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 2022-2023

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RIVM report 2023-0330

Colophon

DOI 10.21945/RIVM-2023-0330

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

Authors:
A. Afrian, J. van Beek, M.J.C. van de Beld, E. Benincà, K.S.M. Benschop, D.S.F. Berry, R.S. van Binnendijk, S. Blomont-Frederick, R. Bodewes, M.C. Boer, P. de Boer, M. van Boven, J.G.M. Brouwer, S. de Bruijn, J. Brummelman, A. Buisman, T.C. van Charldorp, E. op de Coul, J. Cremer, M.A. Davies, J.W. Duijster, E. Duizer, C.A.C.M. van Els, W. Freudenburg-de Graaf, I.H.M. Friesema, T. Garcia Vilaplana, B. de Gier, T. Gordon, C.C.E. van Hagen, S.J.M. Hahné, G. den Hartog, J. Hubert, A. Huiberts, C.E. Hoeve, S. van den Hof, M.I. Hofstee, M. Hooiveld, S. van Iersel, G.A.H. Jol, F. Jongenotter, P. Kaaijk, J. Kaczorowska, C. Kampshoff, J. van de Kassteele, P.B. van Kasteren, J.M. Kemmeren, A.J. King, F.R.M. van der Klis, M. Knijff, M.J. Knol, J.M.A. Kusters, M.S. Lambooij, S.J. Lanooij, E.A. van Lier, E. Lista-de Weever, R. Mariman, A.A.A. Maxwell, S. McDonald, A. Meiberg, A. Meijer, D.L. van Meijeren, H.E. de Melker, M. Middeldorp, W. Miellet, N. Neppelenbroek, A. Niessen, D.W. Notermans, R. Pijnacker, A.J.M. Pluijmaekers, C. van Roekel, M. Rolink, N.Y. Rots, W.L.M. Ruijs, J.F. van Slobbe, B.A. Smagge, N.M. van Sorge, A. Steens, S. Teelen, A.C. Teirlinck, A. Valk, J.W. Vanhommerig, H. Vennema, M.K. Verheul, L.J. Visser, E.R.A. Vos, P.H. Voskuil, M. de Vries, A.J. Wijmenga-Monsuur, J. de Wit, D. Wong, T. Woudenberg

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

Photo cover: iStock

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

Contents

Synopsis **5**
Publiekssamenvatting **6**
Preface **7**
Comprehensive summary **9**
Uitgebreide samenvatting **21**

1 Introduction **33**

2 Vaccination coverage **41**

3 Acceptance of vaccination **51**

4 Burden of disease **61**

5 Adverse events **69**

6 Current National Immunisation Programme **93**
6.1 Diphtheria 94
6.2 *Haemophilus influenzae* disease 99
6.3 Hepatitis B 108
6.4 Human papillomavirus (HPV) 113
6.5 Measles 123
6.6 Meningococcal disease 126
6.7 Mumps 138
6.8 Pertussis 140
6.9 Pneumococcal disease 152
6.10 Poliomyelitis 183
6.11 Rubella 191
6.12 Tetanus 192

7 Immunisation programme in the Dutch Caribbean islands **195**

8 Potential NIP target diseases **203**
8.1 Hepatitis A 204
8.2 Respiratory Syncytial Virus 209
8.3 Rotavirus 216
8.4 Varicella zoster virus (VZV) infection 220

9 COVID-19 **233**

9.1 The COVID-19 epidemiological situation in the Kingdom of the Netherlands 234
9.2 COVID-19 vaccination strategy in the Netherlands 237
9.3 COVID-19 vaccination coverage 249
9.4 COVID-19 vaccine effectiveness 265
9.5 Seroepidemiology of SARS-CoV-2 in the Netherlands 282
9.6 Immunogenicity of COVID-19 vaccines 296
9.7 Adverse events after COVID-19 vaccination 312

10 Vaccines in development for other potential future NIP target diseases **329**

11 List of abbreviations **341**

12 Appendix **349**

Appendix 1 Surveillance methodology 350
Appendix 2 Morbidity and mortality figures 361
Appendix 3 Overview of vaccine changes in the NIP from 2000 395
Appendix 4 Composition of vaccines used in the NIP 401
Appendix 5 Overview of recent RIVM publications (01/07/2022 to 31/06/2023) 405
Appendix 6 Overview of relevant websites 415

Synopsis

The National Immunisation Programme in the Netherlands

Surveillance and developments in 2022-2023

Every year, RIVM tracks how many people fall ill due to a disease that is included in the National Immunisation Programme (NIP). In 2022, more people in the Netherlands got such a disease than in 2021. This is very likely due to the COVID-19 control measures, such as social distancing, being lifted.

As was the case in 2021, no people contracted rubella in 2022. The other diseases that did not occur in 2021, returned in 2022. This is the case for diphtheria (7), measles (6), polio (1), and tetanus (2). Pertussis (129) and mumps (7) occurred more often in 2022 than in 2021, but less often than before the COVID-19 pandemic. Invasive pneumococcal disease also occurred less often in 2022 than before the COVID-19 pandemic.

The number of notifications for meningococcal disease caused by serotype W (2) decreased further since 2018. This is mainly because since that same year, the vaccination against this type of meningococcus is also being given to teenagers. The number of *Haemophilus influenzae* type b (Hib) reports was slightly lower in 2022 (59) than in 2021 (68). The number of children younger than 5 years of age that became very ill because of an Hib infection, did increase (26 in 2021, 29 in 2022), also when compared to the years before the COVID-19 pandemic (39 in 2019, of which 17 younger than 5 years of age).

The number of chronic hepatitis B notifications (815) was higher than in 2022, but lower than before the COVID-19 pandemic: between 2014 and 2019, about 1,000-1,100 people heard they had this disease.

In 2022, at least 1,041,632 children were vaccinated as part of the NIP. They received a total of at least 2,619,654 vaccinations. Also, at least 114,839 pregnant women received a vaccination that protects their baby immediately after birth against, amongst others, whooping cough. This is the maternal pertussis vaccination.

Based on advise by the Health Council of the Netherlands and starting from October 2023, maternal influenza vaccination is offered to pregnant women during the influenza season. Additionally, young babies born on or after 1 January 2024, receive a vaccine against rotavirus. Persons aged 15 or over receive only 2 doses of the HPV vaccine instead of 3, starting from September 2022.

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

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

Publiekssamenvatting

Het Rijksvaccinatieprogramma in Nederland

Surveillance en ontwikkelingen in 2022-2023

Het RIVM houdt elk jaar bij hoeveel mensen een ziekte krijgen waartegen vanuit het Rijksvaccinatieprogramma (RVP) wordt gevaccineerd. In 2022 kregen in Nederland meer mensen zo'n ziekte dan in 2021. Dit komt waarschijnlijk doordat de coronamaatregelen zijn opgeheven, zoals afstand houden.

Net als in 2021 waren er in 2022 geen mensen met rodehond. De andere ziekten die in 2021 niet voorkwamen, waren in 2022 wel weer te zien. Dat zijn difterie (7 mensen), mazelen (6), polio (1) en tetanus (2). Kinkhoest (129) en bof (7) kwamen in 2022 vaker voor dan in 2021, maar wel minder vaak dan in de jaren vóór de coronapandemie. Ook pneumokokken kwam in 2022 iets minder vaak voor dan voor de coronapandemie.

Het aantal mensen met meningokokkenziekte type W (2) is sinds 2018 verder gedaald. Dat komt vooral doordat de vaccinatie tegen dit type meningokokken vanaf dat jaar ook aan tieners wordt gegeven. Ook het aantal meldingen van *Haemophilus influenzae* type B (Hib) was in 2022 iets lager dan in 2021 (59 en 68). Het aantal kinderen jonger dan 5 jaar dat ernstig ziek werd van Hib nam wel toe (26 in 2021, 29 in 2022), ook in vergelijking met de jaren voor de coronapandemie (39 zieken in 2019, van wie 17 onder de vijf jaar).

Het aantal meldingen van chronische hepatitis B (815) was hoger dan in 2021, maar lager dan voor de coronapandemie: tussen 2014 en 2019 hoorden per jaar 1.000 tot 1.100 mensen dat ze deze ziekte hebben.

In 2022 zijn ten minste 1.041.632 kinderen gevaccineerd via het RVP. Zij kregen in totaal minstens 2.619.654 vaccinaties. Ook hebben ten minste 114.839 zwangere vrouwen een vaccinatie gekregen die hun baby vanaf de geboorte beschermt tegen onder andere kinkhoest. Dit is de 22 wekenprik.

Op advies van de Gezondheidsraad wordt de griepvaccinatie vanaf oktober 2023 tijdens het griepseizoen ook aan zwangere vrouwen aangeboden. Verder krijgen jonge baby's die vanaf 1 januari 2024 geboren worden, een vaccin tegen het rotavirus. Personen van 15 jaar of ouder krijgen sinds september 2022 nog maar 2 doses van het HPV-vaccin, in plaats van 3.

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

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

Preface

This report presents an overview of surveillance data and developments in 2022 and the first four to six months of 2023 that are relevant for the Netherlands with respect to diseases included in the current National Immunisation Programme (NIP): diphtheria, *Haemophilus influenzae* serotype b (Hib) disease, hepatitis B, human papillomavirus (HPV) infection, measles, meningococcal disease, mumps, pertussis, pneumococcal disease, poliomyelitis, rubella, and tetanus. It also describes surveillance data for potential target diseases: hepatitis A, respiratory syncytial virus (RSV), rotavirus, varicella zoster virus (VZV) infection. Furthermore, it presents information on COVID-19[1]. In addition, the report presents an overview of vaccines against infectious diseases undergoing clinical trials that are relevant for the Netherlands, including new COVID-19 vaccines.

For developments with regard to influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the Health Council, and the KNCV Tuberculosis Foundation. (See Chapter 1 (Introduction) for these references.)

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

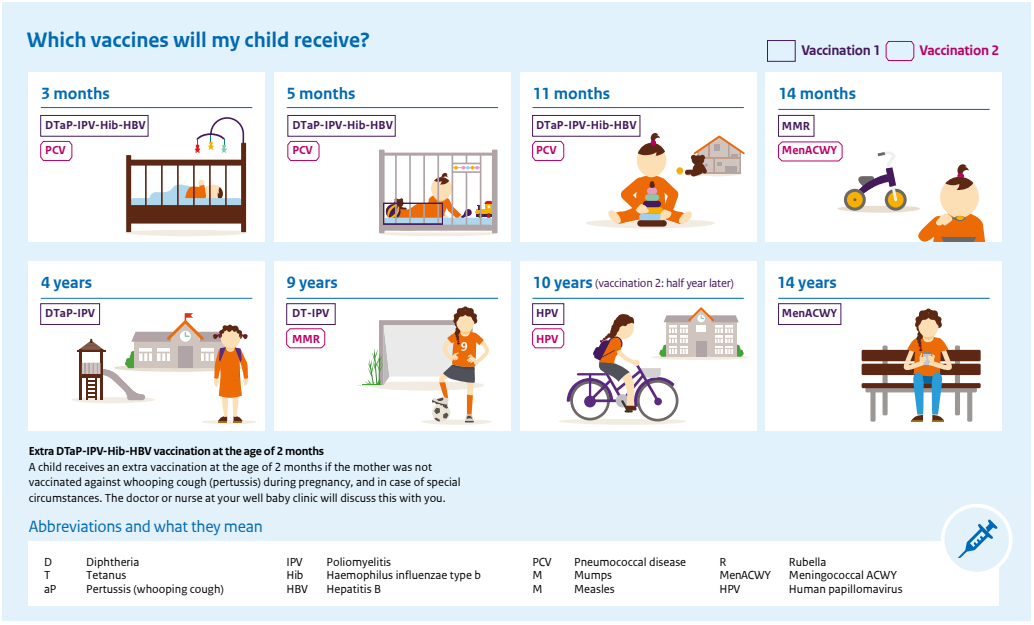
Appendix 1 describes the surveillance methods used to monitor the NIP. Appendix 2 reports on mortality and morbidity figures from 2007 onwards, based on various data sources. Appendix 3 provides an overview of changes in the NIP since 2000, whilst Appendix 4 presents the composition of the vaccines used in the period 2022/2023. Appendix 5 offers an overview of recent publications by the National Institute for Public Health and the Environment (RIVM), and Appendix 6 lists relevant websites.

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

Comprehensive summary

Current NIP vaccination schedule

Figure 1 The NIP vaccination schedule in 2023, including universal HPV vaccination in the year children turn ten.



Source: *https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-english*

Vaccination coverage

The registered vaccination coverage as determined and reported in 2023, was approximately 2%-5% lower than the vaccination coverage that was determined and reported in 2022. For multiple vaccinations, including those for babies, the coverage as determined and reported in 2023 is below 90%, while the WHO target for vaccination coverage for (for instance) measles is 95%.

RIVM is unable to determine precisely how much lower the vaccination coverage is, due to the implementation of the informed consent procedure for data exchange with RIVM in January 2022. As a result, RIVM receives part of the NIP vaccinations anonymously (approximately 5% overall in 2022). Anonymous vaccinations cannot be counted towards the vaccination coverage on a national or a subnational level (because the involved dose, year of birth, sex, and place of residence of the vaccinated person are unknown), so the coverage is reported to be lower than it actually is. The number of vaccinations that cannot be counted for this report is still quite small because it mainly covers NIP vaccinations administered before 2022.

Acceptance of vaccination

Research performed by RIVM reveal the following:
A survey on psychosocial factors of vaccine uptake revealed that in 2022, most parents had positive intention, attitudes and trust towards vaccination and perceived vaccinating their child to be self-evident. However, there are indications that a somewhat higher proportion of parents has become more negative towards the current NIP.

A conversation analytic study shows that if, during a vaccination consultation, parents are invited to ask questions about a vaccine *before* they have made a decision, there is more room for critical questions.

Surveys about the HPV vaccination campaigns for 10-18-year-olds and 19-26-year-olds reveal that the media campaigns did not influence the perceived importance of HPV vaccination, but did lead to a positive development in the overall attitude towards and increased knowledge about HPV vaccination. Additionally, unvaccinated young adult women (19-26 years of age) worry about vaccine safety and have doubts about the benefits of still being vaccinated at their age. Young adult men also have doubts about the benefit of being vaccinated, but mostly report that they have not yet gotten around to it.

Half of the parents of daughters aged 7-10 years, consider HPV vaccination and cervical cancer (CC) screening to be complimentary to each other. Of the other half, parents with low trust in CC screening perceived the risks of HPV and CC as higher than parents with high trust in CC screening, and were more motivated to vaccinate their daughter. Possible changes to the CC screening interval do not seem to influence parents' decision making with respect to HPV vaccination.

COVID-19 vaccine willingness in the Netherlands increased once the decision to be vaccinated was no longer hypothetical (at the end of 2020, right before the original vaccination campaign) but a reality (right after the start of the original campaign in 2021). Furthermore, personal beliefs and social environment play a deciding role in the eventual decision, which is typically made at the moment of receiving the invitation. Later in the vaccination campaign, when the COVID-19 pandemic was in a different phase, beliefs changed and willingness decreased, resulting in lower vaccination willingness. Additionally, later in the vaccination campaign, younger people more often indicated they did not know if they were eligible for vaccination.

Burden of disease

For the year 2022, the estimated total burden of disease caused by (partially) vaccine-preventable diseases was highest for HPV (18,500 disability adjusted life years (DALYs); 74% among women), invasive pneumococcal disease (8,700 DALYs), rotavirus infection (1,500 DALYs), invasive *Haemophilus influenzae* disease (1,500 DALYs), and invasive meningococcal disease (560 DALYs). For most vaccine-preventable diseases, the estimated burden was still somewhat lower in 2022 compared to the estimated burden in 2019, but higher than during the COVID-19 years 2020/2021, when various COVID-19 response measures (e.g. social

distancing and hand hygiene) were in place. Recently implemented additional vaccination of older adults against pneumococcal disease and of adolescents against meningococcal disease also played a part. The burden of invasive *H. influenzae* disease type b was still higher in 2022 than in 2019, as was also the case in 2021 and 2020.

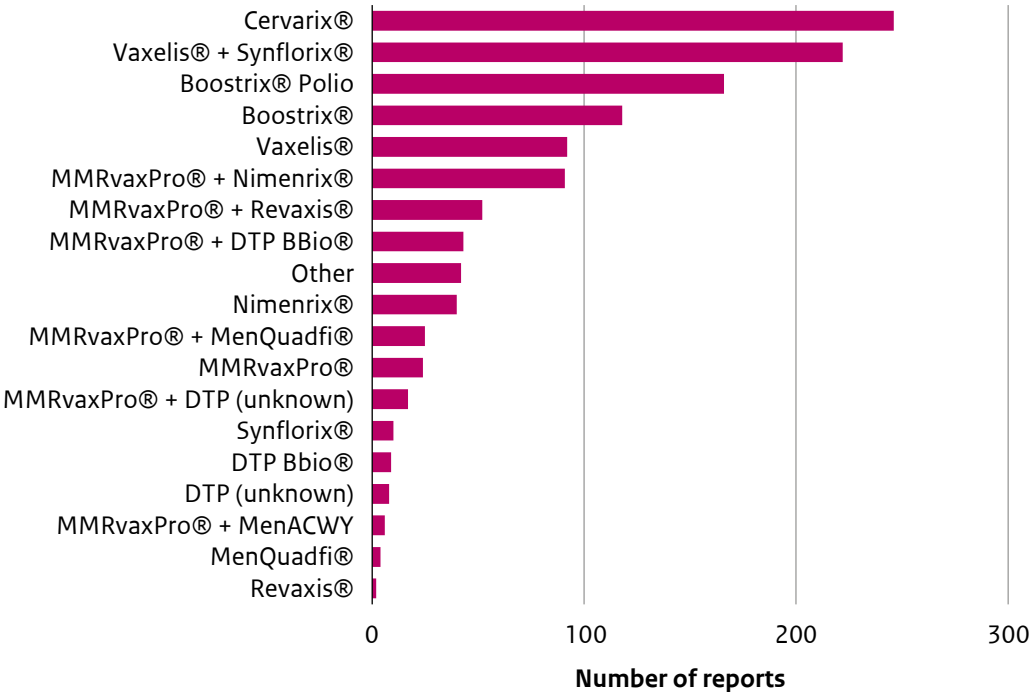
For COVID-19, the estimated burden in 2022 (at least 93,800 DALYs, excluding long-term consequences of the disease) was lower than in 2021 (219,000 DALYs).

Adverse events

In 2022, Lareb received 1,217 notifications representing a total of 4329 adverse events following immunisation (AEFI). This number of reports is lower than in earlier years. The number of reported AEFIs per report was between 3 to 4, which is the same as in earlier years.

No new signals of disturbing adverse events were found.

Figure 2 Number of adverse event reports per suspected vaccine(s) in 2022.



Source: Lareb

Current NIP

Diphtheria

In the Netherlands, seven confirmed diphtheria cases, of which five underaged asylum seekers, were reported in 2022. No cases were reported in 2023 up to and including April (the end of the observation period of this chapter). In 2022 up to and including 21 April 2023, eight EU/EEA countries (including the Netherlands) as well as Switzerland and the United Kingdom, together reported 400 cases of diphtheria among asylum seekers to ECDC.

Haemophilus influenzae disease

The increase in invasive *Haemophilus influenzae* serotype b (Hib) disease in 2020 and 2021 to 0.39 per 100,000 stopped. In 2022, there was a slight decrease to an incidence of 0.32 per 100,000 inhabitants (n=59). In the first 4 months of 2023 (the end of the observation period of this chapter), the number of cases has been similar to the pre-COVID-19 years (n=12). Among children <5 years, Hib incidence has been increasing since 2012 and continued to increase to 3.3 per 100,000 (n=29) in 2022. While in 2020 and 2021, the observed incidences were also higher for older age groups, in 2022, the incidences generally returned to pre-COVID-19 levels. Out of 72 Hib cases with known outcomes from 2022-April 2023, 7 died (1 of whom was <5 years old but sufficiently vaccinated according to age, 5 were aged 60+).

The vaccine effectiveness (VE) against disease in the January 2022-April 2023 period was estimated to be 89% (95%CI 76-95) for those older than 3 months and born in 1993 or after. There was a schedule change from 3+1 to 2+1 in January 2020. According to the age at disease onset, none of the cases that were vaccinated with the 2+1 schedule in the period from 2020 up to and including April 2023 could have been prevented if vaccinated with the former 3+1 schedule.

After a decrease related to the mitigation measures against the COVID-19 pandemic, invasive disease caused by non-typeable *Haemophilus influenzae* (NTHi) and other non-b serotypes has increased to (slightly) higher levels than pre-COVID-19 in 2022 and the first four months of 2023.

Hepatitis B

After a decade-long decline followed by a steeper decline in 2020 and 2021, the number of reported cases of chronic hepatitis B increased from 743 in 2021 to 815 in 2022. The reported number of acute hepatitis B infections remained similar between 2021 and 2022 (n=80, 0.45 per 100,000) following a consistent decrease since 2004. Of the 80 acute hepatitis B notifications, three regarded vaccinated persons. These persons had been vaccinated because they belonged to a risk group.

Human Papillomavirus (HPV) infection

In 2022, the incidence of cervical cancer remained stable with 10.38 new diagnoses per 100,000 women (n=940), compared to 10.41 new diagnoses per 100,000 women (n=948) in 2021. The number of deaths caused by cervical cancer remained relatively stable as well (n=223 compared to 213 in 2021). Slight increases were observed in the mortality rates of (oro) pharyngeal and cervical cancers, whilst the mortality rate of vaginal cancer decreased.

The vaccine effectiveness (VE) of the bivalent vaccine against persistent vaccine-targeted HPV types (HPV types 16 and 18) remained high (>97%) up to twelve years after vaccination with a three-dose regimen and up to seven years after vaccination with a two-dose regimen as found in two prospective cohort studies (HAVANA and HAVANA2). Regarding immunogenicity, high antibody levels against HPV types 16/18 were observed up to 96 months post-vaccination in girls who received 2 doses of the bivalent vaccine (HPV-2D study). In a similar study among boys, the seropositivity of HPV types 16/18 was 100% 7 months post-vaccination among boys who received 2 doses of the vaccine in 2022 at the age of 10 years, whilst the seropositivity rates for HPV types 31, 33, 45, 52, 58 ranged between 43% and 100%.

Cervical screening of women aged <24 (before entry in the cervical cancer screening programme) showed a significant lower prevalence of low-grade and high-grade cervical lesions as well as high-risk HPV infection among fully vaccinated women compared to unvaccinated women. At the beginning of 2023, a catch-up campaign for young men and unvaccinated or partially vaccinated young women born between 1996 up to and including 2003 was launched in the Netherlands.

Measles
In 2022, six cases of measles were reported in the Netherlands, five of which belonged to a cluster that occurred in November. Early on in 2023, a girl deceased due to subacute sclerosing panencephalitis (SSPE), a rare but fatal neurological disorder that results from a persistent measles infection.

Meningococcal disease
Mitigation measures aiming to control the COVID-19 pandemic coincided with a decline in invasive meningococcal disease (IMD). The decline reversed after all measures were lifted in March 2022: the incidence in 2022 was 0.47 per 100,000 (n=78). In the first four months of 2023, 59 IMD cases had already been diagnosed. IMD caused by the vaccine serogroups ACWY was uncommon in 2022-April 2023: IMD-C and IMD-Y were each diagnosed four times, IMD-W occurred twice, and no IMD-A was diagnosed. None of the IMD-ACWY patients were reported to have been vaccinated with MenACWY.

In 2022, serogroup B caused 88% of all IMD cases. The IMD-B incidence was 0.39 per 100,000 population (n=68) in 2022, which is higher than during the COVID-19 years 2020-2021 but slightly lower than during the pre-COVID period (on average 0.43 per 100,000 in 2015-2019). In January-April 2023, 54 IMD-B cases were diagnosed. Four deaths were reported among IMD-B cases in 2022 and four deaths in 2023. Two in each year were aged <5 years. Overall, 71% of IMD-B isolates of 2022-January 2023 were predicted to be covered by 4CMenB and 89% by the MenB-fHbp vaccine. The strain coverage differed slightly by age-group.

Mumps
The number of reported cases of mumps in 2022 is lower than the number observed prior to the COVID-19 pandemic. In 2018 and 2019, the number of reported cases amounted to 73 and 131, respectively, whereas in 2022, 7 cases were reported.

Pertussis
The reduction in the number of notifications (compared to pre-COVID-19) that was observed following the introduction of the COVID-19 control-measures in March 2020 has continued in 2022 and in the first four months of 2023 (end of the observation period of this chapter). In 2022, the overall number of pertussis notifications and the incidence rate (IR) were 129 and 0.7 per 100,000 respectively, which are unprecedentedly low numbers compared to the past 25 years. Besides a reduction of circulation of *B. pertussis* due to the COVID-19 measures, other reasons, such as changed health care seeking behaviour, might also have caused part of the decrease in the number of notifications.

In 2022 and the first four months of 2023, no infections with *B. pertussis* among 0- to 3-month-olds were reported, as was the case in 2021. Therefore, the VE estimate of the maternal Tdap vaccination (74% (95% CI: -32 to 96%)) against infection with *B. pertussis* continues to be based on 8 cases reported between April 2020 and December 2020.

Pneumococcal disease
In the epidemiological year 2021/2022, the incidence of invasive pneumococcal disease (IPD) was low (9.4 per 100,000), mainly due to the COVID-19 mitigation measures. However, after all measures were lifted in March 2022, the incidence increased again to 12.8 per 100,000 in 2022/2023, slightly lower than the average of 15.0 per 100,000 per year in 2015-2019. The incidence in children <5 years was the highest in more than a decade (8.6 per 100,000 in 2022/2023). The increase was mainly due to an increase in serotype 19A (44% of all cases), which is covered by PCV13/PCV15/PCV20 but not by PCV10.

In 2022/2023, four vaccine failures occurred among children: two serotype 23F (following PCV7 and PCV10) and two serotype 14 patients (following PCV10). All but one had known comorbidities. The vaccine effectiveness of at least two doses of PCV10 was estimated at 88% (95% CI: 67-96%).

The PCV13 serotypes that are not covered by PCV10 (i.e., serotypes 3, 6A and 19A), together with serotype 6C (cross-protection of serotype 6A in PCV10) caused 42% of all cases in 2022/2023. PCV15 serotypes + 6C caused 57% and PCV20 serotypes + 6C caused 80% of all cases. For individuals ≥65 years, 80% of IPD was caused by a serotype covered by the 23-valent pneumococcal polysaccharide vaccine (PPV23). Among them, PCV15 and PCV20 (both including 6C) caused 57% and 77% of the cases, respectively. The impact of the recently introduced PPV23 among older adults on PPV23-IPD was estimated at 43-57%, depending on the age-groups and method used.

Poliomyelitis
One case of asymptomatic poliovirus infection was reported in the Netherlands in 2022. This concerned an employee of a vaccine producer located at Utrecht Science Park in Bilthoven, who showed no signs of illness since he was fully vaccinated against poliovirus. In addition, the enterovirus (EV) surveillance demonstrated that a child who was recently vaccinated with bivalent oral polio in Moldavia, was secreting a Sabin 1-Sabin 3 recombinant virus. The child

did not show signs of acute flaccid paralysis. Environmental surveillance activities performed in 2022 have again documented the absence of poliovirus circulation in the Netherlands.

Rubella
Since 2015, no new cases of rubella have been reported in the Netherlands.

Tetanus
In 2022, two women died because of a tetanus infection in the Netherlands. Both women were elderly and therefore not eligible for childhood tetanus vaccination.

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 2022, one case of invasive pneumococcal disease was reported on St. Maarten. No other diseases covered by the NIP were reported in the Caribbean Netherlands.

