Key points

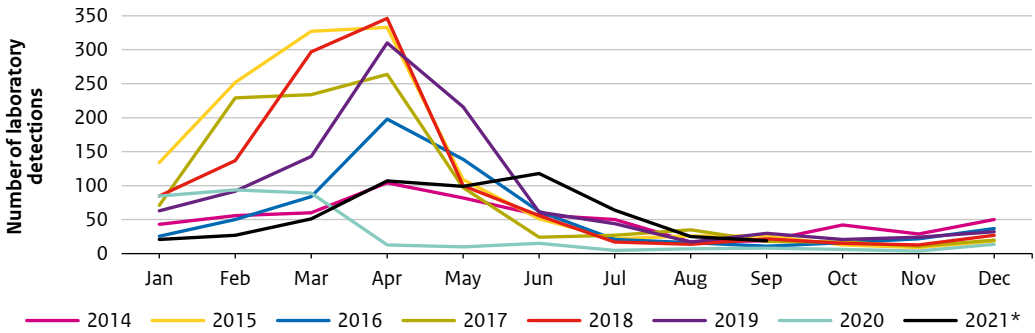
- The number of detected rotavirus cases in 2020 was lower than in 2019. In 2021, up to September, a delayed rotavirus season is observed with a significantly reduced number of rotavirus detections compared to the same period in the years before 2020. The COVID-19 control measures including social distancing likely play a role in this decrease.
- G9P8 was the most prevalent genotype in 2020.
- The Ministry of Health, Welfare and Sport has decided to cease implementation of rotavirus vaccination for high-risk infants in the National Immunisation Programme. The ministry requested a new recommendation from the Health Council. The Health Council recommend implementing universal rotavirus vaccination in the National Immunisation Programme.

### 8.3.2 Tables and figures



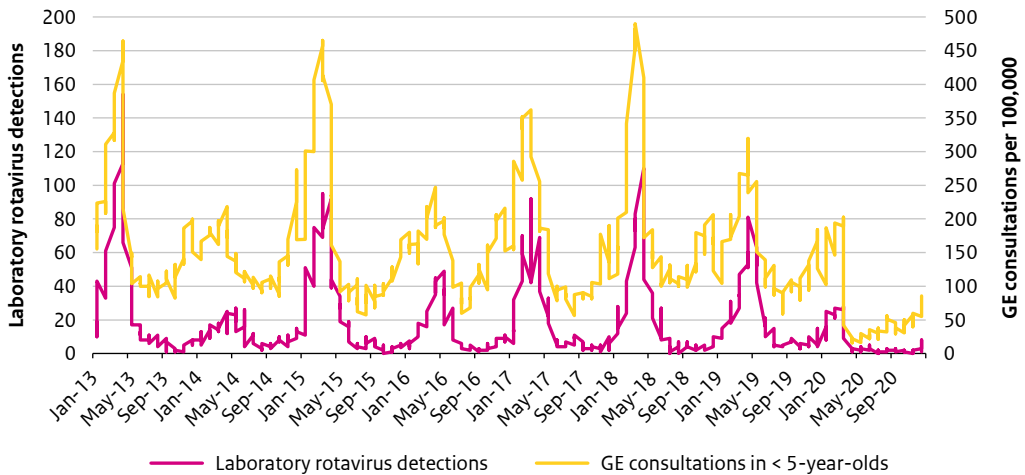
**Figure 8.3.1** Number of reported laboratory rotavirus detections per year in the Netherlands, 2007-2021.

\* Up to and including September 26<sup>th</sup>, 2021.



**Figure 8.3.2** Number of reported laboratory rotavirus detections per month in the Netherlands, 2014-2021.

\* Up to and including September 26<sup>th</sup>, 2021.



**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, 2013-2020.

**Table 8.3.1** Number of rotavirus samples typed per year and identified genotypes, the Netherlands, 2013-2020.

Type	2013	2014	2015	2016	2017	2018	2019	2020	Total
G12P8	1	6	2	0	1	2	1	0	13
G1P8	83	20	25	9	23	7	12	2	181
G2P4	41	29	34	12	12	6	13	5	152
G3P8	51	7	14	23	38	56	40	3	232
G4P8	35	12	137	3	23	3	0	0	213
G9P8	23	49	32	59	20	60	38	11	292
G9P4	1	0	1	0	8	29	24	1	64
Other	52	16	27	12	42	16	17	0	182
<b>Total</b>	<b>287</b>	<b>139</b>	<b>272</b>	<b>118</b>	<b>167</b>	<b>179</b>	<b>145</b>	<b>22</b>	<b>1,329</b>

### 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 Weekly virology report

In 2020, 350 rotavirus detections were reported, which is substantially lower than in 2019 (n=1,053) (Figure 8.3.1). Most rotavirus laboratory detections were reported between January and March (77%) (Figure 8.3.2). Data from 2021, for the period up to and including September 26<sup>th</sup> show 531 rotavirus detections, which is remarkably low for that period of the year (Figure 8.3.2). The peak of the rotavirus season was observed in June 2021, which makes it appear to be a delayed season. The low number of rotavirus detections in 2020, which has continued in 2021 (up to September) is likely due mainly to the COVID-19 control measures, such as the closure of schools and daycare, limited number of visitors per day, social distancing and increased handwashing [1].

The remarkably low seasons in 2014 (n=609 detections) and 2016 (n=682 detections) led to the hypothesis of a shift in the rotavirus seasonal pattern to a biennial pattern. However, the rotavirus seasons in 2017, 2018 and 2019 contradict this hypothesis (Figure 8.3.2).

#### 8.3.3.2 Nivel

The 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 vomiting, diarrhoea, or presumed gastrointestinal infection.



In 2020, 3,455 all-cause GE consultations were reported per 100,000 children younger than five years of age (on average 66 per 100,000 per week) (Figure 8.3.3). This was about half the number of all-cause GE consultations in 2019 (n=7,916 per 100,000, on average 152 per 100,000 per week). This decline is most likely the result of a reduced rotavirus incidence, as well as decreased healthcare utilisation due to COVID-19 control measures [3]. Consultations in 2020 were most frequent between January and March, with 1,948 registered consultations per 100,000 children, which is less than the number of consultations registered in the same period in 2019 (n=2,401 per 100,000).

### 8.3.4 Pathogen

The 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 2020, all of the received samples could be typed (Table 8.3.1). Half of the typed samples (11/22) were identified as rotavirus G9P8, which is higher compared with previous years (2019=26%; 2018=36%; 2017=12%). Besides G9P8, the most prevalent genotype was G2P4, which accounted for 23% (5/22) of the typed samples. Overall, there were few rotavirus samples available for typing in 2020, due to which the genotyping results may not be representative.

### 8.3.5 (Inter)national developments

In April 2020, the Ministry of Health, Welfare and Sport decided to cancel implementation of rotavirus vaccination in the National Immunisation Programme due to the unexpected lower estimates of vaccine effectiveness found in the RIVAR study for high-risk infants [4]. The Ministry asked the Health Council for a new recommendation on rotavirus vaccination. In June 2021, the Health Council advised to implement universal rotavirus vaccination in the National Immunisation Programme [5]. For this to be cost-effective, the price of available vaccines needs to be reduced. The decision to go ahead with the implementation now lies with either the Minister or the Secretary of State in charge of the Health, Welfare and Sport portfolio.

As of May 2021, 107 countries worldwide have introduced rotavirus vaccination in their national immunisation programmes. Four of these countries have either phased or sub-national introductions. Of the ten countries with the highest numbers of rotavirus-related deaths, eight countries introduced rotavirus vaccination (Afghanistan, Angola, Democratic Republic of the Congo, Ethiopia, India, Kenya, Niger, and Pakistan) [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].

#### 8.3.5.1 RIVAR study

Between May 2016 and December 2019, rotavirus vaccination was offered to high-risk infants (i.e. infants with severe congenital pathology, prematurity and/or low birth weight) born in one of the thirteen participating Dutch hospitals as part of the RIVAR project (Risk-Group Infant Vaccination Against Rotavirus). The project was a pilot study on the feasibility and effectiveness of rotavirus vaccination in high-risk infants.

Of the infants eligible for rotavirus vaccination, 49% (726/1482) were vaccinated. Severe rotavirus acute GE occurred in 20 (31%) vaccinated and 18 (43%) unvaccinated infants between 2 and 18 months of age [9]. Vaccine effectiveness for severe rotavirus acute GE in the high-risk infants was lower than expected, namely 30% (95% CI, -40%;65%) compared with previously reported 68% to 98% in healthy infants [10]. It is hypothesised that the unexpectedly lower vaccination effectiveness might be the result of host and pathogen factors. For example, premature infants in the RIVAR study were generally of lower gestational age (GA) compared with a different study [11]. As lower GA is known to be associated with poorer vaccine responses, this may partly explain the lower vaccine effectiveness. Furthermore, vaccine effectiveness may have been influenced by the heterotypic genotype distribution during the study period. Another limitation of the study was the high dropout rate of approximately one third of the participants.

### 8.3.5.2 Vaccine effectiveness

A systematic literature review on the global impact of rotavirus vaccination on hospitalisations and deaths due to diarrhoea among children <5 years old, analysed published data from 2006-2019 with more than 12 months of data before and after rotavirus vaccine introduction [12]. The review shows a reduction in rotavirus hospitalisations between 46-74%, acute GE hospitalisations between 23-47%, and acute GE mortality between 28-46%. The reductions were larger in countries with low child mortality, among younger age groups, and in countries with higher rotavirus vaccination coverage.

Another literature review conducted by the same research group estimated, by means of meta-analysis, the pooled vaccine effectiveness of Rotarix and Rotateq in low-mortality countries [13]. Rotarix VE against laboratory-confirmed rotavirus infection of any severity among children younger than 2 years old was 86% (95% CI: 81-90). RotaTeq vaccine effectiveness among children younger than 1 year was 86% (95% CI: 76-92) and 84% (95% CI: 79-89) for children aged between 1 to 2 years of age. The median vaccine effectiveness was similar for Rotarix (83%; IQR 78-91) and RotaTeq (85%; IQR 81-92) among children younger than 2 years old in low-mortality countries.

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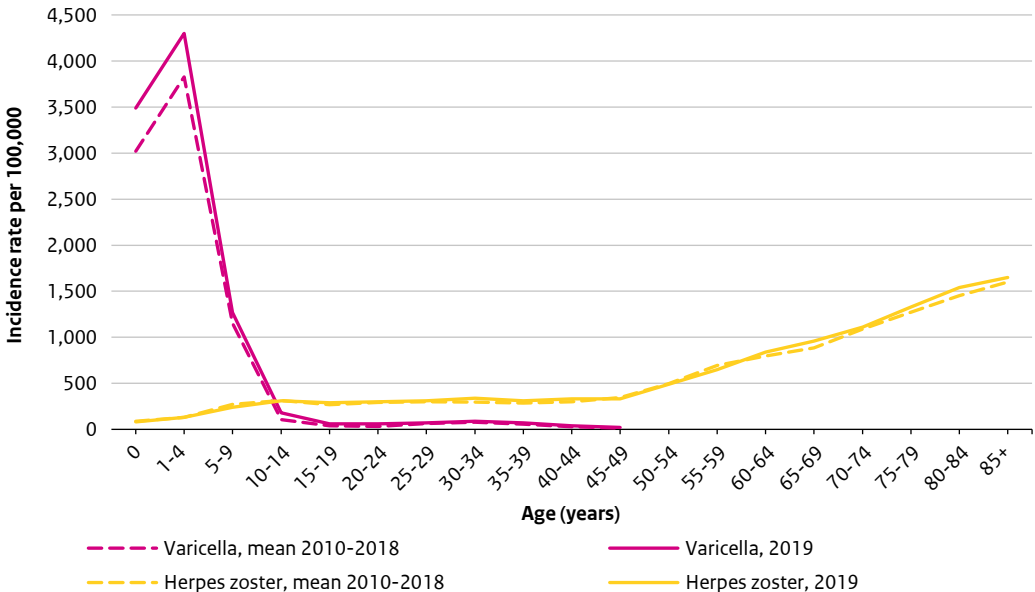
## 8.4 Varicella zoster virus (VZV) infection

E.A. van Lier, A. Buisman, M. Nielen, H.E. de Melker

### 8.4.1 Key points

- VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands did not change in 2019 and was comparable to that in previous years; in 2019, GPs recorded about 52,000 varicella and 95,000 herpes zoster episodes (300 and 550 episodes per 100,000 population, respectively). No data is available yet for 2020, i.e. the presented data concern the period before the beginning of the COVID-19 pandemic.
- First data on real-world effectiveness of Shingrix® highlight the importance of adherence to the second dose to improve effectiveness. Estimated vaccine effectiveness of 2 doses (70.1%) was lower than clinical trial estimates ( $\geq 90\%$ ), likely due to differences in outcome specificity.

### 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 2019 versus mean 2010–2018 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-PCD, using the old (2008-2011) and new methods (2010-2019) (rounded to nearest 10).

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Varicella*	(160)	(110)	(180)									
Varicella**	290	180	210	230								
Varicella***			310	270	250	280	270	250	240	280	260	300
Herpes zoster**	340	360	360	360								
Herpes zoster***			480	490	510	510	530	530	530	530	540	550

\* 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), 2008-2018 [4].

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015*	2016*	2017*	2018*
Varicella	1.7	1.5	1.9	1.7	1.5	1.7	1.9	1.8	2.0	2.0	1.7
Herpes zoster	2.0	2.4	2.1	2.2	2.1	2.1	2.7	2.9	2.8	2.8	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 are admitted more than once within the same year.

\* Data rounded off to 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.

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, 2008-2019 [5].

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Varicella	0	1	2	1	2	1	2	2	4	3	2	3
Herpes zoster	14	20	25	20	21	21	26	33	27	33	36	32

Source: CBS.

### 8.4.3 Epidemiology

VZV epidemiology in the Netherlands in 2019 was comparable to that in previous years (Tables 8.4.1, 8.4.2 and 8.4.3). No data is available for 2020 as of yet, so the presented data concern the period before the beginning of the COVID-19 pandemic. As such, it is not yet known whether varicella incidence in 2020 has changed due to COVID-19 measures. An effect of the COVID-19 pandemic was observed for other vaccine-preventable diseases in the Netherlands [6], and also for varicella in for example China and South Korea [7, 8]. In 2019, general practitioners (GP) recorded about 52,000 varicella and 95,000 herpes zoster (HZ) episodes (300 and 550 episodes per 100,000 population, respectively). The incidence of GP consultations due to varicella episodes per 100,000 population was highest in children aged under 5 years, whereas the incidence of GP consultations due to HZ episodes was highest in those aged 50 years and over (Figure 8.4.1).

According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards [9], the incidence of HZ is higher than it was as calculated using the old method (Table 9.4.1). Mahamud et al. found that national death certificate data tend to overestimate the number of deaths in which HZ is the underlying or contributing cause of death [10]. 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 2019, we would expect 4.3 deaths (range 1.7–6.6) instead of the 32 deaths reported in 2019 (Table 8.4.3).

### 8.4.4 International developments

#### 8.4.4.1 Varicella

A retrospective observational study over the period 2003–2018 showed a significant decrease in hospitalisation rates in Italy after the introduction of varicella vaccination. During the first five years after the introduction of vaccination, hospitalisation rates showed a statistically significant decrease especially among infants <1 year of age (AAPC (average annual percent change) -35.0%) and 1–5 years old (AAPC -35.2%). Total percentage changes were -80.0% and -86.7%, in the age class <1 year old and 1–5 years old, respectively [11]. According to a review of Kaufmann et al., varicella vaccination led to a reduction in moderate/severe varicella and varicella-related hospitalisations in both Italy (1- or 2-dose varicella vaccination programmes implemented successively in eight pilot regions between 2003 and 2011 and nationwide in 2017; long interval between two doses of  $\geq 4$  years) and Germany (1- and 2-dose varicella vaccination programmes implemented in 2004 and 2009, respectively; short interval between two doses of <1 year), despite different vaccination schedules [12]. A retrospective study in Quebec, Canada showed that varicella incidence decreased by 87.3% (95% CI: 86.6–87.9%) in immigrants and by 92.6% (95% CI: 92.4–92.7%) in non-immigrants due to the introduction of childhood varicella vaccination. So, although not covered by the childhood vaccination programme as efficiently as non-immigrants, immigrants benefited substantially from the herd protection effect [13, 14]. Rafferty et al. found that varicella vaccination in Canada reduced HZ risk in children across all age groups, in both vaccinated and unvaccinated individuals. HZ incidence in the unvaccinated group was 64% (RR: 0.36, 95% CI: 0.33–0.39) and 32% (RR: 0.68, 95% CI: 0.64–0.73) higher in the pre-universal vaccination (1993–1999) and universal

vaccination eras (2000–2018), respectively. The decreased impact of vaccination during the universal vaccination era is largely due to the decrease in HZ incidence among unvaccinated children observed after implementation of the universal vaccination programme. Among unvaccinated children, HZ risk was 60% lower after vaccine programme implementation (RR: 0.40, 95% CI: 0.38–0.43) [15].

Prymula et al. assessed the 10-year efficacy and immunogenicity of two doses of a combined MMRV vaccine or one dose of a monovalent varicella vaccine in children from Czech Republic, Lithuania, Poland, Romania, and Slovakia. Vaccine effectiveness against confirmed varicella ranged between 95.4% (Lithuania) and 97.4% (Slovakia) in the MMRV group (two doses) and between 59.3% (Lithuania) and 74% (Slovakia) in the MMR + V group (one dose). Vaccine effectiveness against clinical varicella cases varied from 94.5% in Lithuania to 96.6% in Poland (MMRV group) and 63.6% in Lithuania to 73.3% in Slovakia (MMR + V group) [16]. Habib et al. found that varicella-specific antibody concentrations (anti-VZV and anti-gE antibodies) are a good predictor of protection, given their inverse correlation with varicella occurrence. However, they were not able to find a clear correlate (or surrogate) of protection and suggested that cellular immunity may need to be considered when defining a correlate of protection [17]. According to a literature review, VZV transmission before varicella rash onset seems unlikely, although the possibility of pre-rash respiratory transmission cannot be entirely ruled out [18].

A study among 150 Swiss paediatricians and general practitioners showed that the majority (88%) have a favourable attitude towards childhood varicella vaccination in the setting of a Swiss NITAG recommendation for universal varicella vaccination [19], which is much higher than previously found in the Netherlands (28% among medical doctors of regional public health services and child health clinics) [20].

#### 8.4.4.2 Herpes zoster

Tseng et al. studied the epidemiology of HZ in immunocompetent, unvaccinated adults aged  $\geq 50$  years in Southern California. HZ incidence rate was 9.92/1,000 person-years (95% CI: 9.82–10.01), and only 0.86% of patients had an HZ-related hospitalisation. The case fatality rate was 0.04%. Recurrence rate was 10.96/1,000 person-years (95% CI: 10.18–11.79) with 10-year recurrence risk of 10.26% (95% CI: 9.36%–11.23%) [21]. Forbes et al. quantified the risk of acute non-postherpetic neuralgia (PHN) zoster complications in England. The absolute risks of zoster-specific complications within 3 months of zoster diagnosis were 0.37% (95% CI: 0.34–0.39%) for Ramsay Hunt syndrome, 0.01% (95% CI: 0.0–0.01%) for disseminated zoster, 0.04% (95% CI: 0.03–0.05%) for zoster death and 0.97% (95% CI: 0.92–1.00%) for zoster hospitalisation. For other complications, attributable risks were 0.48% (95% CI: 0.44–0.51%) for neurological complications, 1.33% (95% CI: 1.28–1.39%) for ocular complications, 0.29% (95% CI: 0.26–0.32%) for cutaneous complications and 0.78% (95% CI: 0.73–0.84%) for visceral complications [22]. Van Oorschot et al. conducted a systematic literature review and found an incidence rate of HZ ranging from 5.23–10.9 cases per 1,000 person-years. Studies revealed a trend of increasing incidence of HZ with increasing age and over time [23].

Overall, in the first year of the Australian national HZ immunisation programme (one dose of Zostavax®), when the average time since vaccination was about 8 months, vaccine effectiveness was 63.5% (95% CI: 47.5–74.6%) but fell to 48.2% (95% CI: 30.0–61.7%) in the second year when the average time since vaccination was about 18 months [24]. From 1994–2018, the overall incidence of HZ in the United States increased from 286.0 (95% CI: 259.1–312.8) to 579.6 (95% CI: 554.2–605.0) cases per 100,000 person years. However, since 2007, annual HZ incidence rates have decreased in individuals ≤20 (due to varicella vaccination) and >60 years old (due to HZ vaccination), while continuing to increase in 31- to 60-year-olds [25]. The uptake of HZ vaccine in the United States in adults aged ≥60 years (recommended in 2006) increased from 6.7% in 2008 to 34.5% in 2018, and remained constant in the period 2016–2018 [26]; in 2019, 26.1% of adults aged ≥50 years had ever received a shingles vaccination [27]. In the early phase of implementation of HZ vaccination in Southern California, completion of adjuvanted recombinant zoster vaccine (RZV) series (recommendation: two doses 2–6 months apart) appears suboptimal. Only 67.2% of 31,120 persons aged ≥50 years who received a first dose between 04/01/2018 and 11/30/2018 completed the series within 9 months. Completion varied by race/ethnicity, socioeconomic status, health status, and care-seeking behaviour [28]. Shuvo et al. also showed influence of social determinants of health on timeliness of HZ vaccination (any of the two available vaccines; based on the date of the first vaccination record) among older American adults: odds of later HZ vaccination increased with higher poverty (OR: 1.035, 95% CI: 1.031–1.038), more democratic voters (OR: 1.011, 95% CI: 1.010–1.012), and lack of Internet access (OR: 1.028, 95% CI: 1.024–1.032), but decreased with higher health literacy (OR: 0.971, 95% CI: 0.970–0.973) [29]. Izurieta et al. estimated real-world vaccine effectiveness in the United States of 70.1% (95% CI: 68.6–71.5%) and 56.9% (95% CI: 55.0–58.8%) for 2 and 1 doses RZV, respectively. These estimates are lower than the clinical trial estimates, likely due to differences in outcome specificity. The primary outcome in this study was community (outpatient) HZ, defined by a claim with an ICD-10 diagnosis code for HZ (B020, B021, B022.x, B027–B029) in any position with a claim for HZ-specific antiviral, identified using national drug codes, within 7 days of diagnosis. The 2-dose vaccine effectiveness was not significantly lower for people aged >80 years, for second doses received at ≥180 days, or for individuals with autoimmune conditions. The vaccine was also effective among individuals with immunosuppressive conditions. Two-dose vaccine effectiveness against PHN (defined in the 90–180 days after HZ onset) was 76.0% (95% CI: 68.4–81.8%) [30]. Sun et al. estimated RZV effectiveness in the United States of 85.5% (95% CI: 83.5–87.3%) overall, with an effectiveness of 86.8% (95% CI: 84.6–88.7%) in individuals 50–79 years old compared with 80.3% (95% CI: 75.1–84.3%) in individuals aged 80 years and older. In patients with a history of live zoster vaccine (ZVL) within 5 years of study inclusion, vaccine effectiveness was 84.8% (95% CI: 75.3–90.7%) [31]. Sun et al. found that in Hawaii RZV was 83.5% (95% CI: 74.9–89.2%) effective against HZ and 93.3% (95% CI: 48.7%–99.1%) effective against HZ ophthalmicus [32]. After the introduction of publicly funded ZVL in Ontario, Canada reduced the monthly rate of medically attended HZ by 19.1% (from 4.8 to 3.8 per 10,000 population;  $P < 0.01$ ) and HZ-related emergency department visits and hospitalisations by 38.2% (from 1.7 to 1.0 per 10,000 population;  $P < 0.05$ ) [33]. McGirr et al. showed that second dose completion for RZV in Canada is high but suboptimal and varied across age and geography. In the 6-month and 12-month analytic cohorts, 65.0% and 74.9% received the second RZV dose within 2–6 months and 2–12 months after the first dose, respectively [34].



RZV is indicated for prevention of HZ in adults aged  $\geq 50$  years. A study of Racine et al. suggested that RZV has an acceptable safety profile and induces immunity in an important proportion of  $\geq 18$ -year-old immunocompromised patients too [35]. A post hoc analysis on data from the ZOE-50 and ZOE-70 clinical trials focusing on adults with pre-existing potential immune-mediated diseases showed high efficacy of RZV vaccination of 90.5% (95% CI: 73.5–97.5%) [36]. Curran et al. showed that the RZV reduced the risk of HZ across different frailty subgroups; non-frail 95.8% (95% CI: 91.6–98.2%), pre-frail 90.4% (84.4–94.4%), frail 90.2% (75.4–97.0%) [37]. Kim et al. conducted a sub-cohort analysis of the ZOE-50 and ZOE-70 clinical trials and showed that the RZV is efficacious in Asian adults  $\geq 50$  years. Overall vaccine effectiveness was 95.6% (95% CI: 86.4–99.1%) against HZ and 100% (95% CI: 35.4–100%) against PHN [38].

A study of Schmidt et al. indicated that high levels of psychological stress are associated with increased risk of HZ. Cohen's Perceived Stress Scale (PSS) scores  $< 20$  were not associated with increased hazard ratio of HZ, but thereafter the hazard ratio increased linearly from 1.10 (95% CI: 0.85–1.41) to 2.22 (95% CI: 1.32–3.75) [39]. Kim et al. found an association between the risk for cardiovascular events and antiviral treatment for HZ. Treatment with antiviral agents (adjusted hazard ratio 0.82, 95% CI: 0.71–0.95) and statins (0.71, 95% CI: 0.59–0.85) were significantly associated with lower risk of myocardial infarction and stroke, while use of antithrombotics and steroids was not associated with the risk [40]. Kim et al. study showed that statin use reduced the risk of cardiovascular disease (CVD) by 10%, but the protective effect of statin use against CVD was mitigated by approximately 10% through the development of HZ associated with statin use [41]. Yang et al. found that the increased risk of acute ischemic stroke was not modified by ZVL vaccination and antiviral treatment [42].

#### 8.4.4.3 Cost-effectiveness

Azzari et al. evaluated the cost-effectiveness of a range of varicella vaccination strategies including no vaccination in Italy. The most effective and least expensive strategy was the one with two doses of MMRV (ProQuad®), which resulted in a 66% decrease in varicella cases and a 30% reduction in varicella-related deaths compared with the no vaccination strategy [43]. Akpo et al. evaluated the impact of varicella vaccination strategies and associated cost-effectiveness estimates in the United Kingdom. From the National Health Service perspective, V-MMRV using GSK or MSD varicella-containing vaccines was cost-effective in the short to long term at £20,000 per QALY gained. For MMRV-MMRV, cost-effective benefits would be observed earlier with GSK than with MSD varicella-containing vaccines due to differences in vaccine prices. Without the exogenous boosting hypothesis, HZ incidence decreased through the implementation of universal varicella vaccination [44]. Heininger et al. studied the cost-effectiveness of introduction of varicella vaccination in Switzerland. They compared 2 base-case schedules (no infant vaccination and 10% coverage with infant vaccination) to 3 different universal varicella vaccination schedules using quadrivalent and monovalent vaccines administered at different ages. Incremental cost-effectiveness ratios for the universal varicella vaccination schedules versus the base-case were CHF 31,194–35,403 (Swiss Franc; US \$34,452–39,100) per quality-adjusted life-year from the direct medical cost perspective and CHF 25,245–29,552 (US \$27,881–32,638) from the societal perspective [45]. Pawaskar et al. considered six

two-dose vaccination strategies in Norway, consisting of combinations of two formulations each of a monovalent varicella vaccine (Varivax® or Varilrix®) and a quadrivalent MMRV vaccine (Pro-Quad® or PriorixTetra®), with the first dose given with a monovalent vaccine at age 15 months, and the second dose with either a monovalent or quadrivalent vaccine at either 18 months, 7 or 11 years. According to their analysis, all strategies were cost-saving, with the most cost-saving being two doses of Varivax® at 15 months and 7 years (payer perspective) and two doses of Varivax® at 15 months and 18 months (societal perspective) [46]. Rafferty et al. showed that varicella vaccination in Canada would be cost-saving and highly cost-effective from the societal and healthcare perspective, assuming there was no impact on HZ [47]. Wolff et al. studied four alternative vaccination strategies in Sweden: 1) no vaccination, 2) varicella vaccination with one dose of the live attenuated vaccine at age 12 months and a second dose at age 18 months, 3) HZ vaccination with one dose of the live attenuated vaccine at 65 years of age, and 4) both vaccine against varicella and HZ with the before-mentioned strategies. They concluded that it was cost-effective to vaccinate against varicella but not to vaccinate against HZ [48].

A review of Hodgkinson et al. concluded that current models are sensitive to assumptions on exogenous boosting and suggested that future modelling should include some aspects of agent-based modelling [49]. Luyten et al. argued for sensitivity analyses in which alternative social value judgments about the value of health outcomes are integrated into cost-effectiveness analyses of vaccines. They used the example of VZV vaccination to show the influence of revaluing different types of QALYs for different age groups in line with public preferences; QALYs gained among children through direct varicella protection became more important, whereas QALYs lost indirectly through HZ in adults diminished in value. Weighting of vaccine-related side effects made a large difference. This will be important information for NITAGs and decision makers [50].

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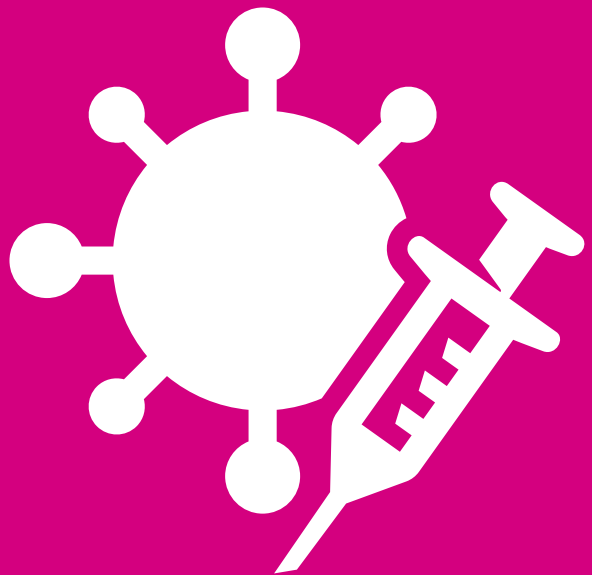
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# 9 COVID-19



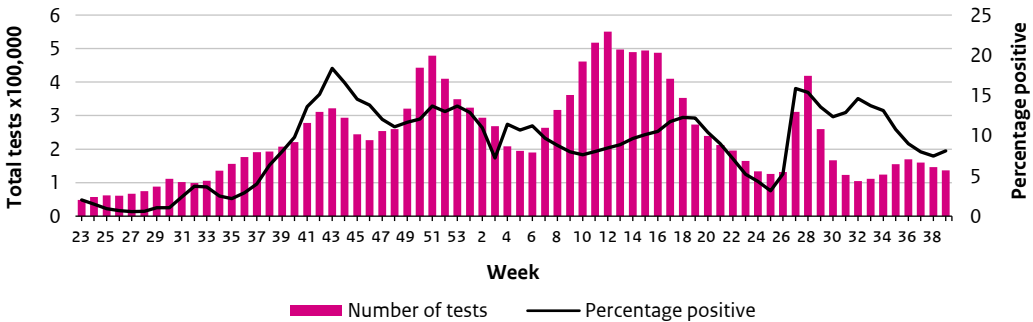
## 9.1 The epidemiological situation of SARS-CoV-2 in the Netherlands

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### 9.1.1 Keypoints

- The Netherlands has seen four COVID-19 waves up to week 38 of 2021, during which COVID-19 control measures were implemented to prevent further spread of the disease. During the pandemic, testing capacity increased every few months.
- The first wave took place at the beginning of the worldwide pandemic after the SARS-CoV-2 virus was introduced into the country by people returning from their holidays, while carnival festivities in the South of the country allowed for unnoticed spread. Mostly the elderly were hit during this wave.
- The second wave hit in September 2020, and lasted through to first few weeks of 2021. This wave no longer hit mostly older people.
- A third wave hit the country from February 2021 until the end of April 2021. Deaths did not increase during this wave, likely as a result from the vaccination campaign.
- The fourth wave occurred in the summer of 2021, most likely again due to introduction of the virus from holiday destinations.

### 9.1.2 Tables and figures



**Figure 9.1.1** Total tests x100,000 and percentage of positive tests for week 26, 2020, until week 38, 2021.

### 9.1.3 SARS-CoV-2 surveillance in the Netherlands

SARS-CoV-2 surveillance in the Netherlands has taken a multi-pronged approach to allow for changes in testing policy over time. At the beginning of the pandemic, testing was restricted to hospitalised SARI (Severe Acute Respiratory Infection) patients, healthcare workers in hospitals with respiratory symptoms, patients  $\geq 70$  years of age, and chronically ill, SARS-CoV-2 symptomatic patients outside hospitals.

Since June 1<sup>st</sup>, 2020, universal testing has been offered to anyone showing symptoms that might indicate infection with SARS-CoV-2. From December 1<sup>st</sup>, 2020 onwards, anyone who has been in close contact with a SARS-CoV-2 positive person can request a test, regardless of whether they experience any COVID-19-related symptoms. These tests are carried out by the municipal health services (GGD), and are either a PCR, loop mediated isothermal amplification (LAMP), or antigen test.

Figure 9.1.1 shows the total number of SARS-CoV-2 tests and the proportion of positive test results, by week, from week 26 in 2020 until week 38 in 2021. Both the number of tests and the proportion of positive results peaked in the autumn of 2020, with a further increase towards the end of the year. This suggests that the transmission of SARS-CoV-2 increased in these periods. It is important to note that in periods during which the number of tests increased, positive test results changed at different rates, as evidenced by the percentage of positive tests as shown in Figure 9.1.1. In some cases, the percentage of positive tests increased even when the total number of tests administered decreased (see weeks 31, 32), or vice versa.

Additional routes for testing exist, mainly through tests administered for admittance to large gatherings such as festivals ('toegangstesten'), tests taken by Dutch travellers to allow entry into their destination country ('reistesten'), tests administered through GP sentinel stations that track flu-like symptoms, and lastly the infection radar, which is not a laboratory test but a survey that asks participants if they have been sick in the previous week. Self-tests are not used for any surveillance-related research.

In addition to nation-wide reporting on positive tests, a few groups of interest are monitored separately: people living at eldercare 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 the 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 contact-tracing role in the Netherlands. The goal of 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 possible 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 the 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**

The first case of COVID-19 in the Netherlands was reported on February 27<sup>th</sup>, 2020. By mid-March, it had become clear that unnoticed community transmission had occurred in the provinces of Noord Brabant and Limburg, most likely due to multiple introductions by Dutch tourists returning from northern Italy and Austria [1]. This was further amplified by the annual carnival celebrations, which last for three days and mostly take place in the south of the Netherlands.

In response, from March 9<sup>th</sup>, 2020 onwards, the Dutch government implemented an expanding range of measures to prevent the spread of SARS-CoV-2, up until the so-called intelligent lockdown that was imposed on March 23<sup>rd</sup>. In the first wave, the number of daily new cases peaked on April 10<sup>th</sup> with about 1,300 new registered cases, while April 7<sup>th</sup> witnessed the highest recorded number of deaths with 232 deceased persons in a single day.

From June 1<sup>st</sup> to 8<sup>th</sup>, the intelligent lockdown measures were eased gradually as the number of cases had decreased greatly, to a total of approximately 100 new confirmed cases per day, while in the week preceding the easing of measures, the number of deaths had decreased to approximately 18 per day. Overall, this first wave mainly hit the elderly.

It should be noted that at the beginning of the pandemic, testing was restricted to hospitalised SARI (Severe Acute Respiratory Infection) patients, healthcare workers in hospitals with respiratory symptoms, patients  $\geq 70$  years of age, and chronically ill, SARS-CoV-2 symptomatic patients outside hospitals. This limited amount of testing led to the underrepresentation of actual cases and likely of SARS-CoV-2-related deaths in the first wave.

After the second wave hit in September 2020, preventative measures were reintroduced and became stricter from mid-October onwards until a complete lockdown was instated on December 15<sup>th</sup>. The second wave started with an increase in incidence in primarily the younger age groups (10-29 years of age) primarily, followed by an increase in the age groups of 40-50 years of age (their parents), and subsequently an increase of cases in the oldest age groups (70+).

During the second wave, testing was universally available from June 2020 onwards to anyone experiencing symptoms, further expanding on December 1<sup>st</sup>, 2020, to include anyone who had been in close contact with a SARS-CoV-2 positive person (as found through contact tracing or the Corona notifier app). Thus, the number of laboratory-confirmed cases was much higher than during the first wave. This second wave peaked twice, with the worst peak in weeks 51 to 53 of 2020. During this time, 78,021 cases were notified (week 51), 1,984 persons were admitted to the hospital (week 53), and 720 persons died (week 51).

January 2021 marked the kick-off of the SARS-CoV-2 vaccination campaign in the Netherlands, starting with nursing-home residents and healthcare workers. A few weeks into the start of the vaccination campaign, daily deaths began to decrease steadily. Therefore, from March 1<sup>st</sup>, 2021 (week 9) onwards, preventative measures were gradually eased. A five-step plan was used to further scale down the measures on a per-region basis.

Simultaneously with the easing of measures, a third wave of SARS-CoV-2 cases swept through the country, peaking in week 16 with 56,295 notifications and 1,853 hospitalisations. Deaths had however continued to decrease, down to 134 in week 16.

Looking at the number of cases, the Netherlands experienced a fourth wave. After gaining 6,571 new cases in week 26, there was an influx of new cases, likely resulting from cases imported from holiday destinations, peaking two weeks later with 70,242 new cases in week 28. After week 26, hospitalisations also began to rise again, peaking in week 30 with 579 new hospitalisations. The number of deaths began to rise slowly from week 29 onwards as well, peaking with 40 deaths in week 32. Since then, the number of weekly deaths have decreased only slightly.

For a more detailed description of the first SARS-CoV-2 waves in the Netherlands, please see the Annual Report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2020/2021 [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 Literature

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## 9.2 SARS-CoV-2 related recommendations from the Health Council of the Netherlands

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### 9.2.1 Keypoints

- The vaccination strategy focused on reducing severe illness and death due to COVID-19 and ensuring that the healthcare system would not be overtaxed. Therefore residents of long-term care facilities, persons with intellectual disabilities living in an institution, and older age groups were prioritised.
- In addition, employees of long-term care facilities, hospital employees providing direct COVID-19 care, and general practitioners were also prioritised.
- Eventually, all persons aged 12 years and older (birth year 2009 and before) were eligible for COVID-19 vaccination with roll-out of the vaccination schedule from old to young, and priority given to risk groups.

### 9.2.2 Tables and figures

**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 8<sup>th</sup>, 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	<a href="#">NL</a> , <a href="#">EN</a>	COVID-19 vaccination strategies
07/12/20	<a href="#">NL</a>	Prioritering vaccinatie COVID-19 voor de CAS-landen
24/12/20	<a href="#">NL</a> , <a href="#">EN</a>	COVID-19 vaccination: BioNTech/Pfizer
04/01/20	<a href="#">NL</a>	Advies uit eerste gezamenlijk overleg OMT en Gezondheidsraad over COVID-19-vaccinatiestrategie
11/01/21	<a href="#">NL</a> , <a href="#">EN</a>	COVID-19 vaccination: The Moderna vaccine and the vaccination strategy
14/01/21	<a href="#">NL</a>	Advies uit tweede gezamenlijk overleg OMT en Gezondheidsraad over COVID-19-vaccinatiestrategie
03/02/21	<a href="#">NL</a>	Interval BioNTech/Pfizer
04/02/21	<a href="#">NL</a> , <a href="#">EN</a>	Ethical and legal considerations COVID-19 vaccination
04/02/21	<a href="#">NL</a> , <a href="#">EN</a>	COVID-19-vaccination: AstraZeneca vaccine
08/03/21	<a href="#">NL</a>	Spoedvragen COVID-19-vaccinatie
17/03/21	<a href="#">NL</a> , <a href="#">EN</a>	COVID-19 vaccination: Janssen vaccine

Date	Links	Title
22/03/21	<a href="#">NL</a>	Aanvulling hoog-risicopatiëntgroepen COVID-19-vaccinatie en toedieningsvormen COVID-19-vaccins
09/04/21	<a href="#">NL</a>	Inzet AstraZeneca-vaccin
09/04/21	<a href="#">NL</a>	Vaccinatie van kinderen
12/04/21	<a href="#">NL</a>	Interval tussen de eerste en tweede vaccinatie
20/05/21	<a href="#">NL</a>	Transmissie na vaccinatie
20/05/21	<a href="#">NL</a>	Interval AstraZeneca-vaccin
02/06/21	<a href="#">NL</a>	Leeftijdsgrens en tweede dosis AstraZeneca-vaccin
02/06/21	<a href="#">NL</a>	Inzet vaccins in huidige fase COVID-19-vaccinatieprogramma
09/06/21	<a href="#">NL</a>	Vaccinatie van kinderen met een medisch risico en ringvaccinatie
17/06/21	<a href="#">NL</a>	Advies Gezondheidsraad en OMT over COVID-19 vaccinatiestrategie voor de korte en middellange termijn
29/06/21	<a href="#">NL</a>	Vaccinatie van adolescenten tegen COVID-19
05/07/21	<a href="#">NL</a>	Heterologe vaccinatie
29/07/21	<a href="#">NL</a>	Vaccinatie van adolescenten tegen COVID-19 met het Moderna-vaccin

### 9.2.3 Recommendations regarding SARS-CoV-2 vaccination strategy

On November 19<sup>th</sup>, 2020, the Health Council of the Netherlands (HC) published their advice regarding COVID-19 vaccination strategies for the moment when vaccines would become available. Three strategies were discussed: 1. Reducing severe disease and death due to COVID-19; 2. Reducing the spread of SARS-CoV-2; 3. Prevention of social disruption. At that time, the council recommended strategy 1 based on the scientific evidence available and current insights into infections and hospitalisations. Given the initial scarcity of vaccines, the HC recommended deploying the vaccines in such a way that they primarily decreased severe illness and death. To this end, the HC advised that 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, should be first in line for vaccination. If these individuals could not be vaccinated, vaccination should be offered to their healthcare workers and caregivers. Healthcare workers that came in close contact with their patients could be considered for vaccination as well. On December 7<sup>th</sup>, the HC expanded this recommendation to the CAS countries, favouring a switch to an age-based priority setting; older age translated to higher priority.

#### 9.2.3.1 Allocation of vaccines

With regard to vaccine allocation, the HC recommended on December 24<sup>th</sup>, 2020, and January 11<sup>th</sup>, 2021, that the vaccines developed by BioNTech/Pfizer (Comirnaty®) and Moderna should be used primarily for the elderly, as they had proven to be highly effective in older age groups and severity of COVID-19 disease increases strongly with age. It was recommended that other vaccines should be offered to healthcare workers vital to the continuation of care.

On February 4<sup>th</sup>, 2021, the AstraZeneca vaccine was recommended for seniors up to 65 years of age and persons in medical risk groups based on the available evidence at that time. On March 8<sup>th</sup>, 2021, the HC expanded their recommendation for deployment of the AstraZeneca vaccine to be expanded to include persons over the age of 65. Lastly, on March 17<sup>th</sup>, 2021, the Janssen vaccine was recommended for seniors over 60, followed by specific risk groups, i.e. individuals with Down Syndrome, individuals with morbid obesity (BMI>40), and patients with neurological afflictions that could lead to respiratory issues.

On March 22<sup>nd</sup>, 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 April 9<sup>th</sup>, 2021, after the EMA added thrombosis with thrombocytopenia syndrome (TTS) to the list of adverse events resulting from the AstraZeneca vaccine, the HC revised its recommendation the AstraZeneca vaccine and stated that it 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 2<sup>nd</sup>, 2021, the HC indicated that its advice remained unchanged on account of the importance of being adequately vaccinated, and insufficient availability of data on the safety and efficacy of heterologous vaccination as an alternative.

#### *9.2.3.2 Changes proposed to intervals between doses*

On January 14<sup>th</sup>, 2021, the HC and the Dutch Outbreak Management Team (OMT) recommended increasing the interval between vaccinations with the BioNTech/Pfizer vaccine to six weeks in order to provide as many people as possible with their first dose of the vaccine. The HC reaffirmed this strategy on February 3<sup>rd</sup>, 2021, for as long as vaccines remained scarce. On March 8<sup>th</sup>, 2021, they recommended no further changes to be made to the vaccination intervals although persons that had been infected with SARS-CoV-2 in the 6 months prior to their first vaccination would no longer require a second dose.

On April 12<sup>th</sup>, 2021, the HC advised that the intervals between the two doses of the BioNTech/Pfizer and Moderna vaccines could be stretched to 12 weeks after all, for as long as these vaccines remained scarce. The recommended interval for AstraZeneca remained 12 weeks and was reaffirmed in the HC's advice published on May 20<sup>th</sup>.

#### *9.2.3.3 Changes proposed to the vaccination strategy*

In two recommendations published on June 2<sup>nd</sup>, 2021, the HC recommended that age groups under 60 should continue to receive mRNA-vaccines. However, Janssen's vector vaccine, which had also been found to potentially cause TTS, was recommended for persons of any age that could not be contacted through regular routes, as it requires a single dose for adequate protection.

The HC and OMT delivered another joint advice on June 17<sup>th</sup>, 2021, in which they expressed a possible future requirement regarding further booster vaccinations. On July 5<sup>th</sup>, 2021, the HC indicated that they did not object to heterologous vaccination, in which a first dose of the AstraZeneca vaccine was followed by a booster vaccination with the BioNTech/Pfizer vaccine.

#### **9.2.4 Recommendations on the inclusion of children in the vaccination strategy**

On April 9<sup>th</sup>, 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 as it had now been approved for use in people of 16 years and over. On June 9<sup>th</sup>, they recommended that use of the BioNTech/Pfizer vaccine should be expanded to risk group children aged 12 and over. Children that could not be vaccinated due to medical reasons could be protected through ring vaccination.

On June 29<sup>th</sup>, the HC further expanded their recommendation by also including children of 12 and over that were not part of a risk group as benefits outweigh the mild adverse effects that may result from vaccination. The benefits were many: reduced hospitalisation and ICU admission of children, decreased incidence of long COVID in children, and decreased circulation of the virus amongst 12- to 17-year-olds, allowing preventative measures to be eased more rapidly and reducing the negative impact these measures can have on children. For the same reasons, the Moderna vaccine was recommended for use in children aged 12-17, as can be found in the HC advice published on July 29<sup>th</sup>, 2021.

## 9.3 COVID-19 vaccination campaign

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### 9.3.1 Keypoints

- The COVID-19 vaccination campaign in the Netherlands started on January 6<sup>th</sup>, 2021. The mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna) have been used from week 1 and 3 2021 onwards, respectively. The vector vaccines Vaxzevria® (AstraZeneca) and COVID-19 Vaccine Janssen® were used from week 6 and 16 2021 onwards, respectively.

### 9.3.2 Tables and figures

**Table 9.3.1** Characteristics of the COVID-19 vaccines that are being used in the Netherlands, weeks 1-33, 2021.

Manufacturer	Brand name	Minimum age (years)	Type	Doses*	Interval target (weeks)	Interval window (weeks)	In use since
BioNTech/Pfizer	Comirnaty®	12	mRNA	2	3	3-6	Week 1
Moderna	Spikevax®	12	mRNA	2	4	3-6	Week 3
AstraZeneca	Vaxzevria®	18**	Recombinant vector	2	6-12	4-14	Week 6
Janssen	The COVID-19 Vaccine Janssen®	18	Recombinant vector	1	-	-	Week 16

\* In principle, each participant receives two doses of the same vaccine if two doses are required. However, from July 6<sup>th</sup>, 2021 onwards, heterologous vaccination of a first dose of Vaxzevria® followed by a second dose of Comirnaty® is allowed, too. An interval of at least 4 weeks is used in that case [3]. Persons who have been infected with SARS-CoV-2 in the past 6 months only need one vaccine dose to be fully vaccinated [1]. On June 4<sup>th</sup>, 2021, this recommendation was revised to eliminate the time restriction: currently, people with a SARS-CoV-2 infection at any moment in the past require only one vaccine dose [2].

\*\* A minimum age of 60 was applied in the Netherlands from April 2<sup>nd</sup>, 2021 [1].

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

Date	Group
<a href="#"><u>Jan 6</u></a>	<ul style="list-style-type: none"> <li>• Employees of long-term care facilities</li> <li>• Hospital employees providing COVID-19 care</li> </ul>
<a href="#"><u>Jan 18</u></a>	<ul style="list-style-type: none"> <li>• Residents of long-term care facilities</li> <li>• Persons with an intellectual disability living in an institution</li> </ul>
<a href="#"><u>Jan 22</u></a>	General practitioners and employees at general practices
<a href="#"><u>Jan 25</u></a>	Residents of long-term care facilities vaccinated by their GPs
<a href="#"><u>Jan 26</u></a> – <a href="#"><u>Feb 5</u></a>	Mobile persons* living at home: persons born; <a href="#"><u>before 1931</u></a> <a href="#"><u>1931 – 1935</u></a> <a href="#"><u>1936 - 1940</u></a>
<a href="#"><u>Feb 12</u></a>	Employees of rehabilitation facilities
<a href="#"><u>Feb 15</u></a>	<ul style="list-style-type: none"> <li>• Persons living at home, born between 1956 - 1960</li> <li>• Employees of disability care facilities</li> </ul>
<a href="#"><u>Feb 22</u></a>	Intramural mental healthcare clients and employees
<a href="#"><u>Feb 25</u></a>	District nursing employees
<a href="#"><u>Mar 2</u></a>	Employees covered by the Social Support Act
<a href="#"><u>Mar 6</u></a>	Mobile persons* living at home, born between 1941 and 1946
<a href="#"><u>Mar 17</u></a>	Mobile adult medical risk groups; persons: <ul style="list-style-type: none"> <li>• with a haematological malignancy</li> <li>• with severe renal failure</li> <li>• with a severe congenital immune disorder</li> <li>• after organ-, stem cell-, or bone marrow transplant</li> <li>• with a neurological disorder that compromises breathing</li> </ul>
<a href="#"><u>Apr 5</u></a>	Immobile persons* living at home, including risk group adults with a neurological disorder that compromises breathing
<a href="#"><u>Apr 6</u></a>	Mobile persons* living at home, born between 1947 and 1951
<a href="#"><u>Apr 16</u></a>	Medical risk groups; persons born between 1961 and 2003: <ul style="list-style-type: none"> <li>• with Down syndrome</li> <li>• with morbid obesity</li> </ul>

Table continues on next page.



**Table 9.3.2** (continued)

Date	Group
<u>Apr 19</u>	Minors belonging to medical risk groups that are at least 16 years old; persons born between 2003 and 2005: <ul style="list-style-type: none"> <li>• Living in an institution;               <ul style="list-style-type: none"> <li>- with a haematological malignancy</li> <li>- with severe renal failure</li> <li>- with a severe congenital immune disorder</li> <li>- after organ, stem-cell or bone-marrow transplant</li> <li>- with a neurological disorder that compromises breathing</li> <li>- with Down syndrome</li> <li>- with morbid obesity (grade 2 or higher)</li> </ul> </li> <li>• Living at home;               <ul style="list-style-type: none"> <li>- with Down syndrome</li> <li>- with morbid obesity (grade 2 or higher)</li> </ul> </li> </ul>
Apr 19 – Apr 30	Mobile persons* living at home, born between or in <u>1952</u> <u>1953 – 1955</u> <u>1961</u> <u>1962</u>
<u>May 6</u>	Medical risk groups; persons who receive annual invitations for influenza vaccination born between 1961 and 2003
<u>May 18</u>	Minors belonging to medical risk groups that are at least 16 years old and living at home; persons born between 2003 and 2005: <ul style="list-style-type: none"> <li>• with a haematological malignancy</li> <li>• with severe renal failure</li> <li>• with a severe congenital immune disorder</li> <li>• after organ, stem-cell or bone-marrow transplant</li> <li>• with a neurological disorder that compromises breathing</li> </ul>
<u>May 25</u>	Military personnel born between 1961 and 2003
May 16 – June 19	Anyone born between or in the years <u>1963</u> – <u>2003</u> , invited in ascending order of birthyear***
<u>June 22</u>	Minors belonging to medical risk groups that are at least 12 years old; persons born between 2004 and 2009: <ul style="list-style-type: none"> <li>• with Down syndrome</li> <li>• who are invited for annual influenza vaccination</li> </ul>
July 2 – July 11	All minors born between or in <u>2004</u> – <u>2009</u> , who are at least 12 years old

\* 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

The COVID-19 vaccination campaign in the Netherlands started on January 6<sup>th</sup>, 2021. The Netherlands only uses COVID-19 vaccines that are approved by the European Medicines Agency (EMA). Table 9.3.1 provides an overview of the characteristics of the four vaccines that are currently in use (up to and including week 33, 2021). The mRNA vaccines Comirnaty® (BioNTech/Pfizer) and Spikevax® (Moderna) have been in use from weeks 1 and 3 2021 onwards, respectively. The vector vaccines Vaxzevria® (AstraZeneca) and COVID-19 Vaccine Janssen® have been in use from weeks 6 and 16 2021 onwards, respectively. With exception of the COVID-19 Vaccine Janssen®, two doses are required to be fully vaccinated with all vaccines in use. Individuals who had been infected with SARS-CoV-2 in the past 6 months only need one dose to be fully vaccinated [1]. On June 4<sup>th</sup>, 2021, this recommendation was revised by removing the time restriction: currently, people with a SARS-CoV-2 infection at any moment in the past require only one vaccine dose [2]. In principle, every individual receives two doses of the same vaccine if two doses are required. However, from July 6<sup>th</sup>, 2021 onwards, there has been no objection to heterologous vaccination where a first dose of Vaxzevria® followed by a second dose of Comirnaty®. This allows anyone who wishes to do so, to replace their second dose of Vaxzevria® with a second dose of Comirnaty®. An interval of at least 4 weeks is used in that case [3].

### 9.3.4 Indication for COVID-19 vaccination

All adults aged 18 years and older (birth year 2003 and before) living in the Netherlands and registered in the *Personal Records Database (BRP)* were eligible for vaccination when the vaccination campaign started. In addition, (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 also eligible for vaccination. Persons living in Belgium or Germany who work in Dutch healthcare were eligible for vaccination in the Netherlands as well [4]. Although this eligible population was formulated when the vaccination campaign started on January 6<sup>th</sup>, the entire defined population was not invited all in once.

Initially, not enough knowledge was available regarding the safety of COVID-19 vaccination during pregnancy. Pregnant women were therefore not eligible for vaccination except when they were at high risk of being exposed. However, from July 19<sup>th</sup>, 2021 onwards, it is recommended that pregnant women should be vaccinated with one of the two mRNA vaccines. By that date, 90,000 pregnant women in the US had been vaccinated with a mRNA vaccine without obvious side effects and/or adverse effects on the child. Moreover it became clear that pregnant women have a higher chance of severe illness due to COVID-19 compared to non-pregnant women [5, 6].

In the course of the year, other target groups also became eligible for vaccination. From April 19<sup>th</sup>, 2021 onwards, individuals in medical risk groups born in 2003, 2004, and 2005 or individuals living in long-term care facilities born in these same years became eligible for vaccination. From the end of June onwards, individuals with Down syndrome, individuals who are eligible for the annual influenza vaccination, and adolescents with grade 2 obesity or higher born between January 1<sup>st</sup>, 2004 and July 1<sup>st</sup>, 2009 also became eligible for vaccination. From July 2021 onwards, all adolescents born in 2004-2009 became eligible, with children born in 2009 allowed to schedule an appointment when they turned 12 years old [4].

### 9.3.5 COVID-19 vaccination strategy

The vaccination strategy focuses on reducing severe illness and death due to COVID-19 and ensuring that the healthcare system does not become overtaxed. As such, residents of long-term care facilities, individuals with an intellectual disability who are living in an institution, and older age groups were prioritised. In addition, employees of long-term care facilities, hospital employees providing direct COVID-19 care and general practitioners were prioritised as they are at increased risk of infecting risk groups and their work is important to ensure that the healthcare system does not become overtaxed. Table 9.3.2 provides an overview of all specified target groups and the date from which an appointment for vaccination could be made.

### 9.3.6 COVID-19 vaccination organizations

The Netherlands relies on multiple organisations to provide vaccinations, with the GGD vaccinating the majority of the population. The organisations that vaccinated (other) specific target groups included general practitioners (GPs), hospitals, and long-term care facilities. In short, residents of long-term care facilities were vaccinated by their institution's doctors or mobile GP teams. Amongst others, GPs vaccinated non-mobile persons and persons born between 1956-1960, and hospitals vaccinated employees providing direct COVID-19 care. The target groups for vaccination organisations can be found in *the most recent vaccination schedule*.

### 9.3.7 Literature

- 1.\* Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Landelijke Coördinatie Infectieziektebestrijding (LCI). COVID-19-vaccinatie Uitvoeringsrichtlijn - Specifieke informatie per vaccin Bilthoven2021 [updated August 23 2021; cited 2021 August 24]. Available from: <https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie#5-1-beschikbare-vaccins>.
2. Rijksoverheid: Ministerie van Volksgezondheid Welzijn en Sport (VWS). Met één vaccin al beschermd na doorgemaakte Covid-infectie 2021 [cited 2021 September 27]. Available from: <https://www.rijksoverheid.nl/actueel/nieuws/2021/06/04/met-een-vaccin-al-beschermd-na-doorgemaakte-covid-infectie>.
- 3.\* Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Landelijke Coördinatie Infectieziektebestrijding (LCI). COVID-19-vaccinatie Uitvoeringsrichtlijn - Simultaan vaccineren en intervallen met andere vaccins Bilthoven2021 [updated August 23 2021; cited 2021 August 25]. Available from: <https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie#8-simultaan-vaccineren-en-intervallen-met-andere-vaccins>.
- 4.\* Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Landelijke Coördinatie Infectieziektebestrijding (LCI). COVID-19-vaccinatie Uitvoeringsrichtlijn - Indicatie voor COVID-19-vaccinatie Bilthoven2021 [updated August 23 2021; cited 2021 August 24]. Available from: <https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie#2-wettelijke-kaders-organisatie-indicatie-en-financiering>.
5. Nederlandse Vereniging voor Obstetrie & Gyneacologie (NVOG). Standpunt Vaccinatie tegen COVID-19 rondom kinderwens, zwangerschap en kraambed. Utrecht; 2021. July 19 2021.
- 6.\* Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Landelijke Coördinatie Infectieziektebestrijding (LCI). COVID-19-vaccinatie Uitvoeringsrichtlijn - Zwangerschap Bilthoven2021 [updated August 23 2021; cited 2021 August 25]. Available from: <https://lci.rivm.nl/richtlijnen/covid-19-vaccinatie#4-6-zwangerschap>.