Recent and upcoming changes to the immunisation schedules in the Dutch overseas territories include the maternal pertussis vaccination (on Bonaire and St. Eustatius) and consequent changes to the corresponding childhood vaccinations, VZV vaccination for all children (Bonaire and Saba), MenACWY vaccination for all children (Bonaire), and HPV vaccination for boys (Bonaire and Saba).

Potential NIP candidates

Hepatitis A
In 2022, 93 hepatitis A cases were reported, corresponding to 0.5 cases per 100,000 population. This is the second year of increase since the low numbers in 2020 (n=50 cases). Infections were mainly seen in 20-49-year-olds. The percentage of travel-related cases was 35%, which is almost back to pre-COVID-19 percentages (2013-2019; mean: 41%) compared to 2020 (18%) and 2021 (21%). The persons who contracted the disease abroad named Asia, Africa and Europe more or less equally.

Respiratory syncytial virus (RSV) infection
Since the summer of 2021, respiratory syncytial virus (RSV) has continuously circulated in the Netherlands, and the number of RSV detections reported in the virological laboratory surveillance only started decreasing a year later, by the end of the summer of 2022, if only a short time. Since week 39 of 2022, the number of RSV detections has increased again. While the absolute numbers of RSV detections were much higher than in previous seasons, the timing of the peak (week 52 of 2022) was within the range of pre-pandemic seasons. As testing practices have probably changed since the COVID-19 pandemic, the number of RSV diagnoses and subsequent outcomes on onset and duration of the RSV season should be interpreted with caution. After a sharp drop in detections from week 2-5 of 2023, the number of detections gradually decreased further and have been at low levels since April 2023.

The number of children <2 years of age that were hospitalised in 2022/2023 with RSV-bronchiolitis followed a similar trend in time as the virological detections. In the winter of 2022/2023, the peak number of hospitalisations (n=100) in 33 hospitals was lower than in the summer peak of 2021 (n=163).

Rotavirus infection
The rotavirus season of 2022 had an early start in October 2021; usually, the season starts in February. This is probably the result of an increase in the number of children susceptible to rotavirus due to an absence of a rotavirus season in 2020 and a mild season in 2021. As a result, the annual number of rotavirus laboratory detections was higher in 2022 than before the COVID-19 pandemic: 1.391 in 2022, compared to an average of 981 detections in 2016-2019 (range: 682-1054). Genotype G3P8 was the most prevalent genotype in 2022, in contrast to previous years when G9P8 was most prevalent. In 2024, universal rotavirus vaccination will be added to the NIP.

Varicella zoster virus (VZV) infection (varicella and herpes zoster)
In 2021, the epidemiology of herpes zoster (incidence of GP consultations, hospitalisations and deaths) in the Netherlands was similar to previous years; GPs recorded about 94,000 herpes zoster episodes (540 episodes per 100,000 population).

For varicella, the incidence of GP consultations and hospitalisations in 2021 was still lower than before 2020 but somewhat higher than in 2020; GPs recorded about 33,000 varicella episodes (190 episodes per 100,000 population). This is probably linked to the COVID-19 measures, which have also limited transmission of VZV.

COVID-19

Epidemiology
A description of last winter's epidemiological developments in the Netherlands (week 21 2022 until week 20 2023) can be found in this year's report on Surveillance of acute respiratory infections in the Netherlands: winter 2022/2023 – SARS-CoV-2, influenza virus, RSV and other respiratory viruses (see this link). Regarding the Dutch Caribbean, early on in 2023, Saba and St. Eustatius reported an increase in cases, although COVID-19-related deaths remained low.

Vaccination campaigns
At the beginning of 2022, the first booster campaign, which had started in November 2021, was still running. During this campaign, booster vaccinations were offered to everyone aged 12 years and over. There were two new vaccination campaigns in 2022 (both in the European and Caribbean part of the Netherlands): the repeat vaccination (second booster) for adults aged 60 years and over and healthcare workers, and the repeat vaccination in the autumn round were available to everyone aged 12 and over.

Vaccination coverage
Up to week 21, 2023, the COVID-19 vaccination coverage for those aged 60 and over was 85.3% for the 2021/2022 booster campaign, 67,2% for the spring repeat vaccination in 2022, and 60.2% for the 2022 autumn round. The COVID-19 vaccination coverage was higher among older age groups than among younger age groups. At the municipal level, a pattern is observed with lower coverage in the Bible Belt and in the north of the Netherlands than in the south. This pattern was observed in all vaccination rounds. In the Caribbean part of the Kingdom of the Netherlands, by week 21 of 2023, the vaccination coverage for the booster campaign for those aged 60 years and over ranged between 15% on St. Maarten and 91% on Saba. For the 2022 autumn campaign, this ranged from <5% on St. Maarten and St. Eustatius to 31% on Saba.

Effects of vaccination
In the February-April 2023 period, the risk of hospitalisation in persons aged 60 years or over who received a bivalent (Omicron BA.1) booster vaccination was 43% lower than in persons who received least one COVID-19 vaccination, but not a bivalent vaccination. For ICU admission, this amounted to 36%. Since October 2022, the relative risk reduction after bivalent booster vaccination has decreased over time.

VE against COVID-19 mortality estimated between January 2021 and January 2022 was >90% for all age groups shortly after the primary series and >85% in all age groups shortly after the first booster vaccination.

Between 26 September and 19 December 2022, relative effectiveness of bivalent (Omicron BA.1) booster vaccination against self-reported Omicron SARS-CoV-2 infection was 31% in 18-59-year-olds and 14% in 60-85-year-olds. Hybrid immunity was more protective against a subsequent Omicron infection than vaccine-induced or infection-induced immunity.

In contrast to some other studies, data from two prospective cohort studies by RIVM (LongCOVID and VASCO) found no evidence of any effect of booster vaccination against long-term symptoms or fatigue after SARS-CoV-2 infections, compared with primary vaccination or no vaccination.

Seroepidemiology
The infection-induced seroprevalence in the Dutch population (assessed in the PIENTER Corona (PICO study)) rose from 26% in November 2021 to 62% in March 2022 following the emergence of Omicron, while the total seroprevalence (i.e., including vaccine-induced antibodies) increased from 87% to 96% and remained high thereafter. A relatively rapid increase in infection-induced seroprevalence was observed in those aged <60 years, which was also reflected by large proportions of breakthrough infections among the vaccinated. Due to the easing of control measures in 2022, overall infection-induced seroprevalence increased to 86% in November 2022. At this point, the majority of the population had acquired hybrid immunity. Only a small proportion of the oldest age groups had not yet been infected.

Within the PICO study in June 2022, 93% was positive for respiratory mucosal spike S1 IgG, while 24% was positive for IgA. Vaccinated participants (mainly aged >11 years) with a known history of infection had significantly higher prevalence and levels of mucosal IgG and especially IgA, compared to participants with no evidence of a past infection. Higher levels, particularly of IgA, reduced the probability of infection within the next six months.

Nearly all participants in the nationwide VASCO study were anti-S1 IgG seropositive after the primary series and first booster, and completely after the second booster. The early response after the primary series varied significantly between vaccine products, with the highest concentrations in Spikevax recipients as well as those with a previous infection, while concentrations were lower in the 60-85 years age group and in the medical risk group for both Comirnaty and Spikevax. Differences between vaccines in early response diminished after the first booster and disappeared completely after the second booster. Overall, waning was slower in the older age group after the first booster, and was not affected by medical risk after the first or second booster.

Immunogenicity
Data from the RIVM corona vaccination trials (CVTs) in community dwelling individuals show that most of the infection-naïve older adults mount a SARS-CoV-2-specific IgG antibody response after the primary series that is lower than in younger adult age groups. Also, T cell responses are lower and show more variability in older adults compared to other adult age groups. In both infected and uninfected persons, booster doses result in an initial increase in antibody levels followed by a decline in antibodies, but waning of antibody levels is slower when a person had been infected before vaccination.

Older adults and specific groups of immunocompromised patients require the first booster dose to reach mean antibody levels similar to levels reached in younger adults. In nursing home residents, solid antibody responses were seen following booster vaccinations, although their antibody responses were slightly lower than in community dwelling older adults.

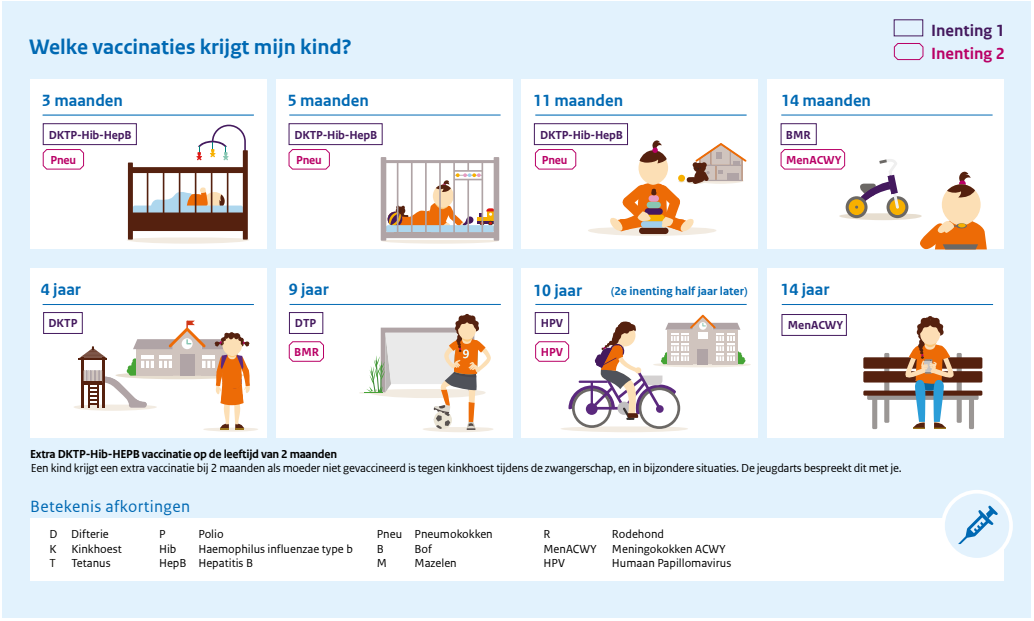
Following vaccination with bivalent COVID-19 vaccine, used for the repeat vaccination in the 2022 autumn round, Omicron Spike protein specific antibodies increased in all adults and children 5-17 years of age. Antibody levels were slightly higher in individuals with hybrid immunity.

There are smaller increases and more variability in T cell response in older adults compared to other adult age groups. The bivalent vaccine induced T cells that are highly cross-reactive against the Spike protein of the Omicron BA.1 and Omicron BA.4/5 variants.

Uitgebreide samenvatting

Huidige vaccinatieschema

Figuur 1 Nederlandse vaccinatieschema in 2022, inclusief universele HPV vaccinatie in het jaar waarin kinderen 10 jaar oud worden.



Bron: https://rijksvaccinatieprogramma.nl/document/vaccinatieschema-rijksvaccinatieprogramma

Vaccinatiegraad

De geregistreerde vaccinatiegraad, zoals bepaald en gerapporteerd in 2023, was ongeveer 2%-5% lager dan bepaald en gerapporteerd in 2022. Voor meerdere vaccinaties, waaronder die voor baby's, ligt de geregistreerde vaccinatiegraad nu onder de 90%, terwijl de WHO-doelstelling voor vaccinatiegraad hoger is; voor mazelen is dit bijvoorbeeld 95%.

Het RIVM weet niet precies hoeveel lager de vaccinatiegraad is. Dat komt doordat het sinds 1 januari 2022 de gegevens van een deel van de vaccinaties anoniem ontvangt (ongeveer 5% in totaal in 2022). Dat gebeurt als mensen geen toestemming geven om hun gegevens met het RIVM te delen. Anonieme vaccinaties kunnen niet worden meegeteld voor de vaccinatiegraad op zowel landelijk als regionaal niveau (omdat geboortejaar, geslacht, woonplaats en betreffende dosis van de gevaccineerde niet bekend zijn), waardoor deze lager wordt gerapporteerd dan hij daadwerkelijk is. Het aantal vaccinaties dat niet kan worden meegeteld voor dit rapport, is nu nog vrij klein. Het gaat namelijk met name om RVP-vaccinaties toegediend vóór 2022.

Acceptatie van vaccinaties

Uit onderzoek van het RIVM blijkt het volgende:
Uit een onderzoek naar de psychosociale factoren van vaccinatiegebruik, bleek dat de meeste ouders in 2022 positieve intentie, houding en vertrouwen hadden ten aanzien van vaccinatie, en het vaccineren van hun kind als vanzelfsprekend beschouwden. Er zijn echter aanwijzingen dat een iets groter deel van de ouders negatiever is geworden ten opzichte van het huidige RVP.

Uit gespreksanalytisch onderzoek blijkt dat als ouders, tijdens een vaccinatieconsult, worden uitgenodigd om vragen te stellen over een vaccin *voordat* ze een beslissing hebben genomen, er meer ruimte is voor kritische vragen.

Uit enquêtes over de HPV-vaccinatiecampagnes voor 10-18-jarigen en 19-26-jarigen blijkt dat de mediacampagnes geen invloed hadden op het waargenomen belang van HPV-vaccinatie, maar wel leidden tot een positieve ontwikkeling in de algemene houding tegenover en meer kennis over HPV-vaccinatie. Bovendien maken niet-gevaccineerde jongvolwassen vrouwen (19-26 jaar) zich zorgen over de veiligheid van vaccins en twijfelen ze aan de voordelen van het nog steeds gevaccineerd worden op hun leeftijd. Ook jongvolwassen mannen twijfelen aan het nut van vaccinatie, maar geven vooral aan er nog niet aan toe te zijn gekomen.

De helft van de ouders van dochters van 7 tot 10 jaar beschouwt HPV-vaccinatie en baarmoederhalskankerscreening als complementair aan elkaar. Van de andere helft ervoeren ouders met weinig vertrouwen in de screening de risico's van HPV en baarmoederhalskanker als hoger dan ouders met veel vertrouwen in de screening, en waren ze meer gemotiveerd om hun dochter te vaccineren. Mogelijke wijzigingen in het screeningsinterval lijken de besluitvorming van ouders met betrekking tot HPV-vaccinatie niet te beïnvloeden.

De vaccinatiebereidheid tegen COVID-19 in Nederland nam toe zodra het besluit om te laten vaccineren niet langer hypothetisch was (aan het eind van 2020, vlak voor de oorspronkelijke vaccinatiecampagne) maar realiteit was geworden (vlak na de start van de oorspronkelijke vaccinatiecampagne in 2021). Persoonlijke overtuigingen en sociale omgeving spelen een doorslaggevende rol in de uiteindelijke beslissing, die doorgaans wordt genomen op het moment dat de uitnodiging wordt ontvangen. Later in de vaccinatiecampagne, toen de COVID-19-pandemie zich in een andere fase bevond, veranderden de overtuigingen en nam de bereidheid af, wat resulteerde in een lagere vaccinatiebereidheid. Daarnaast gaven jongeren later in de vaccinatiecampagne vaker aan niet te weten of ze in aanmerking kwamen voor vaccinatie.

Ziektelast

De geschatte totale ziektelast veroorzaakt door ziekten die (deels) door vaccinatie te voorkomen zijn, was in 2022 het hoogst voor HPV (18.500 disability adjusted life years (DALYs); 74% voor vrouwen), invasieve pneumokokkenziekte (8.700 DALYs), rotavirusinfectie (1,500 DALYs), invasieve ziekte veroorzaakt door *Haemophilus influenzae* (1.500 DALYs) en invasieve meningokokkenziekte (560 DALYs). Voor de meeste ziekten die door vaccinatie te voorkomen

zijn, was de totale geschatte ziektelast in 2022 nog steeds iets lager dan de geschatte ziektelast in 2019, maar hoger dan tijdens de COVID-19 jaren 2020/2021 toen verschillende COVID-19-maatregelen (zoals afstand houden en handen wassen) van kracht waren. Recent is ook aanvullende vaccinatie van ouderen tegen pneumokokkenziekte en adolescenten tegen meningokokkenziekte ingevoerd. De ziektelast van invasieve *H. influenzae* type b was in 2022 nog steeds hoger dan in 2019, net als in 2021 en 2020.

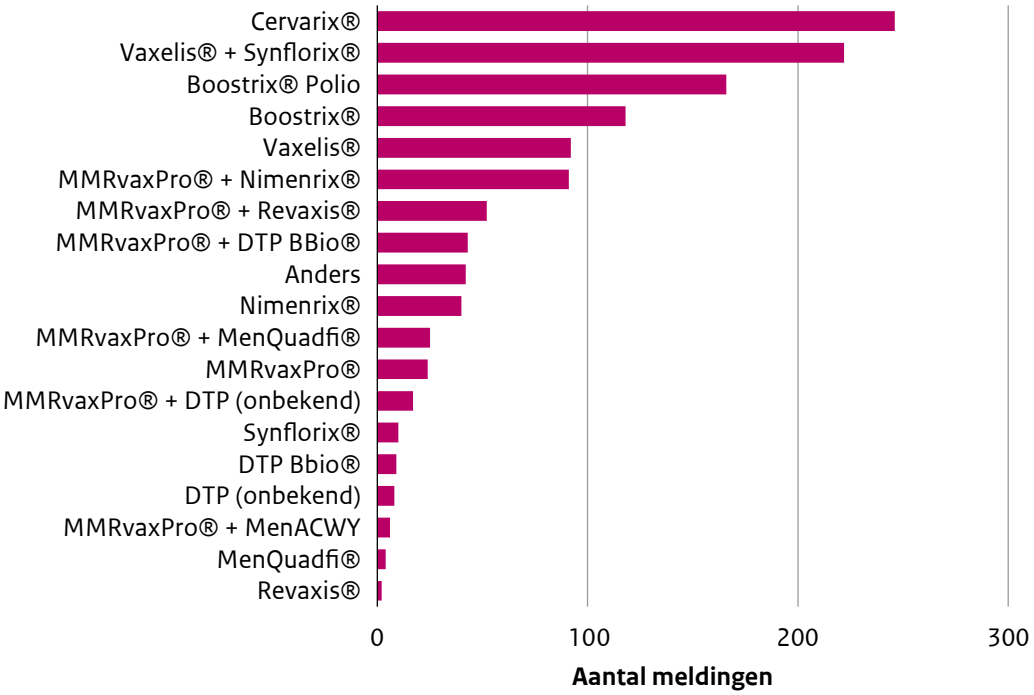
De ziektelast van COVID-19 wordt geschat op ten minste 93.800 DALYs voor 2022 (exclusief langetermijngevolgen van de ziekte). Dit is lager dan in 2021 (219.000 DALYs).

Bijwerkingen

In 2022 ontving Bijwerkingencentrum Lareb 1.217 meldingen van in totaal 4329 mogelijke bijwerkingen van vaccins. Dit aantal meldingen is lager dan het aantal ontvangen meldingen in eerdere jaren. Het aantal geregistreerde mogelijke bijwerkingen na vaccinatie per melding ligt tussen de 3 en 4. Dit is overeenkomstig met eerdere jaren.

Er werden geen nieuwe signalen van verontrustende bijwerkingen gevonden bij kinderen, adolescenten en zwangere vrouwen.

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



Bron: Lareb.

Huidig RVP

Difterie
In Nederland werden in 2022 zeven difteriegevallen gemeld, waarvan vijf minderjarige asielzoekers. In 2023, tot en met april, werden geen difteriegevallen gemeld. In 2022 t/m 21 april 2023, meldden acht EU/EEA landen (waaronder Nederland) en Zwitserland en het Verenigd Koninkrijk, samen 400 difteriegevallen bij asielzoekers.

***Haemophilus influenzae*-ziekte**
De stijging in invasieve Hib-ziekte die in 2020 en 2021 werd gezien en leidde tot een incidentie van 0,39/100.000 is in 2022 licht gedaald, naar een incidentie van 0,32 per 100.000 inwoners (n=59). De eerste 4 maanden van 2023 was het aantal gevallen vergelijkbaar met de jaren vóór COVID-19 (n=12). Bij kinderen jonger dan 5 jaar is de Hib-incidentie sinds 2012 gestaag gestegen, tot 3,3/100.000 (n=29) in 2022. Terwijl in 2020 en 2021 incidenties ook hoger waren voor oudere leeftijdsgroepen, waren deze in 2022 in het algemeen terug naar het niveau van vóór COVID-19. Van de 72 Hib-gevallen met informatie over de uitkomst van de ziekte stierven er in de periode tussen 2022 en april 2023 7 (1 voldoende gevaccineerd kindje van <5 jaar oud, 5 van 60+).

De vaccineffectiviteit (VE) tegen invasieve Hib ziekte werd voor de periode januari 2022-april 2023 geschat op 89% (95% BI 76-95; inclusie individuen van 3 maanden of ouder en geboren vanaf 1993). In januari 2020 vond er een schemawijziging plaats van 3+1 naar 2+1. Afhankelijk van de leeftijd tijdens het optreden van Hib ziekte, had geen van de gevallen die in de periode 2020 tot en met april 2023 met het 2+1-schema waren gevaccineerd kunnen worden voorkomen door vaccinatie met het oude 3+1 schema.

Na een daling als gevolg van de mitigatiemaatregelen tegen de COVID-19-pandemie is het aantal gevallen met invasieve ziekten veroorzaakt door niet-typeerbare *Haemophilus influenzae* (NTHi) en andere niet-b-serotypen in de periode 2022-april 2023 toegenomen tot een iets hogere incidentie dan vóór COVID-19.

Hepatitis B
Na een daling gedurende meer dan tien jaar, gevolgd door een sterkere daling in 2020 en 2021, steeg het aantal gemelde gevallen van chronische hepatitis B van 743 in 2021 naar 815 in 2022. Het gerapporteerde aantal acute hepatitis B-infecties bleef tussen 2021 en 2022 gelijk (n=80, 0,45 per 100.000), na een consistente daling sinds 2004. Van de 80 acute hepatitis B notificaties, waren er 3 in gevaccineerde personen. Deze personen waren gevaccineerd omdat ze tot een risicogroep behoorden.

Humaan Papillomavirus (HPV)-infectie
De incidentie van baarmoederhalskanker is in 2022 stabiel gebleven met 10,38 nieuwe diagnosis per 100.000 vrouwen (n=940) in 2022 ten opzichte van 10,41 nieuwe diagnoses per 100.000 vrouwen (n=948) in 2021. Het aantal sterfgevallen door baarmoederhalskanker bleef eveneens stabiel (n=223 ten opzichte van n=213 in 2021). De mortaliteit van mond-keelholtekanker en baarmoederhalskanker steeg licht in 2022.

De vaccineffectiviteit van het bivalente vaccin tegen persisterende infecties met de vaccintypen HPV 16 en 18 bleef hoog (>97%) tot twaalf jaar na vaccinatie met een drie-doses vaccinatieschema en tot acht jaar na een twee-doses vaccinatieschema (gevonden in prospectieve cohort-studies HAVANA en HAVANA2). In een immunogeniciteitsstudie werden hoge niveaus antilichamen tegen HPV-typen 16/18 waargenomen tot 96 maanden na de vaccinatie bij meisjes die twee doses van het bivalente vaccin ontvingen (HPV-2D studie). In een vergelijkbare studie onder jongens was de seropositiviteit van HPV-typen 16/18 zeven maanden na vaccinatie 100% bij jongens die twee doses van het vaccin kregen op 10-jarige leeftijd, terwijl de seropositiviteit voor de HPV-typen 31, 33, 45, 52 en 58 varieerde van 43% tot 100%.

Cervicale screening van vrouwen jonger dan 24 jaar (vóór de leeftijd van deelname aan het bevolkingsonderzoek baarmoederhalskanker) toonde een significant lagere prevalentie van laaggradige en hooggradige cervicale laesies en van hoog-risico HPV-typen aan bij volledig gevaccineerde vrouwen in vergelijking met niet-gevaccineerde vrouwen. In 2023 is een HPV-vaccinatie inhaalcampagne gestart voor jonge mannen en niet- of onvolledig gevaccineerde jonge vrouwen geboren in de periode 1996 t/m 2003.

Mazelen
In 2022 werden in Nederland zes gevallen van mazelen gemeld. Vijf van deze gevallen behoorden tot een cluster dat zich begin november voordeed. Begin 2023 overleed een meisje als gevolg van subacute scleroserende panencefalitis (SSPE), een zeldzame maar fatale neurologische stoornis die komt door een persistente mazelen infectie.

Meningokokkenziekte
De maatregelen tegen de COVID-19-pandemie vielen samen met een afname van invasieve meningokokkenziekte (IMD). Na het opheffen van alle maatregelen in maart 2022 steeg de incidentie weer: de IMD incidentie was 0,47 per 100.000 (n=78) in 2022. In de periode januari tot en met april 2023 werden al 59 IMD-gevallen gediagnosticeerd. De vaccin-serogroepen ACWY veroorzaakten in de periode 2022-april 2023 niet veel IMD: IMD-C en IMD-Y werden elk vier keer gediagnosticeerd, IMD-W kwam twee keer voor en er werd geen IMD-A gediagnosticeerd. Geen van de gevallen met IMD-ACWY was gevaccineerd met MenACWY.

In 2022 veroorzaakte serogroep B 88% van alle IMD-gevallen. De IMD-B-incidentie was 0,39 per 100.000 (n=68) in 2022, wat hoger is dan tijdens de COVID-19-jaren 2020-2021, maar iets lager dan in de pre-COVID-periode (gemiddeld 0,43 per 100.000 in 2015-2019). In januari-april 2023 werden al 54 IMD-B-gevallen gediagnosticeerd. Vier van de IMD gevallen waren overleden aan hun infectie in 2022 en vier in 2023, allen waren geïnfecteerd met serogroep B. Twee van hen in 2022 en twee in 2023 waren jonger dan 5 jaar. Over het geheel genomen werd voorspeld dat 71% van de IMD-B-isolaten tussen 2022 en januari 2023 gedekt zou zijn door 4CMenB en 89% door het MenB-fHbp-vaccin. De dekking verschilde enigszins per leeftijdsgroep.

Bof
Het aantal gerapporteerde gevallen van bof in 2022 was lager dan de aantal gerapporteerde gevallen voor de COVID-19 pandemie. In 2018 en 2019 was het aantal gerapporteerde gevallen, respectievelijk, 73 en 131, terwijl er in 2022 7 gevallen zijn gerapporteerd.

Kinkhoest
Het lage aantal kinkhoestmeldingen dat werd waargenomen na de invoering van de COVID-19-maatregelen in maart 2020, heeft zich in 2022 en in de eerste vier maanden van 2023 (eind van de observatieperiode voor dit hoofdstuk) doorgezet. In 2022 waren het totale aantal kinkhoestmeldingen en de incidentie, respectievelijk, 129 en 0,7 per 100.000, wat ongekend lage aantallen zijn in vergelijking met de afgelopen 25 jaar. Naast een afname van circulatie van *B. pertussis* door de COVID-19 maatregelen, kunnen ook andere oorzaken, zoals veranderd zorgzoekend gedrag, een deel van de daling van het aantal meldingen hebben veroorzaakt.

In 2022 en de eerste vier maanden van 2023 werden geen infecties met *B. pertussis* gemeld bij kinderen van 0 tot 3 maanden, zoals ook in 2021 het geval was. De VE tegen infectie met *B. pertussis* blijft daarom gebaseerd op acht gevallen die gemeld werden tussen april 2020 en december 2020 (74% (95% CI: -32 tot 96%)).

Pneumokokkenziekte
In het epidemiologische jaar 2021/2022 was de incidentie van invasieve pneumokokkenziekte (IPD) laag (9,4 per 100.000). Dit komt grotendeels door de COVID-19-beperkende maatregelen. Na het opheffen van alle maatregelen in maart 2022, steeg de incidentie naar 12,8 per 100.000 in 2022/2023; dit was nog iets lager is dan vóór COVID-19 (gemiddeld 15,0 per 100.000 per jaar in 2015-2019). Bij kinderen jonger dan 5 jaar steeg de incidentie in 2022/2023 tot het hoogste niveau in meer dan tien jaar (8,6 per 100.000; n=75), vooral vanwege een toename in serotype 19A IPD (44% van alle gevallen <5), welke wordt gedekt door PCV13/PCV15/PCV20, maar niet door PCV10.

In 2022/2023 waren er vier vaccinfalen voor bij kinderen: twee serotype 23F (na PCV7 en PCV10) en twee serotype 14-patiënten (na PCV10). Op een na waren allen bekend met onderliggend lijden. De vaccineffectiviteit van ten minste twee doses PCV10 werd geschat op 88% (95% BI: 67-96%).

De PCV13-serotypen die niet worden gedekt door PCV10 (serotypen 3, 6A en 19A), samen met serotype 6C (kruisbescherming van serotype 6A in PCV10) veroorzaakte 42% van alle IPD gevallen in 2022/2023. PCV15-serotypen + 6C veroorzaakten 57% en PCV20-serotypen + 6C 80%. Bij personen ≥65 jaar werd 80% van de IPD veroorzaakt door een serotype dat wordt gedekt door het 23-valente pneumokokken polysaccharidevaccin (PPV23). PCV15 en PCV20 (beide + 6C) veroorzaakten respectievelijk 57% en 77% van de gevallen. Sinds het najaar van 2020 wordt PPV23 aangeboden aan ouderen. De geschatte impact van PPV23 op vaccintype-IPD in deze leeftijdsgroepen varieerde tussen 43-57%, afhankelijk van de leeftijdsgroepen en de gebruikte methode.

Polio
In 2022 werd in Nederland een geval van asymptomatische poliovirusinfectie gemeld. Het betrof een medewerker van een vaccinproducent op het Utrecht Science Park in Bilthoven, die geen ziekteverschijnselen vertoonde omdat hij volledig was gevaccineerd tegen poliovirus. Daarnaast werd door de enterovirussurveillance aangetoond dat een kind dat onlangs in Moldavië was gevaccineerd met het bivalente orale poliovaccin, een Sabin 1-Sabin 3 recombinant virus uitscheidde. Het kind vertoonde geen tekenen van acute slappe verlamming. Rioolwatersurveillance heeft in 2022 opnieuw de afwezigheid van polioviruscirculatie in Nederland gedemonstreerd.

Rodehond
Sinds 2015 zijn er in Nederland geen nieuwe meldingen van rubella geweest.

Tetanus
In 2022 stierven twee vrouwen aan een tetanusinfectie. Beide vrouwen waren van oudere leeftijd, en waren daardoor niet vanuit het kindervaccinatieprogramma gevaccineerd tegen tetanus.

Het vaccinatieprogramma in Caribisch Nederland

Over het algemeen is de vaccinatiegraad in de Nederlandse overzeese gebiedsdelen, inclusief Caribisch Nederland (Bonaire, Sint-Eustatius en Saba), hoog. In 2022 werd op Sint Maarten één geval van invasieve pneumokokkenziekte gemeld. In Caribisch Nederland zijn geen andere ziekten gemeld die onder het RVP vallen.

Recente en aankomende wijzigingen in de immunisatieschema's in de Nederlandse overzeese gebiedsdelen omvatten de kinkhoestvaccinatie voor moeders (op Bonaire en Sint-Eustatius) en de daaruit voortvloeiende wijzigingen in de overeenkomstige kindervaccinaties, VZV-vaccinatie voor alle kinderen (Bonaire en Saba), MenACWY-vaccinatie voor alle kinderen (Bonaire), en HPV-vaccinatie voor jongens (Bonaire en Saba).

Potentiële RVP-kandidaten

Hepatitis A
Er werden in 2022 93 hepatitis A gevallen gerapporteerd, wat overeenkomt met 0,5 gevallen per 100.000 inwoners. Dit is het tweede jaar sinds de lage aantallen in 2020 (n=50 gevallen) dat er sprake is van een stijging. De meeste infecties werden in de leeftijdsgroep 20-49 jaar gezien. Het percentage reisgerelateerde gevallen was 35%, wat nog maar iets onder de percentages van voor corona is (2013-2019; gemiddeld: 41%) ten opzichte van 2020 (18%) en 2021 (21%). Azië, Afrika en Europa werden ongeveer evenveel genoemd door de patiënten die de infectie in het buitenland hadden opgelopen.

Respiratoir syncytieel virus (RSV)-infectie
Sinds de zomer van 2021 circuleerde voor een jaar lang continue het RS-virus in Nederland. Het aantal laboratorium meldingen en opnames daalde aan het einde van de zomer in 2022, maar begon in de herfst weer te stijgen. Het absolute aantal laboratorium detecties, gemeld door de laboratoria van de virologische weekstaten, was veel hoger dan in voorgaande seizoenen, maar voor de interpretatie van deze aantallen is voorzichtigheid geboden, omdat het testbeleid in veranderd kan zijn. De timing van de piek van het aantal RSV detecties, in week 52 van 2022 was vergelijkbaar met de seizoenen vóór de COVID-19 pandemie. Na de piek daalde het aantal meldingen sterk in de weken 2-5 van 2023 en daalde daarna gestaag door tot een laag niveau in april en mei 2023.

Het aantal kinderen <2 jaar dat in het ziekenhuis werd opgenomen met een RSV-bronchiolitis volgde hetzelfde patroon als dat van de virologische weekstaten. Het aantal opnames in de piek (n=100) lag in de winter van 2022/2023 in 33 ziekenhuizen lager dan in de zomerpiek van 2022 (n=163.

Rotavirusinfectie
Het rotavirusseizoen van 2022 had een vroege start in oktober 2021 in plaats van (zoals gebruikelijk) in februari. Dit is waarschijnlijk het gevolg van een toename van het aantal kinderen dat gevoelig is voor rotavirus door uitblijven van een rotavirus seizoen in 2020 en een mild seizoen in 2021. Het jaarlijks aantal rotavirus detecties in 2022 was hierdoor hoger dan vóór de COVID-19 pandemie: 1,391 in 2022, vergeleken met gemiddeld 981 detecties in 2016-2019 (range: 682-1054). Genotype G3P8 was het meest prevalente genotype in 2022, in tegenstelling tot voorgaande jaren waarin G9P8 het meest voorkomend was. In 2024 zal universele rotavirusvaccinatie worden toegevoegd aan het RVP.

Varicella zoster virus (VZV)-infectie (waterpokken en gordelroos)
De epidemiologie van gordelroos (huisartsenbezoeken, ziekenhuisopnames en sterfgevallen) in Nederland in 2021 was vergelijkbaar met voorgaande jaren; huisartsen rapporteerden ongeveer 94.000 gordelroosepisodes (540 episodes per 100.000 inwoners).

Voor waterpokken was de incidentie van huisartsenbezoeken en ziekenhuisopnames in 2021 nog steeds lager dan voor 2020 maar iets hoger dan in 2020; huisartsen rapporteerden ongeveer 33.000 waterpokkenepisodes (190 episodes per 100.000 inwoners). Dit heeft waarschijnlijk te maken met de COVID-19-maatregelen die ook de overdracht van VZV hebben verminderd.

COVID-19

Epidemiologie
Een beschrijving van de epidemiologische ontwikkelingen van afgelopen winter in Nederland (week 21 2022 t/m week 20 2023) vindt u in het jaarlijkse rapport over surveillance van acute luchtweginfecties in Nederland: winter 2022/2023 (zie deze link). Wat het Nederlandse Caribisch gebied betreft, rapporteerden Saba en Sint-Eustatius begin 2023 een toename van het aantal gevallen, hoewel het aantal COVID-19-gerelateerde sterfgevallen laag bleef.

Vaccinatiecampagnes
Begin 2022 liep de eerste boostercampagne nog, nadat deze in november 2021 was gestart. Tijdens deze campagne werden boostervaccinaties aangeboden aan iedereen van 12 jaar en ouder. In 2022 waren er twee nieuwe vaccinatiecampagnes (zowel in Europees als Caribisch Nederland): de herhaalvaccinatie (tweede booster) voor volwassenen van 60 jaar en ouder en zorgpersoneel, en de herhaalvaccinatie in de najaarsronde waren beschikbaar voor iedereen van 12 jaar en ouder.

Vaccinatiegraad
Tot week 21 2023 was de vaccinatiegraad tegen COVID-19 voor 60-plussers 85,3% voor de boostercampagne 2021/2022, 67,2% voor de herhaalde voorjaarsvaccinatie in 2022, en 60,2% voor de najaarsronde in 2022. De vaccinatiegraad tegen COVID-19 was hoger onder oudere leeftijdsgroepen dan onder jongere leeftijdsgroepen. Op gemeentelijk niveau is een patroon te zien met een lagere dekking in de Bible Belt en in Noord-Nederland dan in het zuiden. Dit patroon is in alle vaccinatierondes gezien. In het Caribische deel van het Koninkrijk der Nederlanden varieerde de vaccinatiegraad voor de boostercampagne in week 21 van 2023 voor 60-plussers tussen 15% op Sint Maarten en 91% op Saba. Voor de najaarscampagne in 2022 varieerde dit van <5% op Sint Maarten en Sint Eustatius tot 31% op Saba.

Effecten van vaccinatie
In de periode februari-april 2023 was het risico op ziekenhuisopname bij personen van 60 jaar of ouder die een bivalente (Omicron BA.1) boostervaccinatie kregen 43% lager dan bij personen die ten minste één COVID-19-vaccinatie kregen, maar niet een bivalente vaccinatie. Voor IC-opname was dit 36%. Sinds oktober 2022 is de relatieve risicoreductie na boostervaccinatie met een bivalent vaccin in de loop van de tijd afgenomen.

De geschatte VE tegen COVID-19-sterfte tussen januari 2021 en januari 2022 was voor alle leeftijdsgroepen >90% kort na de primaire reeks en >85% kort na de eerste boostervaccinatie.

Tussen 26 september en 19 december 2022 bedroeg de relatieve effectiviteit van de bivalente (Omicron BA.1) boostervaccinatie tegen zelfgerapporteerde Omicron SARS-CoV-2-infectie 31% bij 18-59-jarigen en 14% bij 60-85-jarigen. Hybride immuniteit bood meer bescherming tegen een daaropvolgende Omicron-infectie dan vaccin-geïnduceerde of infectie-geïnduceerde immuniteit.

In tegenstelling tot sommige andere onderzoeken vonden twee prospectieve cohortstudies van het RIVM (LongCOVID en VASCO) geen bewijs van enig effect van boostervaccinatie tegen langdurige symptomen of vermoeidheid na SARS-CoV-2-infecties, vergeleken met primaire vaccinatie of geen vaccinatie.

Seroepidemiologie
De infectie-geïnduceerde seroprevalentie onder de Nederlandse bevolking (beoordeeld in de PIENTER Corona (PICO-studie)) steeg van 26% in november 2021 naar 62% in maart 2022 na de opkomst van Omicron, terwijl de totale seroprevalentie (d.w.z., inclusief vaccin-

geïnduceerde antilichamen) steeg van 87% naar 96% en daarna hoog bleef. Er werd een relatief snelle toename van infectie-geïnduceerde seroprevalentie waargenomen bij personen jonger dan 60 jaar, hetgeen ook tot uiting kwam in een groot aantal doorbraakinfecties onder gevaccineerde personen. Als gevolg van de versoepeling van de controlemaatregelen in 2022 is de totale infectie-geïnduceerde seroprevalentie in november 2022 gestegen tot 86%. Op dat moment had de meerderheid van de bevolking hybride immuniteit verworven. Slechts een klein deel van de oudste leeftijdsgroepen was nog niet eerder besmet geweest.

Binnen de PICO-studie in juni 2022 was 93% positief voor respiratoire mucosale piek S1 IgG, terwijl 24% positief was voor IgA. Gevaccineerde deelnemers (voornamelijk ouder dan 11 jaar) met een bekende infectiegeschiedenis hadden significant hogere prevalentie en niveaus van mucosaal IgG en vooral IgA, vergeleken met deelnemers die nog geen eerdere infectie hadden doorgemaakt. Hogere niveaus, vooral van IgA, verminderden de kans op infectie binnen de volgende zes maanden.

Bijna alle deelnemers aan de landelijke VASCO-studie waren anti-S1 IgG seropositief na de primaire serie en de eerste booster, en na de tweede booster allemaal. De vroege respons na de primaire reeks varieerde aanzienlijk tussen de vaccinproducten, met de hoogste concentraties bij zowel ontvangers van Spikevax als bij degenen met een eerdere infectie, al waren de concentraties lager in de leeftijdsgroep van 60-85 jaar en in de medische risicogroep voor zowel Comirnaty and Spikevax. De verschillen tussen vaccins in de vroege respons namen af na de eerste booster en verdwenen volledig na de tweede booster. De afname was in het algemeen langzamer in de oudere leeftijdsgroep na de eerste booster, en werd na de eerste of tweede booster niet beïnvloed door medisch risico.

Immunogeniciteit
Uit gegevens van de coronavaccinatieproeven (CVT's) van het RIVM bij thuiswonende personen, blijkt dat de meeste infectie-naïeve ouderen na de primaire reeks een SARS-CoV-2-specifieke IgG-antilichaamreactie vertonen die lager is dan bij jongere volwassen leeftijdsgroepen. Ook zijn bij oudere volwassenen de T-celreacties lager en vertonen ze meer variabiliteit vergeleken met andere volwassen leeftijdsgroepen. Bij zowel geïnfecteerde als niet-geïnfecteerde personen resulteren boosterdoses in een aanvankelijke stijging van de antilichaamniveaus, gevolgd door een daling van de antilichamen, maar deze afname van antilichaamniveaus is langzamer wanneer een persoon vóór de vaccinatie geïnfecteerd is geweest.

Oudere volwassenen en specifieke groepen immuungecompromitteerde patiënten hebben de eerste boosterdosis nodig om antilichaamniveaus te bereiken die vergelijkbaar zijn met de niveaus die bij jongere volwassenen worden bereikt. Bij bewoners van verpleeghuizen werden solide antilichaamreacties waargenomen na boostervaccinaties, hoewel hun antilichaamreacties iets lager waren dan bij thuiswonende oudere volwassenen.

Na vaccinatie met het bivalente COVID-19-vaccin, gebruikt voor de herhaalde vaccinatie in de najaarsronde van 2022, namen eiwitspecifieke antilichamen van Omicron Spike toe bij alle volwassenen en kinderen van 5-17 jaar. De antilichaamniveaus waren iets hoger bij personen met hybride immuniteit.

Er zijn kleinere stijgingen en meer variabiliteit in de T-celrespons bij oudere volwassenen vergeleken met andere volwassen leeftijdsgroepen. Het bivalente vaccin induceerde T-cellen die zeer kruisreactief zijn tegen het Spike-eiwit van de varianten Omicron BA.1 en Omicron BA.4/5.

1
Introduction

1.1 NIP vaccination schedule

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

The vaccination schedule presented in Figure 1.1 is the routine schedule offered to all children in 2023. In this schedule, DTaP-IPV-Hib-HBV vaccinations are offered at 3, 5, and 11 months. However, children whose mother did not receive a maternal Tdap vaccination at a sufficiently early moment during her pregnancy, and children who had a low birth weight or were born prematurely (before 37 weeks gestation), receive an additional DTaP-IPV-Hib-HBV vaccination at the age of 2 months. Additionally, new-borns to HBsAg-positive mothers are given an HBV vaccination and HBV immunoglobulin, preferably within two hours after birth, but 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 seekers' children receive additional NIP vaccinations to provide them with long-term immunity against NIP target diseases. The youth healthcare physician assesses their vaccination status and offers a personalised vaccination schedule, including an HBV vaccination series. Furthermore, all asylum seekers' infant children are offered an additional MMRo dose at 9 months of age.

Lastly, while Ukrainians who settle in the Netherlands after fleeing the war in Ukraine are not registered as refugees, all Ukrainian children aged 6 to 12 months are offered the additional MMRo vaccine. This is due to a pre-COVID-19 measles outbreak in Ukraine.

1.1.1 Recent changes in the vaccination schedule

In 2022, HPV vaccination was added to the boys' vaccination schedule, and the age at which children are offered HPV vaccination was lowered to the calendar year in which they turn 10. Simultaneously, a catch-up campaign was launched to offer HPV vaccination to all children and adolescents aged 10-18 in 2022 and 2023. At the start of 2023, the catch-up opportunity for HPV vaccination was extended to all adults aged 18-26.

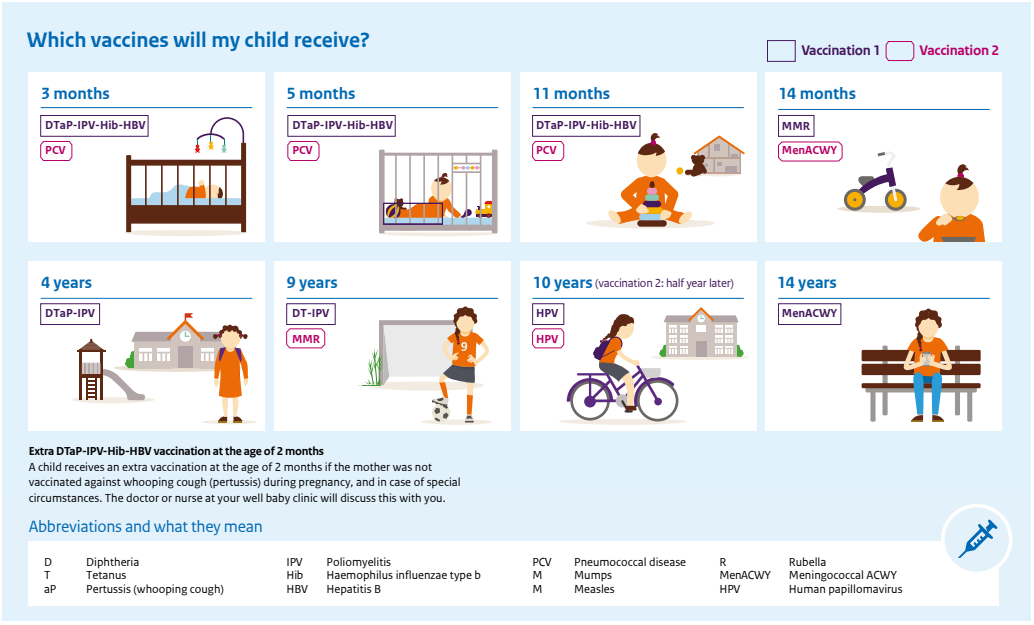
1.1.2 Number of vaccinated children and pregnant women

In 2022, the vaccination schedule consisted of fourteen vaccine doses per child. Of these doses, seven were offered between the ages of 0 and 11 months.

In 2022, at least 1,041,632 children and 114,839 pregnant women were immunised under the Dutch NIP. In total, the children received at least 2,619,654 vaccine doses, while the pregnant women received a total of at least 114,839 vaccine doses: one Tdap vaccine each.

The numbers of vaccinated children and pregnant women, as well as the number of vaccine doses may be higher. The informed consent procedure makes it impossible to know if vaccinations that were registered under the condition of anonymity were offered within the context of the NIP or not.

Figure 1.1 The NIP vaccination schedule in 2023, including universal HPV vaccination in the year children turn 10 years old.



Source: https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-english

1.2 New recommendations and decisions

1.2.1 Rotavirus vaccination

On 23 May 2022, the State Secretary of Health, Welfare and Sport (HWS) decided that vaccination against rotavirus would not be added to the Dutch NIP on the short term due to a lack of available funds [1]. However, on 20 September 2022, the State Secretary amended this decision because financial coverage had been found, adding universal rotavirus vaccination to the Dutch NIP from 2024 onwards [2].

1.2.2 Influenza vaccination

In September 2021, the then State Secretary of HWS decided that in 2021, the influenza vaccine would be available free of charge to the newly defined risk groups, including all pregnant women, as per the Health Council's advice [3]. Due to the short time frame until the start of the

flu season, these new groups could not be actively invited for vaccination in 2021. Instead, they could directly contact their GP to make an appointment.

On 23 May 2022, the new State Secretary of HWS announced that the new risk groups would remain eligible for free influenza vaccination [1]. Because pregnant women are not registered as such at their GP, they will be offered (from 2023 onwards) the influenza vaccine through a cooperation between their obstetric care provider (who informs them of the vaccination) and the Youth Healthcare in their municipality (which administers the vaccine).

1.2.3 Herpes Zoster vaccination

Regarding herpes zoster vaccination for adults aged 60 and over, the State Secretary of HWS published an update on 19 May 2022, indicating his wish to offer this vaccination, provided it can be done cost-effectively and financial coverage can be found [4]. The financial coverage has not yet been found.

1.2.4 HPV vaccination

On 30 August 2022, the Health Council of the Netherlands (HC) issued a renewed advice on the recommended dosage schedules for HPV vaccination [5]. The reason to do so were new scientific insights that had also led the United Kingdom's Joint Committee on Vaccination and Immunisation (JVCI) and the World Health Organization (WHO) to change their stance on this subject. The HC recommended decreasing the number of doses for people aged 15 and over from three to two, with an interval of six months. The HC judged that, as of then, there was inadequate proof to support a further decrease of the number of doses for children under the age of 15. Their schedule was maintained at two doses, also with an interval of six months.

On 30 August 2022, the State Secretary of HWS decided to decrease the number of HPV vaccine doses for people aged 15 and over from three to two, with an interval of 6 months, and to maintain the schedule for children under 15 years of age (also two doses with an interval of 6 months) [6].

1.2.5 NIP vaccination schedule

On 7 September 2022, the HC advised to move four vaccinations to another age group, and replace one of them by another combination vaccine [7] (based on an extensive report with an overview of all pertinent data and insights [8]). The DTaP-IPB-Hib-HBV vaccine at 11 months could be best moved to the age of 12 months, the DTaP-IPV vaccine at age 4 should be swapped for a DTaP vaccine at age 5 or 6, the MMR-2 vaccine offered at age 9 could best be offered between age 2 and 4, and the DT-IPV vaccine offered at age 9 could best be offered at age 14.
On 28 April 2023, the ministry of HWS approved the advised changes to the NIP [9]. The aim is to implement the new NIP schedule from January 2025 onwards.

1.2.6 Meningococcal type B vaccination

On 12 October 2022, the HC advised to not yet offer vaccination against meningococcal disease caused by serotype B to either young children or adolescents [10]. This advice was

based on the fact that there are few disease cases among young children, while the currently available vaccines cause relatively many temporary side effects and are not cost-effective. Among adolescents, there are even fewer disease cases, on top of which it is unclear how long the vaccine would protect them. Furthermore, the vaccine does not induce herd immunity. Reasons for re-evaluation would be an increase in disease cases, or the availability of new vaccines. Additionally, the epidemiological situation is closely monitored.

1.2.7 Pneumococcal vaccination for children

On 20 June 2023, the Health Council advised which pneumococcal vaccine was most appropriate to use for the protection of children [11]. To protect children against the pneumococcal types that currently cause most invasive pneumococcal disease cases, the Health Council advised to offer children either the 13- or the 15-valent vaccine instead of the current PCV-10 vaccine. Once the new PCV-20 vaccine has been approved for children, a re-assessment will be made that includes this vaccine.

1.3 Vaccinations for risk groups

Influenza vaccination is offered through the National Influenza Prevention Programme (NPG) to individuals aged 60 years and over and to those with an increased risk of morbidity and mortality following influenza. Vaccination against tuberculosis is offered to children of immigrants from high-prevalence countries. For developments regarding influenza and tuberculosis, please refer to the reports issued by the Centre for Infectious Disease Control (CIb), the HC, and the KNCV Tuberculosis Foundation [12-15].

On top of the addition of HBV vaccination to the NIP, the Netherlands has an additional vaccination programme in place that targets groups particularly at risk of HBV due to their sexual behaviour, namely men who have sex with men (MSM) and sex workers [16].

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

1.3.1 Mpox outbreak response

Because of the 2022 worldwide mpox outbreak (previously monkeypox), a pre-exposure prophylaxis (PrEP) vaccination campaign was started in July 2022, predominantly among MSM. Specific populations were invited for this campaign, particularly MSM and transgender persons with a lifestyle that puts them at high risk for an mpox infection. Further information about the outbreak and the vaccination campaign can be found in the report 'Sexually transmitted infections in the Netherlands in 2022'.

Additionally, a similar PrEP vaccination campaign was carried out on the Dutch Caribbean islands. High risk populations were invited for vaccination, mainly MSM and HIV positive residents. In total, around 147 residents received at least one dose of the PrEP vaccine, and the campaign ended on 1 March, 2023, after the Carnaval season.

1.4 Vaccination outside of public vaccination programmes

A number of registered vaccines in the Netherlands are available to the public outside of vaccination programmes. Vaccinations registered for infants are those against gastroenteritis caused by rotavirus infection, VZV, and meningococcal B disease (MenB). For both older children and adults, vaccination against influenza, MenACWY and pertussis is available. Specifically for adults, 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 an HAV vaccine simultaneously with their HBV vaccine. They will then receive a discount on the HAV component.

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

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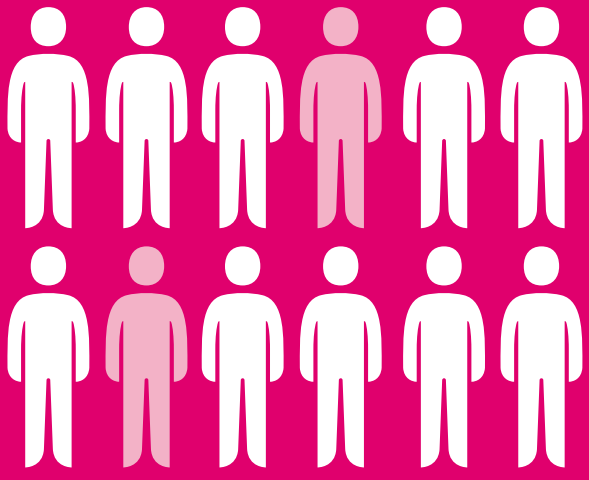
2
Vaccination coverage



M. Knijff, E.A. van Lier

2.1 Key points

- The registered vaccination coverage, as determined and reported in 2023, was approximately 2%-5% lower than last year. For multiple vaccinations, including those for babies, the registered coverage is now below 90%, while the WHO target for (for instance) measles is 95%.
- RIVM is unable to determine precisely how much lower the vaccination coverage is, due to the implementation of an informed consent for data exchange with RIVM in January 2022. As a result, RIVM receives part of the NIP vaccinations anonymously (approximately 5% overall in 2022). Anonymous vaccinations cannot be counted towards the vaccination coverage (because the year of birth, sex, place of residence and the involved dose of the vaccinated person are unknown), so the coverage is reported to be lower than it actually is. The number of vaccinations that cannot be counted for this report is still quite small because it mainly covers NIP vaccinations administered before 2022.