## 9.4 COVID-19 vaccination coverage

D.L. van Meijeren, F. Dijkstra, E.A. van Lier, H.E. de Melker, S. Hahné

### 9.4.1 Key points

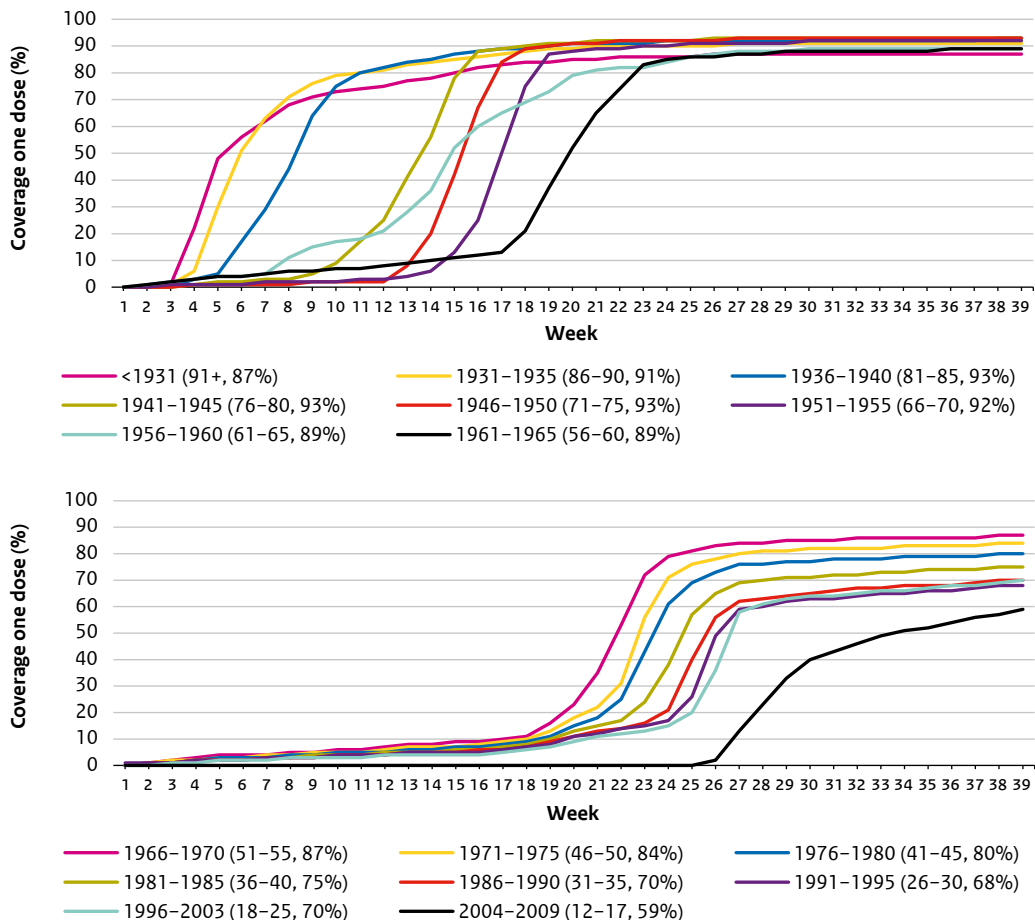
- By the end of week 39, coverage for at least one dose COVID-19 vaccination and full COVID-19 vaccination for individuals born in 2003 or before was between 82-87% and 80-83%, respectively. For individuals born in 2009 or earlier, coverages amounted to 81-84% and 79-81%, respectively, taking into account that for persons born in 2009, only those who had already turned 12 years were included in the denominator.
- High coverage (82-93%) for full COVID-19 vaccination was observed in individuals born in 1965 or before by the end of week 39. In later birth years, however, a less rapid increase, and in certain birth years a stabilisation, of vaccination coverage has already been observed at lower percentages than in older age groups. This indicates that younger age groups might not reach coverage levels for full COVID-19 vaccination as high as those in older age groups in future weeks.
- By the end of week 41, for individuals born in 2003 or before, high coverage (75-84%) was observed for at least one dose COVID-19 vaccination in most municipalities, and about a third of all municipalities, mainly situated in the east and south-east of the country, have reached  $\geq 85\%$  coverage. A few large cities and a few municipalities in the so-called Dutch 'Bible Belt' are exceptions showing lower coverage (mostly 60-74%). The lowest coverage is observed in the municipality of Urk (20-39%).
- Up-to-date and more extensive information about COVID-19 vaccination coverage can be found in the weekly report that is published every Tuesday [here](#).

## 9.4.2 Tables and Figures

**Table 9.4.1** Registered and estimated coverage for at least one dose and full COVID-19 vaccination for birth years 2009 and before and 2003 and before, up to and including week 39, 2021<sup>1-8</sup>.

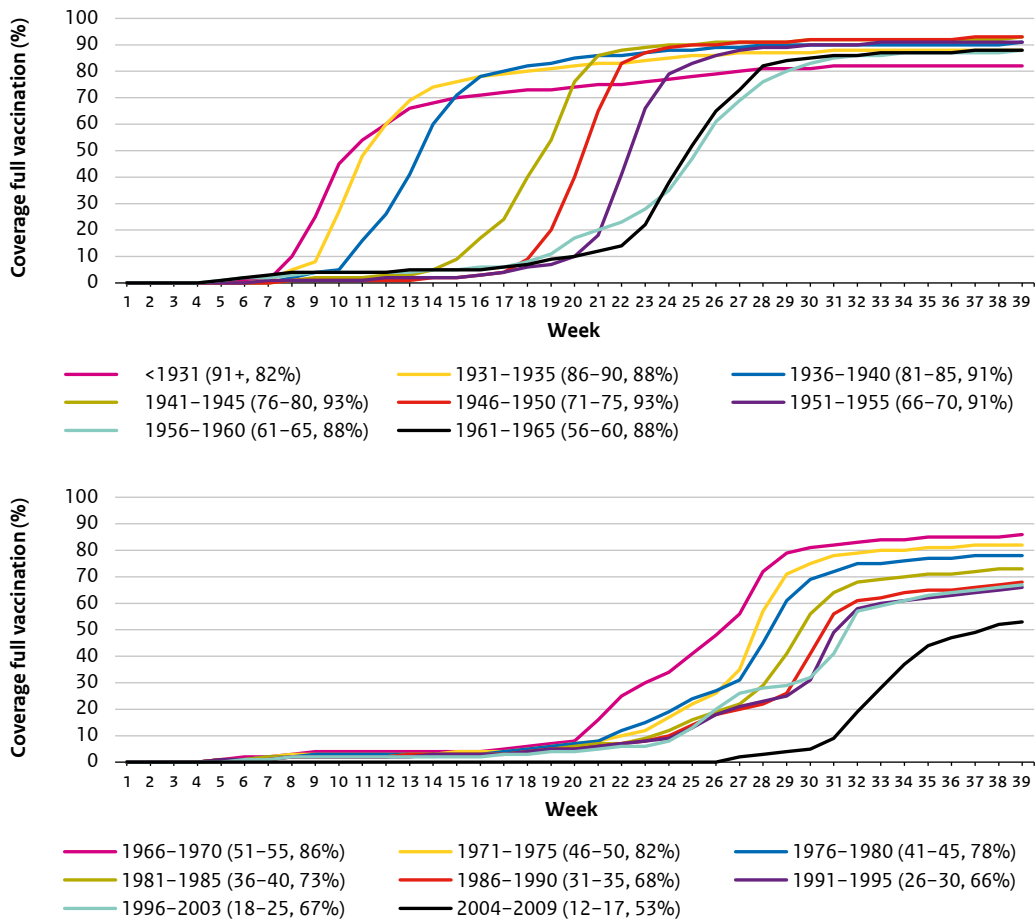
Birth years	At least one dose		Full vaccination	
	Registered coverage	Estimated coverage	Registered coverage	Estimated coverage
2003 and before (18+ years)	82%	87%	80%	83%
2009 and before (12+ years)	81%	84%	79%	81%

1. For registered coverage, the following data sources were used for the numerators: CoronIT for Municipal Health Services (GGD) and COVID-vaccination Information Monitoring System (CIMS) for other implementing organisations, including general practitioners. CIMS includes vaccination information of vaccinated persons who give informed consent to register this information. Data for the denominators were sourced from CIMS (population by age group, 2021).
2. For estimated coverage figures, the following data sources were used for the numerators: CoronIT for GGD and estimated number of vaccinations by other organisations than GGD based on vaccine distribution data. Detailed information on the assumptions being made for the estimated number of vaccinations can be found in the weekly COVID-19 vaccination report, which is published every Tuesday, here. Data for the denominators were sourced from CBS (population by age group, 2020).
3. Individuals born in 2009 are not invited all at the same time since they must turn 12 years first before being allowed the vaccination. Individuals born up to and including June 30<sup>th</sup>, 2009 were invited at the same time. Persons born from July 2009 onwards can make an appointment when they turn 12 years old. To calculate both the registered and estimated coverage in this table, only persons that already turned 12 years old are included in the denominator.
4. Individuals whose age is unknown are included in the estimated coverage for persons born in 2009 and before, but not in the estimated coverage for persons born in 2003 and before.
5. The estimated coverage for persons born in 2003 and before also include persons born in 2004-2009 who are vaccinated by organisations other than the GGD, since these numerators are based on vaccine distribution data in which year of birth cannot be distinguished.
6. Coverage for either at least one dose or full COVID-19 vaccination both includes individuals that received one dose of the Janssen vaccine, since one dose of this vaccine is sufficient to be fully vaccinated.
7. Vaccinated individuals who are not registered in the Personal Records Database (BRP)[1], for example homeless people or migrant workers, are included in the nominator but not in the denominator.
8. Persons for whom a single vaccine dose is sufficient to be fully vaccinated due to prior infection with SARS-CoV-2 are included in both the registered and estimated full COVID-19 vaccination coverage.



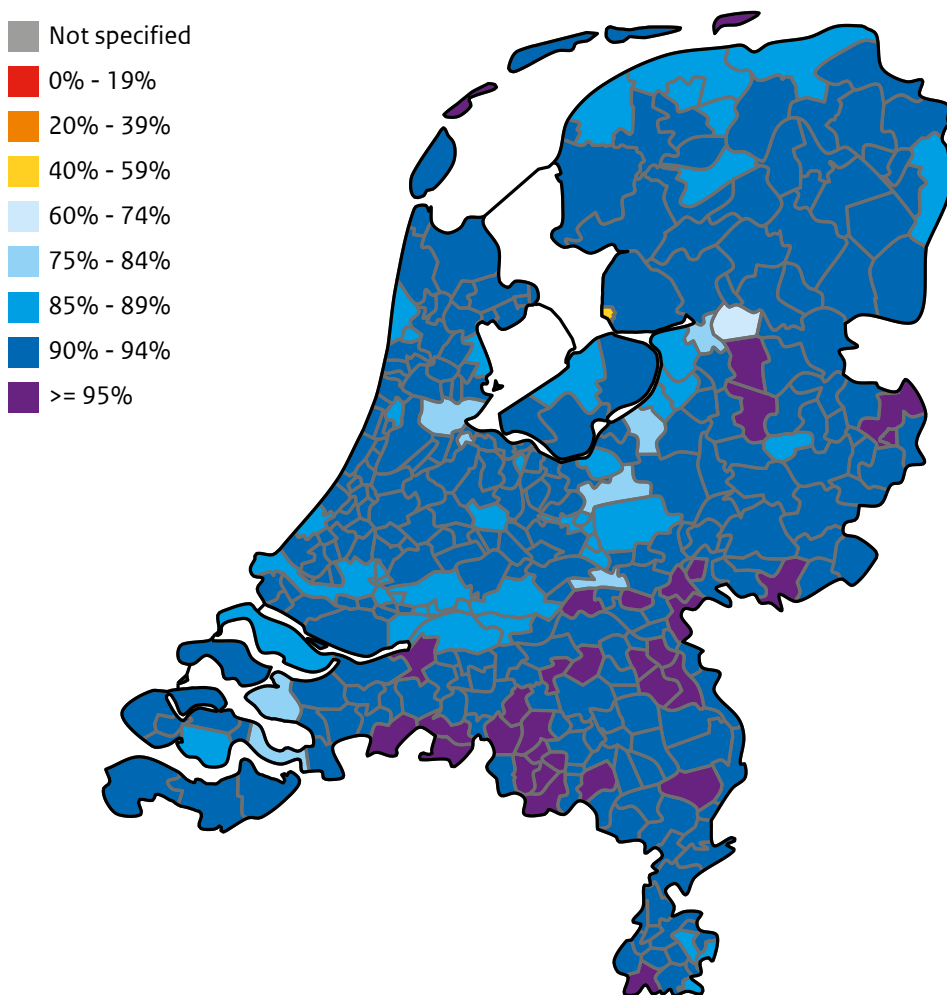
**Figure 9.4.1** Cumulative coverage for at least one dose COVID-19 vaccination, stratified by birth year, for weeks 1-39 of 2021. Age and the percentages representing the coverage in week 39 are shown between parentheses.<sup>1-5</sup>

1. Week numbers are calendar weeks (ISO 8610): week 1 = January 4<sup>th</sup>-10<sup>th</sup>, 2021, week 2 = 11<sup>th</sup>-17<sup>th</sup> January 2021, etc.
2. Data sources for numerators: CoronIT for Municipal Health Services (GGD) and COVID-vaccination Information Monitoring System (CIMS) for other implementing organisations, including general practitioners. Data source for denominators: population by age group, CIMS, 2021. CIMS includes vaccination information of vaccinated individuals who provide informed consent to register this information. Therefore, this figure does not include vaccinated individuals who did not provide informed consent.
3. Persons born in 1956-1960 are vaccinated mainly with Vaxzevria® by their general practitioner. Between March 15<sup>th</sup>-23<sup>rd</sup>, 2021, and April 3<sup>rd</sup>-5<sup>th</sup>, 2021, the Vaxzevria® vaccine was not administered.
4. Vaccinated individuals who are not registered in the Personal Records Database (BRP) [1], for example homeless people or migrant workers, are included in the numerator but not in the denominator.
5. Individuals from birth year 2009 are not invited all at the same time since they must turn 12 years first before being allowed the vaccination. Individuals born up to and including June 30<sup>th</sup>, 2009 were invited at the same time. Persons born from July 2009 onwards can make an appointment when they turn 12 years old. To calculate the coverage in this figure, all persons born in 2009 are included in the denominator for the birth years 2004-2009. If 11-year-olds would be excluded from this denominator, the coverage for birth years 2004-2009 would be 61% instead of 59%.



**Figure 9.4.2** Cumulative coverage for full COVID-19 vaccination, stratified by birth year, for weeks 1-39 of 2021. Age and the percentages representing the coverage in week 39 are shown between parentheses.<sup>1-7</sup>.

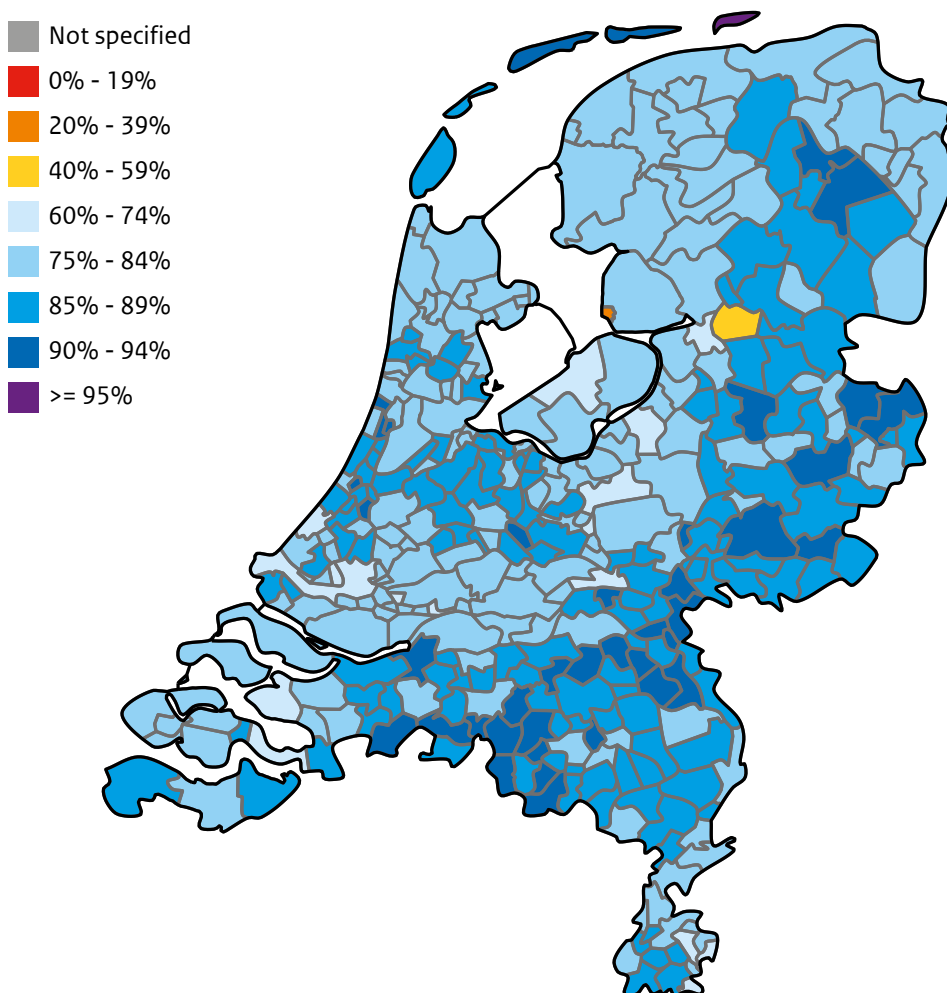
1. Week numbers are calendar weeks (ISO 8610): week 1 = January, 4<sup>th</sup>-10<sup>th</sup>, 2021, week 2 = January 11<sup>th</sup>-17<sup>th</sup>, 2021, etc.
2. Data sources for numerators: CoronIT for Municipal Health Services (GGD) and COVID-vaccination Information Monitoring System (CIMS) for other implementing organisations, including general practitioners. Data source for denominators: population by age group, CIMS, 2021. CIMS includes vaccination information of vaccinated individuals who provide informed consent to register this information. Therefore, this figure does not include vaccinated individuals who did not provide informed consent.
3. Persons born in 1956-1960 are vaccinated mainly with Vaxzevria® by their general practitioner. Between March 15<sup>th</sup>-23<sup>rd</sup>, 2021 and April 3<sup>rd</sup>-5<sup>th</sup>, 2021, the Vaxzevria® vaccine was not administered.
4. Vaccinated individuals who are not registered in the Personal Records Database (BRP) [1], for example homeless people or migrant workers, are included in the numerator but not in the denominator.
5. This figure includes persons that received one dose of the Janssen vaccine, since one dose of this vaccine is sufficient to be fully vaccinated.
6. This figure includes individuals for whom a single vaccine dose is sufficient to be fully vaccinated due to prior infection with SARS-CoV-2.
7. Individuals from birth year 2009 are not invited all at the same time since they must turn 12 years first before being allowed the vaccination. Individuals born up to and including June 30<sup>th</sup>, 2009 were invited at the same time. Persons born from July 2009 onwards can make an appointment when they turn 12 years old. To calculate the coverage in this figure, all persons born in 2009 are included in the denominator for the birth years 2004-2009. If 11-year-olds would be excluded from this denominator, the coverage for birth years 2004-2009 would be 56% instead of 53%.



**Figure 9.4.3** Cumulative coverage for full COVID-19 vaccination, birth years 1955 and before (66 years and older), weeks 1-41, 2021<sup>1-4</sup>.

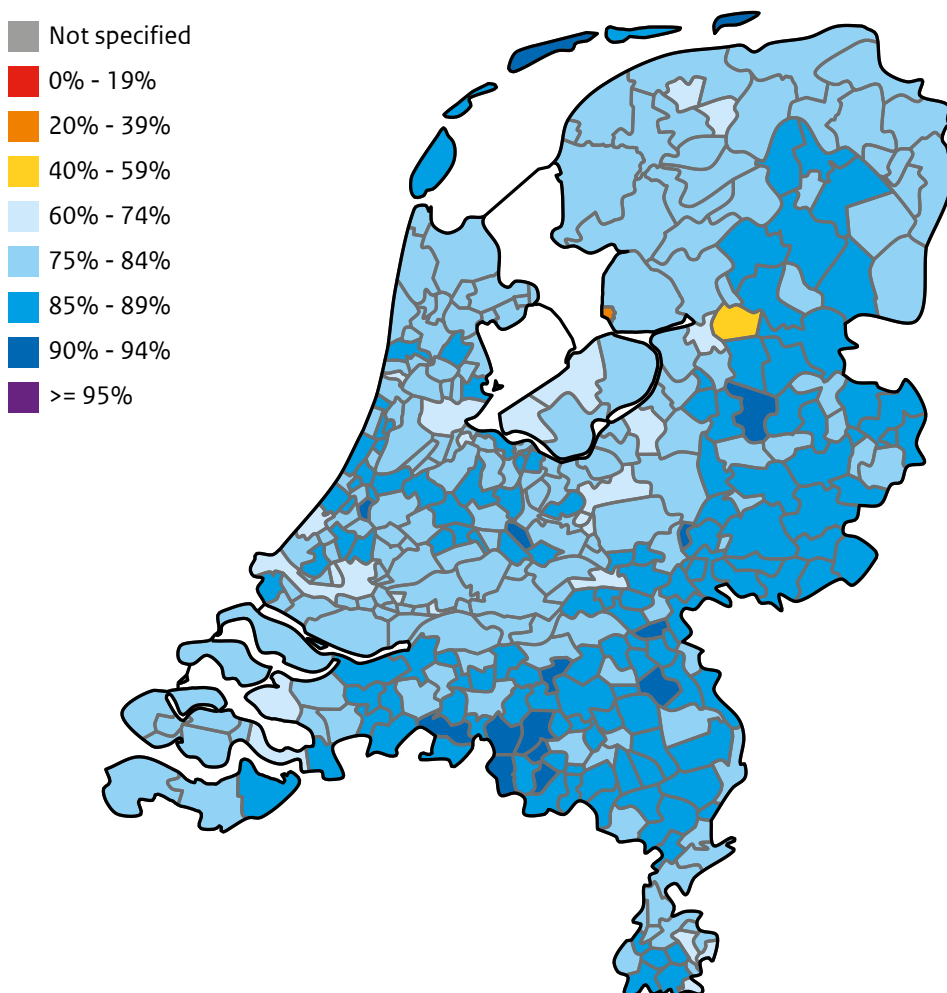
1. Data sources for numerators: CoronIT for Municipal Health Services (GGD) and COVID-vaccination Information Monitoring System (CIMS) for other implementing organisations, including general practitioners. Data source for denominators: population by age group and municipality, CIMS, 2021. CIMS includes vaccination information of vaccinated individuals who provide informed consent to register this information. Therefore, this figure does not include vaccinated individuals who did not provide informed consent.
2. Vaccinated individuals who are not registered in the Personal Records Database (BRP), for example homeless people or migrant workers, are included in the numerator but not in the denominator.
3. This figure includes individuals who received one dose of the Janssen vaccine, since one dose of this vaccine is sufficient to be fully vaccinated.
4. This figure includes persons for whom a single vaccine dose is sufficient to be fully vaccinated due to prior infection with SARS-CoV-2.





**Figure 9.4.4** Cumulative coverage of at least one dose COVID-19 vaccination, birth years 2003 and before (18 years and older), weeks 1-41, 2021<sup>1-2</sup>.

1. Data sources for numerators: CoronIT for Municipal Health Services (GGD) and COVID-vaccination Information Monitoring System (CIMS) for other implementing organisations, including general practitioners. Data source for denominators: population by age group and municipality, CIMS, 2021. CIMS includes vaccination information of vaccinated individuals who provide informed consent to register this information. Therefore, this figure does not include vaccinated individuals who did not provide informed consent.
2. Vaccinated individuals who are not registered in the Personal Records Database (BRP), for example homeless people or migrant workers, are included in the numerator but not in the denominator.



**Figure 9.4.5** Cumulative coverage full COVID-19 vaccination, birth years 2003 and before (18 years and older), weeks 1-41, 2021<sup>1-4</sup>.

1. Data sources for numerators: CoronIT for Municipal Health Services (GGD) and COVID-vaccination Information Monitoring System (CIMS) for other implementing organisations, including general practitioners. Data source for denominators: population by age group and municipality, CIMS, 2021. CIMS includes vaccination information of vaccinated individuals who provide informed consent to register this information. Therefore, this figure does not include vaccinated individuals who did not provide informed consent.
2. Vaccinated individuals who are not registered in the Personal Records Database (BRP), for example homeless people or migrant workers, are included in the numerator but not in the denominator.
3. This figure includes individuals who received one dose of the Janssen vaccine since one dose of this vaccine is sufficient for full vaccination.
4. This figure includes individuals for whom a single vaccine dose is sufficient to be fully vaccinated due to prior infection with SARS-CoV-2.

### 9.4.3 Vaccination strategy

Detailed information on the Dutch vaccination strategy can be found in sections 9.2 and 9.3. In summary, the campaign started on January 6<sup>th</sup>, 2021 and prioritised high age groups, healthcare workers, hospital employees providing direct COVID-19 care, residents of long-term care facilities, and medical risk groups. The organisation administering the vaccinations to the main part of the population was the Municipal Health Service (GGD). Organisations administering vaccinations to (other) specific target groups include general practitioners, hospitals and long-term care facilities.

### 9.4.4 Vaccination coverage by age

By week 39, coverage for at least one dose COVID-19 vaccination and full COVID-19 vaccination for individuals born in 2003 or before had reached between 82-87% and 80-83% respectively (Table 9.4.1). For individuals born in 2009 and before, the coverage had reached between 81-84% and 79-81%, respectively, taking into account that only individuals born in 2009 who had already turned 12 years were included in the denominator.

In week 39, the COVID-19 vaccination campaign was still underway but past its peak. The youngest age groups in particular were still being vaccinated. As the vaccination strategy prioritises, amongst others, high age groups, higher vaccination coverage was seen in older birth years compared to younger birth years in week 39 (Figures 9.4.1 and 9.4.2). In younger age groups, however, a less rapid increase, and in certain younger age groups a stabilisation, of vaccination coverage is already observed at lower percentages than in older age groups (Figures 9.4.1 and 9.4.2). This indicates that younger age groups might not reach coverage levels for full COVID-19 vaccination as high as those in older age groups in future weeks. A potential reason is the fact that younger people in general become less ill after SARS-CoV-2-infection and therefore have a lower vaccination willingness. On the other hand, research by the RIVM shows rising vaccination willingness (49-59% in November 2020, and 91-94% in September 2021) among individuals aged 16-54, although the external validity of this research might not be optimal [2]. The holiday period and the possibility that younger people feel less urgency to be vaccinated as soon as possible might also be reasons for the observation of a slower increase of vaccination coverage among younger age groups. Future weeks will have to show how vaccination coverage develops in younger age groups.

### 9.4.5 Vaccination coverage at the level of municipalities

Figures 9.4.3, 9.4.4, and 9.4.5 show differences in vaccination coverage at the level of municipalities level, that are due to differences in vaccination willingness, since all individuals willing to be vaccinated against COVID-19 could have been fully vaccinated in all municipalities by week 41. Among individuals born in 1955 and before, high coverage (90-94%) is observed in most municipalities, and some municipalities in the east and south-east of the country reach vaccination coverages of  $\geq 95\%$ . Coverage in a few large cities and some Bible Belt municipalities ranges between 75% and 89%. The lowest coverage is observed in the municipality of Urk (40-59%) (Figure 9.4.3). Due to religious considerations, willingness to be vaccinated against COVID-19 is lower in the Dutch Bible Belt. This is in line with lower participation in the National Immunisation Programme (NIP) in these municipalities [3].

For the whole adult population that is eligible for vaccination (all persons born in 2003 or before), similar regional differences are observed (Figures 9.4.4 and 9.4.5). For vaccination with at least one dose (Figure 9.4.4), coverage is  $\geq 75\%$  in nearly all municipalities. Exceptions with lower coverage include a few large cities (60-74%), i.e. Rotterdam, The Hague, and Lelystad, and some Bible Belt municipalities (mostly 60-74%). The highest coverage ( $\geq 85\%$ ) is observed in municipalities in the east and south-east of the country, where some municipalities even reach a coverage of 90-94%. High coverage ( $\geq 85\%$ ) is also observed on the Wadden Islands. The lowest coverage is observed in the municipality of Urk (20-39%) (Figure 9.4.4).

For full COVID-19 vaccination (Figure 9.4.5), coverage has reached 75-84% in most municipalities. Exceptions with lower coverage include a few large cities (60-74%), i.e. Amsterdam, Rotterdam, The Hague, Almere, and Lelystad, and a number of Bible Belt municipalities (mostly 60-74%). The highest coverage (85-89%) is observed in municipalities in the east and south-east of the country, where some municipalities even reach a coverage of 90-94%. High coverage ( $\geq 85\%$ ) is also observed on the Wadden Islands. The lowest coverage is observed in Urk (20-39%) (Figure 9.4.5).

At a more detailed level, lower coverage for full COVID-19 vaccination in the municipalities of Amsterdam, Rotterdam and The Hague is observed mainly in deprived neighbourhoods and among individuals with a migration background. Research by the RIVM shows that individuals with a migration background and/or low socioeconomic status (SES) are generally less willing to be vaccinated against COVID-19 [4, 5]. In Amsterdam, Rotterdam and The Hague, the population includes a relatively large number of people with low SES and/or from a migration background. This is also in line with results for participation in the NIP [6].

#### 9.4.6 Literature

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## 9.5 Effect of vaccination

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### 9.5.1 Keypoints

- A large impact on the COVID-19 burden in the elderly was observed in the first 2-3 months after the vaccination programme in the Netherlands was initiated.
- High vaccine effectiveness (VE) was found against severe COVID-19, including in the period during which the Delta variant was dominant, based on Dutch surveillance data and data from the VECTOR study.
- Based on source and contact tracing, VE against transmission to household members was 71% in the period in which the Alpha variant was dominant.
- Several studies collecting data through questionnaires and blood sampling are ongoing to study VE in the long term.

### 9.5.2 Impact assessment

The impact of the COVID-19 vaccination programme was assessed by comparing COVID-19 incidence among a group targeted for vaccination with the incidence among a group of otherwise comparable individuals not targeted for vaccination. The impact of the first eight weeks of the COVID-19 vaccination programme was quantified by comparing the incidence of positive SARS-CoV-2 tests, COVID-19 related hospitalisations and deaths eight weeks after start of vaccination with incidence in the week preceding start of vaccination in the given target group [1]. Values were standardised by dividing the resulting incidence rate ratio (IRR) by the IRR among an age cohort not yet eligible for vaccination at the time, i.e. 65- to 74-year-olds. The data was standardised this way to account for variations in incidence due to factors other than vaccination. Retrospective analyses were performed for January 1<sup>st</sup> to April 18<sup>th</sup>, 2021. Data from Osiris-AIZ (notifications and deaths) and the COVID-19 hospital registry from Stichting NICE (hospital registrations) were used. Eight weeks after start of the vaccination programme, we observed a relative decline in infections of 56% (95% CI, 51-61%) among people aged 80-84 who lived at home and a decline of 66% (95% CI, 62-70%) among those aged 85 years and over. We estimated a relative decline in infections of 90% (95% CI, 90-91%) among nursing-home residents. Among people living at home, aged 80-84 years and 85 years and over, a relative decrease was estimated of 55% (95% CI, 45-63%) and 69% (95% CI, 63-74%) in hospitalisations, respectively, and 29% (95% CI, -11-55%) and 52% (95% CI, 28-67%) in deaths, respectively, eight weeks into the vaccination campaign. Among nursing-home residents, we estimated a relative decline in deaths of 83% (95% CI, 78-88%). These results showed a large impact on COVID-19 burden in the elderly in the first months after the vaccination programme was initiated in the Netherlands.

### 9.5.3 Vaccine effectiveness

The RIVM employs several methods and data sources to continuously monitor vaccine effectiveness (VE) against positive SARS-CoV-2 tests, COVID-19-related hospitalisations, COVID-19-related deaths, and SARS-CoV-2 transmission in the Netherlands. In addition, specific studies collecting additional data have been set up.

An early VE study among elderly living at home in the spring of 2021 found a VE of 82% (95% CI: 79-84%) against a positive SARS-CoV-2 test, 94% (95% CI: 90-97%) against hospitalisation due to COVID-19, and 94% (95% CI: 85-97%) against death due to COVID-19 [1].

Based on source- and contact-tracing data collected between February and the end of May 2021, we have shown a 71% VE against transmission of SARS-CoV-2 to household members [2]. In this period, the Alpha variant was dominant. The VE against transmission in the period in which the Delta SARS-CoV-2 variant was dominant is monitored and will be made publicly available as soon as possible.

Furthermore, the VE against hospitalisation and ICU admission was estimated using the NICE COVID-19 hospital registry enriched with vaccination data from CIMS. For this estimate, we used an incidence rate-based method. A first report published on August 27<sup>th</sup>, 2021 showed a VE of 95% (95% CI: 94-95%) against hospitalisation and 97% (95% CI: 96-98%) against ICU admission in the period dominated by Delta [3]. No indication for waning of VE against hospitalisation or ICU admission was observed in this report. This is in line with a review by ECDC published on September 1<sup>st</sup>, 2021, showing that while VE against SARS-CoV-2 infection is lower with Delta compared to Alpha variant, the VE against severe disease remains very high [3].

VE against hospitalisation due to COVID-19 was also estimated in the VECTOR study, a test-negative case control study among 6 hospitals in the Netherlands (see [4] for design of the study). In this study, background information including comorbidity and medication use is available. Preliminary results on 623 patients hospitalised (369 cases and 254 controls; median age 65 and 71 years, respectively) between 1 March and 5 July 2021 showed an adjusted VE of 90% (95% CI: 75-96%) after full vaccination and 67% (95% CI: 45-80%) after partial vaccination. No statistical difference in VE was found between age groups or between different medical risk groups. The current results are from the period in which the Alpha variant was dominant. The study will continue in order to monitor VE in the period in which the Delta variant was dominant.

On September 14<sup>th</sup>, 2021, the Health Council recommended refraining from administering booster vaccinations in the general population until evidence shows decreasing VE against severe COVID-19 [5].

#### 9.5.4 Ongoing studies: the CONTEST study and Vaccination Study Corona (VASCO)

The aim of the CONTEST study is to identify and determine the key risk factors for and protective factors against COVID-19 among individuals attending community testing locations in order to inform public health response and strategies. One of the specific aims of the CONTEST study is to estimate VE. The study has a test-negative case-control study design and study participants are recruited prospectively. All persons attending GGD testing locations across the Netherlands are invited to participate in the study by filling out a questionnaire before receiving their test result. Information is collected on demographics, exposure-related variables, signs and symptoms, test results, vaccination history, and underlying chronic conditions. From February 2021 up to August 2021, 20,000 persons were included in the CONTEST study, 6.7% of which tested positive for SARS-CoV-2. Of these participants, 35% were male. The median age was 46 and 62% of participants were highly educated. Of the participants, 25% were vaccinated. Recruitment for this study is still ongoing and results on VE are expected to be available in 2022.

VASCO is a population-based prospective cohort study. At baseline, participants take a fingerpick blood sample at home for serology and complete a questionnaire via the VASCO application. Data collected in the questionnaire includes sociodemographic variables, health status, vaccination, and behaviour regarding COVID-19 measures. During follow-up, participants fill out monthly questionnaires including questions about COVID-19 vaccination, testing for SARS-CoV-2 infection, changes in health status and behaviour regarding COVID-19 measures. At 6 and 12 months after inclusion in the study, and one month after full vaccination, participants again take a fingerpick blood sample. Furthermore, information on SARS-CoV-2 testing and COVID-19 vaccination will be obtained through linkage with the national vaccination register and linkage with GGD registrations where possible. Participants will be followed for 5 years. As of September 2021, 33,288 participants have entered the study. Of these, 23,940 (71.2%) signed the informed consent form and were actually included in the study. Of these, 23,720 (99.1%) filled in the baseline questions and 22,916 (95.7%) sent in the baseline fingerpick sample. Recruitment is still ongoing. In the study, 21,280 (89.7%) of the participants were vaccinated at baseline, of which 14,169 (66.6%) were fully vaccinated. Participants have been vaccinated with Comirnaty® (BioNTech/Pfizer (63.5%), Moderna® (7.5%), Vaxzevria (AstraZeneca) (25.1%) or Janssen (3.7%). In the VASCO study, 36.7% of participants were male, the median age was 62 years, 94.4% of the participants were born in the Netherlands, and 57.4% are highly educated. Based on self-reporting, 9.6% of the participants had a previous SARS-CoV-2 infection. The first results of the study are expected in 2022.

### 9.5.5 Literature

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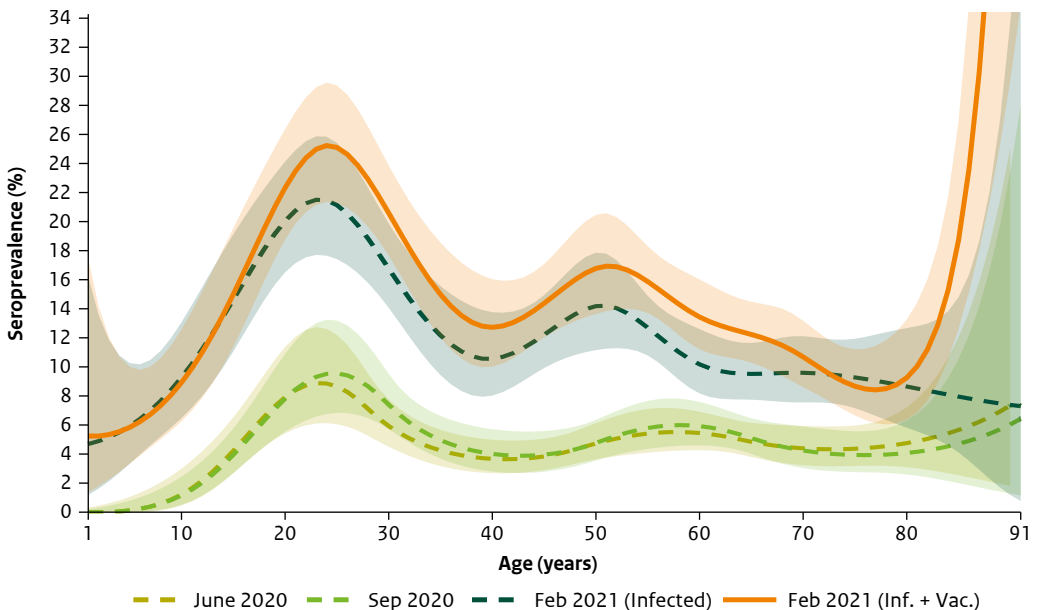
## 9.6 Seroepidemiology of SARS-CoV-2 in the Netherlands

E.R.A. Vos, C.C.E. van Hagen, L.L. van den Hoogen, M. van Boven, R.M. Schepp, G. Smits, J. van Vliet, A.J. Wijmenga-Monsuur, D. Wong, K. Helm, L. Woudstra, R.S. van Binnendijk, F.R.M. van der Klis, G. den Hartog, H.E. de Melker

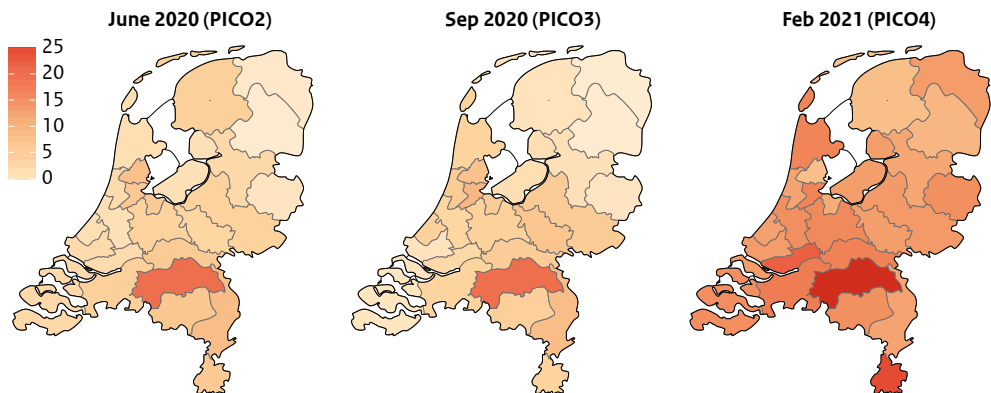
### 9.6.1 Keypoints

- The prospective seroepidemiology PIENTER Corona (PICO) study has provided valuable insights concerning SARS-CoV-2 infections and risk factors in the Netherlands throughout the epidemic. Data from all study-rounds indicate that young adults had been infected most often, especially compared with school-aged children, and data from the latest study round (June 2021) showed that over 90% of Dutch inhabitants of 55 years and older had detectable antibodies, both from natural infection and resulting from vaccination.

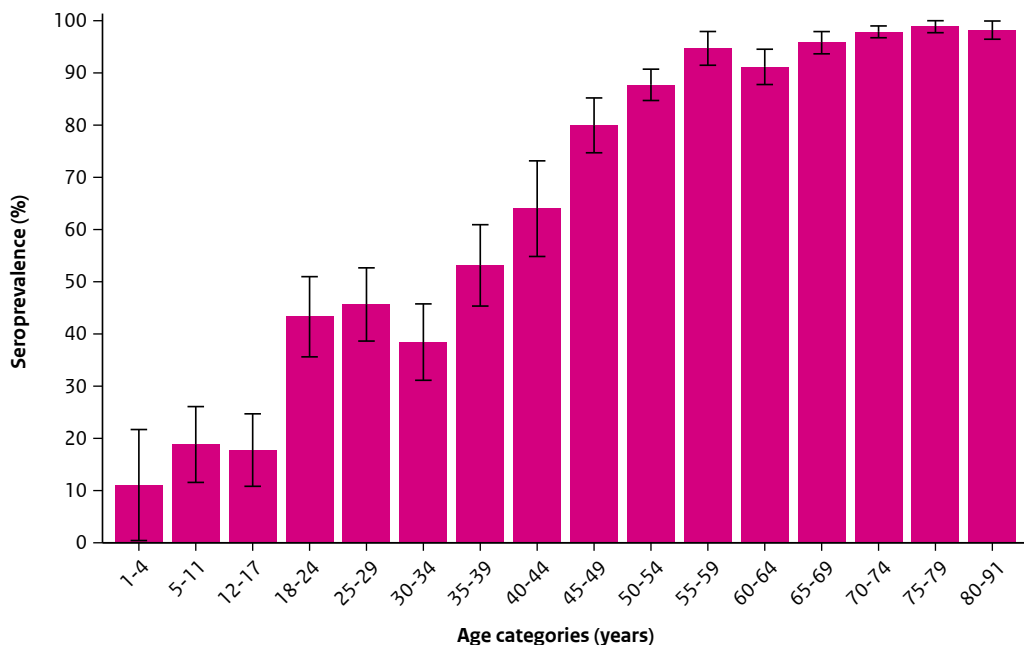
### 9.6.2 Tables and figures



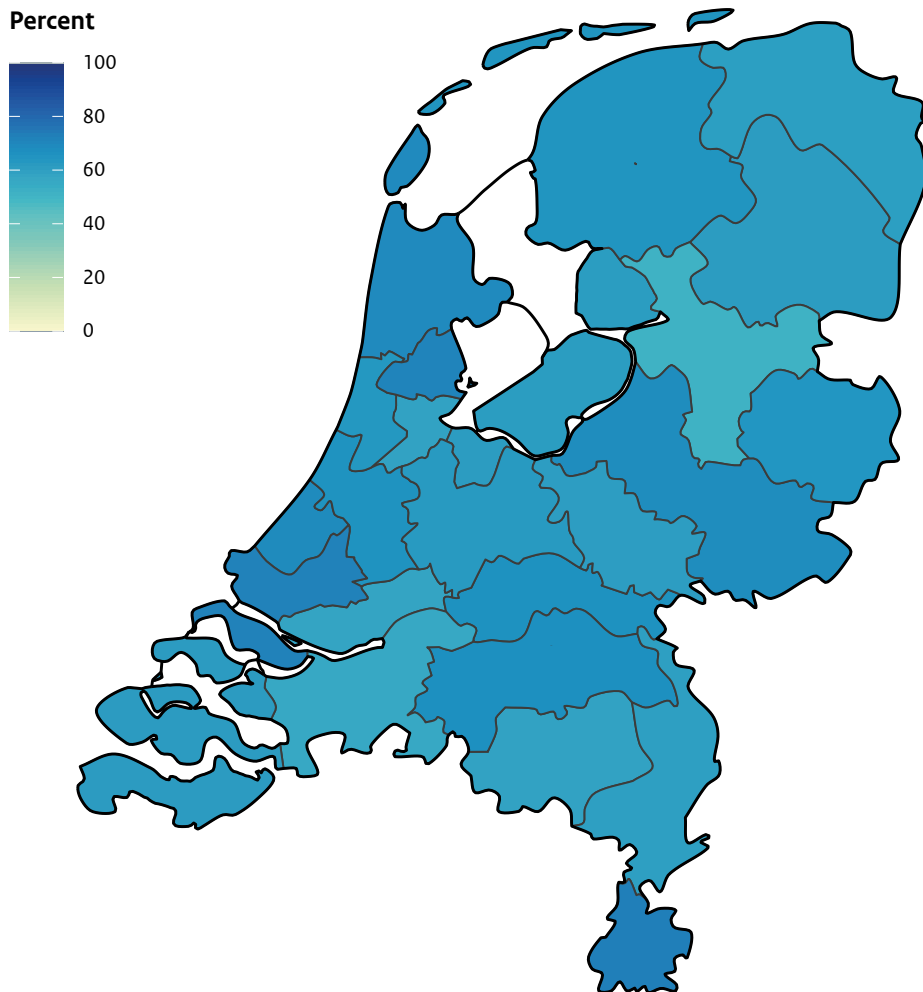
**Figure 9.6.1** Weighted seroprevalence (with 95% confidence intervals) in the general population of the Netherlands in PICO rounds 2, 3 and 4 (June 2020, September 2020, and February 2021, respectively), by age (years) fitted using splines. Note: seroprevalence of PICO round 4 (February 2021) is subdivided into infection-related seroprevalence only (dashed dark green line) and seroprevalence resulting from both infection and/or vaccination (yellow line).



**Figure 9.6.2** Weighted infection-related seroprevalence in the general population of the Netherlands in PICO rounds 2, 3 and 4 (June 2020, September 2020, and February 2021 respectively), by GGD region. Note: Here, seroprevalence in PICO round 4 (February 2021) only includes antibodies derived from infection.

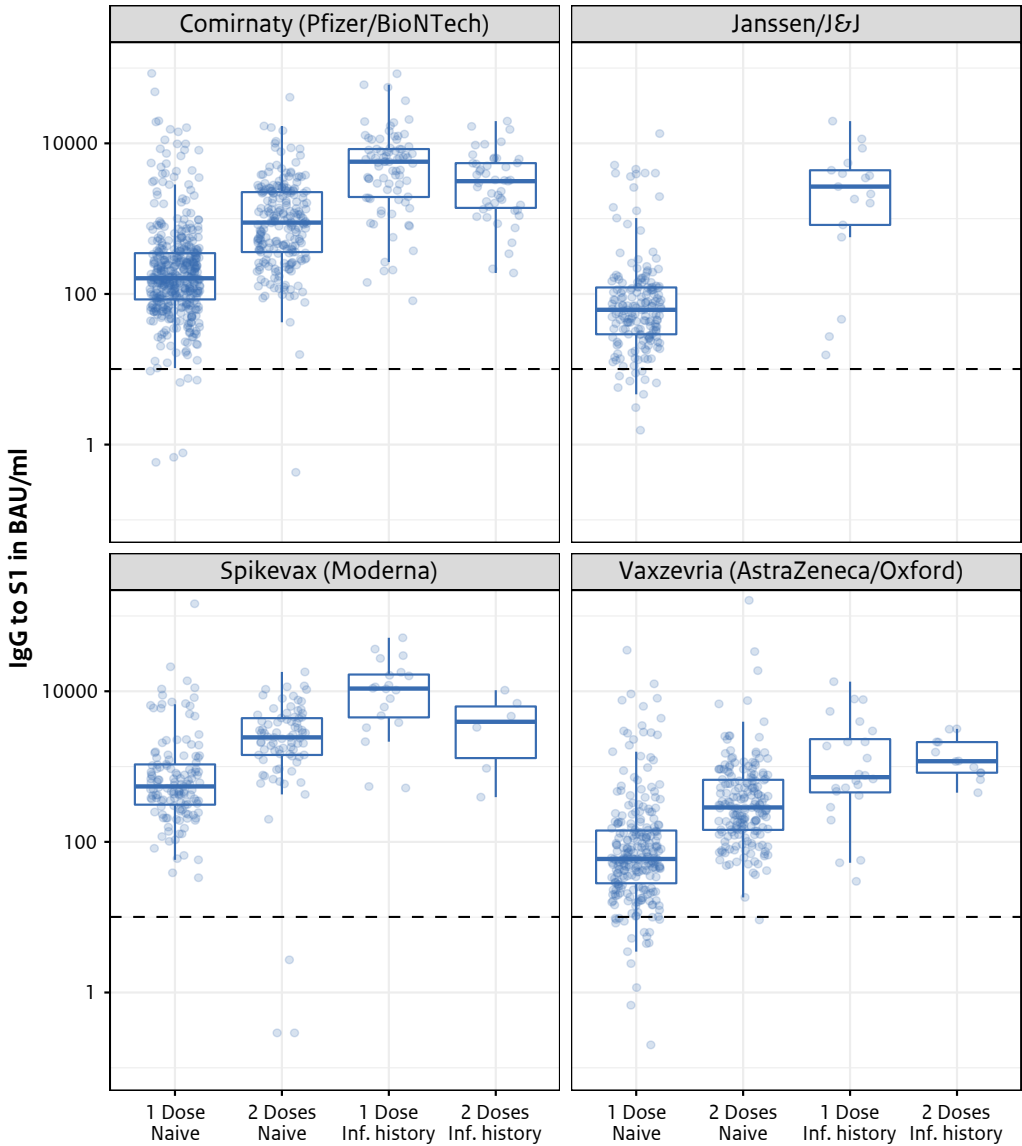


**Figure 9.6.3** Preliminary analysis of weighted total seroprevalence (with 95% confidence intervals) in the general population of the Netherlands in the 5<sup>th</sup> PICO round (June 2021), by age groups. Note: seroprevalence here includes antibodies derived from both infection and/or vaccination.

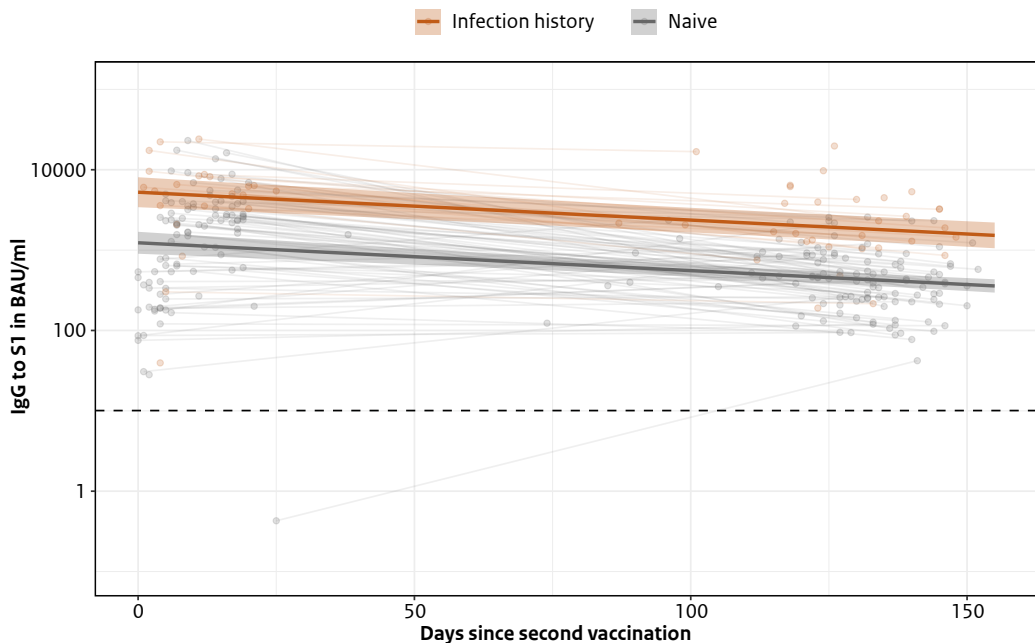


**Figure 9.6.4** Preliminary analysis of weighted total seroprevalence in the general population of the Netherlands in the 5<sup>th</sup> PICO round (June 2021), by GGD region. Note: seroprevalence here includes antibodies derived from both infection and/or vaccination.

[18,65]



**Figure 9.6.5** IgG antibody responses to the SARS-CoV-2 Spike S1 antigen according to infection history, number of doses and vaccine brand in participants aged 18 to 65 years. IgG measurements were taken >14 days after the indicated dose. Median and IQR are provided and individual data are presented as dots. The dotted line represents the cut-off for seropositivity (in BAU/mL).



**Figure 9.6.6** Linear fits (with 95% confidence intervals) of IgG-specific Spike S1 antibodies over time in Comirnaty® fully vaccinated participants aged 18-65 years, by infection history. Individual data are presented in dots, and a generalised estimating equations (GEE) model was used to adjust for repeated sampling. The dotted line represents the cut-off for seropositivity (in BAU/mL).

### 9.6.3 PIENTER Corona (PICO)

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 group of individuals representative of 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 beginning of the SARS-CoV-2 epidemic 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 persons 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 2<sup>nd</sup> in June 2020, the 3<sup>rd</sup> in September 2020, the 4<sup>th</sup> in February 2021, and the 5<sup>th</sup> in June 2021. Data on potential risk factors for 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 the bead-based multiplex immunoassay (MIA) developed at the 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 5<sup>th</sup> round, the participants' age ranged between 1-91 years, and somewhat more women than men participated (57% vs. 43%). Results were weighted to represent the Dutch population. The study will proceed in the coming period: in the last months of 2021, a 6<sup>th</sup> round will be carried out – among current and newly sampled participants – and additional rounds are planned in the coming years.

#### 9.6.4 PICO rounds 1 to 4 (April 2020 – February 2021)

In the first 3 PICO rounds (from April 2020 up to and including September 2020), SARS-CoV-2 anti-spike S<sub>1</sub> was used to determine infection. SARS-CoV-2 vaccines in the Netherlands have been administered since the beginning of 2021, and all are targeted at the spike antigen. Hence, since the 4<sup>th</sup> PICO round, anti-nucleocapsid (N) – induced solely via natural infection – and PCR positivity were used additionally to distinguish antibodies derived from infection and/or vaccination. The overall weighted seroprevalence of IgG antibodies targeted against the spike S<sub>1</sub> antigen of SARS-CoV-2 in the 1<sup>st</sup> round (April 2020) (i.e. derived from infection) was 2.8% (95% CI: 2.1-3.7). This rose to 4.5% (95% CI: 3.8-5.2) in the 2<sup>nd</sup> round (June 2020), and 4.9% (95% CI: 4.1-5.6) in the 3<sup>rd</sup> round (September 2020). In February 2021, 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). On a national level, no differences were observed by sex or ethnic background. Since the Netherlands started SARS-CoV-2 vaccination in January 2021, the 4<sup>th</sup> round of the study (February 2021) made a distinction between seropositivity due to SARS-CoV-2 infection (12%) and resulting from vaccination (2%).

##### 9.6.4.1 Seroprevalence by age

Infection-induced seroprevalence by age is estimated in each PICO study round and shows similar patterns between the different study rounds prior to start of the vaccination programme (Figure 9.6.1, dashed green lines). Young adults display the highest seroprevalence at each timepoint. In February 2021, seroprevalence in this group was above 20%. Although seroprevalence among children of primary school age rose in February 2021 compared to previous rounds, the percentage of individuals with antibodies in this group remains lower than older age groups. Total seroprevalence by age in February 2021 (Figure 9.6.1, continuous orange line) shows a similar pattern as in previous study rounds for all ages below 80 years: a small proportion of those in the working age groups were already vaccinated (foremost care workers), and a steep increase was observed in those above 80 years of age, in line with the age-dependent vaccination rollout in the Netherlands.

#### 9.6.4.2 Seroprevalence by region

Geographical distribution of SARS-CoV-2 seroprevalence in the Netherlands is also monitored in the PICO study. Figure 9.6.2 shows SARS-CoV-2 infection-related seroprevalence per GGD region since 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 compared to the south of the Netherlands. Although seroprevalence was still highest in the southern provinces after the second wave (February 2021, PICO 4<sup>th</sup> round), the difference compared to the other regions had decreased, with the strongest increases in the GGD regions of Twente, Zuid-Holland-Zuid, and Zuid-Limburg.

#### 9.6.4.3 Social distancing

Results from the 2<sup>nd</sup> PICO round showed that social distancing is an important measure in stopping the spread of SARS-CoV-2 [3]. Participants who had followed the recommendation to stay 1.5 metres apart were less likely to test seropositive during the first wave. While seroprevalence among participants who were less compliant with the distancing rule was 5.5%, only 4% of people who did keep their distance during contact with others tested seropositive. Interestingly, participants who mostly had contact with children under the age of 10 were hardly ever infected during those encounters. Likewise, participants who indicated that they had an occupation involving physical contact with children were not more likely to be infected. When attending a meeting or gathering, group size also proved to be an important predictor of infection: among participants who had attended a meeting or gathering (involving more than 20 people) in an indoor environment during the first wave, seroprevalence was 6.2%. This was ~1.5 times higher than people who had not attended such meetings (4.2%).

#### 9.6.4.4 Antibody decay after infection

Data from the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> 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 seven months [5]. Furthermore, it was observed that avidity of these IgG antibodies, an important indicator of antibody-binding strength, increased over time.

### 9.6.5 Preliminary analyses of PICO round 5 (June 2021)

Sampling of the 5<sup>th</sup> round started on June 28<sup>th</sup>, 2021 and samples up to July 20<sup>th</sup>, 2021 were included for the current analysis (median inclusion date June 24<sup>th</sup>, 2021, with 90% of samples collected before July 5<sup>th</sup>, 2021). In preliminary analyses of this 5<sup>th</sup> round, overall weighted total seroprevalence (i.e. both infection- and vaccine-induced humoral immunity) in the general Dutch population was estimated at 63% (95% CI: 62-65%). In accordance with prioritisation of elderly in the vaccination programme, seroprevalence increased significantly with age from 40% in young adults to over 90% in those 55 years and older (Figure 9.6.3).

The geographical distribution of SARS-CoV-2 weighted total seroprevalence in June 2021 (PICO 5<sup>th</sup> round) generally showed similar estimates between GGD regions in the Netherlands, ranging between 52% (GGD IJsselland) and 73% (GGD Zuid-Limburg) (Figure 9.6.4).

Furthermore, preliminary analyses were conducted on humoral responses after vaccination. Overall, most participants had received an mRNA-based vaccine: >95% of all participants aged 70 and over, and 56-69% among those aged 18-60 years had received Comirnaty®. Within the age group 60-69 years, half of the participants were vaccinated with Vaxzevria®. Besides Comirnaty® in the age groups 18-60 years, vaccination with Spikevax® was mostly reported, followed by Janssen COVID-19 vaccine and Vaxzevria®. The mean interval between the two doses of the mRNA-based vaccines was 34 days for Comirnaty® and 32 days for Spikevax®, and for the viral vector vaccine Vaxzevria® 71 days.

In participants without prior evidence of infection, nearly all (99%) seroconverted after the first vaccination with an mRNA vaccine. Likewise, 99% of the participants were seropositive two weeks after the second vaccination. Hence, the COVID-19 vaccine Comirnaty® used in older age groups with two doses, effectively induced humoral immunity in participants up to 91 years of age. After the first dose with Vaxzevria® and after the single vaccination with Janssen, 91% and 99%, respectively, seroconverted after four weeks. Nearly all (99%) presented with SARS-CoV-2 Spike-specific IgG antibodies after the second dose with Vaxzevria®.

Generally, mRNA-based vaccines are highly immunogenic and show the highest antibody levels (Figure 9.6.5). After the first dose, concentrations induced by the vector-based vaccines Vaxzevria® and Janssen COVID-19 vaccine are similar, but both lower than the levels after mRNA-based vaccines Comirnaty® and Spikevax® (note that only participants 18-65 years of age were selected for this analysis to minimise the potential effects of age and time since vaccination). Antibody concentrations increase significantly after the second dose with an mRNA-based vaccine. Following the second vaccination with Vaxzevria®, concentrations are also higher than after the first dose, and higher than after a single vaccination with Janssen COVID-19 vaccine, however substantially lower than after two doses with the mRNA-based vaccines.