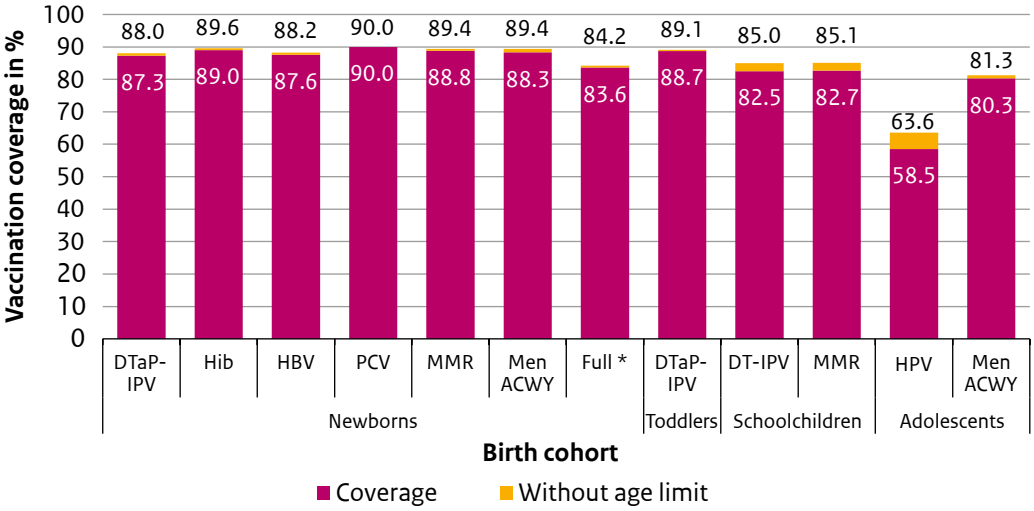
2.2 Tables and figures

Table 2.1 Vaccination coverage (%) per vaccine for age cohorts of new-borns, toddlers, schoolchildren and adolescents in 2006-2023 [1].

	New-borns*								Toddlers*				Schoolchildren*			Adolescent girls*		Adolescents*	
Reporting year	*Cohort*	DTaP -IPV	Hib	HBV [a]	PCV **	MMR	MenC/ ACWY	Full ***	*Cohort*	DTaP -IPV[b]	DTaP -IPV[c]	DTaP -IPV[d]	*Cohort*	DT -IPV	MMR ****	*Cohort*	HPV	*Cohort*	Men ACWY
2006	*2003*	94.3	95.4	15.2	-	95.4	94.8		*2000*	92.5	1.4	93.9	*1995*	93.0	92.9				
2007	*2004*	94.0	95.0	17.1	-	95.9	95.6		*2001*	92.1	1.6	93.7	*1996*	92.5	92.5				
2008	*2005*	94.5	95.1	17.9	-	96.0	95.9		*2002*	91.5	1.6	93.1	*1997*	92.6	92.5				
2009	*2006*	95.2	95.9	18.6	94.4	96.2	96.0		*2003*	91.9	2.0	93.9	*1998*	93.5	93.0				
2010	*2007*	95.0	95.6	19.3	94.4	96.2	96.1		*2004*	91.7	2.6	94.3	*1999*	93.4	93.1				
2011	*2008*	95.4	96.0	19.4	94.8	95.9	95.9		*2005*	92.0	2.6	94.7	*2000*	92.2	92.1				
2012	*2009*	95.4	96.0	19.5	94.8	95.9	95.9		*2006*	92.3	2.1	94.4	*2001*	93.0	92.6	*1997*	56.0		
2013	*2010*	95.5	96.1	19.7	95.1	96.1	96.0		*2007*	92.3	2.4	94.7	*2002*	93.1	92.9	*1998*	58.1		
2014	*2011*	95.4	95.9	51.4	95.0	96.0	95.8		*2008*	92.0	2.4	94.4	*2003*	92.7	92.4	*1999*	58.9		
2015	*2012*	94.8	95.4	94.5	94.4	95.5	95.3		*2009*	91.9	2.2	94.1	*2004*	92.7	92.7	*2000*	61.0		
2016	*2013*	94.2	94.9	93.8	93.8	94.8	94.6		*2010*	91.5	2.1	93.7	*2005*	92.0	92.0	*2001*	61.0		
2017	*2014*	93.5	94.2	93.1	93.6	93.8	93.5	91.2	*2011*	91.1	2.1	93.2	*2006*	90.8	90.9	*2002*	53.4		
2018	*2015*	92.6	93.4	92.2	92.8	92.9	92.6	90.2	*2012*	90.4	2.3	92.7	*2007*	90.0	90.1	*2003*	45.5		
2019	*2016*	92.4	93.1	92.0	92.6	92.9	92.6	90.2	*2013*	90.3	2.2	92.5	*2008*	89.5	89.5	*2004*	45.5		
2020	*2017*	92.6	93.5	92.3	93.0	93.6	93.2	90.8	*2014*	89.9	2.4	92.2	*2009*	89.7	89.7	*2005*	53.0		
2021	*2018*	93.1	93.8	93.0	93.3	93.6	93.3	91.3 (91.9)	*2015*	89.4	2.6	92.0	*2010*	88.9 (91.9)	89.0 (91.9)	*2006*	63.1 (68.0)		
2022	*2019*	92.2 (92.7)#	92.9 (93.3)#	92.2 (92.7)#	92.5 (92.6)#	92.3 (92.7)#	92.0 (92.8)#	90.1 (90.6)#	*2016*	88.5 (89.0)#	2.3	90.8 (91.2)#	*2011*	86.3 (89.7)#	86.4 (89.7)#	*2007*	47.6 (66.4)#	*2006*	84.3 (85.3)#
2023	***2020***	**87.3# (88.0)#**	**89.0# (89.6)#**	**87.6# (88.2)#**	**90.0# (90.0)#**	**88.8# (89.4)#**	**88.3# (89.4)#**	**83.6# (84.2)#**	***2017***	**86.6# (87.1)#**	**2.1#**	**88.7# (89.1)#**	***2012***	**82.5# (85.0)#**	**82.7# (85.1)#**	***2008***	**58.5# (63.6)#**	***2007***	**80.3# (81.3)#**

** Vaccination coverage is assessed at the ages of 2 (new-borns), 5 (toddlers), 10 (schoolchildren), 14 (adolescent girls), and 15 years (adolescents).*
In grey: vaccination coverage including vaccinations given later (reporting year 2021: situation on 2 March 2021, reporting year 2022: situation on 3 March 2022, reporting year 2023: situation on 7 March 2023).
*** Only for new-borns born on or after 1 April 2006.*
**** Key figure for full participation of new-borns: those who received all NIP vaccinations at 2 years of age.*
***** Two MMR vaccinations (in the past 'at least one MMR vaccination' was reported).*
 # The informed consent affects these figures (excluding anonymous vaccinations; underreporting of the actual vaccination coverage). The effect is still limited because it concerns children who largely reached the recommended vaccination age before 1 January 2022.
[a] Percentage for the total cohort. Universal hepatitis B vaccination was introduced in 2011; only risk groups were vaccinated previously.
[b] Revaccinated toddlers.
[c] Toddlers that reached basic immunity at 2–5 years of age were not eligible for revaccination at toddler age.
[d] Sufficiently protected toddlers (sum of [b] and [c]).
Source: Præventis

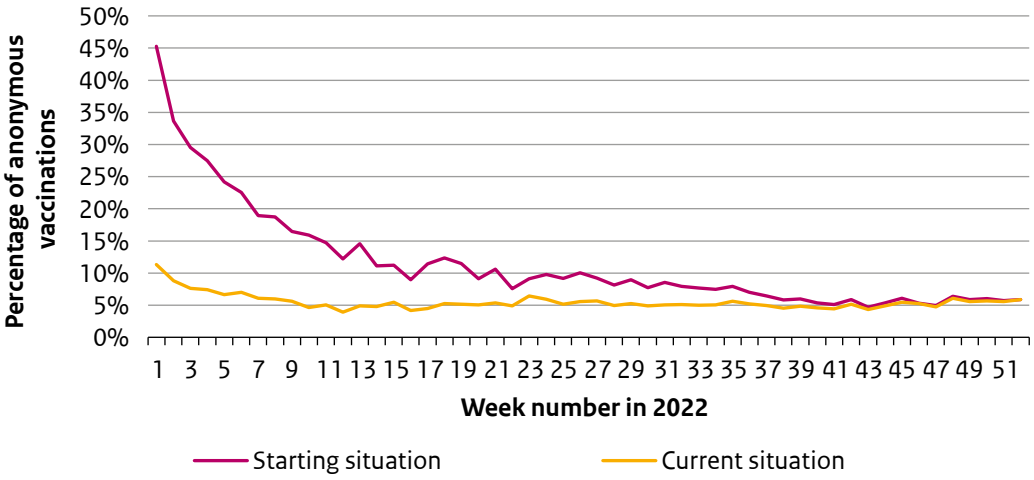
Figure 2.1 Vaccination coverage (%) per vaccination and birth cohort (based on individually registered vaccinations, excluding anonymous vaccinations); determined at 2 years of age (new-borns, born in 2020), 5 years of age (toddlers, born in 2017), 10 years of age (schoolchildren, born in 2012), 14 years of age (HPV: adolescent girls, born in 2008) and 15 years of age (MenACWY: adolescents, born in 2007); in yellow: including vaccinations given later [1].



Meaning of abbreviations: DT(aP)-IPV = diphtheria, tetanus, pertussis, poliomyelitis, Hib = Haemophilus influenzae type b disease, HBV = hepatitis B, PCV = pneumococcal disease, MMR = mumps, measles, rubella, MenACWY = meningococcal ACWY disease, HPV = human papillomavirus infection.

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

Figure 2.2 Development of the percentage of anonymous vaccinations in 2022 by week [1].



2.3 National developments

The registered vaccination coverage, as determined and reported in 2023, was approximately 2%-5% lower than last year (Table 2.1). For multiple vaccinations, including those for babies, the registered coverage is now below 90%, while the WHO target for measles is 95% (Figure 2.1).

Exact figures on the extent of the decrease in vaccination coverage cannot be provided. This is because data on some of the vaccinations has been anonymised since 1 January 2022. This happens when people do not give permission to share their data with RIVM. Anonymous vaccinations cannot be counted towards the vaccination coverage (because the year of birth, sex, place of residence and the involved dose of the vaccinated person are unknown), so the coverage is reported to be lower than it actually is. At the moment, the number of vaccinations that cannot be counted is still quite small, as the reported figures mainly concern children who received their NIP vaccinations before 2022.

In 2022, approximately 5% of all NIP vaccinations were submitted anonymously (Figure 2.2); this is lower than the preliminary 12% that was reported last year. The percentage decreased from 45% in the first week of January to about 5% at the end of 2022. The percentage of anonymous vaccinations also decreased retrospectively. If informed consent is registered at a later date, previously administered vaccinations are still passed on to RIVM, together with personal data. For example, the percentage of anonymous vaccinations for week 1, 2022 has decreased from 45% to 11%. The proportion of anonymous vaccination does not only differ over time, but also per youth health care organisation (ranging from 1% to 29%) and vaccine type (ranging from 3% to 14%).

On the basis of individually registered vaccinations, an estimated percentage of at least 64% of pregnant women with a child born in 2022 took part in the 22-week vaccination that protects babies from whooping cough from birth. As this mainly concerns vaccinations administered in 2022, the impact of the informed consent is greater than for other vaccinations; 13.7% of maternal pertussis vaccinations were registered anonymously. Because this also includes vaccinations administered to mothers of children born in 2023, this percentage cannot be added completely to the aforementioned 64%. Last year, a participation of 66% was reported for mothers of children born in 2021. However, data from three municipal health service (GGD) regions (Amsterdam, Rotterdam-Rijnmond and Limburg-Noord) was not yet complete at that time. Based on additional data, last year's participation is estimated to be 71%.

2.4 International developments

Last year, routine immunisation in the World Health Organization (WHO) European Region was reported to prevent further COVID-19 backsliding in 2021 but fell short of full recovery [2]. This year, although the WHO reported that the European Region achieved high routine immunisation coverage in 2022, it fell short of pre-pandemic levels once again. The WHO European Region achieved 94% average coverage with 3 doses of the diphtheria, tetanus and pertussis vaccine (DTP3) and 93% average coverage with the first dose of measles-containing

vaccine (MCV1) in 2022. While this reflects extensive efforts made by health authorities to recover from declines in routine immunisation coverage experienced during the COVID-19 pandemic, it also indicates uneven success among countries in the European Region [3]. Globally, childhood immunisation was reported to begin recovery after the immunisation backslide caused by the COVID-19 pandemic. The percentage of children who received the DTP3 vaccine was 84% in 2022 compared to 81% in 2021. Despite this improvement, this remains lower than the 86% average coverage reported in 2019 before pandemic-related disruptions, underscoring the need for ongoing catch-up, recovery and system strengthening efforts [4].

The European Immunisation Agenda 2030 outlines the need to achieve 95% coverage for both DTP3 and MCV1 [5]. After a period of low detection in 2021, measles cases have been increasing in the WHO European Region since the beginning of 2022 [6]. By the end of February 2023, the number of reported measles cases already exceeded the number reported for all of 2022 [7]. In the Netherlands, six measles cases were reported in 2022 (see Chapter 6.5). According to the WHO and United Nations Children's Fund (UNICEF), the risk for large outbreaks increased due to relaxation of social distancing practices and other preventive measures implemented during the pandemic as well as to pandemic-related disruptions of routine immunisation. As measles is very contagious, cases tend to rise quickly when vaccination levels decline [8]. Therefore, measles can be an early signal of the presence of immunity gaps. The European Region has also seen increases in other vaccine-preventable diseases following the lifting of public health and social measures necessitated by the pandemic, such as diphtheria and polioviruses [3].

2.5 Literature

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* *RIVM publication.*

3
Acceptance of vaccination

A.J.M. Pluijmaekers, M. de Vries, M. Knijff, E.A. van Lier, S. Teelen, G.A.H. Jol, T.C. van Charldorp, M. Lambooij, M. Rolink

3.1 Key points

Studies performed at RIVM and within the Netherlands have found the following:

- In 2022, a repeated vaccine acceptance survey showed that most parents had positive intentions, attitudes and trust towards vaccination and perceived vaccinating their children to be self-evident. However, there are indications that a somewhat larger proportion of parents have become negative towards the current NIP. This may explain the slight decline in NIP vaccine uptake since the COVID-19 pandemic.
- Results of a conversation analytic study reveal that if, during a vaccination consultation, parents are invited to ask questions about a vaccine before they make a decision, there is more room for critical questions; asking critical questions after the decision would undermine a parent's identity of being a good parent who makes informed decisions.
- Surveys about the HPV vaccination campaigns for 10-18-year-olds and 19-26-year-olds show that the media campaigns did not influence the perceived importance of HPV vaccination, but did lead to a positive development in the overall attitude towards and increased knowledge about HPV vaccination. The main reported reasons for not being vaccinated among unvaccinated young adult women (19-26 years of age) is that they worry about vaccine safety and have doubts about the benefits of being vaccinated at their age. Young adult unvaccinated men share doubts about the benefits of being vaccinated at their age, but mostly report that they simply have not yet gotten around to it.
- HPV vaccination and cervical cancer (CC) screening are seen as complementary to each other by half of the parents of daughters aged 7-10 years. Of the other half of the parents (those who did not see HPV vaccination and CC screening as complementary to each other), those who had low trust in CC screening perceived the risks of HPV and CC as higher than parents with high trust in CC screening, and were more motivated to vaccinate their daughter. Possible changes to the CC screening interval does not appear to influence parents' decision making with respect to HPV vaccination.
- COVID-19 vaccine willingness in the Netherlands increased once the decision to be vaccinated was no longer abstract (right before the vaccination campaign) but a true choice (right after the start of the campaign). Furthermore, personal beliefs and social environment play a deciding role in the eventual decision, which is typically made at the moment of receiving the invitation. Later in the vaccination campaign, beliefs changed because the COVID-19 pandemic was in a different phase, resulting in lower vaccination willingness. Additionally, later in the vaccination campaign, younger people more often indicated they did not know whether they were eligible for vaccination.

3.2 Figures

Figure 3.1 (continues on the next page) Vaccine uptake (V), intention (I), attitude (A), beliefs about vaccination (BV) and infectious diseases (BD), trust (T) and deliberation (D) towards the current NIP among parents of young children (YC) and older children (OC) in 2022 and 2013 (young children only). Psychosocial factors were measured on a 7-point Likert scale and responses were grouped as: 'negative' (score 1-2), 'less pronounced' (3-5) and 'positive' (6-7).

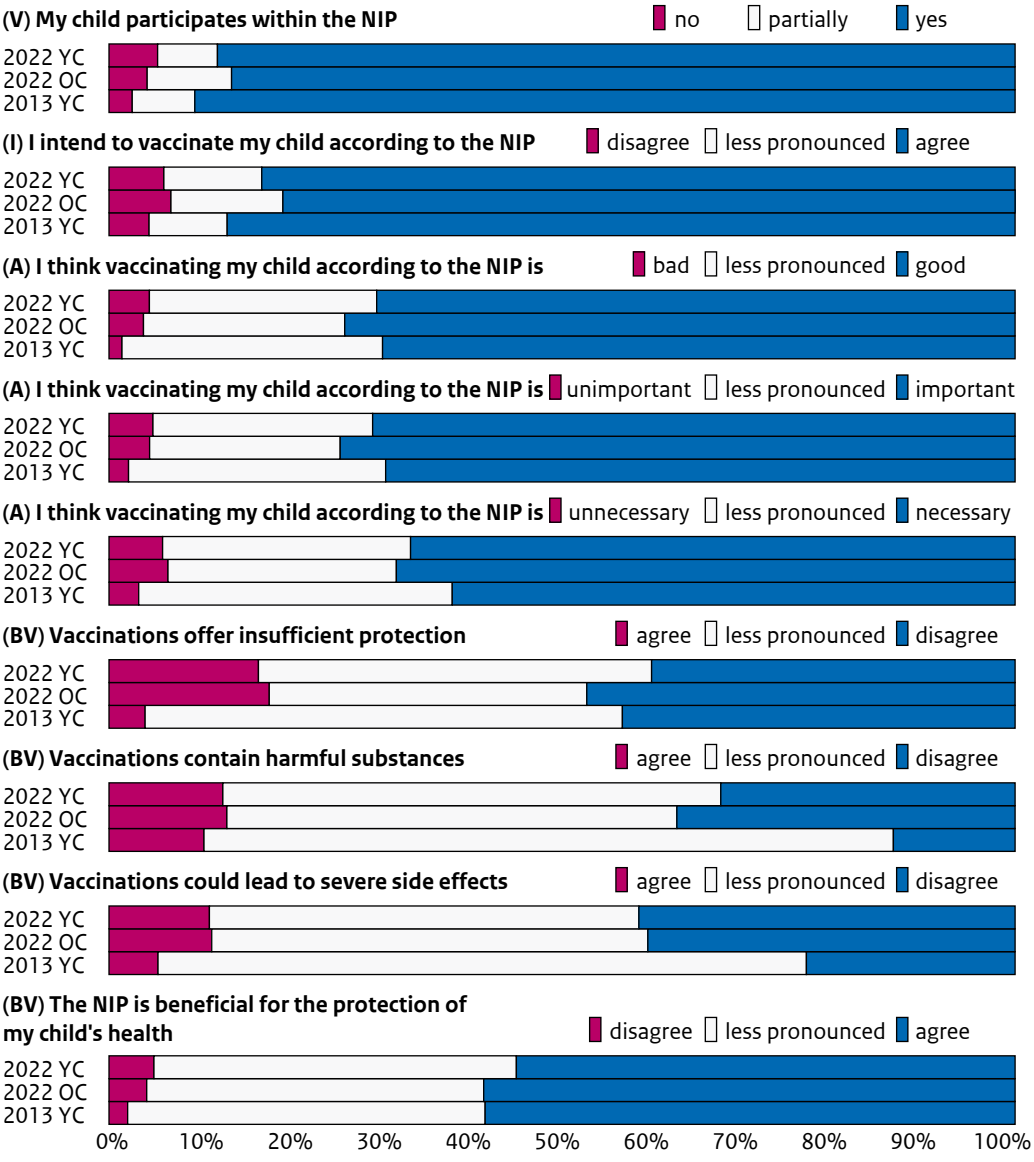
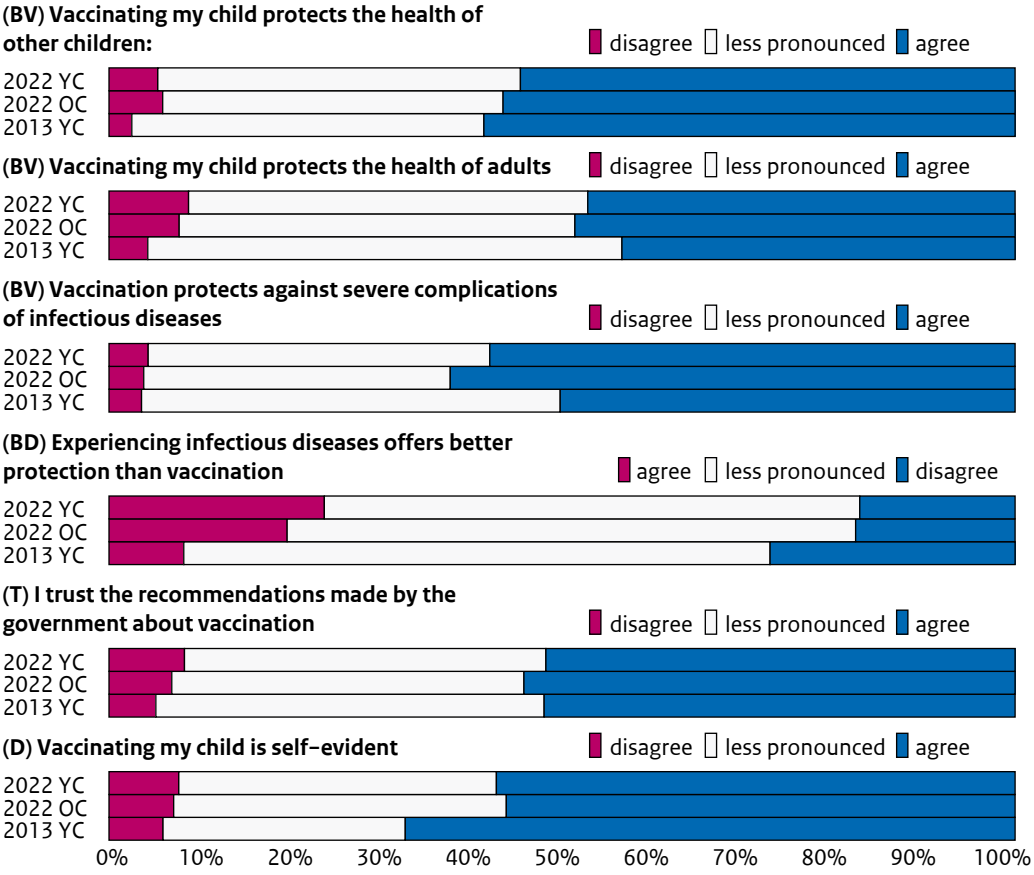


Figure 3.1 (continued) Vaccine uptake (V), intention (I), attitude (A), beliefs about vaccination (BV) and infectious diseases (BD), trust (T) and deliberation (D) towards the current NIP among parents of young children (YC) and older children (OC) in 2022 and 2013 (young children only). Psychosocial factors were measured on a 7-point Likert scale and responses were grouped as: 'negative' (score 1-2), 'less pronounced' (3-5) and 'positive' (6-7).



3.3 Monitoring acceptance of the NIP

In this chapter, we define vaccine acceptance as the timely acceptance of all recommended vaccines according to the National Immunisation Programme (NIP) schedule. Vaccine acceptance is of major importance for a high and homogenous vaccine uptake, and thus for preventing infectious diseases. As there are significant differences in vaccine acceptance within and between Western countries, it is important to monitor acceptance continuously.

This chapter covers relevant recent research at RIVM and in the Netherlands regarding vaccine acceptance, improving vaccine communication campaigns, and the decision-making processes driving vaccine acceptance or refusal.

Additionally, RIVM has started a new research programme, SocioVax, to obtain structural insights into changes in vaccination participation over time and between target groups, as well as into the factors that play a part in this. Additionally, SocioVax aims to offer insights into a) how people can be better informed about vaccinations, b) how people can be better supported in making a decision about being vaccinated or not, and c) how vaccinations can be made as accessible as possible. The SocioVax programme is under development. New insights will be shared in the near future. The insights in this chapter are not yet based on the studies from the SocioVax programme.

3.4 Childhood vaccinations

3.4.1 Survey on psychosocial factors of vaccine uptake

Vaccine uptake within the NIP has declined slightly since the COVID-19 pandemic. In a quantitative study among parents of children eligible for NIP vaccinations, we studied psychosocial factors of vaccine uptake, namely parental intentions, attitudes, beliefs, trust and deliberations (i.e., self-evidence) towards the current NIP, prior to (2013) and two years into the pandemic (2022) [1]. Two surveys were conducted: (1) one among parents of children aged <3.5 years (young children) and parents of children aged 9-14 years (older children) in 2022 (n = 1000 and 1000, (estimated) response = 12.2% and 20.9%, respectively) and (2) one among parents of young children in 2013 (n = 800, response = 37.2%).

In general, both in 2022 and 2013, most parents of young children indicated that their children participated in the NIP (2022 = 88.0%; 2013 = 90.5%), expressed positive vaccination intentions (2022 = 83.1%, 2013 = 87.0%), attitudes (3 items: 2022 = 66.7%-70.9%, 2013 = 62.1%-69.8%) and trust (2022 = 51.8%, 2013 = 52.0%) towards the current NIP and felt that vaccinating their children was self-evident (2022 = 57.2%, 2013 = 67.3%) (Figure 3.1). Scores for psychosocial factors among parents of older children and parents of young children from 2022 were similar (Figure 3.1). However, for all psychosocial factors of vaccine uptake, proportions of parents with negative scores were slightly higher in 2022 than in 2013 (Figure 3.1). The results from multivariate logistic regression analysis suggested that in 2022, parents of young children had significantly higher odds (i.e., likelihood) of a negative attitude towards vaccination (3 items combined: odds ratio (OR) = 2.84, 95% confidence interval (CI) = [1.09, 7.37]) than in 2013. Additionally, they were less likely to regard vaccinations as beneficial. Instead, they more often

believed that vaccinations offer insufficient protection against the infectious diseases they are targeting (OR = 4.89, 95% CI = [3.19, 7.51]), that the NIP is not beneficial for the protection of their children's health (OR = 2.23, 95% CI = [1.15, 4.35]), that vaccinating their children is not a good way to protect the health of other children (OR = 2.24, 95% CI = [1.16, 4.33]) or adults (OR = 2.22, 95% CI = [1.32, 3.75]), that vaccinations could lead to severe side effects later in life (OR = 2.20, 95% CI = [1.35, 3.58]), and that experiencing infectious diseases leads to a better and longer protection than vaccination (OR = 3.18, 95% CI = [2.24, 4.51]). Also, parents of young children were significantly more likely to be distrusting of the government's recommendations on vaccination (OR = 1.73, 95% CI = [1.08, 2.79]) compared to 2013.

Although in 2022, most parents had positive intentions, attitudes and trust regarding vaccination and perceived vaccinating their children to be self-evident, there are indications that they have become more negative towards the current NIP. Monitoring these determinants of vaccine uptake and developing appropriate interventions could contribute to sustaining high vaccine uptake.

3.4.2 Timing the invitation to ask questions during consultations

In order to make an informed decision about vaccination, it is important that parents and children are able to ask questions during the consultation at the Youth Healthcare Services. A conversation analytical study looked into the impact of the moment at which parents and children were invited to ask their questions about HPV vaccination ('do you have any questions about the vaccination?').

Two scenarios were tested: Parents were invited to ask questions about the vaccination either *before* or *after* the parents had shared their vaccination decision with the nurse from the Youth Healthcare Services. When questions were invited by the nurse *before* the vaccination decision was shared, question invitations were seen by parents as an invitation to ask critical questions. While the conversation analytic study indicated that asking 'critical questions' contributes to a parent presenting him/herself as a 'good' parent, inviting questions rarely led to an in-depth conversation about vaccination. One important finding was that providing more explanations about the vaccination seems to provide more opportunities for parents and children to ask questions.