Furthermore, all participants with a history of infection (for this analysis based on IgG antibodies prior to vaccination and/or a positive test (PCR or antigen)) show substantially higher SARS-CoV-2 Spike S1-specific IgG antibody concentrations after their first vaccination than fully vaccinated participants without prior infection vaccinated with the same vaccine. This was true most notably for vaccination with an mRNA-based vaccine, followed by the Janssen COVID-19 vaccine. Notably, the second mRNA-based vaccine dose in those with a previous SARS-CoV-2 infection does not boost the concentration of antibodies any further.

In addition, the potential change over time in IgG concentration and seroprevalence to Spike S1 was analysed for participants 18-65 years of age after two doses of Comirnaty® (i.e. those fully vaccinated with samples in the 4<sup>th</sup> and 5<sup>th</sup> PICO round, n=224) (Figure 9.6.6). Only one participant did not seroconvert, whereas all others remained seropositive over time, including those with a sample up to 3-5 months after their second Comirnaty® vaccination (n=112). As expected, participants with a history of infection show substantially higher SARS-CoV-2 Spike S1-specific IgG levels directly after vaccination, which remain present for the period studied. The rate of antibody decay, however, did not differ between those with and without



prior infection (up to 150 days after the second dose). The estimated half-life of SARS-CoV-2 Spike S1-specific IgG is 87 days (95% CI: 68-122). This is shorter than a previous estimate of IgG half-life following SARS-CoV-2 infection without vaccination in this cohort, which amounted to 158 days (95% CI: 136-189) [5]. It needs to be noted that decay typically is relatively fast after the first few months when short-lived plasma cells disappear. After a few months, the effect of dwindling numbers of antibody-secreting short-lived plasma cells is decreasing and a steadier decay rate is established usually resulting in longer duration of circulating antibody estimates later after the immunisation event.

Finally, it should be noted that only humoral data are presented here. Comparison of vaccine-induced immunity between vaccines may look different when evaluating cellular immunity too. Still, data of vaccinated and convalescent participants show a strong correlation between Spike S1 antibody concentrations and virus neutralisation [6], indicating that higher concentrations of antibodies do contribute to protection against disease [7].

### 9.6.6 Literature

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## 9.7 Pathogen surveillance

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### 9.7.1 Keypoints

- The RIVM sequences randomly selected SARS-CoV-2-positive specimens from both Municipal Health Centres and hospitals to continuously monitor the increase or decrease of Variants Of Concern (VOCs).
- From March up to May 2021, the Alpha variant caused nearly 100% of all infections, while from June 2021, the Delta variant started to expand rapidly, causing almost 100% of infections from August 2021 onwards.
- When comparing the proportion of different VOCs of SARS-CoV-2 infections between unvaccinated and vaccinated SARS-CoV-2 infected individuals, we found that vaccinated individuals had a higher risk of being infected with the Beta, Gamma or Delta variant while unvaccinated individuals had a higher risk of being infected with the Alpha variant.

Since the world-wide spread of SARS-CoV-2, the virus has been slowly but steadily evolving through introduction of mutations in its genome. Although many mutations are synonymous, multiple substitutions in functional domains of the spike protein are present in these variants, some of which have significant impact on transmissibility, severity and/or immunity. Such a variant is called a Variant-of-Concern (VOC). As of September 1<sup>st</sup>, 2021, four 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) and Delta (B.1.5617.2, first detected in December 2020 in India). All four VOCs contain substitutions in the receptor binding domain (RBD) and N-terminal domain (NTD) of the Spike protein, which are known to be the main target of neutralising antibodies. Several studies have shown decreased sensitivity of VOCs for convalescent and post-vaccination sera in vitro, with little to no reduction in sensitivity for the Alpha variant, the highest reduction in sensitivity for Beta and to a lesser extent for Gamma and Delta [1-3]. The Delta variant has the highest estimated transmissibility of all current SARS-CoV-2 VOCs and is outcompeting all variants in countries in which it is present. It is expected to become dominant worldwide in the coming months if trends continue.

Through the Dutch national SARS-CoV-2 surveillance programme, the RIVM sequences randomly selected SARS-CoV-2-positive specimens from both GGD Municipal Health Centres and hospitals, ensuring proper geographical distribution across all provinces. By means of this surveillance, the increase or decrease of VOCs is monitored continuously (see [link](#)). From January 2021, the Alpha variant started to expand rapidly and quickly became the dominant strain in the Netherlands. From March up to May 2021, the Alpha variant caused nearly 100% of all infections with only a very small percentage of infections caused by the Beta or Gamma variant. From June 2021, the Delta variant started to increase expand rapidly and it has been causing nearly 100% of all infections from August 2021 onward. The Beta, Gamma and Alpha variants have virtually disappeared.

The rapid global spread of first Alpha and later Delta sparked fear for escape from pre-existing immunity and selection of these variants in vaccinated individuals. Real-world evidence indeed suggests lower vaccine effectiveness against the Delta variant compared with the Alpha variant [4, 5]. This lower effectiveness is clear for any infection, but VE against severe disease is still high for the Delta variant. This is also shown on the basis of Dutch surveillance data (see section 9.5).

In addition to sequencing of randomly selected specimens, the RIVM also sequences additional specimens of partially or fully vaccinated cases or persons with a reinfection. This oversampling allows detailed investigation of variants as seen during infection after vaccination or re-infection. We compared the proportion of the different VOCs between unvaccinated and (partly) vaccinated cases. Being fully vaccinated was significantly associated with being infected with the Beta, Gamma or Delta variant compared to the Alpha variant (adjusted OR: 3.1 (95% CI: 1.3-7.3), 2.3 (95% CI: 1.2-4.4), and 1.9 (95% CI: 1.4-2.5), respectively). The association for partial vaccination was less strong and not significant for Beta and Gamma, but still significant for Delta (adjusted OR: 1.8 (95% CI: 1.4-2.2)). Interestingly, we did not find a significant association between previous infection and the Beta, Gamma or Delta variant (adjusted OR: 1.4 (95% CI: 0.5-3.7), 0.3 (95% CI: 0.0-1.9), and 1.0 (95% CI: 0.6-1.5), respectively). These results suggest that the vaccines currently used in the Netherlands provide somewhat less protection against infection with the Delta variant than against infection with the Alpha variant.

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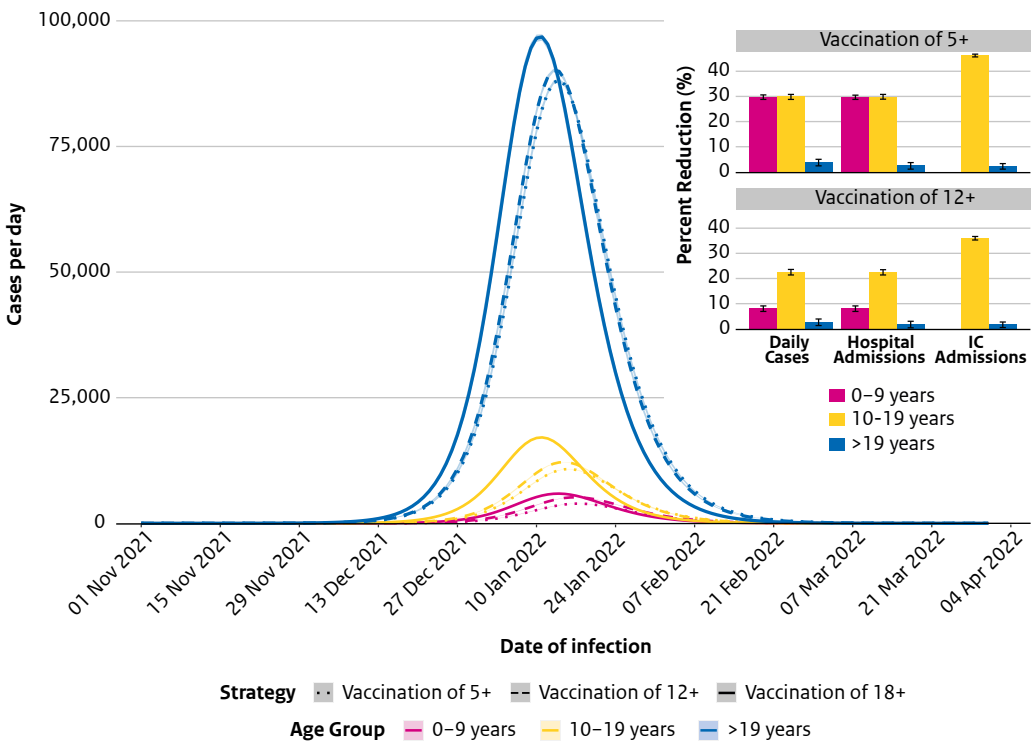
## 9.8 Vaccine modelling

K. Ainslie

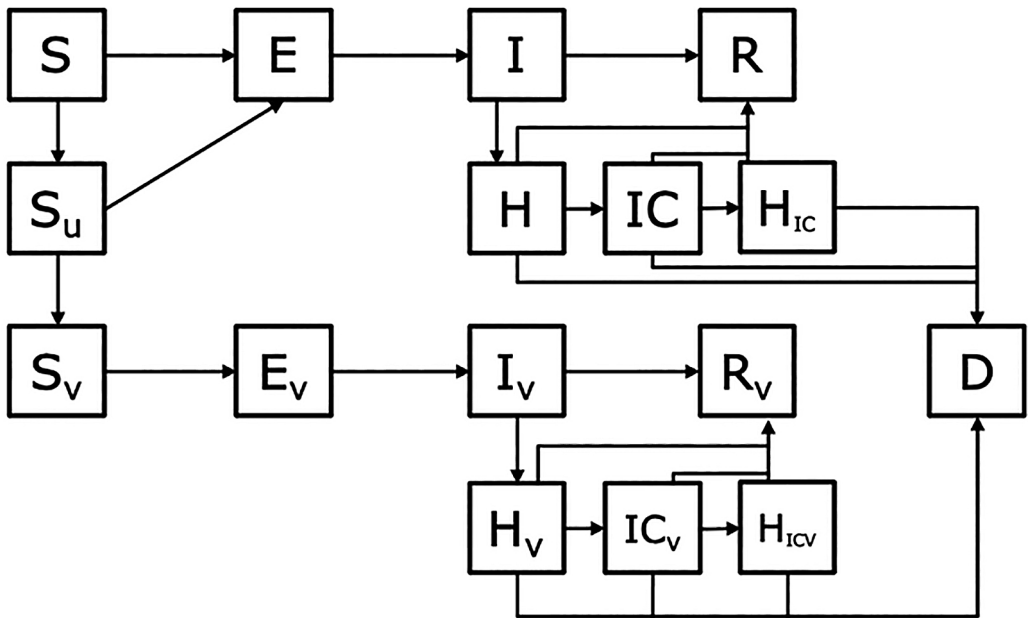
### 9.8.1 Keypoints

- A compartmental transmission model was used to aid policy decisions relating to the Dutch COVID-19 vaccination campaign.

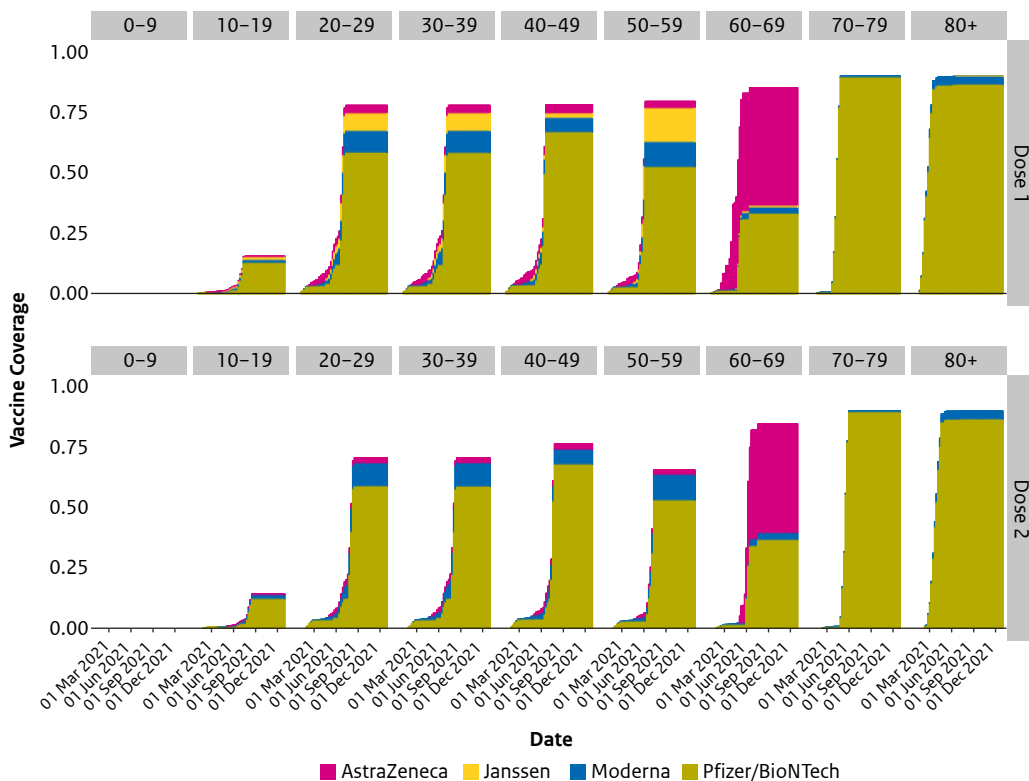
### 9.8.2 Tables and figures



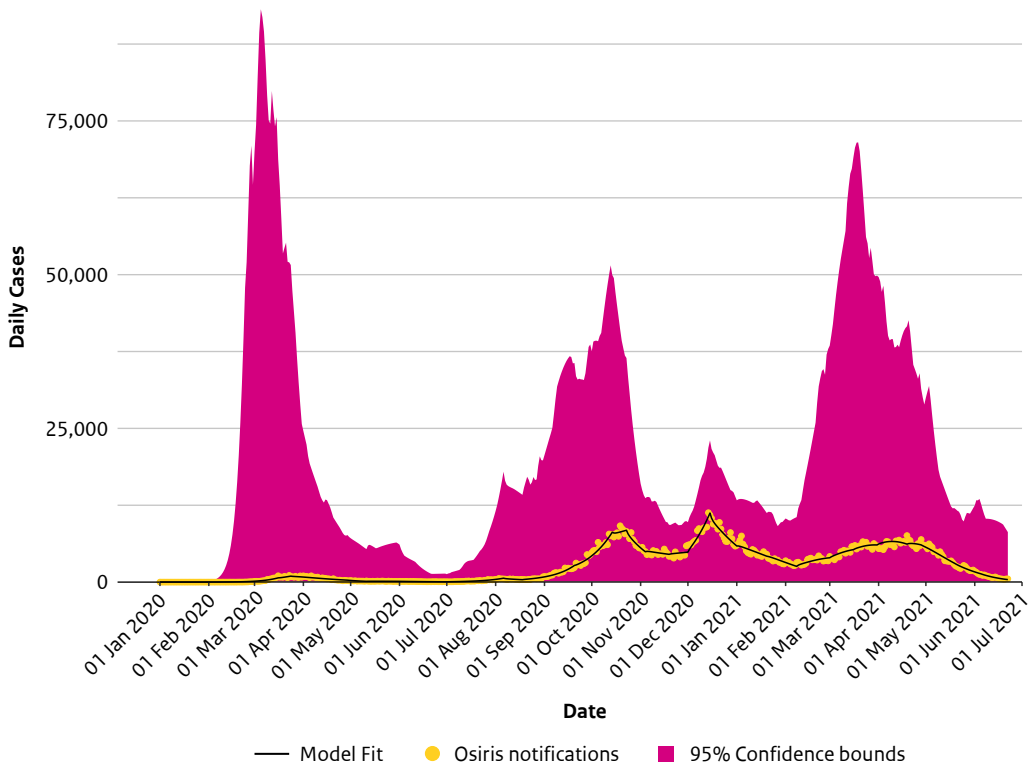
**Figure 9.8.1** Daily cases of COVID-19 for different vaccination strategies: vaccination in adults only (18+, solid line), vaccination in individuals  $\geq 12$  years (12+, dashed line), and vaccination in individuals those  $\geq 5$  years (5+, dotted line). The main figure shows daily cases under the different vaccination strategies by age group, and the figure inset shows the percent reductions in disease outcomes in 5+ and 12+ vaccination strategies compared to the 18+ strategy. This figure shows modelled disease outcomes forward in time from 22 June 2021 until 31 March 2022 and assumes that non-pharmaceutical control measures are relaxed on 1 November 2021. This figure was previously published in Ainslie et al. [2].



**Figure 9.8.2** Basic conceptual model diagram. This diagram does not include the additional states after the second dose of vaccination or the age structure in the model. S = susceptible, E = exposed, I = Infectious, R = Recovered, H = hospitalised, IC = In intensive care, HIC = return to the hospital ward following treatment in IC, Su = vaccinated but not yet protected, D = dead. States with subscript V indicate individuals who are vaccinated and protected by vaccination. This figure was previously published in [2].



**Figure 9.8.3** Vaccination coverage in the Netherlands over time by age group (columns), dose (rows) and vaccine (colour).



**Figure 9.8.4** Model fit to Osiris notification data with 95% confidence bounds from January 1<sup>st</sup>, 2020 to June 22<sup>nd</sup>, 2021. This figure was previously published in [2].

### 9.8.3 Introduction

The first vaccine against COVID-19 was approved by the European Medicines Agency (EMA) on December 21<sup>st</sup>, 2020 [1]. Three other vaccines have since been approved by the EMA and are included in the Dutch COVID-19 vaccination programme (see Section 9.3). To aid policy decisions relating to the roll-out of the Dutch COVID-19 vaccination campaign, we developed a compartmental transmission model. This model allows us to simulate expected disease outcomes, such as the number of cases, hospitalisations or ICU admissions, under different vaccination strategies (Figure 9.8.1). We use data from Dutch and international sources to inform the model so that we can incorporate characteristics of SARS-CoV-2 transmission, population susceptibility, and vaccine distribution and effectiveness. For example, when vaccine supply was limited in early 2021, we used our model to determine the trade-offs between delaying the second dose of vaccines with 2-dose regimens to maximise the number of individuals with partial protection and fully protecting vulnerable age groups sooner. We also used the model to inform vaccination policy in the Netherlands regarding the vaccination of 12- to 17-year-olds and the impact of vaccinating this group with respect to disease outcomes (Figure 9.8.1) [2-4]. All vaccination modelling analyses are published in [2, 3].

### 9.8.4 Model

We developed a deterministic age-structured compartmental susceptible-exposed-infectious-recovered (SEIR) model extended to include states for severe disease outcomes and vaccination status. The population is partitioned into 10-year age groups (0-9, 10-19, ..., 70-79, 80+). Within each age group we further partition the population into those who are unvaccinated, vaccinated with 1 dose, or vaccinated with 2 doses and then finally into disease states: susceptible (S), infected but not yet infectious (E), infectious (I), hospitalized (H), in intensive care (IC), return to the hospital ward after intensive care (HIC), recovered (R), and dead (D) (Figure 9.8.2). We assume several different modes of vaccine protection: 1) reduction in susceptibility to infection, 2) reduction in risk of hospitalization if a vaccinated individual is infected, and 3) reduction in risk of infecting others (transmission) if a vaccinated person is infected.

### 9.8.5 Data sources

To make realistic modelling projections, we use a number of surveillance data sources to inform model parameterisation. Due to the age-structured nature of the model, we can incorporate differences in contact patterns within and between age groups. To accurately reflect contact patterns throughout 2020 and 2021, we use contact matrices that are estimated on the basis of the different rounds of the PICO study [5-7]. Additionally, the objective of this model is to accurately model the expected outcomes of different vaccination strategies, requiring real-time information about the distribution of different vaccines within the population. The rate of vaccination for each age group is extracted from the Dutch vaccine distribution schedule (Figure 9.8.3) based on vaccine availability, the eligibility of different groups to receive vaccines, and current safety guidelines over time. The model also needs to account for vaccine characteristics, such as vaccine effectiveness (VE). We use information from Dutch studies [8-10] and the international literature to update the estimates of VE assumed in the model. Finally, to calibrate the model to the pandemic situation in the Netherlands and



estimate the transmission rate that reflects the patterns of cases over time, we fit the model to Osiris case notification data (Figure 9.8.4). The data is fit piecewise to correspond with the correct contact patterns and non-pharmaceutical interventions [11] within each time window. By re-estimating the transmission rate when control measures change, the estimate of transmission rate implicitly incorporates control measures that cannot be modelled explicitly, such as wearing masks or a curfew. Additionally, by estimating the transmission rate for different time points, we can incorporate differences in transmission rate due to virus variants and other factors influencing transmission. Using the model fits, we can then simulate forward in time to determine what might happen in the coming months.

A full description of the model and data sources used to inform model parameters have previously been described [2].

### 9.8.6 Literature

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## 9.9 Safety of COVID-19 vaccines

J.M. Kemmeren

### 9.9.1 Keypoints

- National health authorities and the European Medicines Agency (EMA) continually monitor adverse events following immunisation (AEFI) in people who have received a vaccine.

### 9.9.2 Tables and figures

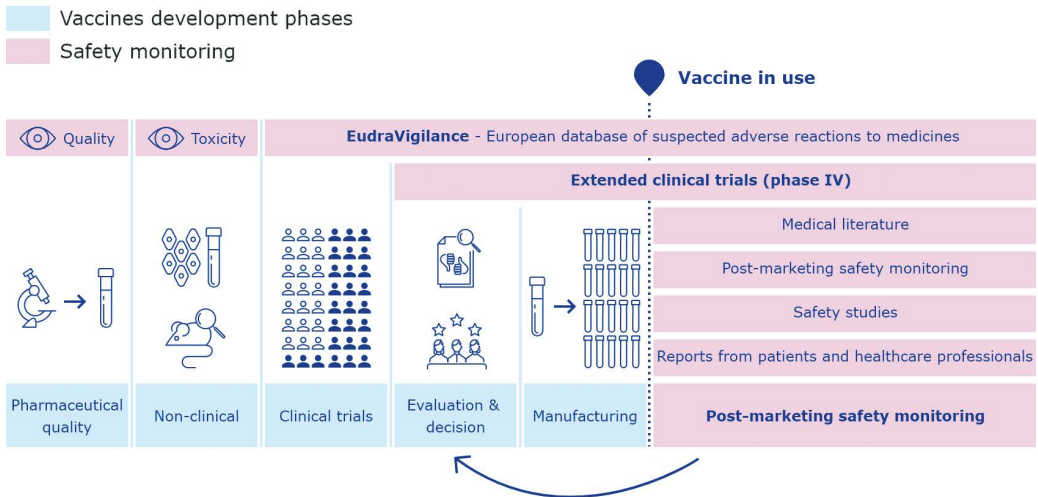


Figure 9.9.1 How vaccine safety is studied.

**Table 9.9.1** Number of reports after the first and second doses per vaccine up to 4 July 2021\*.

Vaccine	Number of reports		
	After 1st vaccination	After 2nd vaccination	Total
AstraZeneca (Vaxzevria®)	32,847	1,213	34,060
Pfizer/BioNTech (Comirnaty®)	25,800	11,867	37,667
Moderna vaccine	8,046	5,182	13,228
Janssen vaccine	8,343	-	8,343
Vaccine unknown	140	15	155

\*For the most recent information, see the Lareb page on [adverse effects after coronavirus vaccination](#).

**Table 9.9.2** Most reported local reactions and systemic events per vaccine up to 04/07/2021\*

Adverse event	Pfizer	Moderna	AstraZeneca	Janssen
Headache	17,320	6,660	24,143	6,097
Malaise	17,282	7,146	22,669	5,730
Myalgia	17,130	7,117	20,862	5,170
Fatigue	18,097	6,886	20,760	5,410
Chills	11,146	5,471	21,776	5,130
Pain at injection site	12,617	6,604	13,131	2,454
Fever	7,166	4,501	16,060	4,279
Nausea	8,987	3,710	11,830	2,922
Joint pain	8,320	3,289	12,579	2,802
Swelling at injection site	4,390	3,307	4,399	662

\*For the most recent information, see the Lareb page on [adverse effects after coronavirus vaccination](#).

### 9.9.3 Monitoring by the EMA

Following approval of COVID-19 vaccines, it is important to monitor the safety of these vaccines to inform vaccination policy and maintain public confidence. Certain rare or very rare side effects may emerge when millions of people are vaccinated. EU law requires that the safety of vaccines must be monitored while they are in use in routine clinical practice. Therefore, national health authorities and the European Medicines Agency (EMA) continually monitor adverse events following immunisation (AEFI) in people who have received a vaccine.

#### 9.9.3.1 Infrastructure

EMA has set up an infrastructure to support safety monitoring of COVID-19 vaccines. This is important because exceptionally large numbers of people receive COVID-19 vaccines once they are authorised (see [link](#)).

A pharmacovigilance plan for COVID-19 vaccines sets out how EMA and the national competent authorities in the EU Member States identify and evaluate any new information that arises promptly, including any safety signals that are relevant to the benefit-risk balance of these vaccines. This plan also ensures that regulators can take any appropriate regulatory actions and communicate these to the public as quickly as possible.

The monitoring activities in the plan apply to all vaccines, but they take place on a larger scale during this pandemic:

- Collecting exposure data to COVID-19 vaccines
- Adopting specific safety signal detection and management measures
- Setting up a European infrastructure for monitoring COVID-19 treatments and vaccines
- Using real-world data from clinical practice
- Applying exceptional transparency measures

EMA's guidance on preparing risk management plans for COVID-19 vaccines helps marketing authorisation applicants develop risk management plans for COVID-19 vaccines. These risk management plans set out how the company will monitor and report on safety and how it will characterise and manage risks following authorisation of a COVID-19 vaccine.

Companies need to submit monthly safety reporting summaries for COVID-19 vaccines in addition to periodic safety update reports, and put processes in place to manage a high volume of safety reports. They need to carry out further studies on COVID-19 vaccines that receive conditional marketing authorisation.

Additional considerations in this guidance address traceability tools that can help record who has received which vaccine and from which batch.

EMA also commissioned the ACCESS project (vACCine Covid-19 monitoring readinESS). This project, which is described in the next section, started May 2020 and ended 15 February 2021 (see [link](#)).

#### 9.9.3.2 ACCESS

ACCESS is a public-academic partnership of 22 European research centres to conduct preparatory research into data sources and methods that can be used to monitor the safety, effectiveness and coverage of COVID-19 vaccines in clinical practice.

With regard to safety monitoring, ACCESS delivered the following deliverables which have gone through EMA and stakeholder review (see [link](#)):

1. List of adverse events of special interest (AESIs).  
A list of 37 events of interest is created. The list of AESIs, definitions and codes is available (see [link](#)).
2. Background rates of AESIs.
  - Protocol background rates of AESIs (see [link](#)).
  - For results of background rate calculations (see [link](#)).
3. Template protocols for different types of studies to be adapted for full implementation to local situation.
  - Signal detection based on cohort event monitoring (from [link](#)):
    - Cohort event monitoring to assess safety of COVID-19 vaccines using patient reported events, a protocol template from the ACCESS project.
  - Rapid assessment of new safety signals based on electronic health record data (EHR):
    - Rapid assessment of COVID-19 vaccines safety concerns through electronic health records: a protocol template from the ACCESS project.
  - Safety signal evaluation studies (EHR or hospital-based):
    - Safety evaluation of COVID-19 vaccines through electronic health records: a protocol template from the ACCESS project.
    - Safety Protocol for Hospital Case-Based Monitoring of Specific Adverse Events Following COVID-19 Vaccines: A Protocol Template from the ACCESS project.

In the meantime, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance have started a Cohort Event Monitoring study (see [link](#)). The primary aim is to generate incidence rates of patient-adverse drug reactions (ADRs) by COVID-19 vaccine brand in near real-time. The secondary aim is to describe differences in ADR incidence rates between different vaccine batches used across the participating countries. In different countries, at the national level, data will be collected directly from a cohort of vaccine recipients in near real-time. The common core data from different countries will be pooled and analysed at the European level. Lareb is the participant on behalf of the Netherlands.

#### 9.9.4 Number of Reports in the Netherlands

The spontaneous reporting system managed by the National Centre for Pharmacovigilance Lareb receives AEFI reports for all COVID-19 vaccines. Up to July 4<sup>th</sup>, 2021, Lareb received 93,453 reports. Of these, 66,724 were for the first vaccination and 14,756 for the second (for the most recent information, see [link](#)). There is a considerably higher number of reports after the second dose of both Pfizer and Moderna compared to the number of reports after the second dose of AstraZeneca (see Table 9.9.1).

The reports relate to about 16.5 million vaccinations in all, approximately 11.8 million doses from Pfizer/BioNTech (Comirnaty®), 2.8 million from AstraZeneca (Vaxzevria®), 1.3 million from Moderna and 600,000 from Janssen. These figures are based on the Corona dashboard of the central government (see [link](#)).

## 9.9.5 Reactogenicity

### 9.9.5.1 Overview from Lareb

All reports received contain a total of 440,266 AEFIs (see [link](#)). Table 9.9.2 shows the most frequently reported local reactions and systemic events per vaccine.

### 9.9.5.2 International literature

In clinical trials of the mRNA-based vaccines, frequently reported reactions included injection site pain, fatigue, and headache [1, 2]. Reactions were generally mild to moderate, and often resolved within a couple of days after onset. Continued monitoring of reactogenicity outside clinical trial settings showed similar results. Among COVID-19 vaccine recipients who participated in V-safe, an active surveillance system for collecting information on solicited local and systemic reactions in the United States (US), injection site pain (67.8%), fatigue (30.9%), headache (25.9%) and myalgia (19.4%) were most frequently reported [3]. Reactogenicity was greater after the second dose for both Pfizer-BioNTech and Moderna vaccine recipients, especially for systemic reactions, including fatigue (53.9%), headache (46.7%), myalgia (44.0%), chills (31.3%), fever (29.5%), and joint pain (25.6%). A greater percentage of Moderna than Pfizer-BioNTech participants reported reactogenicity, and persons 65 years and older reported less reactogenicity than younger persons.

Based on the phase 2/3 trials in the United Kingdom (UK), Brazil and South Africa, the (recombinant) ChAdOx1-S vaccine (AstraZeneca) is well tolerated with a lower reactogenicity profile in older adults than in younger adults [4]. The most commonly reported solicited systemic reactions were similar to those seen after vaccination with mRNA vaccines, including fatigue, headache, feverishness, and myalgia. Most of the reported local and systemic events were mild to moderate in severity, and compared with the first vaccination, fewer adverse events were reported after the second dose. In a study assessing vaccine safety in a community setting, 58.7% of vaccinated individuals reported local side effects after the first dose of ChAdOx1 nCoV-19; 33.7% reported systemic side effects [5]. Headache (22.8%), fatigue (21.1%), chills and shiver (14.7%) were most frequently reported.

In a phase 3 trial evaluating the efficacy and safety of the Ad26.COV2.S (Janssen) vaccine, injection site pain was the most common local reaction (48.6%) among vaccine recipients [6]. Headache (38.9%), fatigue (38.2%), myalgia (33.3%), and nausea (14.2%) were the most common systemic reactions. More solicited adverse events were reported by participants 18 to 59 years of age than by those 60 years of age or older. Reactogenicity was transient and most solicited adverse events resolved in one to two days after vaccination [7].

### 9.9.6 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 reported by Lareb are have been updated up to the moment of the writing of the present report. For the most recent numbers, see [link](#).

### 9.9.6.1 Anaphylaxis

#### 9.9.6.1.1 Overview from Lareb

Up until July 4<sup>th</sup>, 2021, Lareb received 222 reports of a severe allergic reaction, of which 136 after vaccination with Pfizer/BioNTech (Comirnaty®), 51 after AstraZeneca (Vaxzevria®), 30 after Moderna and 5 after vaccination with Janssen. There was an established anaphylactic reaction in 62 reports. In the other reports, there were symptoms (such as extensive rash or swelling around the eyes or throat) that may be associated with a severe allergic reaction. The first symptoms of anaphylactic reactions usually started in the first 15-30 minutes after vaccination. For some it took up to a few hours before the complaints were at their most severe. All patients were treated and recovered quickly and adequately.

#### 9.9.6.1.2 International literature

Anaphylaxis as an adverse event following immunisation is generally uncommon, occurring at a rate of less than 1 per million doses for most vaccines [8]. Between December 14<sup>th</sup>, 2020 and January 18<sup>th</sup>, 2021, after 9,943,247 doses of the Pfizer-BioNTech vaccine and 7,581,429 doses of the Moderna vaccine were administered in the US, a total of 66 cases of anaphylaxis were detected [9]. From these 66 cases, 47 occurred following Pfizer-BioNTech vaccine (4.7 cases/million doses), and 19 following Moderna vaccine (2.5 cases/million doses). Common signs and symptoms in anaphylaxis cases were generalised urticaria, diffuse erythematous rash, angioedema, respiratory and airway obstruction symptoms, and nausea. Twenty-one (32%) of the 66 cases reported a prior episode of anaphylaxis from other exposures. No deaths from anaphylaxis after vaccination with either vaccine were reported.

Cases of suspected anaphylaxis have also been reported for the ChAdOx1-S vaccine (AstraZeneca). EuroVigilance, a system for managing and analysing information on suspected side effects of medicines authorised for use in the European Economic Area (EEA), reported 41 suspected cases out of approximately 5 million vaccinations in the UK (data lock point: 16 February 2021) [10]. After further review by the Pharmacovigilance Risk Assessment Committee (PRAC), the European Medicines Agency's (EMA) safety committee, it was concluded that a link to the vaccine was likely in at least some of these cases [11].

No severe allergic reactions or anaphylaxis caused by Ad26.COVS.2 (Janssen) have been recorded in the setting of clinical trials. One confirmed case of anaphylaxis has been reported in a large open label study in South Africa, where 500,000 healthcare workers were vaccinated with this vaccine [12].

### 9.9.6.2 TTS/VITT

#### 9.9.6.2.1 Overview from Lareb

A combination of thrombosis and low platelet count has been described as a rare side effect in the package inserts of the AstraZeneca and Janssen vaccines. It is now referred to as 'thrombosis with thrombocytopenia syndrome' (TTS). Up until June 17<sup>th</sup>, 2021, Lareb received 44 cases reporting a combination of thrombosis and low platelet count [13]. In 29 reports (65.9%), one or more heparin-induced thrombocytopenia (HIT) tests were performed (BioNTech/Pfizer n=5, AstraZeneca n=23, Janssen n=1). In 12 reports, the patient had a positive

ELISA and/or HIPA confirming Vaccine Induced Prothrombotic Immune Thrombocytopenia/ Vaccine-Induced Immune Thrombotic Thrombocytopenia (VIPIT/VITT). Ten of these patients were vaccinated with AstraZeneca (first dose n=9, vaccination moment unknown n=1). One patient was vaccinated with Janssen and another patient had his second administration of BioNTech/Pfizer. However, since this patient had been treated with heparin during an endovascular aortic aneurysm repair twelve days after vaccination, it could not be determined whether this was HIT or VIPIT/VITT caused by the BioNTech/Pfizer COVID-19 vaccine. The 11 confirmed VIPIT/VITT cases associated with AstraZeneca and Janssen concerned 5 men and 6 women. Their median age was 63 years (range 27-67 years). The time to onset varied between 6 and 19 days. Of these, two patients died, four patients had not recovered at the time of reporting, four were recovering and as per July 7<sup>th</sup>, 2021, the outcome was unknown for one patient. Another five AstraZeneca reports were strongly suggestive of VIPIT/VITT based on clinical judgement (first administration n=3, vaccination moment unknown n=2). In these reports, diagnostic tests were not supportive or test results were missing. Symptoms started between 9 and 20 days after vaccination. At the time of reporting, three patients were recovering and two had not recovered. In ten reports (22.7%), no HIT test was performed.

#### 9.9.6.2.2 *International literature*

Several cases of an unusual combination of thrombosis and thrombocytopenia after the use of the ChAdOx1-S (AstraZeneca) vaccine in vaccination campaigns were reported [14-16]. After intensive review of all available data, PRAC concluded that a causal relationship between vaccination with the AstraZeneca vaccine and this very rare syndrome of thrombosis with thrombocytopenia (TTS), is plausible [10]. TTS was estimated to occur in 1 in 100,000 vaccinated people [17]. The Medicines & Healthcare products Regulatory Agency (MHRA) in the UK reported an overall incidence after first or unknown doses of 14.7 per million doses, with a higher reported incidence rate in younger age groups following the first dose compared to older groups (20.1 per million doses in those aged 18-49 years versus 10.8 per million doses in those aged 50 years and over) [18]. An observational study performed in Denmark and Norway reported that increased rates for venous thromboembolism were observed within 28 days of vaccination with ChAdOx1-S, corresponding to 11 excess events per 100,000 vaccinations, including 2.5 excess cerebral venous thrombosis events per 100,000 vaccinations (or 1 per 40,000 vaccine recipients) [19]. A study on the background incidence of TTS itself [20] also demonstrated that thrombosis with concomitant thrombocytopenia is very rare, with an unadjusted overall incidence rate of less than 5 per 100,000 person-years.

As of April 21<sup>st</sup>, 2021, approximately 7.98 million doses of the Janssen COVID-19 vaccine had been administered in the US. In the period from March 2<sup>nd</sup> to April 21<sup>st</sup>, 2021, the VAERS received 15 reports of TTS [21]. Thirteen TTS cases occurred among women aged 18-49 years, and two occurred among women aged ≥50 years. No cases were reported among men. TTS reporting rates were 7 cases per million doses administered to women aged 18-49 years and 0.9 per million doses administered to women aged ≥50 years. The rate was highest among women aged 30-39 years, with 11.8 TTS cases per 1 million doses administered. No more than a few cases of TTS syndrome have been reported after vaccination with mRNA vaccines. A lower frequency of TTS was found than among those who were not vaccinated [22].



### 9.9.6.3 Myocarditis/pericarditis

#### 9.9.6.3.1 Overview from Lareb

Up until July 9<sup>th</sup>, 2021, Lareb received 16 reports of inflammation of the heart (myocarditis) and 42 of inflammation of the pericardium (pericarditis) [23]. These concerned 38 reports relating to the Pfizer/BioNTech vaccine and 20 relating to the Moderna vaccine; 39 after the first dose and 18 after the second dose (unknown: n=1). Of all reports, 34 were men and 24 women, 10 were between 20-30 years of age, 20 between 30-50 years, and 28 older than 50 years. At the moment, there is not enough data to determine whether there is a connection with COVID-19 vaccination. The EMA investigates all reports of myocarditis or pericarditis. The background incidence of myocarditis and pericarditis is 1 to 10 in 100,000 people.

#### 9.9.6.3.2 International literature

Myocarditis and pericarditis can occur following infections or immune diseases. The incidence in the EEA ranges from 1 to 10 in 100,000 people per year, depending on the cause [24]. Post-immunisation myocarditis is a known rare adverse event of vaccination, particularly smallpox vaccination [25]. Myocarditis occurring after vaccination with mRNA vaccines has not been reported in trials, but cases have been reported after the roll-out of vaccination programmes, mostly in male adolescents or young adults [26-30]. Symptoms such as chest pain or shortness of breath often started within several days after vaccination, and more often after getting the second dose [31]. Most patients responded well to treatment.

EMA's safety committee (PRAC) has concluded that myocarditis and pericarditis can occur in very rare cases following vaccination with the COVID-19 vaccines Comirnaty® and Spikevax [32]. The Committee therefore recommends listing myocarditis and pericarditis as new side effects in the product information for these vaccines, together with a warning to raise awareness among healthcare professionals and people taking these vaccines. In reaching its conclusion, the Committee has taken into consideration all currently available evidence. This included an in-depth review of 145 cases of myocarditis in the European Economic Area (EEA) among people who received Comirnaty® and 19 cases among people who received Spikevax®. PRAC also reviewed reports of 138 cases of pericarditis following the use of Spikevax® and 19 cases following the use of Spikevax®. As of 31 May 2021, around 177 million doses of Comirnaty® and 20 million doses of Spikevax® had been given in the EEA. The Committee concluded that the cases primarily occurred within 14 days after vaccination, more often after the second dose and in younger adult men. In five cases that occurred in the EEA, the individuals in question died. They were either of advanced age or had concomitant diseases. Available data suggest that the course of myocarditis and pericarditis following vaccination is similar to the typical course of these conditions, usually improving with rest or treatment.

At this point in time, no causal relationship with myocarditis or pericarditis could be established with two other COVID-19 vaccines authorised in the EEA, COVID-19 Vaccine Janssen and Vaxzevria®, and the Committee has requested additional data from the companies that market these vaccines.

#### 9.9.6.4 Systemic capillary leak syndrome (SCLS)

##### 9.9.6.4.1 Overview from Lareb

Systemic Capillary Leak Syndrome (SCLS) is a severe disease in which fluid leaks out of the capillaries. This causes low blood pressure, swelling of especially the arms and legs, thickening of the blood and too little albumin in the blood. In Europe six cases were reported to the EMA in which the syndrome occurred after vaccination with the AstraZeneca vaccine. In three cases, the patients were found to have been previously diagnosed with SCLS. One person has died. Up until July 4<sup>th</sup>, 2021, Lareb has not received any report of this syndrome after vaccination with the AstraZeneca vaccine, but one report was received for a patient who had received the Janssen vaccine. This concerned a man between the ages of 50 and 60 who died.

##### 9.9.6.4.2 International literature

A very small number of cases of capillary leak syndrome occurred in people who were vaccinated with the AstraZeneca vaccine. The MHRA received 8 reports for more than 45 million administered doses of AstraZeneca vaccine [18]. The PRAC reviewed 6 cases, of which most occurred in women and within 4 days of vaccination. Three of those affected had a history of SCLS and one of them subsequently died [33]. Some cases of SCLS mentioned in the literature appeared to be triggered by SARS-CoV-2 infection [34]. SCLS is generally a very rare syndrome with fewer than 500 cases reported worldwide [35].

#### 9.9.6.5 Death

##### 9.9.6.5.1 Overview from Lareb

Up until July 4<sup>th</sup>, 2021, there have been 448 reports of death after corona vaccination [36, 37]. It concerns 263 people aged 80 or older, 132 people between the ages of 65 and 79 and 51 people under the age of 65. The exact age of two people is unknown. Most reports were about the vaccine from Pfizer/BioNTech (Comirnaty®). This is the most commonly used corona vaccine and also the vaccine that is mainly used in the elderly population.

Death after vaccination does not mean that a side effect of the vaccine is the cause of death. In most reports, pre-existing health problems are the most obvious explanation for the patient's death. In a number of reports, however, side effects may have contributed to the deterioration of an already fragile health situation or dormant underlying condition, whether or not due to old age. These are known side effects of the COVID-19 vaccines such as fever, nausea and general malaise. Five patients died after thrombosis in combination with a low platelet count following administration of the AstraZeneca vaccine.

##### 9.9.6.5.2 International literature

Reports of death after administration of a COVID-19 vaccine are rare [38]. In the US, where more than 331 million doses of COVID-19 vaccines were administered between December 14<sup>th</sup>, 2020 and July 6<sup>th</sup>, 2021, the VAERS received 5,946 reports of death (0.0018%) in individuals who received a COVID-19 vaccine. It is not clear whether there was a causal relationship with the vaccine (healthcare providers are required to report any death after vaccination).

In the period from December 27<sup>th</sup>, 2020 to February 15<sup>th</sup>, 2021, the Norwegian Medicines Agency received 100 reports of suspected fatal adverse reactions in nursing-home patients after the administration of Comirnaty® [39]. It was concluded that vaccination may, in a few cases, have accelerated a process of dying that had already begun and that therefore the benefits versus risk must be carefully weighed up for the frailest patients.

In the period from December 9<sup>th</sup>, 2020 to June 23<sup>th</sup>, 2021, the MHRA in the UK received 439 reports in which the patient died shortly after vaccination with Comirnaty®, 936 reports for Vaxzevia®, five for the Moderna vaccine, and 23 where the vaccine brand was unspecified [18]. Most of these were in elderly people or persons with underlying illness. Review of the reports and patterns of reporting does not suggest that the vaccines played a role in the fatalities.

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10

# Vaccines in development for other potential future NIP target diseases



N.Y. Rots

## 10.1 Chapter overview

An update of information with regards to vaccines in development against infectious diseases, that have reached the clinical testing phase and are relevant for the Netherlands is given in the table below. Generally speaking, developing a vaccine 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 1 to 2 years, phase II 2 to 3 years, and phase III 4 to 6 years. However, with COVID-19 vaccines we have seen that in a pandemic it is possible to develop a vaccine within 1 year, from research to market authorisation.

Pfizer received a fast-track designation for its Streptococcus group B and Lyme vaccines, both currently being tested in phase II trials. Valneva has received fast-track designation from the FDA and PRIME designation from EMA for their Chikungunya vaccine, which is currently being tested in phase 3. Results are expected mid-2021.

The Coronavirus SARS-CoV-2 vaccines in development are shown in a separate table. According to the *WHO COVID-19 vaccine tracker*, as per September 2nd, 2021, more than 296 vaccines are being developed, 112 of which are being tested in clinical trials. The European Medicines Agency (EMA) has granted conditional approval for four vaccines, and another four vaccines are currently under evaluation in a rolling review. The European Commission (EC) has signed purchase agreements for COVID-19 vaccines with seven manufacturers. Of these COVID-19 vaccines, only the vaccines that are relevant for the Netherlands and are being tested in humans are included in the overview. COVID-19 vaccine development is changing quickly. For more information, please refer to the *WHO COVID-19 vaccine tracker* and landscape, which are updated twice per week.

## 10.2 Bacteria

Vaccine	Status, clinical phase
<i>Chlamydia</i>	
• Adjuvanted chlamydia vaccine CTH522 (SSI/Imperial College London)	I completed, safe, humoral and cellular immune response
<i>Clostridium difficile</i>	
• Toxoid inactivated (Pfizer)	III, FDA fast track
• Recombinant toxoid VLA84, genetic fusion (Valneva)	II completed III waiting for partner
• Recombinant protein adjuvant (GSK)	I
<i>Helicobacter pylori</i>	
• HP3 (Chiron/Novartis)	I/II completed, limited protective immunity, not pursued
• Oral recombinant vaccine (China)	III discontinued
<i>Lyme</i>	
• 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
<i>Meningococcal ABCWY</i>	
• MenABCWY recombinant conjugated (Novartis/GSK)	IIIB 15-25 year olds booster dose study
• MenABCWY recombinant conjugated, 2 <sup>nd</sup> generation (GSK)	I
• Nimenrix-Trumemba combinations (Pfizer)	III adolescents, young adults
<i>Moraxella catarrhalis, non-typeable Haemophilus influenzae COPD</i>	
• Recombinant COPD reduction with adjuvant (GSK)	II
<i>Shigella</i>	
• Live attenuated single-strain,	I completed
• Inactivated trivalent whole cell	II
• Chemical glycoconjugate	I
• Recombinant glycoconjugate (biconjugate)	III
• Conjugate outer membrane (Novartis/GSK)	II



Vaccine	Status, clinical phase
<i>Staphylococcus aureus</i>	
• Conjugate (SA4Ag, 4 antigen) (Pfizer)	III, FDA fast track 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
<i>Streptococcus group A</i>	
• 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, AIOH adjuvanted	I
<i>Streptococcus group B</i>	
• CPS-protein conjugate (mono and trivalent) (GSK)	II maternal
• 6-valent polysaccharide CRM197 conjugated vaccine (Pfizer)	II maternal, FDA fast track
• Recombinant fusion antigen (Minervax APS)	I
<i>Pneumococcus*</i>	
• (Killed) whole-cell vaccine	II
• Protein-based vaccine (GSK)	II
• Protein-based vaccine (Sanofi)	II
<i>Tuberculosis (all forms, all ages)</i>	
• Live attenuated vaccine BCG	On market but low efficacy
• 2, 3 or 4 antigen adjuvanted fusion protein (GSK/Areas, Areas)	II(b)
• Subunit adjuvanted recombinant fusion protein (Areas/Sanofi/SSI)	II completed
• Modified Recombinant BCG	II
• Recombinant Subunit (GSK, Sanofi)	II
• Live attenuated (MTBVAC)	IIb started in 2018
• Lysate of NTM	III
• Killed whole cell (booster) (Areas)	I
• Viral vector (Oxford)	I

\* For conjugate serotype specific vaccines, see section 6.9 on pneumococcal disease.

### 10.3 Viruses

Vaccine	Status, clinical phase
<i>Chikungunya</i>	
• Live recombinant measles virus-based, Merck V184 (Merck)	II completed
• Virus-like particle (NIAID)	I/II completed
• Live attenuated (Valneva)	III FDA fast track, PRIME EMA
<i>Cytomegalo (CMV)</i>	
• Glycoprotein B bivalent	I and III
• Replication defective V160 (MSD)	II
• RNA vaccine (Moderna)	I
<i>Dengue</i>	
• Live recombinant (tetraivalent) (Butantan/NIAID)	III
• Live-attenuated (tetraivalent) TDV (Takeda)	III
• Inactivated (tetraivalent) V180 (Merck)	I
• Recombinant Subunit (tetraivalent) (GSK)	I/II
• Live attenuated, Dengavaxia (Sanofi)	Registration approved for 9-45 years of age, for seropositive people only
<i>Ebola</i>	
• 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)	I
• Recombinant nanoparticle based (Novavax)	III
• Recombinant Viral vector (GSK)	II
• VRC-EBOADC069-0-VP (Okairos/NIAID)	I
<i>Epstein-Barr</i>	
• Recombinant gp350, glycoprotein subunit	II
• Live attenuated vaccines	On hold
<i>Hepatitis C</i>	
• Recombinant, heterologous viral vector (GSK)	II

Vaccine	Status, clinical phase
<i>Hepatitis E</i>	
• Recombinant protein (Hecolin®) (Xiamen Innovax Biotech)	IV Approved in China, not registered in EU
<i>Herpes simplex</i>	
• HSV-529 replication defective live attenuated (Sanofi)	I
<i>Herpes zoster (Shingles)</i>	
• Recombinant (Shingrix, GSK)	Approved in US and EU
• Inactivated V212 (Merck)	III, on hold
<i>HIV</i>	
• Recombinant protein (GSK)	II
• Viral vector Prime/boost (Sanofi)	II
• Ad26 Mos HIV vaccine (Janssen vaccines)	III
• DNA (GeoVax)	II completed
<i>Hookworm</i>	
• iBio	I
<i>Noro</i>	
• Virus-like particles (bi-valent) (Takeda)	II
• Oral tablet vaccine (Vaxart)	I
<i>MERS-CoV</i>	
• MVA-MERS-S	I
• DNA (GeneOne Life Science/Inovio)	II started in August 2021
<i>Parainfluenza type I</i>	
• Live attenuated	I-II
<i>Respiratory syncytial (RSV) (17 in clinical development)</i>	
• Live attenuated (Sanofi/NIH)	II paediatric
• Live attenuated (Intravacc)	I paediatric
• Inactivated whole cell	0
• Nanoparticle-based (Novavax)	III maternal data 2021, FDA fast track
• 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
• Subunit, F-protein (Janssen)	I maternal, elderly

Vaccine	Status, clinical phase
• Subunit, F-protein (Merck)	II elderly-maternal I elderly
• Gene-based vector MVA (Bavarian Nordic)	II
• Gene-based vector AV (Janssen)	II elderly II elderly-paediatric
• Gene-based vector AV (Vaxart)	I paediatric
• Gene-based vector AV (GSK)	II paediatric
• RNA vaccine (Moderna)	I
<i>Typhoid</i>	
• TT-Conjugate (Bharat Biotech)	III published
<i>West Nile</i>	
• Inactivated (NIAID)	I completed
• Chimeric vaccine; live attenuated recombinant (ChimeriVax) (NIAID/Acambis)	II
• Recombinant subunit (NIAID/Hawaii Biotech)	I completed
<i>Zika</i>	
• DNA (GeneOne Life Science/Inovio/NIAID)	II
• RNA (Moderna)	I
• Live attenuated	II
• Whole inactivated (Sanofi, Takeda, NIAID)	II (Sanofi did not start phase III limited funding Barda)

Source: WHO and clinicaltrial.gov, websites of pharmaceutical companies.

## 10.4 SARS-CoV-2 vaccines

Company	Status
<i>Inactivated whole virus</i>	
• Sinovac (China)	EMA review
• Bharat Biotech	III
• Valneva*	III
<i>Live attenuated virus</i>	
• Meissa vaccines	I
• Intranasal vaccine (Conagenix/SII)	I
<i>Non-replicating Viral vector</i>	
• ChAd# (Oxford University/AstraZeneca)	EMA approved
• Ad5 (CanSino Beijing Institute Biotech)	Registration in China
• Ad26# (Janssen Pharmaceutical)	EMA approved
• Ad26, Sputnik V (Gamaleya Res. Ins)	EMA review
• ReiThera/Leukocare/Univercells	II/III
• Ad5, adjuvanted, oral vaccine (Vaxart)	I
• MVA (Ludwich Maximilinas University Munich)	I
<i>Replicating Viral Vector</i>	
• MVA (MSD/Inst Pasteur/Themis/University of Pittsburg)	Development discontinued
• Intranasal flu (Beijing Wantai Bio/Xiamen university)	II
• rVSV (Israel Institute for Biological Research)	II/III
<i>Protein (sub-unit)</i>	
• Matrix M adjuvant* (Novavax)	III, EMA review
• ASO3 adjuvant# (Sanofi/GSK)	III
• ASO3 or CPG and aluminium adjuvant (Clover/GSK/Dynavax)	II/III
• MF59 adjuvanted (University of Queensland)	I
• Kentucky Bioprocess	I/II
• Vaxine Meditox, CinnaGen (Advax adj)	II
• Medigen/NIAID, Dynavax (CpG 1018 adj)	II
• TT-conjugate, adjuvanted (Finlay inst. Cuba)	III
• COVAXX	III
• UMCGroningen Akston	I/II

Company	Status
<b>RNA</b>	
• LNP encapsulated mRNA <sup>#</sup> , mRNA-1273 (Moderna)	EMA approved 12-18 EMA review II 6 mos-11 yrs
• LNP encapsulated mRNA <sup>#</sup> , Comirnaty (BioNTech/Fosun/Pfizer)	EMA approved II maternal and 6 mos-11 yrs
• Imperial College London (LNP)	I
• Curevac <sup>#</sup>	III, EMA review, VE 49%
• Acturus Duke/NUS	II
• Sanofi Pasteur Translate Bio	II
• GSK	I
<b>DNA</b>	
• DNA plasmid electroporation (Inovio/IVI)	II/III
• Zydus Cadila Healthcare Limited	III
• Genexine consortium	I/II
• Adjuvanted (Osaka University/Takara bio)	II/III
<b>VLP</b>	
• Medicago	II/III
• SII SpyBiotech (HBsAg RBD S)	I/II
• Radboud University (MF59)	I

# COVID-19 vaccines with EC contract.

\* COVID-19 vaccines with EC contract negotiations.



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## 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
AAPC	average annual percentage change
ADEM	acute disseminated encephalomyelitis
ADHD	attention deficit hyperactivity disorder
ADR	adverse drug reactions
AEFI	adverse event following immunisation
AES	adverse events
AESI	adverse event of special interest
AGE	acute gastroenteritis
AFP	acute flaccid paralysis
aP	acellular pertussis
ARI	acute respiratory infection
BAU/mL	binding antibody units per milliliter
BCG	Bacillus Calmette-Guérin
BERT	booster against pertussis
BES	Bonaire, St. Eustatius, Saba
BI	betrouwbaarheidsinterval
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	cluster of differentiation 4
CDC	Centres for Disease Control and Prevention
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
CN	Caribbean Netherlands
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
cPCV7	pneumococcal vaccine containing 7 non-PCV13 serotypes
CRM	cross-reactive material conjugate
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
cVDPV	circulating vaccine derived polio virus
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
DTP	combination of diphtheria, tetanus and pertussis vaccines
DTP-IPV-HBV-Hib	combination of diphtheria, tetanus, pertussis, inactivated polio, hepatitis B virus and <i>Haemophilus influenzae</i> type b vaccines
EBV	Epstein-Barr virus
EC	European Commission
ECDC	European Centre for Disease Control and Prevention
EEA	European Economic Area
EHR	electronic health record
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
EUL	Emergency Use Listing
EV	enterovirus
EVI	study of early effects of vaccine immunisation
FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
fhbp	factor H-binding protein
Fim <sub>3</sub>	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
GEE	generalised estimating equations
GGD	municipal health services; gemeentelijke gezondheidsdiensten
GMC	geometric mean concentrations
GNV	gender neutral vaccination
GOV	girls only vaccination
GP	general practitioner
GPEI	Global Polio Eradication Initiative
GPLN	WHO Global Polio Laboratory Network
GW	genital warts
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	Health Council
HCP	healthcare professionals
HepB	hepatitis B virus
Hi	<i>Haemophilus influenzae</i>

Hia	<i>Haemophilus influenzae</i> type a
Hib	<i>Haemophilus influenzae</i> type b
Hie	<i>Haemophilus influenzae</i> type e
Hif	<i>Haemophilus influenzae</i> type f
HIPA	heparin-induced platelet aggregation
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HPV	human papillomavirus
HPV2D	study to monitor the immunogenicity of a two-dose schedule of HPV vaccination
hrHPV	high-risk human papillomavirus
HSV	herpes simplex virus
HZ	herpes zoster
ICU	intensive care unit
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICPC	International Classification of Primary Care
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IE	international units; internationale eenheden
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IKNL	Netherlands Comprehensive Cancer Organisation; Integraal Kankercentrum Nederland
IL	interleukin
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
IU	international units
JGZ	youth health care; jeugdgezondheidszorg
LBR	Landelijke Basisregistratie Ziekenhuiszorg
LINH	Netherlands Information Network of General Practice; Landelijk informatienetwerk huisartsenzorg
LMR	National Medical Registration; Landelijke Medische Registratie
LNP	lipid nanoparticles
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	Meningococcal serogroup A
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenE	Meningococcal serogroup E
MenW	Meningococcal serogroup W
MenX	Meningococcal serogroup X
MenY	Meningococcal serogroup Y
MERS-CoV	Middle East respiratory syndrome-coronavirus
MHRA	Medicines & Healthcare products Regulatory Agency
MIA	multiplex immunoassay
MLST	multilocus sequence typing
MLVA	multiple locus variable number of tandem repeat analysis
MMR	combination of measles, mumps and rubella vaccines
MMRV	combination of measles, mumps, rubella and Varicella vaccines
MNT	maternal and neonatal tetanus
MNTE	Maternal and Neonatal Tetanus Elimination initiative
mOPV <sub>2</sub>	monovalent type 2 Oral Polio Vaccine
MPV	maternal pertussis vaccination
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
MSM	men who have sex with men
NIAID	National Institute of Allergy and Infectious Diseases
NIBSC	National Institute for Biological Standards and Control
NICE	Dutch National Intensive Care Evaluation; Nationale Intensive Care Evaluatie
NICU	neonatal intensive care unit
NIP	National Immunisation Programme
NIVEL	Netherlands Institute for Health Services Research; Nederlands Instituut Voor onderzoek van de Eerstelijngestgezondheidszorg
NKR	Netherlands Cancer Registry
NTD	N-terminal domain
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NRLBM	Netherlands Reference Laboratory for Bacterial Meningitis
nOPV <sub>2</sub>	novel type 2 oral polio vaccine
NTHi	nontypeable <i>Haemophilus influenzae</i>
NTM	neurotrimin
NWKV	Dutch Working Group for Clinical Virology; Nederlandse Werkgroep voor Klinische Virologie
OMT	Outbreak Management Team
OMV	outer membrane vesicles
OPV	oral polio vaccine

OR	odds ratio
OSIRIS	Dutch information system for infectious disease surveillance; Online systeem voor infectieziekten registratie binnen ISIS
OSIRIS-AIZ	Dutch information system for infectious disease surveillance for general infectious diseases; Online Systeem voor algemene 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
PDA's	patient decision aids
PEV	parechovirus
PHN	postherpetic neuralgia
POI	premature ovarian insufficiency
PorA	porin A protein
POTS	postural orthostatic tachycardia
PPV	pneumococcal polysaccharide vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
PRAC	Pharmacovigilance Risk Assessment Committee
PrEP	pre-exposure prophylaxis
Prn	pertactin
Ptx	pertussis toxin
PV	poliovirus
QALY	quality-adjusted life year
qPCR	real-time polymerase chain reaction
RBD	receptor binding domain
RCV	rubella containing vaccine
RIVM	Netherlands National Institute for Public Health and the Environment
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RV	rubella virus
RZV	recombinant zoster vaccine (Shingrix®)
SARI	severe acute respiratory infection
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCLS	systemic capillary leak syndrome
SDM	shared decision making
SEIR	susceptible-exposed-infectious-recovered
SES	socioeconomic status
SH	small hydrophobic gene

SIA	supplementary immunisation activity
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SPC	summary of product characteristics
ST	sequence type
STI	sexually transmitted infection
Tdap	tetanus, diphtheria and pertussis vaccine
tOPV	trivalent oral polio vaccine
TT	tetanus toxoid
TTS	thrombocytopenia syndrome
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VIPIT/VITT	Vaccine Induced Prothrombotic Immune Thrombocytopenia/ Vaccine-Induced Immune Thrombotic Thrombocytopenia
VLP	virus-like particle
VOC	variant of concern
VPDs	vaccine-preventable diseases
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
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 notification 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 <i>Haemophilus influenzae</i> type b	C	from December 2008 onwards
Hepatitis B disease	B2	from 1950 onwards

Disease	Category	Periods of notification by legislation
Invasive pneumococcal disease	C	from December 2008 onwards
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

<sup>a</sup> Only for cases born from 2006.