When inviting questions *after* the vaccination decision was shared, parents risked that asking critical questions could contradict with their identity as a good parent, possibly portraying themselves as making uninformed decisions, i.e., only after agreeing to (or refusing) the vaccination did they come up with a range of (critical) questions about it.

If nurses want to encourage questions and a conversation, they should provide information about the vaccination first before inviting questions or asking a decision about the vaccination.

3.5 HPV

3.5.1 Campaign effect evaluations

As part of the evaluations of the media communication campaigns for the HPV vaccination campaigns aimed at children aged 10 to 18 years [2] and at young adults aged 19 to 26 years [3], surveys were carried out among the target populations. To evaluate the campaign targeting 10-18 years old, 4 repeated surveys were conducted (measurements before, during, and after the media campaign) among 100 to 150 participants in each of the 4 specific target populations at which the campaign was directed: boys and girls aged 13-18 years, and parents of children aged 9-10 and 13-18 years. The survey for the 19-26 age group campaign was repeated twice (before and after the media campaign) among 398 and 415 respondents aged 19-26 years, respectively.

The surveys showed that on average, participants recognised both media campaigns better than other campaigns issued by the central government. While a positive development was found in the overall attitude towards HPV vaccination, and participants' knowledge about HPV had significantly increased following the media campaigns, the participants' perceived importance of HPV vaccination appeared to not have been influenced by any of the media campaigns.

By checking the retention of the campaign messages, the surveys showed that the media campaigns clearly conferred most of the messages, which were still remembered at the time of the concluding measurements, i.e., message retention was long-lasting. Message retention in young adults was lowest for the messages that the vaccine would be free for only a short amount of time, and where they could find further information. In children aged 13-18 years, messages about the HPV vaccine were retained better than messages about HPV itself. Parents retained the messages about the protective capacity of the HPV vaccine better than the information about HPV itself.

3.5.2 Obstacles to HPV vaccination for 18-26-year-olds

In April 2023, a survey was performed to gain insights into the obstacles young adults face in receiving an HPV vaccine. For (currently) unvaccinated women, the most important reasons not to be vaccinated were worries about vaccine safety and doubts about the benefits of being vaccinated at their age. The latter reason for not being vaccinated (yet) also played a role for (currently) unvaccinated men, but the reason they most often reported for not being vaccinated (so far) was that they had not gotten around to it yet. 20% of the men and 16% of the women indicated that they intended to be vaccinated in 2023.

3.5.3 Influence of cervical cancer screening on HPV vaccination decision making and attitudes

Semi-structured interviews were held with 30 parents of daughters aged 7-10 years who will receive an invitation for HPV-vaccination in the coming years. The interviews were thematically analysed, indicating various possible influences of cervical cancer (CC) screening on parental HPV vaccination decision making.

Half of the parents consider the CC screening programme and HPV vaccination as being complementary to each other. For the other half of the parents, those who did not perceive the two prevention programmes to be complementary, the beliefs they held about the screening programme turned out to influence their vaccination intent. When the effectiveness of screening was believed to be low, parents were more motivated to vaccinate their daughters. Additionally, for some of these parents, awareness of the screening programme's existence was related to a higher risk perception of HPV and CC, thus increasing the urgency they felt about vaccinating their daughters. Those parents who believed that the screening programme was effective, believed that the probability of developing CC was low and had decided not to vaccinate their daughters or were still in doubt about that decision. These parents perceived the screening programme as a sufficient preventive measure for early CC detection, making vaccination redundant.

Parental decision making for HPV vaccination does not seem to be influenced by a potential increase of the screening interval (vaccinated = longer interval between consecutive rounds of CC screening); participation in routine five-yearly CC screening was seen as very important, regardless of vaccination status. Screening remained important to the parents because of their positive beliefs about the effectiveness of the HPV vaccine, their negative beliefs about the aetiology of CC, as well as ethical aspects. These ethical considerations related to the risk of missing CC cases if screening is offered less often, possibly influenced by a potential decrease in the social norm of partaking in the screening programme (resulting from longer screening intervals), and to the autonomy their daughters should have in participating in the screening programme and after which intervals to do so.

Apart from information about HPV, CC and the HPV vaccine, parents indicated they would like to know more about the screening programme and possible changes made to it. Specifically, parents would prefer more information about the reasoning behind changing screening intervals on the basis of vaccination status and proof that this is safe, the possibility of being screened every five years regardless of vaccination status, and the general procedure of the screening programme.

3.6 COVID-19

Research shows that in the Dutch population, willingness to vaccinate oneself against COVID-19 increased once the decision to vaccinate became more concrete: in November 2020, before the start of the COVID-19 vaccination programme, average willingness to vaccinate was 48%, while in January 2021, after the vaccination programme had started, willingness was 75%. Indeed, the decision to vaccinate was typically made once the invitation was received (the so called cue to action) [4]. The decision to be vaccinated was predicted by the beliefs held about the vaccination, as well as the social context [4, 5]. For the COVID-19 primary vaccination series, beliefs about vaccine safety and one's own health- and social benefits, played an important role in the vaccination decision. Socially, the conviction that being vaccinated would contribute to a solution to the crisis played an important role, as did the decisions made by friends and family [4, 5].

Three-weekly recurring surveys looking into developments of adherence to COVID-19 control measures and vaccination intent, showed that the decision for the booster/repeat-vaccinations was formed differently than the decision for primary vaccination. In contrast to primary vaccination, intent to receive a repeat vaccination decreased over time: in October 2022, 10% of the participants who received primary vaccination had received their repeat-vaccination and 52% intended to, while in January 2023, only 47% of all respondents had indeed been vaccinated (10% indicated they were planning on still being vaccinated). Additionally, the percentage of participants that were in doubt about being vaccinated or not, dropped from 21% in October 2022, to 13% in January 2023, while the 17% of participants that did not want to be vaccinated in October 2022, rose to 30% in January 2023 (results from survey round 31 [6]).

Vaccination willingness for the repeat-vaccinations was strongly associated with age (results from survey round 33 [6]). Notably, younger participants indicated more often than their older counterparts that they did not know whether or not they qualified for vaccination, and that they had not received enough information to be able to make a decision (results from survey round 32 [6]). Overall, the most common reasons to not receive a repeat-vaccination were low perceived usefulness of the repeat-vaccination, trust in the immune system, and the perception that at that moment, the COVID-19-situation was not serious enough to warrant vaccination (results from survey round 31 [6]).

3.7 Other studies from the Netherlands: adolescents

When it comes to vaccinating adolescents, the decision for vaccinating is no longer solely made by the parents [7]. The views held by adolescents and their parents play separate roles, but also influence each other [7]. Concerns about side effects (both proven and theorised) remain an influential negative factor in the decision-making process [8]. Parental acceptance of, specifically, the HPV vaccine is also associated with the age of vaccination (younger age equals greater hesitancy) and the child's gender (greater hesitancy for vaccinating boys) [8]. This may be because parents perceive the risk that HPV poses to their sons as lower than the risk to their daughters [8].

A study regarding the MenACWY vaccination, found that parents and (especially) their adolescent children perceived a social norm that favours partaking in the childhood vaccination programme [7]. However, compared to their parents, adolescents participating in the study felt more comfortable refusing MenACWY vaccination, which might be tied in with the observed lower perceived risk of not being vaccinated among these adolescents, and which in turn could possibly be linked to their lesser knowledge. Lastly, this study found that most parents and adolescents prefer adolescent vaccinations to be offered at individual appointments, rather than during mass vaccination events.

3.8 Literature

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* *RIVM publication.*

4
Burden of disease

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

4.1 Key points

- The estimated total burden of disease caused by (partially) vaccine-preventable diseases for the year 2022 was highest for HPV (18,500 disability-adjusted life years (DALYs); 74% among women), invasive pneumococcal disease (8,700 DALYs), rotavirus infection (1,500 DALYs), invasive *Haemophilus influenzae* disease (1,500 DALYs), and invasive meningococcal disease (560 DALYs).
- For most vaccine-preventable diseases, the estimated burden was still somewhat lower in 2022 compared to the estimated burden in 2019 (the last year before the COVID-19 pandemic), but higher than during the COVID-19 years 2020/2021, when various COVID-19 response measures (e.g. social distancing and hand hygiene) were in place. Additional vaccination against pneumococcal disease (older adults, start in 2020) and meningococcal ACWY disease (adolescents, start in 2018; newborns, meningococcal ACWY instead of meningococcal C vaccine since 2018) was also implemented, leading to protection against these types and thus to a lower burden of disease.
- The burden of invasive *H. influenzae* disease specifically for type b was higher in 2022 than in 2019 (before the COVID-19 pandemic), as it was in 2021 and 2020.
- The burden of COVID-19 is estimated to be 93,800 DALYs for 2022, where 93% of the burden is due to premature death because of COVID-19. This is an underestimation of the actual burden, since long-term consequences of the disease have not been taken into account. For COVID-19, the burden was lower in 2022 than in 2021.

4.2 Tables and figures

Table 4.1 Estimated annual burden of disease in DALYs in 2018–2022, and DALYs per 100 infections in 2022 in the Netherlands (with 95% uncertainty intervals) [1-3].

Disease	DALYs (95% uncertainty interval)					DALYs/100 infections in 2022
	2018	2019	2020	2021	2022	
Diphtheria	3 (3-4)	0 (0-0)	3 (3-4)	0 (0-0)	11 (9-13)	150 (120-180)
Hepatitis A virus infection	100 (62-170)	90 (55-150)	28 (17-45)	42 (26-69)	50 (30-83)	11 (8-15)
Hepatitis B virus infection (acute)	130 (120-140)	140 (130-150)	110 (99-110)	170 (150-180)	66 (61-71)	18 (17-19)
Human papillomavirus infection[a]						
- Females	12,200 (11,500-13,000)	12,700 (12,000-13,500)	11,800 (11,100-12,600)	13,500 (12,800-14,300)	13,600 (12,800-14,400)	n/a
- Males	4,800 (4,000-5,700)	4,800 (4,000-5,700)	4,500 (3,700-5,400)	4,900 (4,100-5,900)	4,900 (4,100-5,800)	n/a
Invasive *H. influenzae* disease	1,000 (960-1,100)	970 (920-1,000)	1,000 (970-1,100)	890 (840-950)	1,500[b] (1,400-1,600)	410 (390-430)
Invasive meningococcal disease	1,100 (960-1,300)	890 (740-1,100)	400 (300-510)	280 (190-380)	560[c] (440-700)	690 (630-740)
Invasive pneumococcal disease	10,800 (10,100-11,400)	9,500 (8,900-10,000)	6,200 (5,800-6,600)	5,200 (4,900-5,500)	8,700[d] (8,200-9,200)	390 (370-410)
Measles	5 (4-5)	16 (15-18)	0.4 (0.3-0.5)	0 (0-0)	1 (1-2)	2 (2-2)
Mumps	0.6 (0.5-0.6)	1 (1-1)	0.5 (0.5-0.5)	0.01 (0.01-0.01)	0.1 (0.1-0.1)	0,4 (0,4-0,4)
Pertussis	2,000 (1,900-2,100)	2,600 (2,500-2,800)	390 (370-420)	32 (30-35)	60 (55-67)	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	1,200 (470-2,400)	1,100 (440-2,300)	390 (160-790)	920 (360-1,900)	1.500 (580-3,000)	0,5 (0,3-1)
Rubella	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	n/a
Tetanus	1 (1-1)	0 (0-0)	11 (9-12)	0 (0-0)	2 (2-2)	75 (71-79)

DALY= disability-adjusted life year.
n/a = not applicable; no cases occurring in 2022 or unknown number of infections (HPV).
For HPV, the disease burden for 2018–2021 is somewhat higher than previously reported due to a resolved error regarding the CFR for oropharyngeal cancer.

[a] *To estimate the burden, the numbers of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV were used. The most recent year of available data on the incidence of anogenital warts was 2020. Therefore, the incidence rate for 2020 was carried forward to 2021–2022; in addition, the incidence for 2017–2019 has been updated. The most recent year of available data on the incidence of high-grade cervical lesions was 2021; the incidence rate for 2021 was carried forward to 2022.*

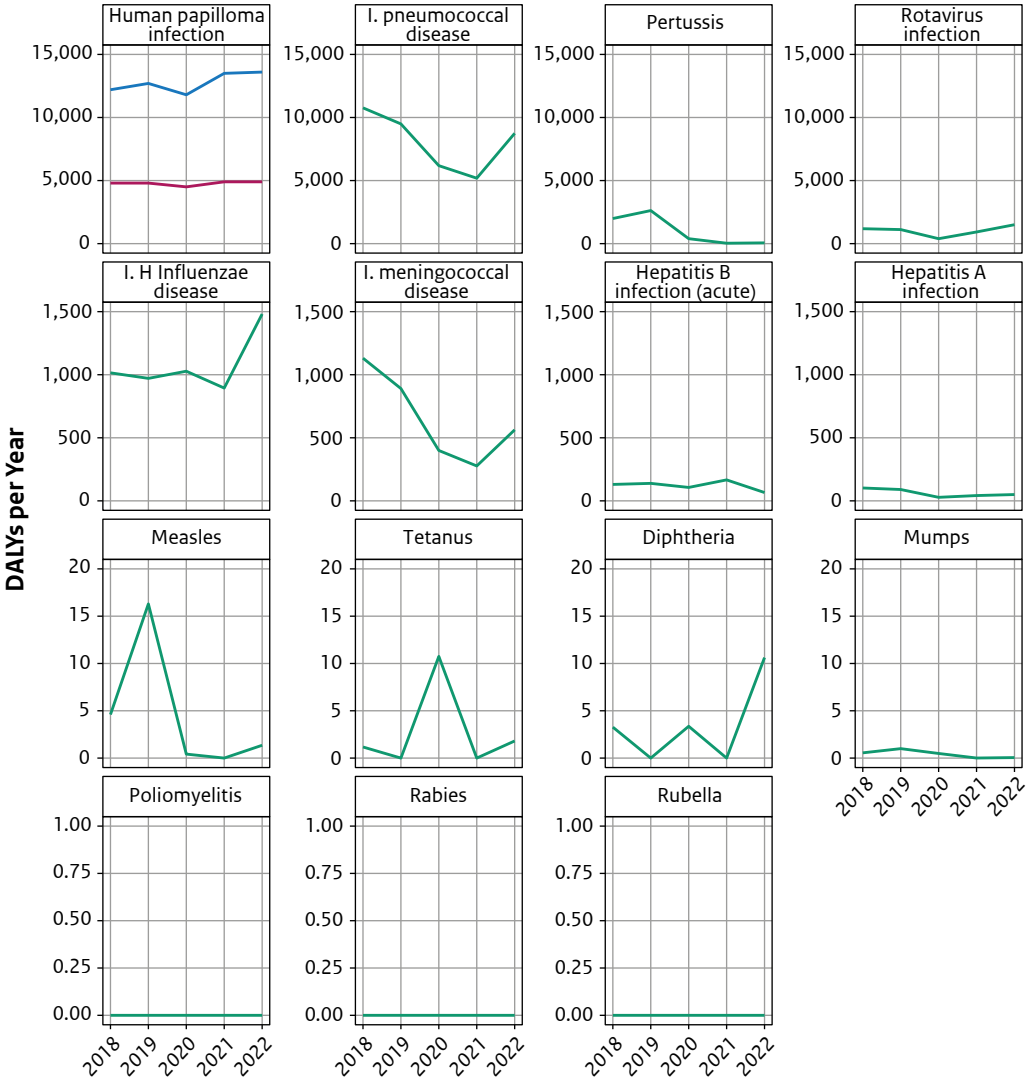
[b] *Proportion of disease burden due to disease caused by vaccine-preventable type b in 2022: 28%.*

[c] *Proportion of disease burden due to disease caused by vaccine-preventable type C in 2022: 3%; proportion caused by type B in 2022: 91%; proportion caused by type W in 2022: 2%.*

[d] *Proportion of disease burden due to disease caused by vaccine-preventable types 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (PCV10) in 2022: 5%; proportion caused by types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F (PPV23) in 2022: 80%.*

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 2018–2022 [1-3].



Notes:

1. *DALY= disability-adjusted life year; for HPV, the disease burden for 2018–2021 is somewhat higher than previously reported due to a resolved error regarding the CFR for oropharyngeal cancer.*
2. *Vaccination against rabies, hepatitis A and rotavirus infection is not included in the NIP.*
3. *For the three invasive bacterial diseases and HPV, only certain serotypes are covered by the vaccines used: Haemophilus influenzae serotype b (Hib), meningococcal serotypes A, C, W, and Y, PCV10 pneumococcal serotypes for children, PPV23 serotypes for older adults, and HPV16/18.*
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 pink line shows the burden for females, the blue line shows the burden for males.*
5. *Note that the y-axes are not the same for all diseases.*

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

4.3 Burden of NIP diseases

In this section, we present an update of the disease burden of (partially) vaccine-preventable diseases in the 2018–2022 period, expressed in disability-adjusted life years (DALYs). We present the same estimates as published in the 'State of infectious diseases in the Netherlands, 2022', 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, 2022' [3], and estimates for COVID-19 from the report 'Annual report Surveillance of acute respiratory infections in the Netherlands: winter 2022/2023'[4]. Estimates for human papillomavirus (HPV) infection were derived from a separate analysis [2] and updated for more recent years using the Global Burden of Disease (GBD) 2010 life expectancy. For HPV, the disease burden for 2018–2021 is somewhat higher than previously reported due to a resolved error regarding the CFR for oropharyngeal cancer. Note that the calculation method used for HPV is not fully comparable to that used for other diseases: instead of using the number of incident infections (which is unknown), the number of cases with cancer, anogenital warts and high-grade cervical lesions attributable to HPV was used. All DALY estimates were rounded up or down: to three significant digits for numbers ≥10,000, to two significant digits for numbers between 10 and 10,000, and to one significant digit for numbers <10.

Table 4.1 shows the estimated DALYs per year in the 2018–2022 period and the DALYs per 100 infections in 2022 (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 2022 was zero because no cases were reported. For mumps, measles, tetanus, and diphtheria, the disease burden in 2022 was estimated to be relatively low, while the highest burden was estimated for HPV infection, followed by invasive pneumococcal disease, rotavirus infection, invasive *Haemophilus influenzae* disease, and invasive meningococcal disease.
The incidence of pertussis and rotavirus infection is known to surge every few years (Figure 4.1). For most vaccine-preventable diseases, the estimated burden in 2022 is still somewhat lower compared to the estimated burden in 2019, but higher than during the COVID-19 years 2020/2021. This is probably still an effect of the previous implementation of COVID-19 control measures, such as social distancing and hand hygiene (see also [5-7]).
In addition, the Netherlands started vaccinating older adults against pneumococcal disease in the autumn of 2020. Furthermore, meningococcal ACWY vaccination for adolescents was provided through a catch-up campaign in 2018-2019 and has been included in the NIP from 2020 onwards, whereas new-borns have been vaccinated with meningococcal ACWY instead of meningococcal C vaccine since 2018. These introductions might have affected incidence and thus the burden of disease.
After two years with no reported invasive meningococcal serogroup C cases, and therefore no burden, the proportion of the burden of invasive meningococcal disease due to serogroup C in 2022 was 3%. The proportion of the burden of invasive meningococcal disease due to serogroup W decreased further: from 42% in 2018 to 29% in 2019, 14% in 2020, 6% in 2021, to 2% in 2022. In 2022, the burden of the PCV10-preventable pneumococcal serotypes was only 5% of the total burden due to invasive pneumococcal disease, whereas the burden of the

PPV23 preventable pneumococcal serotypes was 80%. The proportion of invasive *H. influenzae* disease burden in 2022 due to the vaccine-preventable *H. influenzae* disease serotype b (Hib), is 28%; comparable to the years 2018/2019. This proportion increased in 2020 (47%) and 2021 (50%), due to an increase of Hib and a decrease of non-typeable and other serotype invasive *H. influenzae* disease. The latter development was probably due to the COVID-19 control measures. The absolute number of DALYs due to Hib had increased in 2020 and 2021 and was still relatively high in 2022 (2018: 290 DALYs, 2019: 270 DALYs, 2020: 480 DALYs, 2021: 450 DALYs, 2022: 420 DALYs). Possible reasons for the increase in Hib are under investigation (see also section 6.2).

It must be noted that the total disease burden for pneumococcal disease, meningococcal disease, and *H. influenzae* disease is higher than presented here, as the analyses were limited to (laboratory-confirmed) invasive disease. Furthermore, the burden of these diseases, as well as of HPV infection, is not fully preventable through vaccination because not all serotypes are covered by the vaccine. Finally, the disease burden related to hepatitis B virus infection has also been underestimated. The analyses only reflect the (future) burden of new cases of hepatitis B virus infection in the 2018–2022 period because the disease burden of (chronic) hepatitis B cases infected prior to this period is not included.

4.4 Burden of COVID-19

The disease burden of COVID-19 in 2022 is estimated to be 93,800 DALYs (95% uncertainty interval 91,600-96,100), where 93% of the burden is due to premature death because of COVID-19 [4]. In 2021 the burden was estimated to be 219,000 DALYs (95% uncertainty interval 215,000-223,000).
The burden for COVID-19 is underestimated since long-term consequences of the disease have not been taken into account. Furthermore, there is insufficient data about the epidemiology and long-term impact of COVID-19 at this time to properly estimate the disease burden in DALY/100 cases [4].

4.5 Literature

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* *RIVM publication.*

5
Adverse events

J.M. Kemmeren

5.1 Key points

- In 2022, Lareb received 1,217 notifications representing a total of 4,329 adverse events following immunisation (AEFI). This number of reports is lower compared to the number of reports received in earlier years. The number of reported AEFIs per report was between 3 to 4, which is the same as in earlier years.
- No new signals of disturbing adverse events were found in children, adolescents or pregnant women.

5.2 Tables

Table 5.1 Number of reports per dose and suspected vaccine(s) [1].

Vaccines	Total 2021	Total 2022	0-2m	3-4m	5-6m	7-8m	9-10m	11-12m	13-14m	15-16m	17-23m	2-5yrs	6-9yrs	10-14yrs	15-19yrs	Pregnant women	Other/Unknown
Vaxelis® + Synflorix®	320	**222**	1	84	56	4	1	57	17	1	1						
Vaxelis®	104	**92**	21	21	7	1	1	8	3	3	4	17	5	1]			
Synflorix®	10	**10**		1	4	1		3	1								
MMRVaxPro® + Nimenrix®	193	**91**							52	33	4	2					
MMRVaxPro® + Menquadfi®	-	**25**							19	5	1						
MMRVaxPro® + MenACWY (unknown)	-	**6**							2	3							1
MMRVaxPro®	46	**24**							10	6		1	5	1	1		
Nimenrix®	58	**40**							4	1	1	1	1	32			
Menquadfi®	-	**4**							1	3							
Boostrix Polio®	233	**166**										164					2
MMRVaxPro® + Revaxis®	118	**52**										1	51				
MMRVaxPro® + DTP Bbio®	8	**43**											43				
MMRVaxPro® + DTP (unknown)	-	**17**											16	1			
Revaxis®	11	**2**											2				
DTP Bbio®	-	**9**											9				
DTP (unknown)	-	**8**											7	1			
Cervarix®	128	**246**											45	155	46		
Boostrix®	186	**118**														118	
Combined with vaccines not in NIP	35	**41**		1				1	2			4	13	16	3	1	
Vaccinated within old schedule	12	**1**	1														
Total 2022		**1217**	**23**	**107**	**67**	**6**	**2**	**69**	**111**	**55**	**11**	**190**	**197**	**207**	**50**	**119**	**3**
Total 2021	1,462		35	167	90	6	5	98	155	94	14	240	153	163	44	197	1
Total 2020	1,475		58	165	94	7	5	143	145	86	22	292	144	87	26	198	3
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 (continues on the next page) Reported severe adverse events per vaccination moment [1].

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
Skin conditions																
Rash, eczema	1	6	6	1	1	5	29	21	5	18	16	10	3	3		125
Skin discolouration		8	1					1								10
Urticaria	1		3			3	6	2		8	2	3	2	2	1	33
Respiratory symptoms																
Apnoea, dyspnoea, irregular breathing	3	10	3				1	1		1		4		3		26
Breath-holding spells		1				1	1	1								4
Neurologic symptoms																
Ataxia, spasms, tics									1		1	1				3
Autism spectrum disorder											1					1
Delirium febrile											1					1
Febrile convulsion, seizures, tonic convulsion, epilepsy	1	2				2	8	7		2	1	3		1		27
Facial paresis/Bell's palsy												2				2
Hypotonic-hyporesponsive episode	5	4	1				1									11
Migraine											1	2	2	1		6
Status epilepticus								1								1
(Pre)syncope										5	14	25	3			47
Extensive swelling of vaccinated limb	**1**	**2**	**4**			**4**	**1**	**1**		**20**	**3**			**4**	**1**	**41**
Body temperature ≥40.5 - ≤42°C		**1**	**1**			**1**	**8**	**4**	**1**	**4**	**7**	**1**				**28**
Persistent crying					**1**											**1**
Abscess																
Injection site abscess			2			2										4
Injection site abscess sterile																
Immune mediated disorders																
Acute haemorrhagic oedema of infancy							1									1
Autoimmune disorder																
Autoimmune thyroiditis											1					1
Immune thrombocytopenia		1					1				1					3
Systemic lupus erythematosus																
Type 1 diabetes mellitus																

Table 5.2 (continued) Reported severe adverse events per vaccination moment [1].

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
Dehydration			1													1
Death*			1													1
Sudden Infant Death Syndrome (SIDS)																
Adverse events with fatal outcome																
Encephalitis/meningitis	1															1
Postural orthostatic tachycardia (POTS)																
Vaccine failure																
Fibromyalgia												1				1
Kawasaki's disease																
Juvenile idiopathic arthritis																
Complex regional pain syndrome (CRPS)																1
Adverse events concerning pregnancy																
Foetal death*															1	1
Stillbirth															1	1
Amniotic cavity infection															1	1

** For a full descriptions of the causes of death: see yearly report of Lareb [1].*

5.3 Spontaneous Reporting System

5.3.1 Reports

The enhanced passive surveillance system managed by the National Pharmacovigilance Centre Lareb receives AEFI reports for all vaccines. In this chapter an overview will be given of the AEFIs received by Lareb in 2022 for vaccines covered by the NIP. The AEFIs reported after COVID-19 vaccination are described in chapter 9.07.

In 2022, Lareb received 1,217 reports with a total of 4,329 AEFIs (Table 5.1) [1]. This number of reports is lower compared to the number of reports received in earlier years (2018: n=1,519, 2019: n=2,009, 2020: n=1,475, 2021: n=1,462), despite the fact that, from 2022, an extra group has been added to the NIP (i.e., boys now also receive an invitation for HPV vaccination). Most reported AEFIs were injection site reactions (n=1,152), fever (n=393), malaise (n=258), headache (n=216), fatigue (n=198), nausea (n=194), myalgia (n=121) and vomiting (n=105).

For most vaccines, the number of reports is lower or within the range of the last years (see Table 5.1). Especially the number of reports following maternal pertussis vaccination is remarkably lower compared to 2020 and 2021. Although it has not been established, increased alertness immediately following the introduction of this vaccination may be a possible explanation for this trend.
For HPV vaccination, an increase in the number of reports was seen compared to the most recent years. This can be explained by the introduction of HPV vaccination among boys, a new target group in the NIP.
The number of reported AEFIs per report was 3 to 4 which is similar to earlier years. Due to the implementation of an informed consent for data exchange with the RIVM in January 2022, it is not possible to precisely determine how much vaccine doses are given. A reliable estimation of the number of AEFIs per vaccine dose is therefore not possible,

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. No reports of postural orthostatic tachycardia syndrome (POTS) and one report of fibromyalgia after HPV vaccination was received.