### 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

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.

**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, please see the [annual RIVM report on 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 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. For invasive meningococcal disease and invasive *H. influenzae* disease, clinical laboratories in the Netherlands send in all invasive (i.e. from normally sterile sites) isolates. For invasive pneumococcal disease, all clinical laboratories send in all positive isolates from CSF. Since 2004, nine sentinel clinical laboratories distributed throughout the country have been sending in all invasive isolates positive for *Streptococcus pneumoniae*. These nine sentinel laboratories cover approximately 25% of the Dutch population. Since 2008, for children aged under 5, all clinical laboratories send in all invasive isolates positive for *Streptococcus pneumoniae*. In addition to positive isolates, normally sterile PCR positive material (e.g. CSF or blood) can also be sent to the NRLBM for further typing. This means that we have nationwide laboratory surveillance for invasive meningococcal disease and invasive *H. influenzae* disease. Since 2004, sentinel surveillance for invasive pneumococcal disease covering 25% of the Dutch population for all ages has been in place. Since 2008, nationwide surveillance for invasive pneumococcal disease for children aged under 5 has been implemented.

#### *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-eerstelijjn>). 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 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].

### **A1.1.2.3 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:

$VE (\%) = 1 - [PCV / (1 - PPV/PPV)]$ , 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. In response to the recent changes in vaccination coverage, the PPV has been adjusted by birth cohort since last year. For each birth cohort, the vaccination coverage as reported in the national vaccination coverage report was used. This resulted 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 ( $N_{\text{blood}}=10,128$ ) [25], 2006-2007 ( $N_{\text{blood}}=7,904$ ) [26], and 2016-2017 ( $N_{\text{blood}}=5,745$ ). 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](http://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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## Appendix 2 Morbidity and mortality figures

### Diseases included in the current NIP

Diphtheria								ICD10: A36								
Year	Age (years)						Total	Male			Female					
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr			
<i>Mortality (source: CBS)</i>																
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									
<i>Hospitalisations** (source: Prismant/DHD/CBS)</i>																
2000	0	0	0	0	0	0	0									
2001	0	0	0	1	0	0	1	Male 1-4 yr								
2002	0	0	0	0	0	0	0									
2003	0	1	0	0	0	1	2			Female 1-4 yr	Female 5-9 yr					
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			Female 10-19 yr						
2010	0	0	0	0	0	1	1	Male 10-19 yr								
2011	0	0	0	0	0	1	1			Female 10-19 yr						
2012	0	0	0	0	0	0	0									
2013	0	0	0	0	0	0	0									
2014	0	0	0	0	0	2	2	Male 1-4 yr								
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									

\* 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 is not always actually 0, but can also be a few cases.

## Diphtheria

ICD9: 032  
ICD10: A36

Year	Age (years)						Total	Male 0-9 yr		Male 10-49 yr		Male 50+ yr	
	0	1-4	5-9	10-19	20-49	50+		0-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	50+ yr

### 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.

## Haemophilus influenzae

Year	Age (years)						Total	Gender and Age Group										
	0	1-4	5-9	10-19	20-49	50+		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
<b>Notifications* (serotype b; source: Osiris)</b>																		
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											

### Laboratory diagnoses (serotype b; source: NRLBM)

2001	3	5	0	1	4	4	17											
2002	6	9	0	0	7	8	30											
2003	4	7	2	2	3	11	29											
2004	8	7	2	2	7	21	47											
2005	9	17	3	0	4	8	41											
2006	3	8	3	1	5	3	23											
2007	3	8	2	0	2	9	24											
2008	3	4	1	2	2	12	24											
2009	6	3	1	0	8	13	31											
2010	2	7	0	1	4	23	37											
2011	3	2	0	2	5	10	22											
2012	2	5	2	2	6	11	28											
2013	6	7	1	0	4	10	28											
2014	6	3	2	1	5	12	29											
2015	3	10	1	0	5	15	34											
2016	7	14	1	1	4	17	44											
2017	4	9	4	0	7	21	45											
2018	8	10	1	1	6	17	43											
2019	10	7	0	2	5	15	39											
2020	11	17	5	0	10	25	68											

\* Notifiable since 2009.

## Haemophilus influenzae

Year	Age (years)						Total	Gender and Age Group											
	0	1-4	5-9	10-19	20-49	50+		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
2001	9	13	2	3	11	55	<b>93</b>												
2002	13	18	0	2	22	53	<b>108</b>												
2003	21	19	5	4	20	60	<b>129</b>												
2004	19	14	2	3	15	72	<b>125</b>												
2005	21	24	3	1	19	64	<b>132</b>												
2006	14	12	8	4	21	61	<b>120</b>												
2007	7	14	5	1	9	79	<b>115</b>												
2008	11	14	2	3	18	60	<b>108</b>												
2009	11	8	3	2	18	87	<b>129</b>												
2010	8	10	1	3	15	106	<b>143</b>												
2011	11	6	3	6	20	93	<b>139</b>												
2012	12	11	2	4	26	85	<b>140</b>												
2013	11	11	2	2	16	117	<b>159</b>												
2014	16	6	5	1	22	111	<b>161</b>												
2015	15	14	4	1	27	129	<b>190</b>												
2016	19	16	2	1	22	130	<b>190</b>												
2017	12	20	6	3	34	149	<b>224</b>												
2018	21	15	3	8	32	157	<b>236</b>												
2019	17	15	0	4	36	155	<b>227</b>												
2020	18	24	7	5	24	125	<b>203</b>												

## 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+														
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: Prismaant/DHD/CBS)

2000	1	2	2	8	80	32	127													
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	15	20	40													
2016^	0	0	0	0	25	20	50													
2017^	0	0	0	0	20	20	40													
2018^	0	0	0	0	15	20	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 is not always actually 0, but can also be a few cases.

## Hepatitis B

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr
<i>Notifications (Acute; source: Osiris)</i>													
2001	0	0	2	23	163	33	221						
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						

<i>Notifications (Chronic; source: Osiris)</i>													
2001	2	7	12	158	1,018	159	1,356						
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						

\* 1 case without information on gender.

\*\* 2 cases without information on gender.



Human papillomavirus							ICD10: C53			
Year	Age (years)						Total	Male 0 yr	Male 1-4 yr	Male 5-9 yr
	0	1-4	5-9	10-19	20-49	50+		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	

*Mortality (cervical cancer; source: CBS)*

2000	0	0	0	0	73	185	<b>258</b>			
2001	0	0	0	0	66	177	<b>243</b>			
2002	0	0	0	0	45	142	<b>187</b>			
2003	0	0	0	0	47	167	<b>214</b>			
2004	0	0	0	0	49	154	<b>203</b>			
2005	0	0	0	0	52	183	<b>235</b>			
2006	0	0	0	0	44	170	<b>214</b>			
2007	0	0	0	0	57	147	<b>204</b>			
2008	0	0	0	0	51	193	<b>244</b>			
2009	0	0	0	0	40	169	<b>209</b>			
2010	0	0	0	0	43	162	<b>205</b>			
2011	0	0	0	0	46	143	<b>189</b>			
2012	0	0	0	0	42	173	<b>215</b>			
2013	0	0	0	0	47	176	<b>223</b>			
2014	0	0	0	0	50	148	<b>198</b>			
2015	0	0	0	0	49	158	<b>207</b>			
2016	0	0	0	0	50	179	<b>229</b>			
2017	0	0	0	0	44	162	<b>206</b>			
2018	0	0	0	0	50	167	<b>217</b>			
2019	0	0	0	0	26	171	<b>197</b>			
2020*	0	0	0	0	52	177	<b>229</b>			

*Registrations (cervical cancer; source: NKR)*

2001	0	0	0	0	338	272	<b>610</b>			
2002	0	0	0	0	334	316	<b>650</b>			
2003	0	0	0	0	325	292	<b>617</b>			
2004	0	0	0	1	376	326	<b>703</b>			
2005	0	0	0	0	365	321	<b>686</b>			
2006	0	0	0	0	370	320	<b>690</b>			
2007	0	0	0	0	416	327	<b>743</b>			
2008	0	0	0	0	376	328	<b>704</b>			
2009	0	0	0	0	385	339	<b>724</b>			
2010	0	0	0	0	399	332	<b>731</b>			
2011	0	0	0	0	381	354	<b>735</b>			
2012	0	0	0	1	403	328	<b>732</b>			
2013	0	0	0	0	379	281	<b>660</b>			
2014	0	0	0	0	418	321	<b>739</b>			
2015	0	0	0	0	389	321	<b>710</b>			
2016	0	0	0	0	451	356	<b>807</b>			
2017	0	0	0	1	433	337	<b>771</b>			
2018	0	0	0	0	466	375	<b>841</b>			
2019	0	0	1	0	510	394	<b>905</b>			
2020**	0	0	0	0	435	361	<b>796</b>			

\* 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
	0	1-4	5-9	10-19	20-49	50+		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	

Mortality (vulva cancer; source: CBS)^

2001	0	0	0	0	1	177	178			
2002	0	0	0	0	3	142	145			
2003	0	0	0	0	5	167	172			
2004	0	0	0	0	3	154	157			
2005	0	0	0	0	7	183	190			
2006	0	0	0	0	3	170	173			
2007	0	0	0	0	6	147	153			
2008	0	0	0	0	7	193	200			
2009	0	0	0	0	1	169	170			
2010	0	0	0	0	1	162	163			
2011	0	0	0	0	2	143	145			
2012	0	0	0	0	8	173	181			
2013	0	0	0	0	0	176	176			
2014	0	0	0	0	2	148	150			
2015	0	0	0	0	4	158	162			
2016	0	0	0	0	3	179	182			
2017	0	0	0	0	44	162	206			
2018	0	0	0	0	50	167	217			
2019	0	0	0	0	26	171	197			
2020*	0	0	0	0	52	177	229			

Registrations (vulva cancer; source: NKR)^

2001	0	0	0	0	24	193	217			
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	371	409			
2018	0	0	0	0	42	384	426			
2019	0	0	0	0	50	407	457			
2020**	0	0	0	0	42	382	424			

\* 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
	0	1-4	5-9	10-19	20-49	50+		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	

*Mortality (vagina cancer; source: CBS)^*

2001	0	0	0	0	1	19	20			
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			

*Registrations (vagina cancer; source: NKR)^*

2001	0	0	0	0	6	33	39			
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	53	54			
2019	0	0	0	0	3	39	42			
2020**	0	0	0	0	6	64	70			

\* 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
	0	1-4	5-9	10-19	20-49	50+		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	

Mortality (penis cancer; source: CBS)^

2001	0	0	0	0	2	21	23			
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			

Registrations (penis cancer; source: NKR)^

2001	0	0	0	0	9	78	87			
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	151	164			
2018	0	0	0	0	12	173	185			
2019	0	0	0	0	11	190	201			
2020**	0	0	0	0	15	221	236			

\* 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
	0	1-4	5-9	10-19	20-49	50+		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	

Mortality (oropharynx cancer; source: CBS)^

2001	0	0	0	0	7	62	69			
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			

Registrations (oropharynx cancer; source: NKR)^

2001	0	0	0	0	68	355	423			
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	45	634	680			
2020**	0	0	0	0	42	631	673			

\* 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
	0	1-4	5-9	10-19	20-49	50+		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

Mortality (anus cancer; source: CBS)^

2001	0	0	0	0	4	30	34			
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			

Registrations (anus cancer; source: NKR)^

2001	0	0	0	0	20	105	125			
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	218	243			
2018	0	0	0	0	29	258	287			
2019	0	0	0	0	21	224	245			
2020**	0	0	0	0	29	301	330			

\* 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			Female					
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr			
<i>Mortality (source: CBS)</i>																
2001	0	0	0	0	0	0	0									
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									
<i>Notifications (source: Osiris)</i>																
2001	0	3	4	3	7	0	17									
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	423	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	1	4	0	1	10	1	17									
2018	3	4	0	2	14	1	24									
2019	4	15	17	10	37	1	84									
2020	0	1	0	0	1	0	2									

\* 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			Female			
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr	
2000	1	4	3	1	6	0	15							
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							

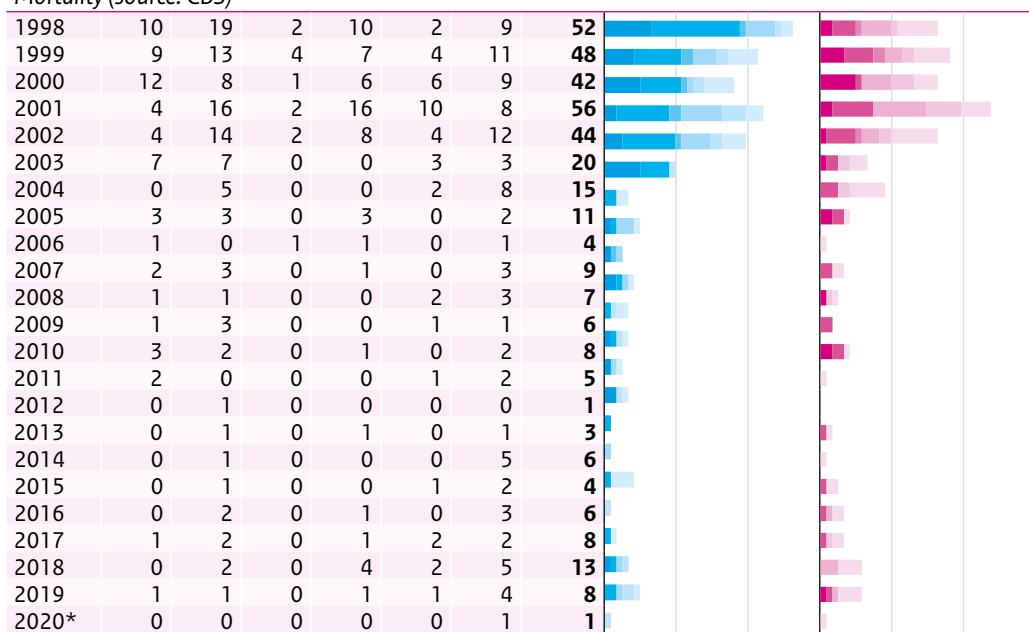
\* Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases is not always actually 0, but can also be a few cases.

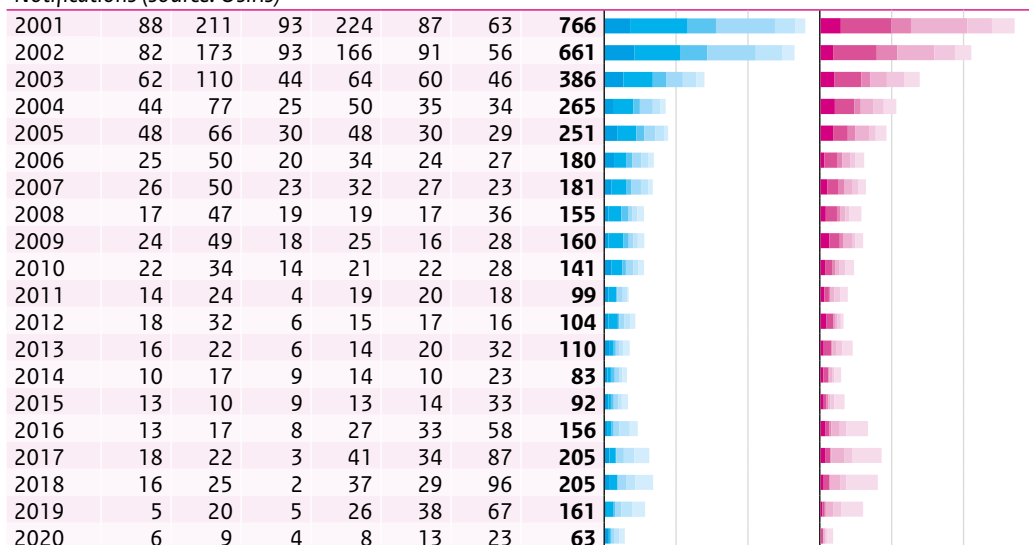


Meningococcal disease							ICD10: A39			
Year	Age (years)						Total	Male 0 yr	Male 1-4 yr	Male 5-9 yr
	0	1-4	5-9	10-19	20-49	50+		Male 10-19 yr	Male 20-49 yr	Male 50+ yr
							Female 0 yr	Female 1-4 yr	Female 5-9 yr	
							Female 10-19 yr	Female 20-49 yr	Female 50+ yr	

Mortality (source: CBS)



Notifications (source: Osiris)



\* 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+		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
<i>Laboratory diagnoses (all serogroups; source: NRLBM)</i>																		
2001	91	197	82	194	86	69	<b>719</b>											
2002	79	154	84	148	86	62	<b>613</b>											
2003	61	98	37	54	56	45	<b>351</b>											
2004	50	75	27	45	31	43	<b>271</b>											
2005	41	63	29	45	30	34	<b>242</b>											
2006	25	49	22	32	23	24	<b>175</b>											
2007	30	51	20	30	27	28	<b>186</b>											
2008	15	47	18	18	22	39	<b>159</b>											
2009	25	47	18	23	16	28	<b>157</b>											
2010	23	34	13	18	21	28	<b>137</b>											
2011	15	23	4	18	19	22	<b>101</b>											
2012	18	28	7	11	17	16	<b>97</b>											
2013	19	21	6	15	19	37	<b>117</b>											
2014	10	16	10	12	11	23	<b>82</b>											
2015	12	10	5	14	15	33	<b>89</b>											
2016	14	15	7	24	28	63	<b>151</b>											
2017	16	21	3	41	35	82	<b>198</b>											
2018	15	25	3	33	28	101	<b>205</b>											
2019	6	19	5	27	34	68	<b>159</b>											
2020	5	9	4	9	13	28	<b>68</b>											

<i>Laboratory diagnoses (serogroup C; source: NRLBM)</i>																		
2001	20	53	27	105	43	29	<b>277</b>											
2002	13	39	30	73	42	25	<b>222</b>											
2003	11	6	0	1	16	8	<b>42</b>											
2004	1	1	1	0	7	7	<b>17</b>											
2005	0	0	0	0	2	2	<b>4</b>											
2006	0	1	0	0	2	1	<b>4</b>											
2007	2	0	1	1	4	2	<b>10</b>											
2008	2	0	0	0	4	5	<b>11</b>											
2009	1	1	0	0	2	5	<b>9</b>											
2010	2	0	0	2	2	0	<b>6</b>											
2011	0	0	0	0	1	2	<b>3</b>											
2012	2	0	0	0	1	0	<b>3</b>											
2013	0	1	0	0	1	4	<b>6</b>											
2014	0	0	0	0	1	2	<b>3</b>											
2015	2	0	0	0	3	3	<b>8</b>											
2016	0	0	0	1	2	3	<b>6</b>											
2017	1	0	0	1	1	6	<b>9</b>											
2018	0	0	0	0	1	2	<b>3</b>											
2019	0	0	0	0	1	5	<b>6</b>											
2020	0	0	0	0	0	0	<b>0</b>											

## Meningococcal disease

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr

### 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	5	8						
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						

### Laboratory diagnoses (serogroup B; source: NRLBM)

2001	68	142	54	88	37	33	422						
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						

## Meningococcal disease

ICD9: 036.0-4, 036.8-9  
ICD10: A39

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr

Hospitalisations\* (source: Prismant/DHD/CBS)

1999	114	251	98	170	66	53	<b>755</b>						
2000	98	233	109	132	64	55	<b>694</b>						
2001	114	295	113	268	85	66	<b>949</b>						
2002	106	238	110	182	72	47	<b>767</b>						
2003	72	135	46	64	57	44	<b>421</b>						
2004	54	101	46	58	31	45	<b>336</b>						
2005	45	70	36	45	19	27	<b>244</b>						
2006	35	50	28	40	20	21	<b>196</b>						
2007	23	58	17	22	28	18	<b>166</b>						
2008	18	48	15	14	11	30	<b>136</b>						
2009	28	49	26	25	14	13	<b>156</b>						
2010	21	37	12	20	13	18	<b>122</b>						
2011	18	27	12	20	13	11	<b>103</b>						
2012	15	26	11	11	9	12	<b>84</b>						
2013	16	22	4	14	17	25	<b>99</b>						
2014	10	15	13	11	10	16	<b>75</b>						
2015^	15	15	10	15	10	25	<b>90</b>						
2016^	15	20	10	20	30	35	<b>135</b>						
2017^	15	30	5	50	30	55	<b>180</b>						
2018^	15	30	5	30	20	65	<b>160</b>						

\* 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 is not always actually 0, but can also be a few cases.

Mumps							ICD10: B26			
Year	Age (years)						Total	Male 0 yr	Male 1-4 yr	Male 5-9 yr
	0	1-4	5-9	10-19	20-49	50+		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	

Mortality (source: CBS)

2001	0	0	0	0	0	0	0	0											
2002	0	0	0	0	0	0	2	2											
2003	0	0	0	0	0	0	0	0											
2004	0	0	0	0	0	0	0	0											
2005	0	0	0	0	0	0	1	1											
2006	0	0	0	0	0	0	0	0											
2007	0	0	0	0	0	0	0	0											
2008	0	0	0	0	0	0	0	0											
2009	0	0	0	0	0	0	0	0											
2010	0	0	0	0	0	0	0	0											
2011	0	0	0	0	0	0	0	0											
2012	0	0	0	0	0	0	0	0											
2013	0	0	0	0	0	0	0	0											
2014	0	0	0	0	0	0	0	0											
2015	0	0	0	0	0	0	0	0											
2016	0	0	0	0	0	0	0	0											
2017	0	0	0	0	0	0	0	0											
2018	0	0	0	0	0	0	0	0											
2019	0	0	0	0	0	0	0	0											
2020*	0	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												

\* 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	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr

Hospitalisations\* (source: Prismant/DHD/CBS)

2000	0	0	0	0	0	2	2											
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											

\* 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.

Pertussis								ICD10: A37								
Year	Age (years)						Total	Male			Female					
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr			

Mortality (source: CBS)

2001	0	0	0	0	0	0	0	0											
2002	0	0	0	0	0	0	0	0											
2003	0	0	0	0	0	0	0	0											
2004	1	0	0	0	0	0	0	1											
2005	0	0	0	0	0	0	0	0											
2006	0	0	0	1	0	0	0	1											
2007	0	0	0	0	0	0	0	0											
2008	0	0	0	0	0	0	1	1											
2009	0	0	0	0	0	0	0	0											
2010	0	0	0	0	0	0	0	0											
2011	1	0	0	0	0	0	0	1											
2012	2	0	0	0	0	0	0	2											
2013	0	0	0	0	0	0	0	0											
2014	1	0	0	0	0	0	0	1											
2015	1	0	0	0	0	0	0	1											
2016	1	0	0	0	0	0	1	2											
2017	1	0	0	0	0	0	1	2											
2018	1	0	0	0	0	0	0	1											
2019	2	0	0	0	0	0	0	2											
2020*	1	0	0	0	0	0	1	2											

Notifications (source: Osiris)

2001	307	1,164	3,400	1,342	1,212	605	8,030												
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												

\* 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			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr

Hospitalisations\* (source: Prismant/DHD)

2000	171	37	12	5	0	5	230						
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	5	0	10	0	10	175						
2016^	155	15	0	5	5	10	190						
2017^	145	15	0	10	0	10	180						
2018^	110	10	0	5	0	5	135						

\* 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 is not always actually 0, but can also be a few cases.



## Pneumococcal disease

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr
<i>Notifications IPD* (source: Osiris)</i>													
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						

### Laboratory diagnoses IPD (<5 years, 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					50						
2018	40	28					68						
2019	33	28					61						
2020	15	17					32						

## Pneumococcal disease

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr

Laboratory diagnoses IPD (all ages, sentinel labs covering 25% of Dutch population; source: NRLBM)

2004	30	20	10	12	88	444	<b>604</b>										
2005	24	30	3	8	95	480	<b>640</b>										
2006	11	23	4	4	83	516	<b>641</b>										
2007	11	24	10	12	110	519	<b>686</b>										
2008	10	14	4	5	100	474	<b>607</b>										
2009	8	10	4	10	110	478	<b>620</b>										
2010	9	12	6	4	83	459	<b>573</b>										
2011	11	7	8	7	95	506	<b>634</b>										
2012	4	7	3	3	81	540	<b>638</b>										
2013	4	3	4	6	110	525	<b>652</b>										
2014	5	11	5	5	67	454	<b>547</b>										
2015	10	5	1	9	95	547	<b>667</b>										
2016	6	5	3	4	66	547	<b>631</b>										
2017	8	8	5	4	60	531	<b>616</b>										
2018	7	9	5	5	67	595	<b>688</b>										
2019	9	13	3	4	61	503	<b>593</b>										
2020	5	7	4	2	45	316	<b>379</b>										

Mortality IPD (all ages, sentinel labs covering 25% of Dutch population; source: NRLBM)

2005	3	0	0	0	1	101	<b>105</b>										
2006	0	1	0	0	3	91	<b>95</b>										
2007	0	0	0	0	7	82	<b>89</b>										
2008	0	1	0	0	7	82	<b>90</b>										
2009	1	1	1	0	4	75	<b>82</b>										
2010	0	0	0	0	6	52	<b>58</b>										
2011	0	0	0	0	3	65	<b>68</b>										
2012	0	0	0	0	6	68	<b>74</b>										
2013	0	0	0	0	1	75	<b>76</b>										
2014	0	1	0	1	1	75	<b>78</b>										
2015	1	0	0	0	4	72	<b>77</b>										

## Pneumococcal disease

ICD9: 481  
ICD10: J13

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr
2001	0	0	0	0	6	51	57						
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						

## Hospitalisations pneumococcal pneumonia\*\* (source: Prismant/DHD)

2000	32	75	48	41	360	1,257	1,817						
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	10	10	25	380	2,125	2,540						
2017^	5	5	5	15	275	2,180	2,485						
2018^	5	10	5	15	290	2,455	2,785						

\* 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 is not always actually 0, but can also be a few cases.

Poliomyelitis								ICD10: A80										
Year	Age (years)						Total	Male			Female							
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr					
<i>Mortality (acute; source: CBS)</i>																		
2001	0	0	0	0	1	0	1											
2002	0	0	0	0	0	0	1											
2003	0	0	0	0	0	0	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											
<i>Notifications (source: Osiris)</i>																		
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											

\* 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
	0	1-4	5-9	10-19	20-49	50+		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

Hospitalisations\* (source: Prismant/DHD)

2000	0	0	0	0	0	0	0												
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												

\* 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 is not always actually 0, but 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
	0	1-4	5-9	10-19	20-49	50+		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	

Mortality (source: CBS)

2001	0	0	0	0	0	0	0	0											
2002	0	0	0	0	0	1	0	1											
2003	0	0	0	0	0	0	0	0											
2004	0	0	0	0	0	0	0	0											
2005	0	0	0	0	0	1	0	1											
2006	0	0	0	0	0	0	0	0											
2007	0	0	0	0	0	0	0	0											
2008	0	0	0	0	0	0	0	0											
2009	0	0	0	0	0	0	0	0											
2010	0	0	0	0	0	0	0	0											
2011	0	0	0	0	0	0	0	0											
2012	0	0	0	0	0	0	0	0											
2013	0	0	0	0	0	0	0	0											
2014	0	0	0	0	0	0	0	0											
2015	0	0	0	0	0	0	0	0											
2016	0	0	0	0	0	0	0	0											
2017	0	0	0	0	0	0	0	0											
2018	0	0	0	0	0	0	0	0											
2019	0	0	0	0	0	0	0	0											
2020*	0	0	0	0	0	0	0	0											

Notifications (source: Osiris)

2001	0	2	0	0	2	0	4	4											
2002	0	0	0	0	3	0	3	3											
2003	0	0	0	1	0	0	1	1											
2004	2	4	12	33	14	0	65	65											
2005	9	28	66	166	78	2	349	349											
2006	0	0	0	0	4	1	5	5											
2007	0	0	0	0	1	0	1	1											
2008	0	0	0	0	2	0	2	2											
2009	0	0	0	4	2	1	7	7											
2010	0	0	0	0	0	0	0	0											
2011	0	0	0	0	1	2	3	3											
2012	0	0	0	0	1	0	1	1											
2013	0	10	37	7	3	0	57	57											
2014	0	1	0	0	1	0	2	2											
2015	0	0	0	0	1	0	1	1											
2016	0	0	0	0	0	0	0	0											
2017	0	0	0	0	0	0	0	0											
2018	0	0	0	0	0	0	0	0											
2019	0	0	0	0	0	0	0	0											
2020	0	0	0	0	0	0	0	0											

\* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

## Rubella (acquired)

ICD9: 056  
ICD10: B06

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr

Hospitalisations\* (source: Prisma/DHD)

2000	0	0	0	0	1	0	1												
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												

\* 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 is not always actually 0, but 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
	0	1-4	5-9	10-19	20-49	50+		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	

Mortality (source: CBS)

2001	0	0	0	0	0	3	3			
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			

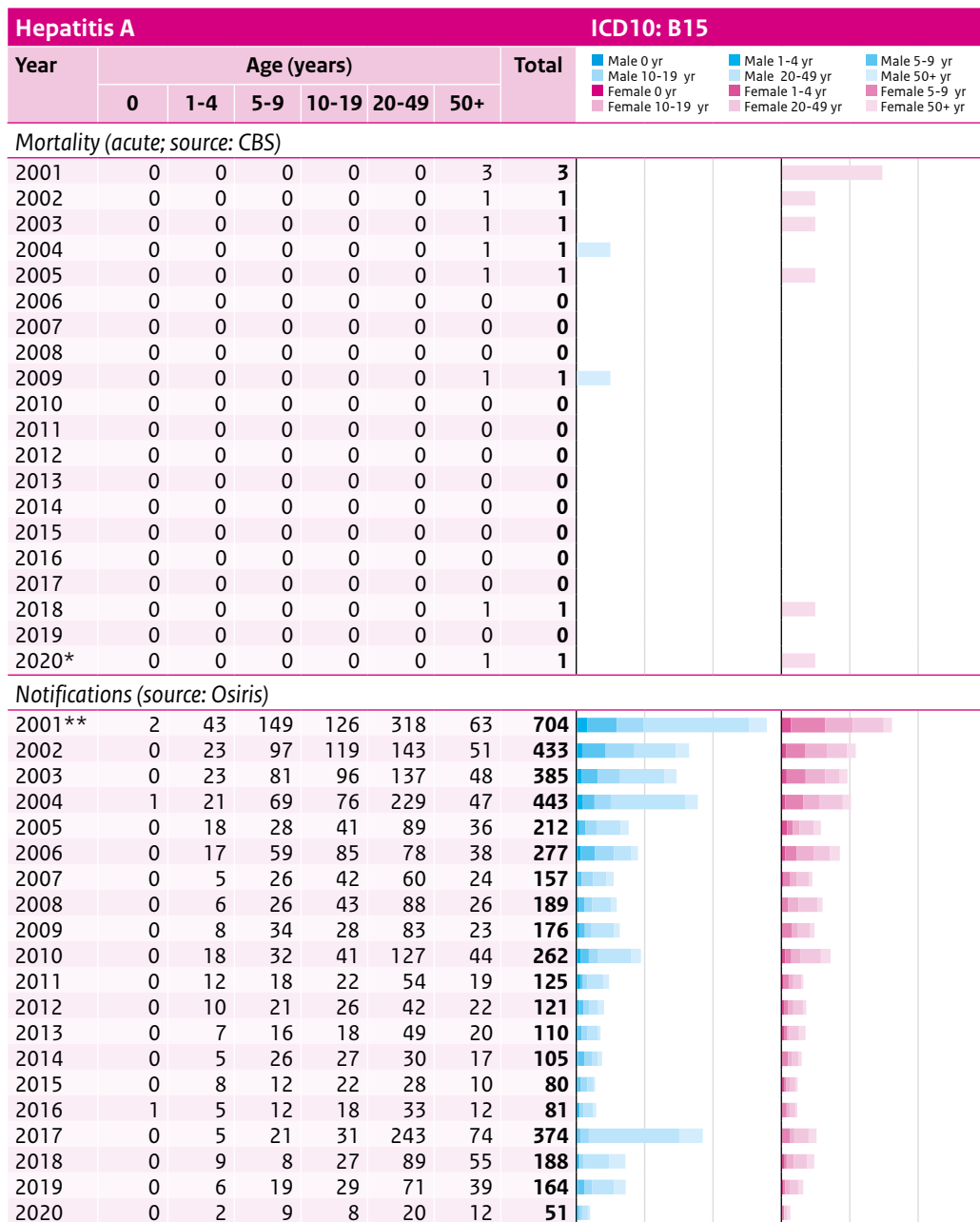
Notifications (source: Osiris)

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			

\* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.



## Potential NIP target diseases



\* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

\*\* Age is unknown for 3 patients.

## Rotavirus

Year	Age (years)						Total					
	0	1-4	5-9	10-19	20-49	50+						
<i>Hospitalisations* (source: Prismant/DHD)</i>												
2001	1,154	2,277	147	0	0	184	<b>3,762</b>					
2002	1,180	2,208	148	0	0	160	<b>3,696</b>					
2003	1,298	2,287	160	0	0	202	<b>3,947</b>					
2004	1,240	2,011	160	16	51	298	<b>3,776</b>					
2005	1,729	2,744	199	19	83	443	<b>5,217</b>					
2006	1,990	3,254	272	26	109	737	<b>6,388</b>					
2007	1,532	2,323	189	23	139	722	<b>4,928</b>					
2008	1,933	2,702	211	47	274	1,288	<b>6,455</b>					
2009	2,171	2,924	220	45	301	1,636	<b>7,297</b>					
2010	2,534	3,398	262	60	329	1,845	<b>8,428</b>					
2011	1,754	2,294	167	56	305	1,502	<b>6,078</b>					
2012	1,470	1,985	148	71	329	1,392	<b>5,395</b>					
2013	1,774	3,195	218	69	331	1,889	<b>7,477</b>					
2014	669	1,383	83	26	117	753	<b>3,030</b>					
2015^	1,334	3,139	208	52	153	1,509	<b>6,394</b>					
2016^	711	1,915	121	29	34	670	<b>3,481</b>					
2017^	1,107	2,961	178	31	22	957	<b>5,256</b>					
2018^	1,202	3,215	193	33	24	1,039	<b>5,708</b>					
2019^	1,115	2,980	179	31	23	963	<b>5,291</b>					
2020^	342	811	55	15	0	295	<b>1,518</b>					

\* 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.

^ The estimates from 2015-2017 are based on the five previous years (2010-2014).

## Varicella (chickenpox)

ICD9: 052  
ICD10: B01

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr
2001	0	1	1	0	1	0	3	1	1	1	0	0	0
2002	2	0	0	0	1	1	4	2	0	0	0	0	2
2003	0	1	0	1	0	4	6	1	1	0	0	0	4
2004	0	1	0	0	0	3	4	1	1	0	0	0	2
2005	0	0	0	0	0	1	1	0	0	0	0	0	1
2006	0	0	1	0	1	1	3	1	1	0	0	0	1
2007	1	1	0	1	1	1	5	2	2	0	0	0	1
2008	0	0	0	0	0	0	0	0	0	0	0	0	0
2009	0	0	0	0	0	1	1	0	0	0	0	0	1
2010	0	0	0	0	0	2	2	1	0	0	0	0	1
2011	1	0	0	0	0	0	1	1	0	0	0	0	0
2012	0	0	0	0	0	2	2	1	0	0	0	0	1
2013	0	0	0	0	0	1	1	1	0	0	0	0	0
2014	0	0	0	0	1	1	2	1	0	0	0	0	1
2015	0	0	0	0	0	2	2	1	0	0	0	0	1
2016	0	0	0	0	0	4	4	2	0	0	0	0	2
2017	1	1	0	0	0	1	3	1	1	0	0	0	1
2018	0	0	1	0	0	1	2	1	0	0	0	0	1
2019	0	0	0	0	0	3	3	1	0	0	0	0	2
2020*	0	0	0	0	0	2	2	1	0	0	0	0	1

## Hospitalisations\*\* (source: Prisma/DHD/CBS)

2000	44	95	14	6	38	14	211	100	100	100	100	100	100
2001	62	104	19	3	36	9	233	100	100	100	100	100	100
2002	47	113	17	4	29	9	219	100	100	100	100	100	100
2003	78	121	10	6	41	17	273	100	100	100	100	100	100
2004	89	115	20	7	26	12	269	100	100	100	100	100	100
2005	64	119	9	1	28	17	238	100	100	100	100	100	100
2006	108	132	17	4	33	19	313	100	100	100	100	100	100
2007	69	92	19	4	24	23	231	100	100	100	100	100	100
2008	74	111	19	3	38	26	271	100	100	100	100	100	100
2009	67	92	18	6	37	22	242	100	100	100	100	100	100
2010	81	136	21	7	39	31	315	100	100	100	100	100	100
2011	67	118	13	5	34	40	277	100	100	100	100	100	100
2012	63	96	17	6	29	42	253	100	100	100	100	100	100
2013	58	102	18	7	45	51	281	100	100	100	100	100	100
2014	76	112	22	6	49	56	321	100	100	100	100	100	100
2015^	55	105	20	15	45	70	305	100	100	100	100	100	100
2016^	60	115	25	15	50	80	345	100	100	100	100	100	100
2017^	70	115	25	15	50	65	335	100	100	100	100	100	100
2018^	45	85	20	15	55	75	290	100	100	100	100	100	100

\* 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 is not always actually 0, but can also be a few cases.

## Herpes zoster (shingles)

ICD9: 053  
ICD10: B02

Year	Age (years)						Total	Male			Female		
	0	1-4	5-9	10-19	20-49	50+		0 yr	1-4 yr	5-9 yr	10-19 yr	20-49 yr	50+ yr
2001	0	0	0	0	1	12	13						
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						

## Hospitalisations\*\* (source: Prisma/DHD/CBS)

2000	2	6	4	9	68	274	363						
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						

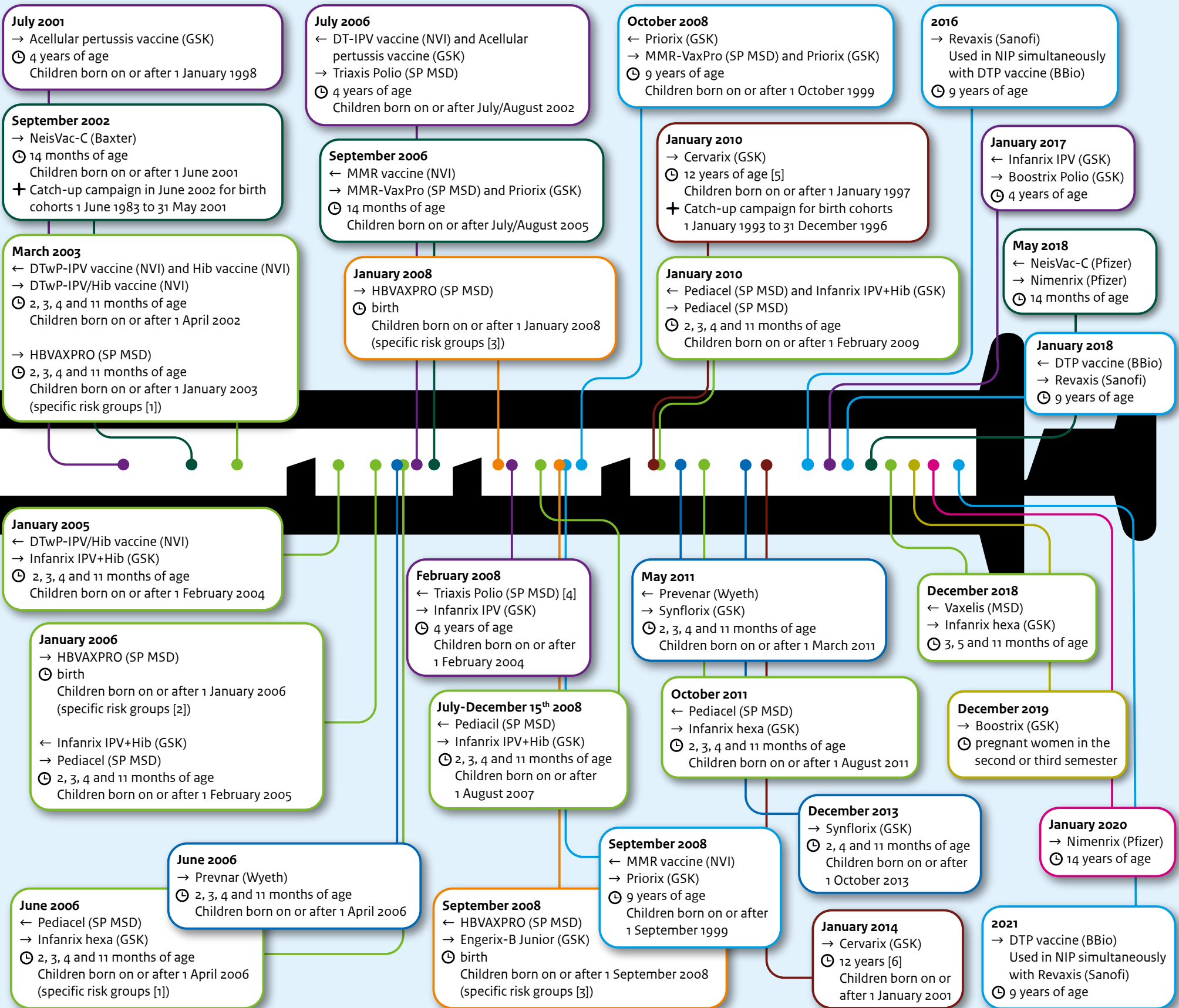
\* Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

\*\* 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 is not always actually 0, but can also be a few cases.



## Appendix 3 Overview of vaccine changes in the NIP from 2000



### Legend

- ⌚ Age of vaccination
- + Additional campaign for specific groups of children

[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.

[4] Used until March 2008.

[5] Only girls were vaccinated and received three doses of HPV vaccine: at 0, 1 and 6 months.

[6] Only girls were vaccinated and received two doses of HPV vaccine: at 0 and 6 months.

## Appendix 4 Composition of vaccines used in the NIP

Vaccine	Composition
<i>M-M-R VaxPro / MSD</i>	
EU/1/06/337 Mumps, measles and rubella vaccine 0.5 ml	Measles virus <sup>1</sup> (Enders' Edmonston) <sup>3</sup> , >1000 TCID <sub>50</sub> <sup>4</sup> Mumps virus <sup>1</sup> (Jeryl Lynn, Level B) <sup>3</sup> , >12,500 TCID <sub>50</sub> <sup>4</sup> Rubella virus <sup>2</sup> (Wistar RA 27/3) <sup>3</sup> , >1000 TCID <sub>50</sub> <sup>4</sup>  <sup>1</sup> produced in chick embryo cells <sup>2</sup> produced in WI-38 human diploid lung fibroblasts <sup>3</sup> live attenuated <sup>4</sup> 50% tissue culture of infectious doses
<i>Boostrix Polio / GSK</i>	
RVG 35123 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine (adsorbed, reduced antigen) 0.5 ml	Diphtheria toxoid <sup>1</sup> , >2 IU Tetanus toxoid <sup>1</sup> , >20 IU <i>Bordetella pertussis</i> antigens Pertussis toxoid (PT) <sup>1</sup> , 8 µg Filamentous haemagglutinin (FHA) <sup>1</sup> , 8 µg Pertactin (PRN) <sup>1</sup> , 2.5 µg Inactivated poliovirus type 1 poliovirus (Mahoney) <sup>2</sup> , 40 DU type 2 poliovirus (MEF-1) <sup>2</sup> , 8 DU type 3 poliovirus (Saukett) <sup>2</sup> , 32 DU  <sup>1</sup> adsorbed to aluminiumhydroxide (Al(OH) <sub>3</sub> ), hydrated, 0.3 mg Al <sup>3+</sup> and aluminiumphosphate (AlPO <sub>4</sub> ), 0.2 mg Al <sup>3+</sup> <sup>2</sup> produced in Vero cells
<i>Boostrix / GSK</i>	
RVG 35121 Diphtheria, tetanus and pertussis (acellular component) vaccine (adsorbed, reduced antigen) 0.5 ml	Diphtheria toxoid <sup>1</sup> , >2 IU Tetanus toxoid <sup>1</sup> , >20 IU <i>Bordetella pertussis</i> antigens Pertussis toxoid (PT) <sup>1</sup> , 8 µg Filamentous haemagglutinin (FHA) <sup>1</sup> , 8 µg Pertactin (PRN) <sup>1</sup> , 2.5 µg  <sup>1</sup> adsorbed to aluminiumhydroxide (Al(OH) <sub>3</sub> ), hydrated, 0.3 mg Al <sup>3+</sup> and aluminiumphosphate (AlPO <sub>4</sub> ), 0.2 mg Al <sup>3+</sup>

Vaccine	Composition
<i>Vaxelis / MCM Vaccine B.V.</i>	
EU/1/15/1079 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis and <i>Haemophilus</i> type b vaccine (adsorbed) 0.5 ml	Diphtheria toxoid <sup>1</sup> , >20 IU Tetanus toxoid <sup>1</sup> , >40 IU <i>Bordetella pertussis</i> antigens <sup>1</sup> : Pertussis toxoid, 20 µg Filamentous haemagglutinin, 20 µg Fimbriae type 2 and 3, 5 µg Pertactin, 3 µg Hepatitis B surface antigen <sup>2,3</sup> Inactivated poliovirus <sup>4</sup> : Inactivated type 1 poliovirus, 40 DE Inactivated type 2 poliovirus, 8 DE Inactivated type 3 poliovirus, 32 DE <i>Haemophilus influenzae</i> type b polysaccharide (Polyribosylribitol Phosphate), 3 µg Conjugated to meningococcal protein <sup>2</sup> , 50 µg  <sup>1</sup> adsorbed on aluminiumphosphate, 0.17 mg Al <sup>3+</sup> <sup>2</sup> adsorbed on amorphous aluminium hydroxyphosphate sulfate, 0.15 mg Al <sup>3+</sup> <sup>3</sup> produced in yeast ( <i>Saccharomyces cerevisiae</i> ) cells by recombinant DNA technology <sup>4</sup> produced in Vero cells <sup>5</sup> or equivalent antigenic quantity determined by a suitable immunochemical method
<i>REVAXIS / SP</i>	
RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria toxoid <sup>1</sup> , >2 IU Purified tetanus toxoid <sup>1</sup> , >20 IU Inactivated poliovirus type 1 <sup>2</sup> , 40 DU Inactivated poliovirus type 2 <sup>2</sup> , 8 DU Inactivated poliovirus type 3 <sup>2</sup> , 32 DU  <sup>1</sup> adsorbed to aluminium hydroxide, 0.35 mg (as aluminium) <sup>2</sup> produced in Vero cells
<i>Engerix-B Junior / GSK</i>	
RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen recombinant (S protein) <sup>1,2</sup> , 10 µg  <sup>1</sup> adsorbed to aluminium hydroxide, hydrated, 0,25 mg Al <sup>3+</sup> <sup>2</sup> produced on genetically engineered yeast cells ( <i>Saccharomyces cerevisiae</i> )

Vaccine	Composition
<i>Engerix-B / GSK</i>	
RVG17316 Hepatitis B (rDNA) vaccine (adsorbed) 1 ml	Hepatitis B-virus surface antigen <sup>1,2</sup> , 20 µg <sup>1</sup> adsorbed on aluminium hydroxide, hydrated, 0.5 mg Al <sup>3+</sup> <sup>2</sup> produced on yeast cells ( <i>Saccharomyces cerevisiae</i> ) with recombinant DNA technology
<i>Cervarix / GSK</i>	
EU/1/07/419	Human papillomavirus type 16 L1 protein <sup>1,2,3</sup> , 20 µg Human papillomavirus type 18 L1 protein <sup>1,2,3</sup> , 20 µg <sup>1</sup> adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL) <sup>3</sup> , 50 µg <sup>2</sup> absorbed on aluminium hydroxide, hydrated (Al(OH) <sub>3</sub> ), 0.5 mg Al <sup>3+</sup> in total <sup>3</sup> 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 <i>Trichoplusia ni</i>
<i>Nimenrix / Pfizer</i>	
EU/1/12/767 Conjugated meningococcal group A, C, W-135 and Y vaccine 0.5 ml	<i>Neisseria meningitidis</i> -group A polysaccharide <sup>1</sup> , 5 µg <i>Neisseria meningitidis</i> -group C polysaccharide <sup>1</sup> , 5 µg <i>Neisseria meningitidis</i> -group W-135 polysaccharide <sup>1</sup> , 5 µg <i>Neisseria meningitidis</i> -group Y polysaccharide <sup>1</sup> , 5 µg <sup>1</sup> conjugated to tetanus toxoid carrier protein, 44 µg
<i>Synflorix / GSK</i>	
EU/1/09/508 Pneumococcal polysaccharide conjugate vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 1 <sup>1,2</sup> , 1 µg Pneumococcal polysaccharide serotype 4 <sup>1,2</sup> , 3 µg Pneumococcal polysaccharide serotype 5 <sup>1,2</sup> , 1 µg Pneumococcal polysaccharide serotype 6B <sup>1,2</sup> , 1 µg Pneumococcal polysaccharide serotype 7F <sup>1,2</sup> , 1 µg Pneumococcal polysaccharide serotype 9V <sup>1,2</sup> , 1 µg Pneumococcal polysaccharide serotype 14 <sup>1,2</sup> , 1 µg Pneumococcal polysaccharide serotype 18C <sup>1,3</sup> , 3 µg Pneumococcal polysaccharide serotype 19F <sup>1,4</sup> , 3 µg Pneumococcal polysaccharide serotype 23F <sup>1,2</sup> , 1 µg <sup>1</sup> adsorbed on aluminium phosphate, 0.5 mg Al <sup>3+</sup> in total <sup>2</sup> conjugated to protein D (derived from non-typeable <i>Haemophilus influenzae</i> ) carrier protein, 9–16 µg <sup>3</sup> conjugated to tetanus toxoid, 5–10 µg <sup>4</sup> conjugated to diphtheria toxoid, 3–6 µg

More extensive product information can be found at: [www.cbg-meb.nl](http://www.cbg-meb.nl) and [www.emea.europa.eu](http://www.emea.europa.eu).



## Appendix 5 Overview of recent RIVM publications (01/07/2020 to 31/06/2021)

### Vaccination coverage

1. Middeldorp M, van Lier A, van der Maas N, Veldhuijzen I, Freudenburg W, van Sorge NM, et al. Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020. *Vaccine*. 2021;39(7):1039-43.

### Acceptance of vaccination

1. de Munter AC, Ruijs WL, Ruiters RA, van Nimwegen DJ, Oerlemans AJ, Ginkel Rv, et al. Decision-making on maternal pertussis vaccination among women in a vaccine-hesitant religious group: Stages and needs. *PloS one*. 2020;15(11):e0242261.
2. van Zoonen K, Ruijs WLM, De Melker HE, Bongers MEJ, Mollema, L. How to increase awareness of additional vaccinations; the case of maternal pertussis vaccination. *BMC public health*. 2021;21(1):1257.
3. Lima PdOB, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. *Vaccine*. 2020;38(34):5516-24.
4. Environment NlPHat. Verkenning factoren van invloed op deelname aan COVID-19 vaccinatie: National Institute for Public Health and the Environment; 2021. Available from: <https://www.rivm.nl/documenten/verkenning-factoren-van-invloed-op-deelname-aan-covid-19-vaccinatie>.

### Burden of disease

1. Middeldorp M, van Lier A, van der Maas N, Veldhuijzen I, Freudenburg W, van Sorge NM, et al. Short term impact of the COVID-19 pandemic on incidence of vaccine preventable diseases and participation in routine infant vaccinations in the Netherlands in the period March-September 2020. *Vaccine*. 2021;39(7):1039-43.
2. Wyper GMA, Assunção RMA, Colzani E, Grant I, Haagsma JA, Lagerweij G, et al. Burden of Disease Methods: A Guide to Calculate COVID-19 Disability-Adjusted Life Years. *International Journal of Public Health*. 2021;66(4).

### Adverse events

1. van den Boogaard J, de Gier B, de Oliveira Bressane Lima P, Desai S, de Melker HE, Hahné SJM, et al. Immunogenicity, duration of protection, effectiveness and safety of rubella containing vaccines: A systematic literature review and meta-analysis. *Vaccine*. 2021;39(6):889-900.
2. Immink MM, Koole S, Bekker MN, Groenendaal F, Kemmeren JM, de Melker HE, et al. Background incidence rates of adverse pregnancy outcomes in the Netherlands: Data of 2006-2018. *Eur J Obstet Gynecol Reprod Biol*. 2021;256:274-80.

## Current NIP

### *Diphtheria*

1. Berbers G, van Gageldonk R, van de Kasstele J, Wiedermann U, Desombere I, Dalby T, et al. Widespread circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. *Nature Communications*. 2021;12.

### *Haemophilus influenzae disease caused by type b (Hib) and other serotypes*

N/a

### *Hepatitis B*

1. Sonneveld MJ, Veldhuijzen IK, van de Laar TJW, Op de Coul ELM, van der Meer AJ. Decrease in viral hepatitis diagnoses during the COVID-19 pandemic in the Netherlands. *J Hepatol*. 2021.
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6. Thesis Hella Pasmans March 2021. Natural and vaccine derived immunity against the Human Papilloma Virus.

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N/a

### *Meningococcal disease*

1. Freudenburg-de Graaf W, Knol MJ, van der Ende A. Predicted coverage by 4CMenB vaccine against invasive meningococcal disease cases in the Netherlands. *Vaccine*. 2020;38(49):7850-7.
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### *Mumps*

N/a

### *Pertussis*

1. Versteegen P, Pinto MV, Barkoff AM, Van Gageldonk PGM, Van de Kasstele J, Van Houten MA, et al. Responses to an acellular pertussis booster vaccination in children, adolescents, and young and older adults: A collaborative study in Finland, the Netherlands, and the United Kingdom. *EBioMedicine*. 2021;65.
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### *Pneumococcal disease*

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### *Poliomyelitis*

1. Benschop K, Duizer E. Enterovirus surveillance as a tool for poliovirus detection in the Netherlands: update for 2020. 2021.
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*

1. van den Boogaard J, et al., Immunogenicity, duration of protection, effectiveness and safety of rubella containing vaccines: A systematic literature review and meta-analysis. *Vaccine*, 2021. 39(6): p. 889-900.

### *Tetanus*

1. Berbers G, van Gageldonk R, van de Kasstele J, Wiedermann U, Desombere I, Dalby T, et al. Widespread circulation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. *Nature Communications*. 2021;12.

## **Potential NIP target diseases**

### *Hepatitis A*

N/a

### *Respiratory syncytial virus*

1. Andeweg SP, Schepp RM, van de Kasstele J, Mollema L, Berbers GAM, van Boven M. Population-based serology reveals risk factors for RSV infection in children younger than 5 years. *Sci Rep*. 2021;11(1):8953.
2. Teirlinck AC, Broberg EK, Berg AS, Campbell H, Reeves RM, Carnahan A, et al. Recommendations for respiratory syncytial virus surveillance at national level. *The European respiratory journal*. 2021.
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5. Zylbersztejn A, Pembrey L, Goldstein H, Berbers G, Schepp R, van der Klis F, et al. Respiratory syncytial virus in young children: community cohort study integrating serological surveys, questionnaire and electronic health records, Born in Bradford cohort, England, 2008 to 2013. *Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin*. 2021;26(6).

### Rotavirus

1. Quee FA, de Hoog MLA, Schuurman R, Bruijning-Verhagen PCJ. Community burden and transmission of acute gastroenteritis caused by norovirus and rotavirus in the Netherlands (RotaFam): a prospective household-based cohort study. *The Lancet Infectious Diseases*. 2020;20(5):598-606.
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### Varicella zoster virus (VZV) infection

1. Luyten J, van Hoek AJ. Integrating Alternative Social Value Judgments Into Cost-Effectiveness Analysis of Vaccines: An Application to Varicella-Zoster Virus Vaccination. *Value Health*. 2021;24(1):41-9.

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3. de Gier B, Andeweg S, Joosten R, Ter Schegget R, Smorenburg N, van de Kasstelee 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).
4. Verberk JDM, Vos ERA, Mollema L, van Vliet J, van Weert JWM, de Melker HE. Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. *BMC Infect Dis*. 2019;19(1).
5. Vos ERA, den Hartog G, Schepp RM, Kaaijk P, van Vliet J, Helm K, et al. Nationwide seroprevalence of SARS-CoV-2 and identification of risk factors in the general population of the Netherlands during the first epidemic wave. *Journal of Epidemiology and Community Health*. 2020;jech-2020-215678.

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12. Verberk JDM, et al, Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. *BMC Infectious Diseases*, 2019. 19(1): p. 470.
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## Appendix 6 Overview of relevant websites

### General information for NIP professionals

RIVM website for professionals:

<http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/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](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](http://www.rivm.nl/Onderwerpen/M/Meldingsplicht_infectieziekten)

Cervical cancer screening programme:

[https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek\\_baarmoederhalskanker\\_voor\\_professionals](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](http://www.rivm.nl/vaccinaties)

Volksgesondheidszorg.info:

<https://www.volksgesondheidszorg.info/>

Cervical cancer screening programme:

[https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek\\_baarmoederhalskanker](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 2019:

<https://www.rivm.nl/publicaties/vaccinatiegraad-en-jaarverslag-rijksvaccinatieprogramma-nederland-2019>

Adverse events in the Netherlands Vaccination Programme, reports in 2010 and review 1994–2010:

<http://www.rivm.nl/bibliotheek/rapporten/205051004.pdf>

## 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](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](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/>

### **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/Griepvaccinatie>

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 Influenza and Other Respiratory Infections in the Netherlands:

<https://www.rivm.nl/bibliotheek/rapporten/2019-0079.pdf>

### *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 vaccination*

Landelijk Coördinatiecentrum Reizigersadviesing  
(National Coordination Centre for Information for Travellers):

<https://www.lcr.nl/Index.htm>





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