In 2022, Lareb received two serious reports of adverse events following maternal pertussis vaccination (1). One report described a stillbirth following Tdap vaccination (Boostrix®) during pregnancy. Placental examination showed an infection of the placenta and one of the umbilical vessels, consistent with severe chorioamnionitis and placental discharge. Two systematic reviews showed a slightly increased risk of chorioamnionitis following Tdap vaccination during pregnancy, although this was not associated with the risk of non-pertussis infections, spontaneous abortion or stillbirth and maternal or neonatal death [2, 3].

The second report described a case of intrauterine foetal death (IUFD) following Tdap vaccination (Boostrix®) during pregnancy. Obduction showed a high winding index in the umbilical cord, with signs of decreased foetal perfusion, which may have contributed to

the IUFD. However, Tdap vaccination during pregnancy has never been associated with an increased risk of stillbirth including IUFD [2, 3].

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

5.3.2 Signals/overviews

On the basis of the reports, the following analyses were conducted in 2022 [1]:

1. HPV vaccination in boys.
   In 2022, boys received the HPV vaccine for the first time. The reports received by Lareb in the first half year did not give reasons for action.

2. HPV vaccination in 9-10 year olds.
   The administration of HPV vaccination has been brought forward from 12-13 years to the year when adolescents turn 10. Lareb did not notice a clear difference in side effects between the various age groups.

3. Tdap vaccination during pregnancy.
   Lareb analsed differences in the pattern of side effects in children who received the DKTP-Hib-HepB vaccine (Vaxelis®) where:
   (a) the mother did have a Tdap vaccination during pregnancy
   (b) the mother did not receive Tdap vaccination during pregnancy. The adverse reaction pattern between the two groups is mostly similar.
   The percentage of serious reports is slightly lower in the group of children whose mother did receive a Tdap vaccination during pregnancy.

5.4 International Developments

5.4.1 Vaccines targeting diseases included in the current NIP

5.4.1.1 Meningococcal vaccines

No safety issues were reported for conjugate meningococcal ACWY vaccines [4-14].
The results of three studies showed the safety of meningococcal B vaccines [15-17].

5.4.1.2 MMR/MMRV vaccines

The MMR, MMRV and measles-containing vaccines are generally well tolerated [18-22], even in patients with underlying disorders [23, 24], in infants exposed in utero to TNF inhibitors [25], in preterm children [26], or co-administrated with an inactivated enterovirus 71 vaccine or typhoid conjugate vaccines [27-29]. However, on the basis of a case report, the understanding of the prevalence and duration of vaccine-derived rubella virus shedding was highlighted [30].

5.4.1.3 Pneumococcal vaccines

Three studies showed some adverse risks following pneumococcal vaccination. A case study reported an association of Erythema Multiforme following hepatitis A and pneumococcal vaccination [31], Parmar *et al.* described cardiac adverse events (mostly myopericarditis) following pneumococcal vaccination [32], and Zheng *et al.* reported a small increased risk for shoulder conditions following pneumococcal conjugate vaccination among elderly persons who received intramuscular vaccinations, which may be due to needle overpenetration [33]. However, most studies showed the safety of PCV10 [34], PCV13 with or without PPV23 [35-45], PCV15 with or without PPV23 [46-57], PCV20 [58-63], PCV21 [64] PPV23 [65], and unspecified PCVs [66] even in patients with underlying diseases [67]. One observational study confirmed the safety of PCV13 in infants, although the incidence and severity of adverse events was higher in premature children [26].

5.4.1.4 DTaP-IPV-HBV-Hib vaccines

Several studies showed the safety of infant tetravalent, pentavalent and hexavalent vaccines [68-79]. Oral polio vaccine is also well tolerated [80]. One observational study confirmed the safety of hexavalent vaccines in infants, although the incidence and severity of adverse events was higher in premature children [26]. Another study reported that the safety profile of penta- and hexavalent vaccines in preterm infants was generally similar to those seen in full-term infants, with the exception of an increase in cardiorespiratory adverse events such as apnoea, bradycardia and desaturation following vaccination in preterm infants [81]. Regarding clarifying factors that may play a role on the risk of AEs, Ma *et al.* showed that genetic predisposition is associated with the risk of AEs following DTaP-Hib vaccination [82].
In adults, a case of ITP was reported following DTaP-IPV vaccination [83], but Tdap vaccination is shown to be safe in adults with obstructive airway diseases and pregnant women [84-89].

5.4.1.4.1 Hepatitis B vaccine

Several studies demonstrated the safety of the hepatitis B vaccines [126-129], even given as a booster [130], in coadministration with other vaccines [131] or in patients with underlying diseases [67, 132, 133]. In China, only seven cases of SAEs following Hepatitis B vaccination were reported from January 2010 to January 2022 [134]. A 3-antigen recombinant hepatitis B vaccine showed a good safety profile but is associated with more adverse reactions than a single-antigen hepatitis B vaccine [135]. A new nano adjuvant (PF3) for an enhanced hepatitis B vaccine showed an acceptable biosafety equivalent to that of aluminium adjuvant [136].

5.4.1.5 HPV vaccines

5.4.1.5.1 2vHPV, 4vHPV and 9vHPV vaccines

Several studies showed the safety of 2vHPV vaccines [90-96], 4vHPV vaccines [93, 94, 96-101], 9vHPV vaccines [93, 95, 100-103] or unspecified HPV vaccines [24, 104, 105].
In earlier years, reports of a possible association between primary ovarian insufficiency were published. However, an review of data in VAERS does not suggest a safety concern [106]. Furthermore, over the years, a number of case reports described the onset of systemic lupus erythematosus following HPV vaccination, although all patients showed rapid remission with

glucocorticoid and immunosuppressive therapy [107]. An update on recent clinical trials and real-world reporting showed that following herpes zoster and influenza vaccination, HPV vaccination is the third most common to have headache as an AE [108].

5.4.1.5.2 New vaccines

In clinical trials, a novel Escherichia coli-produced HPV-16/18 bivalent vaccine, as well as a novel Escherichia coli-produced HPV-6/11 bivalent vaccine showed an acceptable safety profile [93, 109].

5.4.2 Vaccines targeting diseases that may be included in the NIP in the future

5.4.2.1 Varicella vaccines

Several studies showed the safety of live attenuated varicella vaccines [21, 22, 106, 110], even in paediatric patients with underlying diseases [24]. One case report described a confirmed case of extensive neonatal varicella disease in a neonate after being exposed to a vaccine varicella rash that developed following maternal postpartum vaccination [111].

5.4.2.2 Herpes Zoster vaccines

Several studies showed the safety of a recombinant zoster vaccine in adults [112-114], even in patients with underlying diseases [67, 115-119].

Rare adverse events, occurring less than 1% of the time, have been seen with both vaccine types and include disseminated herpes zoster with the live zoster vaccine, and Guillain-Barré syndrome with the recombinant vaccine [120]. Headache is also commonly reported after RZV [108, 121] and a case report described varicella infection reactivation after routine zoster vaccination [122].

Data collected through a pregnancy registry does not support a relationship between the occurrence of congenital varicella syndrome or major birth defects and varicella vaccine exposure during pregnancy, although the small number of exposures cannot rule out a low risk [123].

5.4.2.3 Hepatitis A vaccines

One case report described an association of erythema multiforme following administration of the hepatitis A and pneumococcal vaccines [31]. Other studies did not found safety issues for the hepatitis A vaccine [110, 124, 125].

5.4.2.4 Rotavirus vaccines

A good safety profile was demonstrated for rotavirus vaccines [137, 138], even in preterm children [139] and in infants exposed in utero to TNF inhibitors [25]. One study showed the safety of a hexavalent reassortant rotavirus vaccine [140].

5.5 Literature

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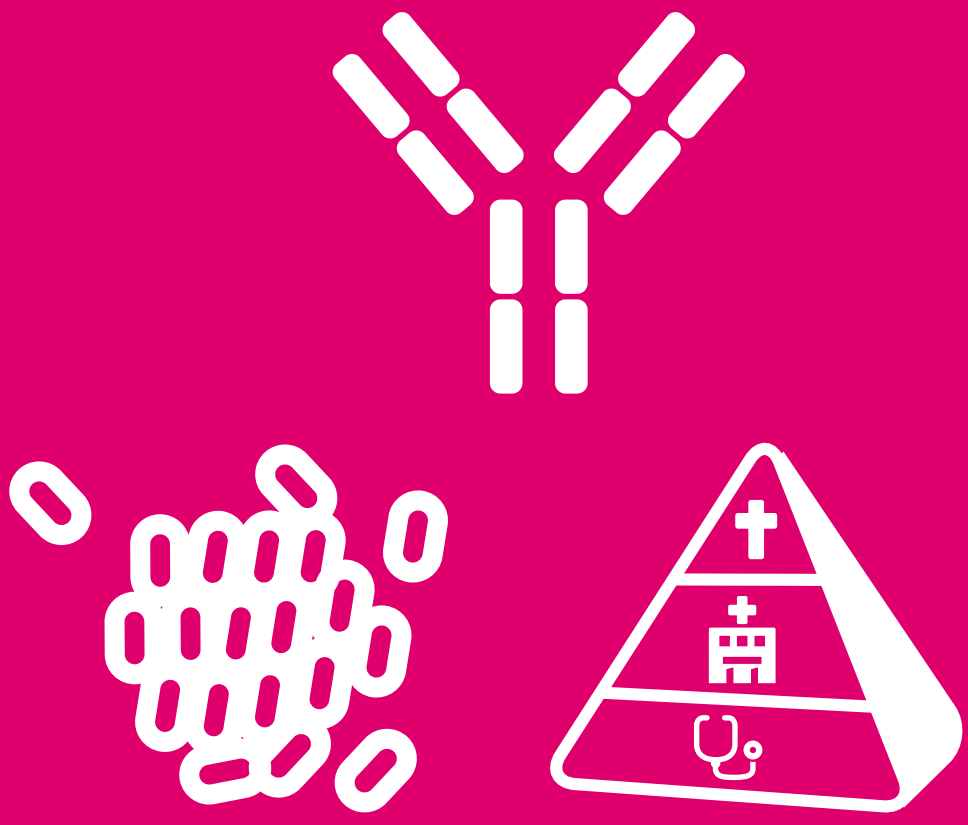
6
Current National Immunisation Programme



6.1 Diphtheria

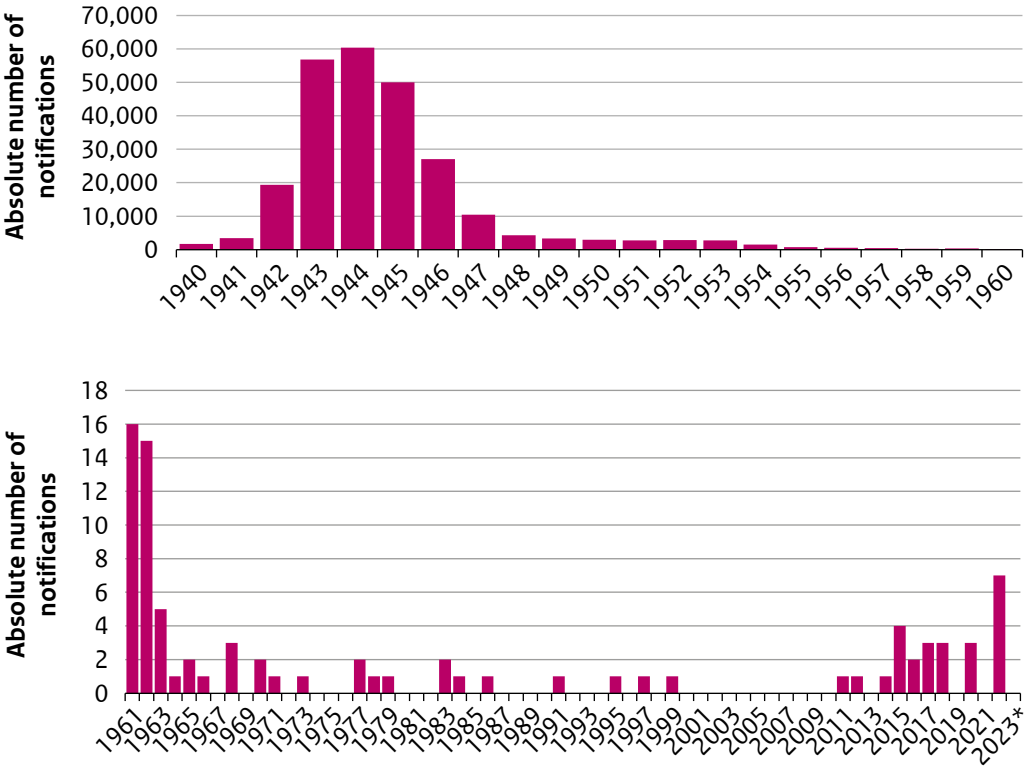
D.L. van Meijeren, M.J.C. van den Beld, D.W. Notermans, H.E. de Melker

6.1.1 Key points

- In the Netherlands, seven confirmed diphtheria cases were reported in 2022 and no cases in 2023 up to and including April. Five of these cases involved under aged asylum seekers.
- From early 2022 up to and including 21 April 2023, 400 cases of diphtheria among asylum seekers were reported to ECDC by eight EU/EEA countries, Switzerland, and the United Kingdom, including the five asylum seekers in the Netherlands
- In 2022, the RIVM received 14 *C. diphtheriae* and 3 *C. ulcerans* strains for confirmation testing. Five of the *C. diphtheriae* and one of the *C. ulcerans* strains tested positive for exotoxin production.
- In 2023 up to and including April, the RIVM received 2 *C. ulcerans* strains for confirmation testing, of which one strain tested positive for exotoxin production.

6.1.2 Tables and figures

Figure 6.1.1 Annual number of diphtheria notifications for 1940-1960 (above) and 1961-2023* (below). Until 2009, only infections with *Corynebacterium diphtheriae* were notifiable. From 2009 onwards, infections with *C. ulcerans* are notifiable too.



** Up to and including April.*

Table 6.1.1 Laboratory results of confirmation testing for *C. diphtheriae** and *C. ulcerans* at RIVM for 2016-2023**. Date of arrival at the laboratory is used for year of classification. Pos = positive, Neg = negative, NC = non-conclusive.

	Corynebacterium diphtheriae					*Corynebacterium ulcerans*				
	PCR		Elek			PCR		Elek		
	Pos	Neg	Pos	NC	Neg	Pos	Neg	Pos	NC	Neg
2016	1	12	1	n/a		1	2	n/a	1	
2017	1	9	0	0		2	0	n/a	2	
2018	0	7	0	0		2	1	1	1	
2019	0	7	n/a	n/a		0	8	n/a	n/a	
2020	1	3	n/a	1		1	5	n/a	1	
2021	0	7	n/a	n/a		0	2	n/a	n/a	
2022	5	9	3	0	2	1	2	0	0	1
2023*	0	0	n/a	n/a	n/a	1	1	1	0	1

** For comparability, strains from 2022 and 2023 include C. belfantii, since this was a biovar of C. diphtheriae in previous years.*
*** Strains that were sent to RIVM up to and including April 2023.*

6.1.3 Epidemiology

In the Netherlands, seven confirmed diphtheria cases were reported in 2022 and no cases in 2023 up to and including April (Figure 6.1.1). Five out of the seven cases involved under aged asylum seekers, with an infection caused by *C. diphtheriae*, diagnosed in October and November 2022. Four of these cases involved cutaneous diphtheria, of which in two cases throat carriage was also demonstrated. In the fifth case, only throat carriage was demonstrated. None of the patients died. It is unclear where the patients got infected and also their vaccination status is unknown.

The sixth and seventh reported cases both involved cutaneous diphtheria, caused by an infection with *C. ulcerans*. Both patients may have been infected by their cat, but this has not been confirmed. Their vaccination status is unknown. One patient was born a few years before, and the other patient a few years after the introduction of childhood vaccination against diphtheria. The patients were not related to each other.

6.1.4 Pathogen

In 2022, RIVM received fourteen *C. diphtheriae* and three *C. ulcerans* strains isolated from wounds or ulcera. In 2023, for the period up to and including April, RIVM received no *C. diphtheriae* strains and two *C. ulcerans* strains, one from a skin swab and one from unknown material. Out of the seventeen strains in 2022 and the two strains in 2023, seven positive test results regarding exotoxin production were found. These seven strains refer to the seven confirmed diphtheria cases that were reported in 2022, of which one case had disease onset in 2022 and was diagnosed in 2023. See Table 6.1.1 for details on laboratory results for the respective strains.

6.1.5 International developments

From early 2022 up to and including 21 April 2023, 400 cases of diphtheria among asylum seekers, caused by an infection with *C. diphtheria*e, were reported to ECDC by Germany (162), the UK (74), Austria (72), France (27), Belgium (25), Switzerland (25), Norway (7), the Netherlands (5), Italy (2), and Spain (1). Most cases were male, aged 8-49 years and born in Afghanistan or Syria, but for many other cases, the country of origin is unknown. Most cases (~70%) concerned cutaneous diphtheria, while ~15% concerned respiratory diphtheria (sometimes in combination with cutaneous diphtheria). Fewer than 10% of the cases were asymptomatic, and for a small part of the cases the type was unknown. Up to February 2023, ECDC was not aware of any transmission into the broader EU/EEA population [1]. In the 2016-2020 period, an average of 26 *C. diphtheria*e cases was reported annually in the EU/EEA and the UK (excluding Switzerland). ECDC published a Rapid Risk Assessment concerning the increase of diphtheria cases among migrants in October 2022 [2], with an update in December 2022 [3]. Up to and including 8 March 2023, two fatal cases were reported by ECDC [1].

Among the typed *C. diphtheria*e isolates in Europe, three different sequence types were identified. Within each sequence type, genetic clustering of the recent cases was shown. Because not many isolates were subjected to further typing, the information available is too limited to draw firm conclusions and investigations led by the ECDC are ongoing [2].

The increase in the number of cases may have various causes: a larger amount of asylum seekers may come from countries where diphtheria is endemic, circulation of diphtheria may be increasing in the countries of origin, and/or there may be an increased risk of transmission during their journey to Europe or in a setting such as asylum seekers' reception centres [2]. Diphtheria is endemic in the middle East, Eastern Europe, Asia, the South Pacific, Africa and South America. In the past seven years, outbreaks of respiratory diphtheria have occurred in Bangladesh, Myanmar, Haiti, Indonesia, South Africa, Ukraine, Venezuela, Vietnam, and Yemen [4, 5]. In the past twenty years, the vaccination coverages of three doses of DTP vaccine has increased in the African, South-East Asian and Eastern Mediterranean region to, respectively, 72%, 91% and 84% in 2022. However, in the American region, the vaccination coverage decreased to 83% [6].

6.1.6 Literature

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6.1.7 Other RIVM publications

Vandebriel RJ, Stalpers CAL, Vermeulen JP, Remkes M, Schmelter M, *et al.* Development of a cell line-based in vitro assay for assessment of Diphtheria, Tetanus and acellular Pertussis (DTaP)-induced inflammasome activation. Vaccine 2022; 40(38):5601-5607.

6.2 *Haemophilus influenzae* disease

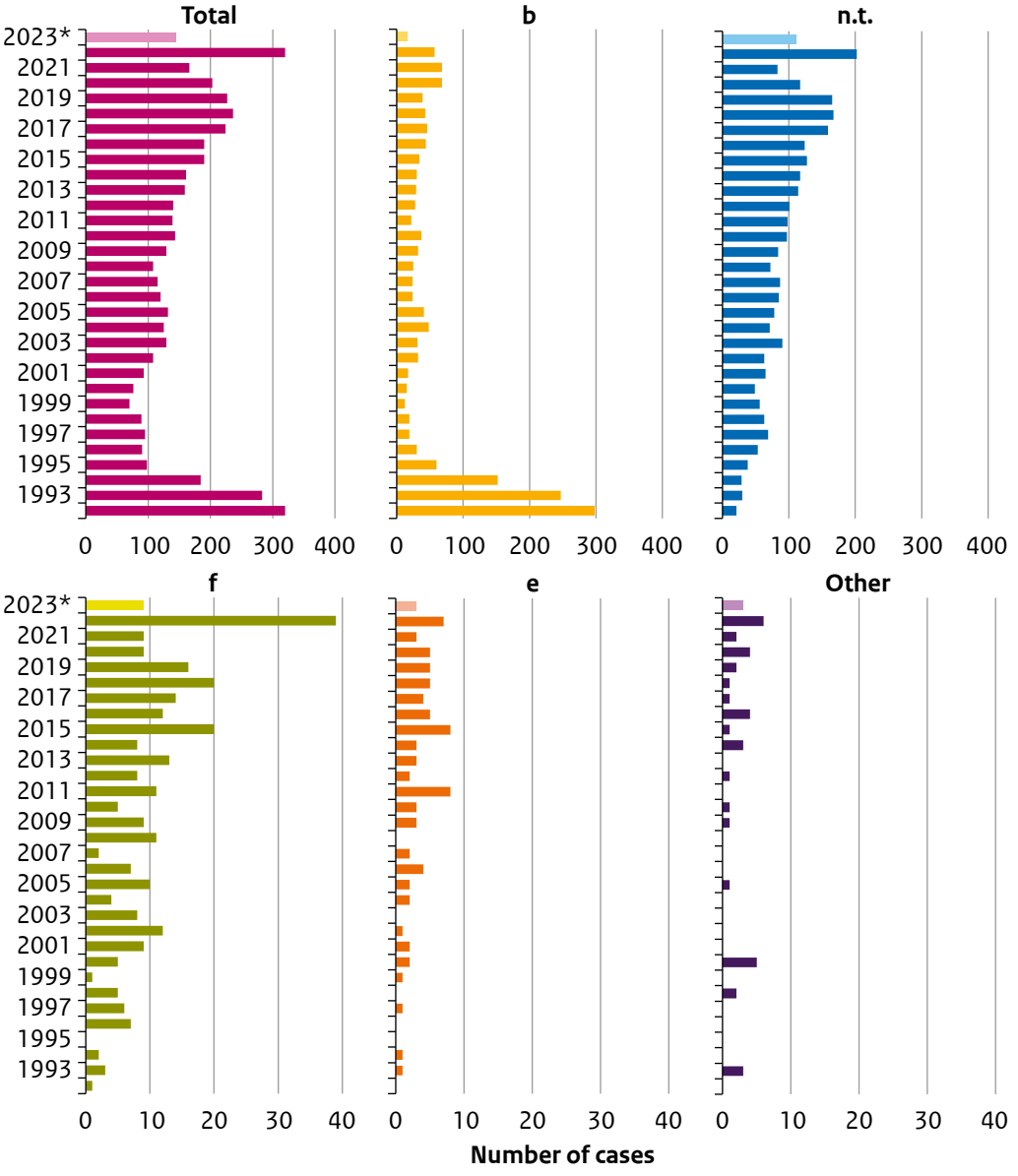
A. Steens, T. Garcia Vilaplana, W. Freudenburg-de Graaf, R. Mariman, H.E. de Melker, N.M. van Sorge

6.2.1 Key points

- In 2020 and 2021, the invasive *Haemophilus influenzae* serotype b (Hib) disease incidence was higher than observed before (0.39/100,000 in both years). In 2022, it slightly decreased again to an incidence of 0.32 per 100,000 inhabitants (n=59). In the first 4 months of 2023, the number of cases has been similar to the pre-COVID-19 years (n=12).
- The invasive Hib disease incidence among children <5 years old has been increasing since 2012 and continued to increase in 2022 to 3.3/100,000 (n=29).
- Vaccine effectiveness (VE) against disease in January 2022-April 2023 was estimated to be 89% (95%CI 76-95) for those older than 3 months and born in 1993 or after.
- While in 2020 and 2021, the observed incidences were also higher for older age groups, in 2022, the incidences generally returned to pre-COVID-19 levels.
- There was a schedule change from three primary doses + a booster (3+1) to two primary doses + a booster (2+1) in January 2020. In the period spanning from 2020 up to and including April 2023, according to the age at disease onset, none of the cases that were vaccinated with the 2+1 schedule could have been prevented if vaccinated with the former 3+1 schedule.
- Out of 72 Hib cases with known outcomes from 2022 through April 2023, 7 died (1 was <5 years old but sufficiently vaccinated according to age, 5 were aged 60+).
- After a decrease related to the mitigation measures against the COVID-19 pandemic, invasive disease caused by non-typeable *Haemophilus influenzae* (NTHi) and other non-b serotypes have increased to (slightly) higher levels than pre-COVID-19 in 2022 and the first four months of 2023.

6.2.2 Tables and figures

Figure 6.2.1 Number of *Haemophilus influenzae* invasive disease cases per serotype, 1992-2023*. Note: the 'Other' category includes serotype a and serotype d, but since 2017, no serotype d has been observed. Corresponding numbers thus indicate serotype a.



* *Up to and including April 2023.*

Figure 6.2.2 Age-specific incidence rate of *Haemophilus influenzae* type b (Hib) invasive disease, 2001-2022.

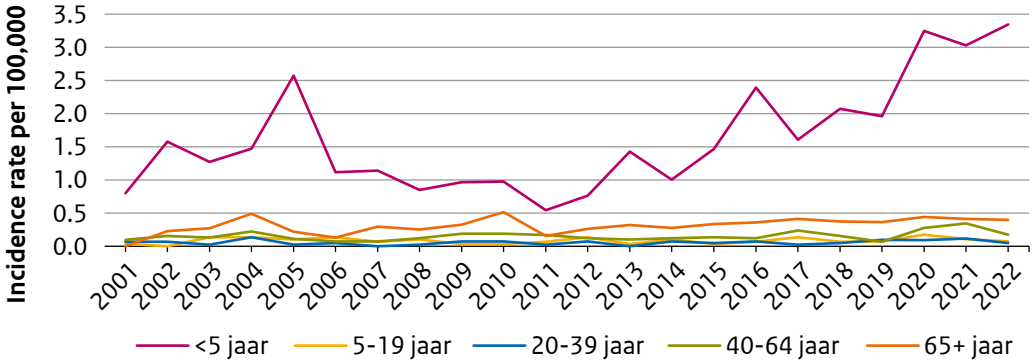


Figure 6.2.3 Estimated incidence of invasive *Haemophilus influenzae* serotype b (Hib) disease by year, age group and vaccination status for children <5 years from 2005-2022, with a 3-year moving average (note the different y-axes for not (sufficiently) vaccinated groups).

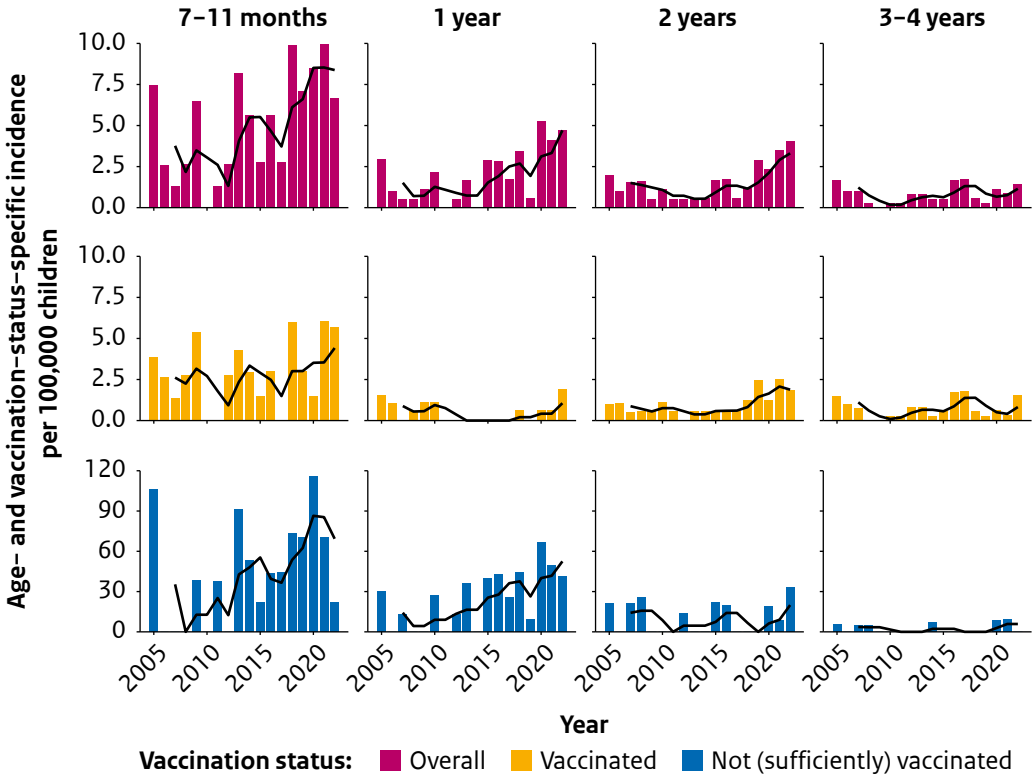
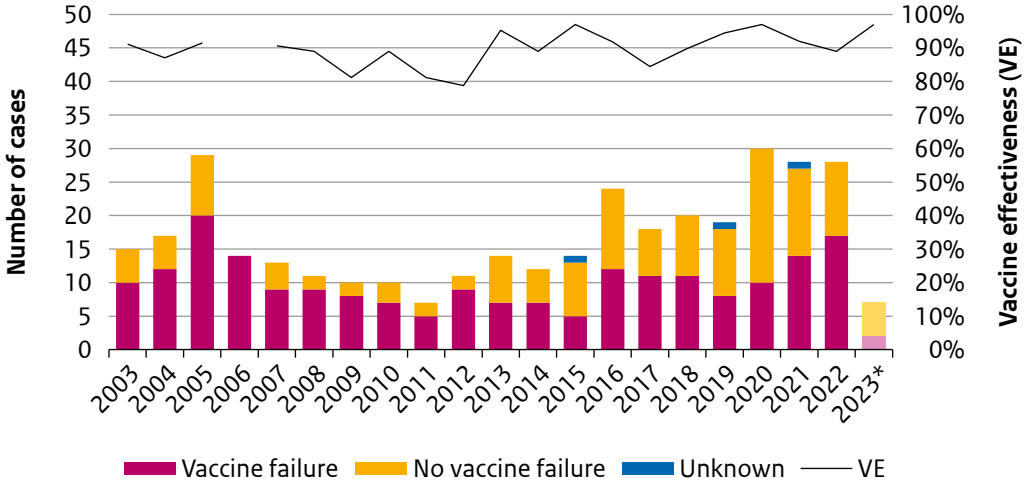


Figure 6.2.4 Number of *Haemophilus influenzae* type b (Hib) cases in cohorts eligible for vaccination (i.e. born after 1 April 1993) and at least 3 months of age, by vaccination status and estimated vaccine effectiveness, 2003-2023*. Note: in 2006, VE could not be estimated because 100% of the cases was vaccinated.



** Up to and including April.*

Figure 6.2.5 Age-specific incidence of non-typeable *Haemophilus influenzae* (NTHi) disease, 2001-2022.

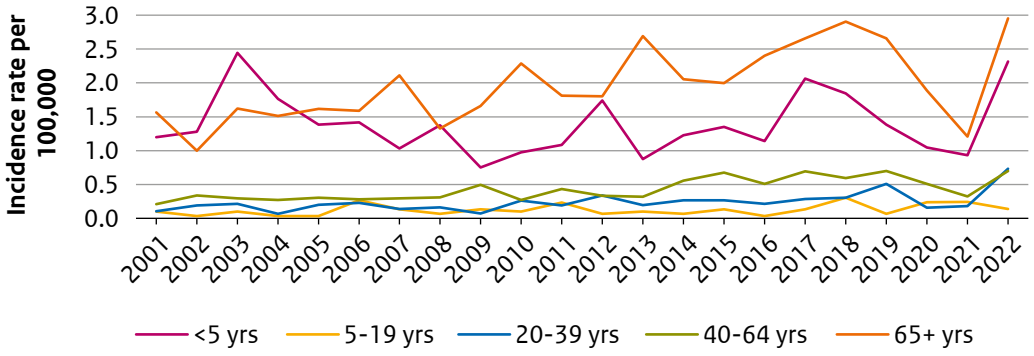
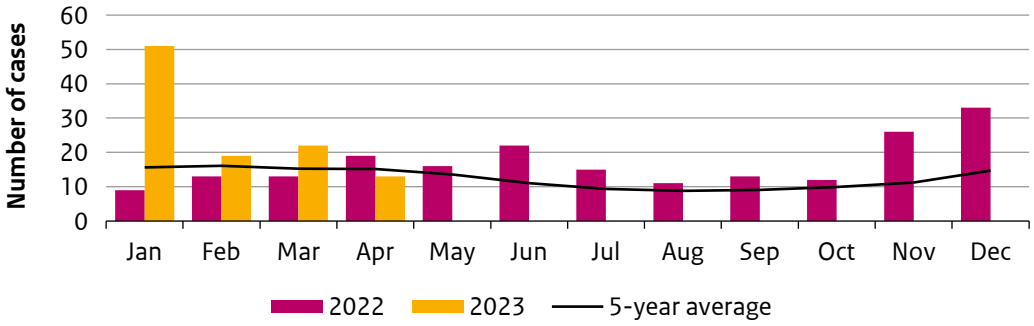


Figure 6.2.6 Number of cases with invasive disease caused by non-typeable *Haemophilus influenzae* (NTHi) in 2022 (violet) and January-April 2023 (yellow) by month compared with the pre-COVID monthly 5-year moving average (2015-2019).



6.2.3 *Haemophilus influenzae* serotype b (Hib)

Invasive Hib disease can present itself as epiglottitis, meningitis, sepsis, pneumonia, and septic arthritis. To confirm an infection with Hib, the isolate needs to be serotyped. Since 1959, all *Haemophilus influenzae* (Hi) isolates from invasive infections in the Netherlands, are submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) for serotyping. Only Hib is currently vaccine-preventable and has been notifiable since December 2008. Information of notified cases is linked to the information on isolates of the NRLBM [1]. For non-b Hi infections, only limited case information is available.

6.2.3.1 Hib epidemiology

6.2.3.1.1 Incidence

Hib vaccination was introduced in the Netherlands in April 1993. After an initial decrease following vaccination, the number of Hib cases fluctuated around 30 cases per year, with a maximum of 48 cases in 2004 (range in 1996-2019: 12-48, Figure 6.2.1). In 2020 and 2021, the incidence was 0.39/100,000 each year (n=68); this was higher than observed in earlier years (between 0.15-0.27/100,000 after the 2004 peak), despite the preventive measures because of the COVID-19 pandemic that led to decreases in other respiratory invasive bacterial diseases [2]. In 2022, the incidence slightly decreased again to 0.32/100,000. In the first 4 months of 2023, the number of cases has been similar to the pre-COVID-19 years (n=12).

Focusing on specific age groups, the 2022 incidence in <5-year-olds (3.3/100,000; n=29) was the highest since the decrease following vaccine introduction. The incidence among <5-year-olds has been steadily increasing since 2012 (Figure 6.2.2). In 2022, when COVID-preventive measures were still partly in place, half of the annual number of cases already occurred in the first 4 months (n=14), while in January-April of 2023, 'only' 6 cases have been observed, which is similar to the years 2017, 2020, and 2021.

For children <5 years, we performed separate detailed analyses on small age groups separately for vaccinated and not sufficiently vaccinated (termed unvaccinated) children. The estimated Hib incidence in unvaccinated children was much higher compared to the incidence in vaccinated children of the same age (see Figure 6.2.3). The incidence decreased with age in unvaccinated children, but in vaccinated children, the incidence in 2-year-olds was higher than for 1-year-olds (though, still much lower than in unvaccinated children). The increasing trend observed over time differed by vaccine status; for unvaccinated children, the increase was observed earlier (from 2009) and at a younger age (from 7-11 months) compared to vaccinated children (N.B. small numbers). In vaccinated children, the increase was observed among 2-year-olds from 2018. These age- and vaccination-status-specific results may indicate that different mechanisms have caused the increased incidence in <5-year olds, although no conclusions can be drawn. Increased transmission/colonisation, possibly as a result of the lower antibody concentrations in the population [3], might play a role, as well as possibly faster waning of vaccine protection with age in recent cohorts. It is being investigated whether the kind of vaccine product plays a role in the latter.

In 2020 and 2021, the observed incidences were not only higher in those aged <5 years but also in older age groups (Figure 6.2.2). In 2022, the incidences generally returned to pre-COVID-19 levels; for those aged 5 years and older, the incidence was 0.18/100,000 in 2022 (n=30) versus 0.15/100,000 on average in 2015-2019.

6.2.3.1.2 Disease outcome and underlying medical conditions

Disease outcome is known for 58 Hib patients in 2022. Of these, 5 patients died (9% of those with known information; outcome missing for 2 cases); 1 fatal case was under 5 years of age, had comorbidities and was sufficiently vaccinated against Hib; the other fatal cases were adults. During the first 4 months of 2023, 2 older adults died from Hib. In the pre-COVID-19 period, 0 or 1 fatal Hib cases were reported annually (0-4%), but during that period, outcome data was not available for several cases (69% available data in 2016-2019), which complicates comparison. During 2020 and 2021, 4 (6%) and 3 (5%) cases, respectively, died of Hib; in these years, outcome was unavailable for 2 and 5 cases.

It is often unknown whether or not a Hib patient has an underlying medical condition; for patients aged <5 years, this was reported for ~50%, while for older patients, the percentage with data on comorbidities was even lower. Out of the children aged <5 years with reported information in the period from 2015 onwards, about 20% had a reported underlying medical condition. Prematurity, a known risk factor for Hib, is largely unknown despite being enquired about through OSIRIS since mid-2021.

6.2.3.1.3 Vaccine history and vaccine effectiveness

In 2022 and 2023 (up to and including April), 30 and 7 Hib cases, respectively, were reported among vaccine-eligible cohorts (born from 1 April 1993 onwards) and at least 3 months of age (first dose in the standard schedule; Figure 6.2.4). Of these cases, 18 (49%) were not (sufficiently) vaccinated and 19 (51%) were sufficiently vaccinated (i.e. received at least 2 vaccinations with at least 2 weeks between the second vaccination and the date of diagnosis).

The proportion that was sufficiently-vaccinated was similar to earlier years (Figure 6.2.4). The overall VE of Hib vaccination in 2022 among those eligible for vaccination and >3 months old was estimated using the 'screening method' (see Appendix 1). The estimated VE was 89% (95% CI: 76-95) (Figure 6.2.4), which is not significantly different from earlier years.

We also looked at the VE by small age groups, and aggregated years for sufficient power (2008-2012, 2013-2017, 2018-2022). In this analysis, using Poisson regression, it was shown that the VE of those aged 7-11 months or 1 year was 90% or higher, with a lower limit of the 95% CI of ≥70% for all investigated time periods. In 2-year-olds, however, the VE was ≥90% in 2008-2012 and 2013-2017, but was slightly lower in 2018-2022 (84%, 95%CIs: 59%-93%). In 3-4-year-olds, the VE was ≤81% in all investigated time periods (though with wide CIs).

In 2022-23, most vaccinated cases (n=16/19) were younger than 5 years, and 6 (32%) of those had a reported underlying medical condition (NB, much information on comorbidity was missing); at least 2 with a known immune disorder. Out of the 16 eligible but not (sufficiently) vaccinated cases older than 3 months in 2022-23 for which information about the opinion about vaccination was available, 7 reported to be Reformed orthodox, and 4 to be generally critical of vaccination. The not (sufficiently) vaccinated children were between 0 and 2 years of age.

In January 2020, the standard vaccination schedule for Hib was changed from a 3+1 schedule with primary vaccination at 2, 3 and 4 months to a 2+1 schedule with primary vaccination at 3 and 5 months. The booster for both schedules is at 11 months of age. Since the schedule change, 9 cases occurred in infants aged <5.5 months, which is the cut-off used for being protected through vaccination in the 2+1 schedule. More specifically, all 9 cases occurred in infants younger than 3.5 months and therefore younger than the cut-off for protection in the 3+1 schedule. This means that, on the basis of the age of infection, none of the 9 infants could have been prevented through vaccination with the former 3+1 schedule.

6.2.3.2 Haemophilus influenzae disease caused by non-b serotypes

In 2022, 202 cases of invasive non-typable *Haemophilus influenzae* (NTHi) disease were diagnosed, resulting in an incidence of 1.15 per 100,000 (Figure 6.2.5). As expected, this was higher than during the COVID-19 years 2020 (0.67/100,000) and 2021 (0.47/100,000) but it also exceeded numbers of pre-COVID-19 cases (on average 0.87/100,000). The highest number of cases was observed in June as well as from November 2022 to January 2023 (Figure 6.2.6). In the first 4 months of 2023, 105 cases of NTHi disease have been diagnosed. As observed previously, the incidence has been highest among persons aged 65 and over (2.9 per 100,000; n=104) and children under 5 years of age (2.2 per 100,000; n=20) (Figure 6.2.5).

Last year we reported an increase in serotype F disease (Hif) at the start of 2022. Analysis of whole genome sequence data showed that all isolates belong to clonal complex (CC) 124. However, within this CC, substantial genetic variability was observed, making a common source unlikely. Overall, in 2022, 39 cases were diagnosed in comparison to 9-20 annually in the 2015-2021 period. The increase was mainly seen among those aged 65 years or over (n=24; 61% of cases). From January to April 2023, 9 Hif cases have been diagnosed.

Other Hi serotypes that have been diagnosed in 2022 are serotypes a (Hia) and e (Hie). These serotypes were also diagnosed slightly more often compared to other years but numbers are still low (6 Hia cases, 7 Hie cases). In 2023, up to and including April 2023, 3 cases of serogroup a and 3 of serogroup e have been diagnosed. No Hi serotype d disease has been found since 2017.

6.2.4 (Inter)national developments

6.2.4.1 Hib

In Portugal, Hib vaccine failures in <18-year-olds were characterised using prospective surveillance data of the 2010-2021 period [4]. In Portugal, Hib vaccination is administered at 2, 4, 6 and 18 months, with as a primary series a hexavalent vaccine and as a booster a pentavalent vaccine. The vaccine coverage is estimated to have been >95% since 2000. Of all Hi isolates, 51% was NT-Hi and 29% was Hib. In the 2016-2021 period, the Hib incidence was higher (0.29/100,000) than in the 2010-2015 period (0.10/100,000). During the study period, all Hib cases were <18 year (73% <5 years), and of these, 63% involved vaccine failure. Half of all vaccine failures occurred among children too young to have received the booster. In the Netherlands, most vaccine failures occur following the booster, which is given at 11 months. As in the Netherlands, most Hib cases were among previously healthy children.

6.2.4.2 Non-b Haemophilus influenzae

A systematic review including 94 studies involving 2701 patients reported increases in Hif incidence worldwide in the era of Hib vaccination [5]. As we have seen in the Netherlands, over time, the Hif incidence has increased worldwide. Globally, there is little genetic variability; the majority belonged to CC-124, just like the Dutch cases. The case fatality rate is high (14% found in the review; note, no data on outcome is available for Dutch Hif cases).

Another serotype that internationally gets attention is serotype a. While Hia has been increasing in the Americas [6] and specifically in the Arctic region [7], it has also increased in the UK [8]. The increase in the UK started in children in 2015, but other age groups, mainly 65-years and older, are now also affected, although the incidence remains low (0.03/100,000). Eight percent of the invasive Hia infections was reported to be fatal. ST1511 is a recently emerging clone that has increased in UK over time. Note that attempts are being made to make a Hia vaccine, but market availability is not yet close.

US surveillance data was used to investigate secondary transmission of invasive disease caused by *Haemophilus influenzae* to know whether prophylaxis should (also) be advised to contacts of non-b *Haemophilus influenzae* disease cases, as is being done for Hib in the US [9]. Clusters were defined as cases of invasive disease caused by the same serotype diagnosed in the same county that occurred within ≤60 days of one another during 2011–2018. For NTHi, <14 days instead of <60 days were used, and data was analysed for the 2015-2018 period. Subsequently, information on the cases in potential clusters was reviewed and WGS was performed. Of the 1584 investigated cases caused by encapsulated Hi, 157 potential clusters were reviewed, resulting in the identification of 5 pairs of secondary transmission (3x Hif, 1x Hia, 1x Hie, no Hib). Furthermore, of the 2426 cases with NTHi, 3 pairs of secondary

transmission were identified. So, although secondary transmission of non-b Hi was rare, this analysis shows that it can occur. Note that, in the US, antibiotic chemoprophylaxis is advised for household contacts and in childcare facilities in the eventuality of Hib cases, which may explain the absence of secondary Hib cases.

6.2.5 Literature

1.* van den Boogaard J, van der Ende A, Westerhof A, Ruijs WLM, de Melker HE, Knol MJ. Voldoen medisch microbiologische laboratoria en de GGD aan de landelijke meldingsplicht voor invasieve Hib-ziekte? Infectieziekten bulletin. 2019.

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3.* National Institute for Public Health and the Environment (RIVM). The National Immunisation Programme in the Netherlands. Surveillance and developments in 2021-2022. 2022.

4. Marques JG, Inacio Cunha FM, Bajanca-Lavado MP, Portuguese Study Group on *Haemophilus influenzae* Invasive Disease in C. *Haemophilus influenzae* Type b Vaccine Failure in Portugal: A Nationwide Multicenter Pediatric Survey. Pediatr Infect Dis J. 2023.

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8. Bertran M. Persistent increase in invasive *Haemophilus influenzae* serotype a (Hia) disease: prospective national surveillance, 2008/09 to 2021/22, England. 16th EMGM conference 2023.

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* *RIVM publication.*

6.3 Hepatitis B

T. Woudenberg, K.S.M. Benschop, A. Meiberg, J. Cremer, A.J. King, E. Op de Coul, H.E. de Melker

6.3.1 Key points

- Of the total number of 911 reported hepatitis B cases in 2022, 9% had an acute infection (n=80) and 91% had a chronic infection (n=815) (type of infection unknown for 16 reported cases).
- The incidence of acute hepatitis B notifications in 2022 (n=80) increased slightly compared to 2021 and was 0.45 per 100,000 population. Incidence is lower compared with the incidence in 2019 (0.61 per 100,000), the last year before the COVID-19 pandemic.
- Among the 80 acute hepatitis B notifications, three vaccinated persons were reported. Their age indicated that they were vaccinated because they belonged to a risk group.
- The number of newly diagnosed chronic HBV infections (n=815) was higher than in 2020 and 2021 and amounted to 4.6 per 100,000 population.
- Among both men and women, sexual contact was the most frequently reported risk factor for acute HBV infection.
- In 2022, genotype A continued to be the dominant genotype among acute HBV cases with 55% of 49 genotyped cases, followed by genotypes F and B (both 14%).

6.3.2 Tables and figures

Figure 6.3.1 Incidence of acute HBV infections in men and women by year in the Netherlands 1976-2022, and chronic HBV infections 2000-2022.

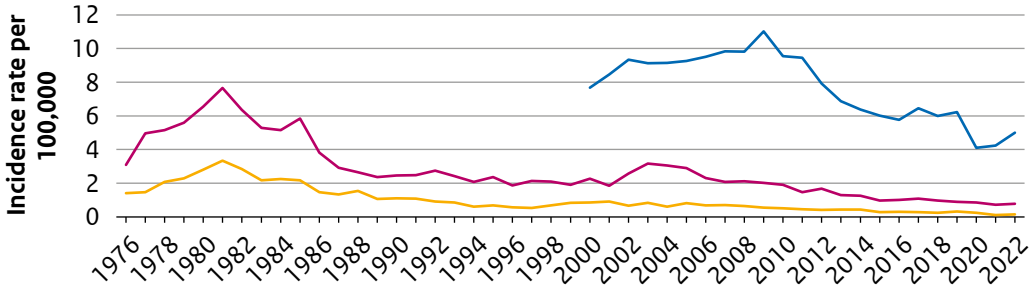


Figure 6.3.2 Optimised maximum parsimony tree based on the full-length sequence of HBV cases in the Netherlands in 2022 by reported transmission route (n=49).

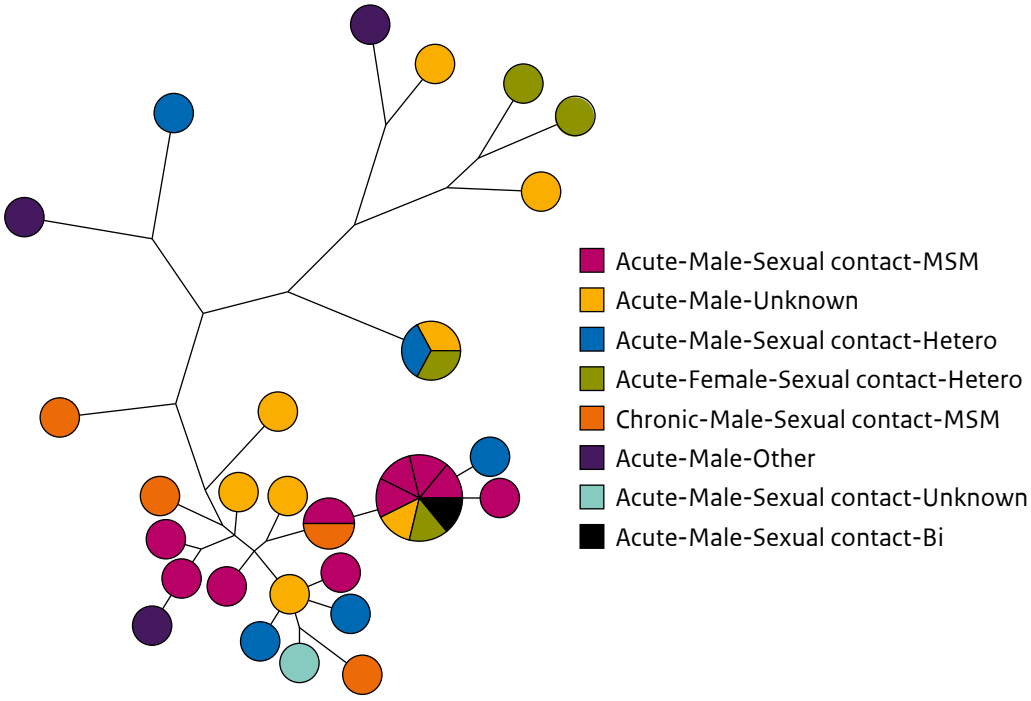


Figure 6.3.3 Genotype distribution of acute HBV cases in the Netherlands from 2004 to 2022.

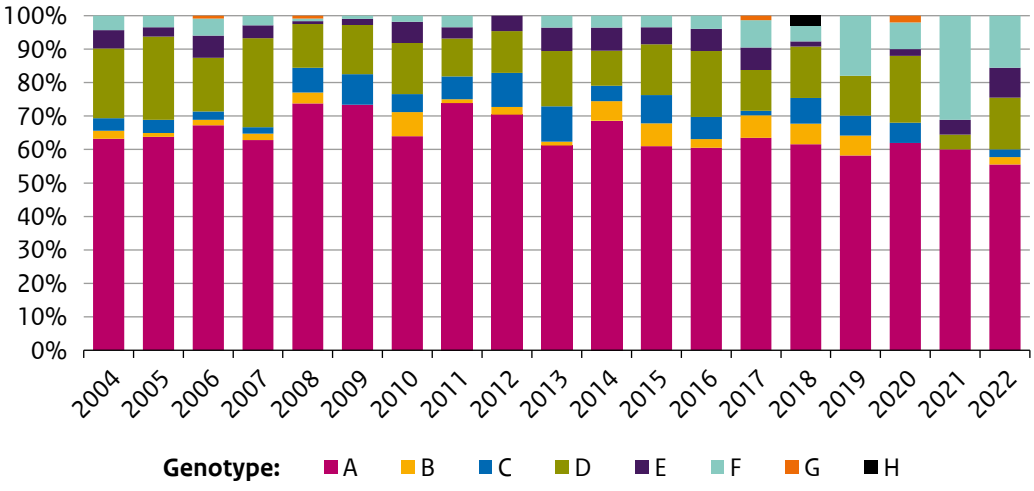
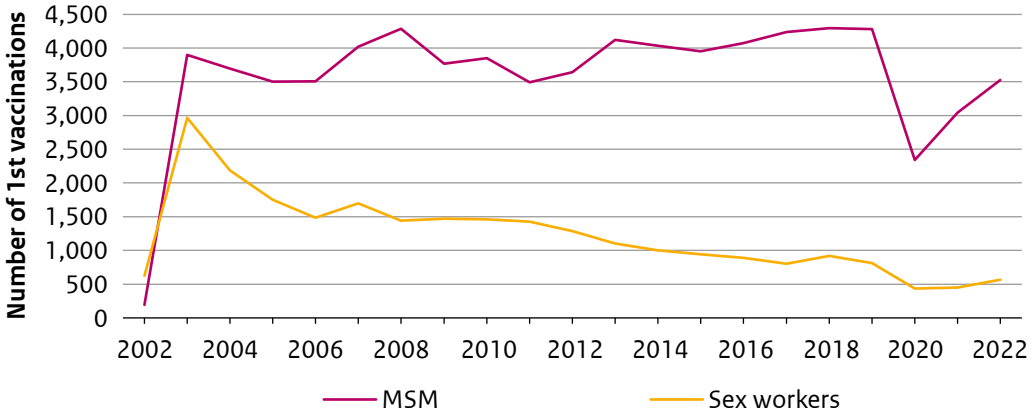


Figure 6.3.4 Number of first vaccinations per year from 2002 up to and 2022 in the programme for MSM and sex workers.



6.3.3 Epidemiology

In 2022, 911 hepatitis B infections were reported to RIVM, of which 831 (91%) were chronic/unknown infections, and 80 (9%) were acute infections.

6.3.3.1 Acute HBV epidemiology

The number of notified acute HBV infections in 2022 amounted to 80, an 8% increase compared with 2021, when 74 cases were notified. The incidence of acute HBV notifications in 2022 was 0.45 per 100,000 population, 0.77/100,000 among men and 0.15/100,000 among women. The HBV incidence over time is shown in Figure 6.3.1. The mean age of patients with acute HBV infection was 45 years and was higher in men (46) than in women (39). Out of the 80 reported cases, 3 patients (4%) were vaccinated, 69 (96%) were unvaccinated, while for 8 patients the vaccination status was unknown. The three vaccinated persons were found positive for acute hepatitis B infection at the ages of 33, 48 and 66 years, indicating that they were vaccinated because they belonged to a risk group. No cases of acute hepatitis B were reported among 0-19-year-olds; the youngest patient was 20 years old. 16 (20%) patients with acute hepatitis B were admitted to hospital in 2022. One patient died. In 2022, most cases of acute HBV infection (60%; among men 60% (40 out of 67 cases), and among women 62% (8 out of 13 cases)) were acquired through sexual contact. For 24% of the reports of acute HBV infection, the most likely route of transmission remained unknown despite source tracing. One case was infected due to injecting drug use (IDU, 1%) and for 12 cases (15%), the route of transmission was registered as 'other'. Most patients with acute hepatitis B were born in the Netherlands (73%).

6.3.3.2 Chronic HBV epidemiology

The number of chronic HBV notifications was around 1,000-1,100 per year from 2014 to 2019 (incidence 5.8-6.4 per 100,000) but declined to 722 cases in 2020 and 743 cases in 2021 (incidence 4.2 per 100,000) (Figure 6.3.1). Since chronic hepatitis B is largely asymptomatic, the number of new diagnoses is highly influenced by testing practices. The number of people tested for HBV infection annually is unknown, but the lower number in 2020 and 2021 is probably related to the COVID-19 pandemic. The number of chronic HBV notifications was 815 in 2022, an increase since 2020 (n = 722 and 2021 (n = 743). In 2022, 92% of the chronic HBV patients whose country of birth was known, were born abroad. The number of newly diagnosed chronic HBV infections in people born abroad is about 67 times higher than that of people born in the Netherlands (28.3 compared to 0.4 per 100,000 population). The number of notifications per country of birth fluctuates over time. In 2022, the most frequently reported countries of birth were Turkey (n=75, 9%), China (n=73, 9%), the Netherlands (n=63, 8%), Syria (n=59, 7%), and Afghanistan (n=43, 5%). A large proportion of cases (43%) acquired chronic HBV infection through vertical transmission. In 42% of the reports of chronic HBV infection, the most likely route of transmission was unknown. Sexual contact was the source of infection for 5%. Transmission also occurred via other routes such as needle stick injuries (1%), or via injecting drug use (IDU, 1%) and other (9%).

6.3.4 Pathogen

Samples for genotyping are collected from all patients with an acute HBV infection, from MSM patients with a chronic infection and from people with an HBV infection detected through the vaccination programme for behavioural risk groups. In 2022, 72 out of the 80 acute HBV cases (90%) and 6 out of the 11 chronic HBV cases from risk groups were available for molecular typing. PCR amplification and sequencing gave results for 49 samples of acute HBV infections for the full-length genome. An optimised maximum parsimony tree of these sequences by the most likely transmission route is shown in Figure 6.3.2. In 2022, six different genotypes were found (Genotype A, B, C, D, E, F) among notified acute cases and three different genotypes among notified chronic cases of HBV. The largest cluster of cases continues to be among genotype A infected cases, the most common genotype for acute HBV in the Netherlands (Figure 6.3.3). Of acute cases with genotype information, 55% were genotype A. Genotype F and D were the second-most detected genotype among acute cases, (both: n=7, 14%). Genotype A was also most common among chronic cases in risk groups (4/7; 57%), whereas genotype F was not observed among chronic cases of HBV.

6.3.5 (Inter)national developments

6.3.5.1 HBV vaccination programme for risk groups

Hepatitis B vaccinations have been introduced incrementally in the Netherlands, from targeted programs for high-risk groups, starting with high-risk groups and certain patient groups in 1983, and wrapping up with a universal program for children in the National Immunization Program since 2011. In between, universal prenatal screening was implemented in 1989 to detect and prevent vertical transmission from mother to baby. Subsequently, men who have sex with men, drug users, sexworkers and heterosexuals with frequently changing

sexual contacts, were invited to be vaccinated in 2002. A year later, children of migrants from countries with high hepatitis B prevalence were also invited for hepatitis B vaccination. Since 2011, the hepatitis B vaccine has been included in the DKTP-Hib-HepB vaccine within the National Immunization Program.

The number of first vaccinations given as part of the HBV vaccination programme for high behavioural risk groups (men who have sex with men and sex workers) has been relatively constant over the years up to 2019 (Figure 6.3.4). The decrease in vaccinations in 2020 and 2021 is likely related to the COVID-19 pandemic. In 2022, the number of vaccinations rose again but did not reach the same level as in the years before 2020.

6.3.5.2 Trends of acute and chronic HBV in EU/EEA.

The overall trend for acute hepatitis B cases in the EU/EEA has shown a steady decline from 2012–2021, as observed in the Netherlands [1]. According to ECDC, the decrease is most likely related to national hepatitis B vaccination programmes. For both acute and chronic cases in EU/EEA countries, a steeper decline in rates of new diagnoses was observed in 2020 and 2021 compared to the trajectory in earlier years. In the Netherlands, this was especially the case for chronic cases of HBV, whereas the number of newly reported cases of acute HBV remained stable in COVID-19 pandemic years. ECDC suggests that the steeper decline during the COVID-19 pandemic may be the result of a combination of changes in healthcare seeking behaviours and testing practices in EU/EEA countries.

6.3.5.3 Towards ending viral hepatitis

In 2021, the Netherlands and Italy were the first countries to have achieved regional targets for control of hepatitis B through immunisation set by the European Region office of WHO. One of these targets is to reach a vaccination coverage over 90% of three hepatitis B vaccinations as part of a universal new-born vaccination programme. Other targets are to provide evidence on effective measures to prevent perinatal transmission of hepatitis B and seroprevalence data on screening pregnant women for hepatitis B. Another eight countries have followed the example of the Netherlands and Italy and had their achievements of hepatitis B control targets validated by WHO European Region. More countries reaching elimination targets makes it more likely for the European region to reach the ultimate goal of eliminating viral hepatitis as a public health threat by 2030 [2].

6.3.6 Literature

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6.4 Human papillomavirus (HPV)

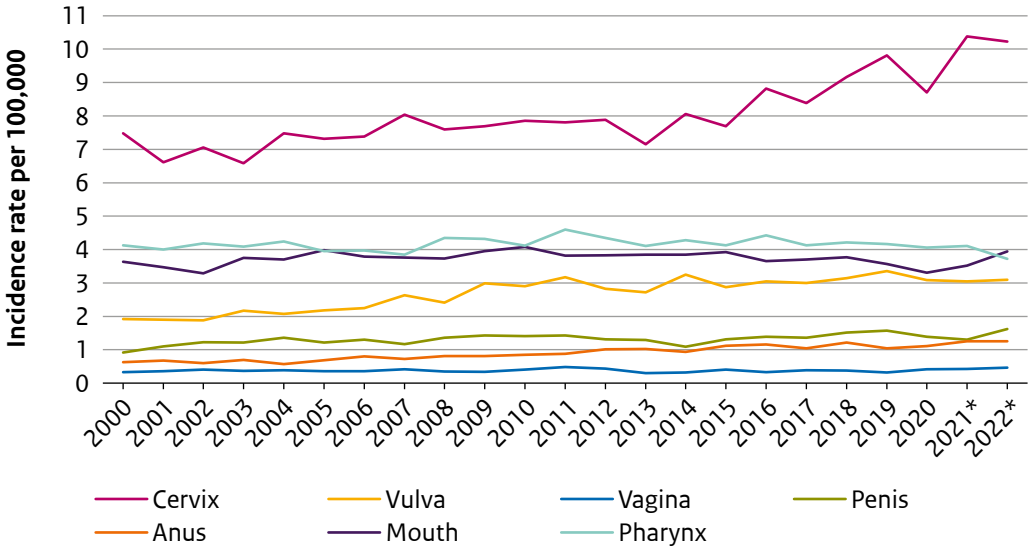
J.W. Duijster, M. Middeldorp, J.G.M. Brouwer, J.A.M. Kusters, A. King, H.E. de Melker

6.4.1 Key points

- In February 2023, an HPV vaccination catch-up campaign started, in which adult males and previously unvaccinated or partly vaccinated women born in the years 1996 up to and including 2003 are invited for HPV vaccination.
- Seven months after the first dose of vaccination in boys vaccinated in 2022, antibody levels against HPV16 and HPV18 were high.
- The vaccine effectiveness (VE) of the bivalent vaccine against persistent vaccine-targeted HPV types (types 16 and 18) remained high (above 97%) up to 12 years post vaccination with a 3-dose regimen, and up to 8 years post vaccination with a 2-dose regimen.
- Among women up to the age of 24, significant beneficial early effects of HPV vaccination on the occurrence of (pre-)cancerous lesions and high-risk HPV were shown.

6.4.2 Tables and figures

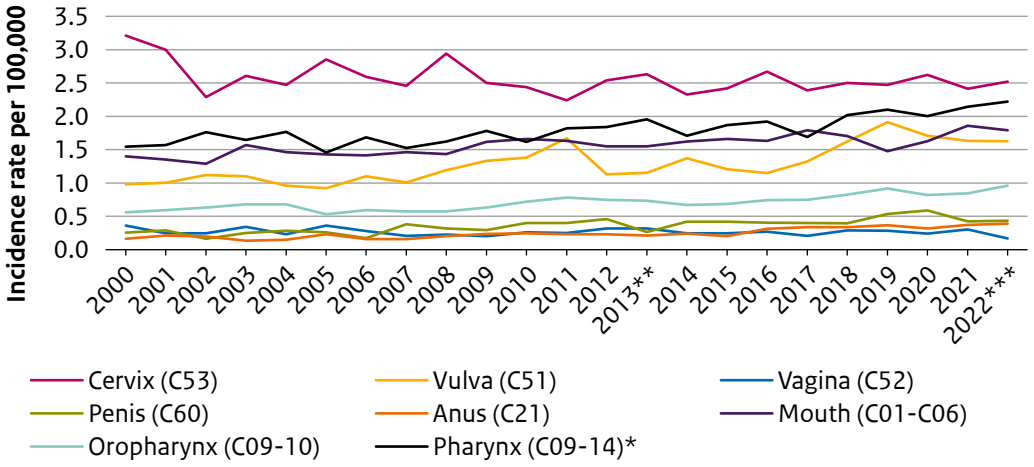
Figure 6.4.1 Incidence rates** (per 100,000, standardised by European standardised rates) of cervical, vulvar, vaginal, penile, anal, mouth/oral and pharyngeal cancer in the Netherlands, 2000-2022.



** Preliminary incidence rates.*

*** Incidence rates were obtained from the Netherlands Cancer Registry, IKNL (iknl.nl/nkr-cijfers, accessed 20 March 2023).*

Figure 6.4.2 Incidence rates per 100,000 of deaths related to cervical, anogenital, mouth, oropharyngeal and pharyngeal cancers in the Netherlands, 2000-2022.

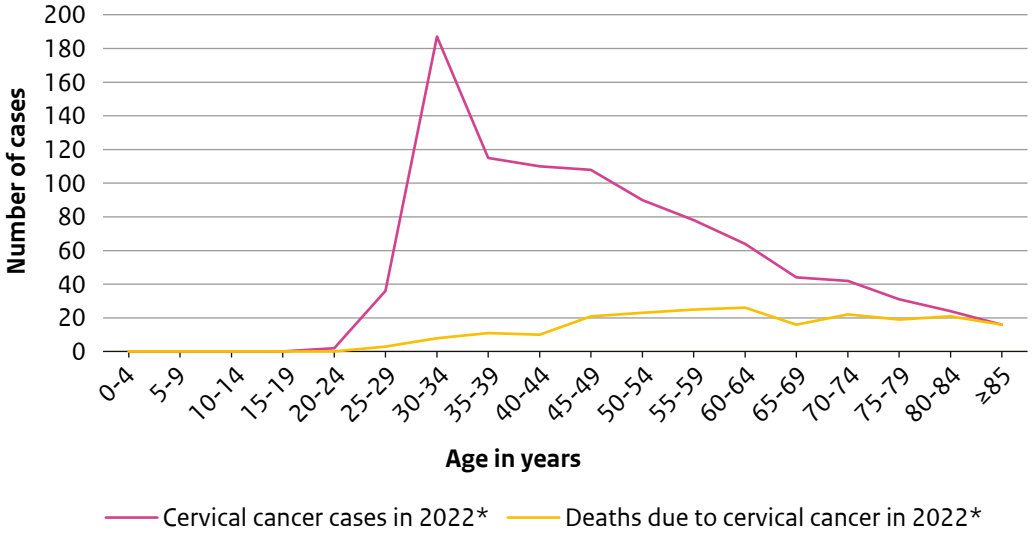


** Number of deaths due to pharynx cancer includes the number of oropharynx cancer deaths.*

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

**** Preliminary incidence rates.*

Figure 6.4.3 Absolute number of newly diagnosed cervical cancer cases and absolute number of deaths due to cervical cancer in 2022*.



** Preliminary data.*

Table 6.4.1 Vaccine effectiveness against incident and persistent HPV infections (twelve months) in young women eligible for three doses of HPV vaccination in the HAVANA study up to twelve years post vaccination.

	Adjusted* VE (95% CI)	
	Incident infections	**Persistent infections**
Vaccine types (16/18)	77.7% (68.8-84.1%)	96.8% (90.0-99.0%)
Cross-protective types (31/33/45)	48.1% (31.8-60.6%)	64.7% (42.0-78.5%)
hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59)	12.2% (2.1-21.2%)	19.5% (4.9-31.8%)
hrHPV types 9-valent vaccine (16/18/31/33/45/52/58)	32.6% (21.6-42.1%)	46.6% (32.4-57.9%)

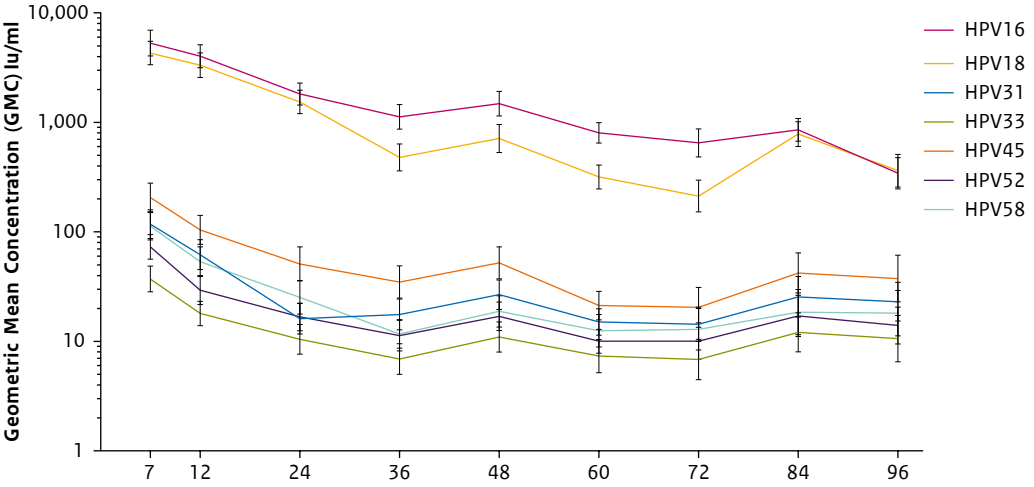
** Adjusted for age, urbanisation degree, ever used contraception, and ever had sex. CI, confidence interval; VE, vaccine effectiveness.*

Table 6.4.2 Vaccine effectiveness against incident and persistent HPV infections (twelve months) in young women eligible for two doses of HPV vaccination in the HAVANA2 study up to eight years post vaccination.

	Adjusted* VE (95% CI)	
	Incident infections	**Persistent infections**
Vaccine types (16/18)	88.1% (69.4-95.3%)	100%
Cross-protective types (31/33/45)	45.5% (10.5-66.8%)	82.1% (37.4-94.9%)
hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59)	18.3% (1.2-32.4%)	33.2% (7.6-51.7%)
hrHPV types 9-valent vaccine (16/18/31/33/45/52/58)	39.6% (21.4-53.6%)	57.2% (30.5-73.7%)

** Adjusted for age, ever used contraception, and ever had sex. CI, confidence interval; VE, vaccine effectiveness.*
Note: Due to low numbers of 12-month persistent infections, VE estimates against type-specific persistent infections could not be calculated.

Figure 6.4.4 Geometric Mean Concentrations (GMCs; IU/mL) of HPV types 16/18/31/33/45/52/58 at 7, 12, 24, 36, 48, 60, 72, 84, and 96 months after the first dose among girls in the HPV-2D study*.



** Preliminary data.*

6.4.3 Epidemiology

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

In 2022, incidence rates of HPV-related cancers in the Netherlands ranged from 0.47 new diagnoses per 100,000 women for vaginal cancer to 10.23 new diagnoses per 100,000 women for cervical cancer (preliminary data, Figure 6.4.1). The preliminary incidence rate of cervical cancer in 2022 was comparable to the previous year. Preliminary mortality rates in 2022 were estimated at 2.52 per 100,000 women for cervical cancer and 0.17 per 100,000 women for vaginal cancer (preliminary data, Figure 6.4.2). For pharyngeal cancer and oropharyngeal cancer, the mortality rates slightly increased compared to previous years, thereby continuing the trend of increasing mortality for these cancers since the year 2000 (preliminary data, Figure 6.4.2). In absolute numbers, preliminary data show that 2,372 women were diagnosed with HPV-related cancers (in cervix, vulva, vagina, anus, mouth, or pharynx) and 1,614 men were diagnosed with HPV-related cancers (in anus, mouth, pharynx, or penis) in

the Netherlands in 2022 [8]. Also, 645 women and 554 men died of HPV-related cancers in 2022 [9]. The age-specific number of cervical cancer diagnoses and deaths caused by cervical cancer in the Netherlands are shown in Figure 6.4.3.

6.4.4 Current/ongoing research

6.4.4.1 HPV among vaccinated and unvaccinated adolescents (HAVANA)

A prospective cohort study (HAVANA) among vaccinated and unvaccinated 14- to 16-year-old girls eligible for the catch-up campaign, which was initiated in 2009, is still ongoing. The primary aim of this study is to monitor the effect of three doses of the bivalent (2-valent) HPV vaccine on HPV type-specific presence among vaccinated and unvaccinated women. Vaginal self-swabs collected in this cohort were tested for the presence of HPV DNA. Vaccine effectiveness (VE) against incident and persistent infections is determined every year. Up to twelve years post vaccination, a high VE against both incident and 12-month persisting vaccine-type infections (HPV16/18) (78% and 97%, respectively) was observed for the 2-valent vaccine (Table 6.4.1). Moreover, the VE against cross-protective HPV types 31/33/45 was 48% (95% CI: 32, 61) for incident infections and 65% (95% CI: 42, 79) against 12-month persisting infections. VE estimates up to twelve years post vaccination against incident and persistent infections are shown in Table 6.4.1. Type-specific VE estimates up to 12 years post vaccination against 12-month persistent infections were 96% (95% CI: 87, 99) for HPV16, 100% (model did not converge due to absence of persistent HPV18 infections among vaccinated participants) for HPV18, 78% (95% CI: 56, 89) for HPV31, -11% (95% CI: -134, 47) for HPV33, and 55% (95% CI: -50, 87) for HPV45. VE estimates between 76% and 88% against incident infections were found for HPV types 16, 18 and 45. VE estimates against incident HPV31 and HPV33 infections were 48% (95% CI: 26, 63) and 34% (95% CI: 0, 58) respectively.

6.4.4.2 HAVANA2

In 2016, a second prospective cohort study (HAVANA2) was initiated among vaccinated and unvaccinated girls who were eligible for the two-dose HPV vaccination schedule in 2014 (birth cohort 2001). A follow-up of this cohort is performed annually, where the girls are asked to complete a questionnaire and hand in a vaginal self-swab. VE against incident infections could be estimated up to eight years post vaccination. This resulted in a VE of 88% (95% CI: 69, 95) against incident vaccine type (HPV types 16/18) infections. The pooled VE estimate for 12-month persistent HPV16/18 infections was 100% (model did not converge due to absence of persistent HPV16/18 infections among vaccinated participants). Moreover, the VE against cross-protective HPV types 31/33/45 was 46% (95% CI: 11, 67) for incident infections and 82% (95% CI: 37, 95) for 12-month persisting infections. VE estimates up to eight years post vaccination against incident and persistent infections (type-specific and combined endpoints) are shown in Table 6.4.2. Type-specific VE estimates up to 8 years post vaccination against incident infection were 85% (95% CI: 56, 95) for HPV16, 96% (95% CI: 66, 99) for HPV18, 60% (95% CI: 22, 79) for HPV31, 27% (95% CI: -64, 67) for HPV33, and 74% (95% CI: -28, 95) for HPV45. We found a VE against incident HPV58 infections of 9% (95%CI: 2, 73). No persistent type-specific HPV16/18/31/45 infections were observed among vaccinated participants. For persistent HPV33 infections, the VE was 43% (95% CI: -155, 87).

6.4.4.3 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 girls (birth cohort 2001) who were eligible for vaccination with a two-dose schedule, started in 2014. Annually, the participants complete a web-based questionnaire and provide self-collected finger-prick blood. Up to 96 months of follow-up, the seropositivity for vaccine types HPV16/18 was 100% (data not shown). In the first 36 months post vaccination, a decrease in geometric mean concentrations (GMCs) of HPV16/18 antibody levels was observed (Figure 6.4.4). Next, HPV 16/18 antibody levels more or less stabilised until 96 months post vaccination. HPV16/18 antibody levels were still high 96 months post vaccination with a GMC of 782 IU/mL and 257 IU/mL, respectively. GMCs were considerably lower for HPV types 31, 33, 45, 52, 58.

Since 2022, boys are also invited for routine HPV vaccination in the Netherlands at the age of 10 years. Therefore, a cohort study to examine the kinetics in antibody levels among routinely vaccinated boys (birth cohort 2012) was initiated in 2022. Up to seven months post vaccination, seropositivity for vaccine types HPV16/18 was 100%. HPV16/18 antibody levels were high 7 months post vaccination with GMCs of 7,717 IU/mL and 3,496 IU/mL, respectively. The GMCs for HPV types 31, 33, 45, 52 and 58 were considerably lower than the GMCs for HPV16/18 at 7 months post vaccination. The observed GMC for HPV16 was higher among routinely vaccinated boys (birth cohort 2012 vaccinated at 10 years of age) compared to the GMC of routinely vaccinated girls (birth cohort 2001 vaccinated at 12 years of age) 7 months post vaccination with a 2-dose schedule (7,717 IU/mL versus 5,303 IU/mL, respectively).

6.4.4.4 Early effect of bivalent vaccination on cervical cytology outcomes among young Dutch women
In the Netherlands, the first cohort of women who were eligible for HPV vaccination in the NIP enter the cervical cancer screening programme in 2023. Yet, about 2% of the Dutch women has undergone cervical screening before the age of entry into the screening programme (i.e., so-called 'opportunistic screening'), mostly due to presence of gynaecological symptoms. By linking data on vaccination status from Praeventis, the immunisation register of the Netherlands, to the cervical screening data from PALGA, the Dutch National Pathology Databank, the early effects of HPV vaccination on any presence of cytological abnormalities were assessed [16]. A total of 42,171 women born between 1993-2002 were included in the analyses with follow-up periods ranging from 3 to 10 years. HPV vaccine uptake of the women in the cohort ranged from 47 to 62%; 2% of both the vaccinated and unvaccinated women had a cervical sample taken before the age of 25. The prevalence of both LSIL and HSIL was significantly higher among unvaccinated compared to fully vaccinated women, with odds ratios of 0.70 (95%CI 0.61-0.80; VE 30.1% [20.1%-38.7%]) and 0.39 (95%CI 0.30-0.51; VE 60.8% [49.3%-69.8%]), respectively. The effects were less pronounced when compared to incompletely vaccinated women. Overall, hrHPV prevalence was significantly lower among fully vaccinated women (OR 0.70; 95%CI 0.63-0.79) and incompletely vaccinated women (OR 0.78; 95%CI 0.62-0.97) compared to unvaccinated women. Yet, at an age of 24 years, the hrHPV prevalence was similar for unvaccinated and fully vaccinated women. The prevalence of LSIL, HSIL and hrHPV did not differ between women vaccinated at 12/13 years and women who were vaccinated at catch-up age (13-16 years). A total of 184 unvaccinated, 52 fully vaccinated

and 14 incompletely vaccinated women were diagnosed with CIN3, adenocarcinoma in situ (AIS) or carcinoma before the age of 25. The odds of diagnosis with CIN3/AIS/carcinoma were significantly lower for fully vaccinated women (0.28; 95%CI 0.19-0.41) as compared to unvaccinated women, whereas the odds of diagnosis with CIN1/CIN2/CIN-not otherwise specified (NOS) were not statistically different between vaccinated and unvaccinated women [16].

6.4.5 (Inter)national developments

6.4.5.1 Impact of HPV vaccination

Real-world data on the impact of HPV vaccination is becoming increasingly available. In a Norwegian study, the effectiveness of HPV vaccination was assessed in women who have been vaccinated outside the vaccination programme [10]. The vaccination status of women born between 1975 and 1996 who were ineligible for routine HPV vaccination was linked to the cancer registry data. The total cohort consisted of 832,732 women, 46,381 of whom received at least 1 dose of a 2-valent, 4-valent or 9-valent HPV vaccine. In total, 24,750 unvaccinated women and 191 vaccinated women were diagnosed with a cervical intraepithelial neoplasia grade 2 or worse (CIN2+). The majority (77.0%) of the vaccinated women with a CIN2+ diagnosis received their first HPV vaccination at an age of ≥20 years. Among women who were vaccinated before the age of 20 years, a protective effect of the vaccine against CIN2+ was observed as compared to unvaccinated women (incidence rate ratio [IRR] 0.62; 95%CI 0.46-0.84). Such effect was not observed among women who received their first dose of vaccination at an age of ≥20 years (IRR 1.22; 95%CI 1.03-1.43) [10].

The population-based effectiveness of 2-valent HPV vaccination in reducing the risk of cervical abnormalities was also assessed in an Italian cohort from the Ancona province [11]. Women born between 1990 and 1993 with at least one Pap smear between the age of 25 and 30 years were included in the analyses. Women in the birth cohorts 1991-1993 were offered the HPV vaccination in a catch-up campaign from 2009 onwards free of charge until their 26th birthday. A total of 4,664 women were included in the analyses, 24.0% (n=1,118) of whom were vaccinated. Overall, 107 (2.3%) low-grade squamous intraepithelial lesions or worse Pap smears (LSIL+), 70 (1.5%) CIN1+ histological abnormalities and 35 (0.8%) CIN2+ histological abnormalities were identified among the participating women. The proportion of women with cytological or histological abnormalities increased by age. Compared to unvaccinated women, women vaccinated with at least one dose had significant lower proportions of LSIL+ (1.8% vs. 2.5%), CIN1+ (0.9% vs. 1.7%) and CIN2+ (0.4% vs. 0.9%), which was reflected by ORs of 0.55 (95%CI 0.33-0.91) for LSIL+, 0.43 (95%CI 0.22-0.86) for CIN1+ and 0.31 (95%CI 0.11-0.91) for CIN2+ in multivariable logistic regression. The atypical squamous cells (ASC) of undetermined significance or worse Pap smears (ASC-US+) did not differ by vaccination status. The outcomes of this cohort study indicated considerable effectiveness of the HPV vaccination catch-up campaign in preventing cervical abnormalities [11].

Among a cohort of men who have sex with men (MSM) in Canada aged 16-30 years, the prevalence of incident and persistent anal HPV infections was assessed at two time points with an interval of around twelve months [12]. A lower prevalence of incident anal infections with vaccine-preventable HPV types was found among men who received the first dose of vaccination within five years following their anal sexual debut compared to men who had been sexually active for more than five years before vaccination (weighted prevalence ratio [95%CI]: 0.15 [0.03-0.68] for a 4-valent vaccine type and 0.37 [0.16-0.86] for a 9-valent vaccine type).

6.4.5.2 Reduced dosing schedule

Currently, a two-dose HPV vaccination schedule is most commonly implemented in immunisation programmes worldwide. However, the use of a one-dose schedule has been under consideration for several years. In a study comparing the immune responses in women who received either one, two or three doses of a 4-valent HPV vaccine, high and sustained immune responses were observed up to ten years post-vaccination [14]. Neutralising antibodies against HPV16 and HPV18 were detected in, respectively, 96.0% and 96.9% of the blood samples drawn 10 years after a single dose of vaccination, whereas all samples were drawn from women who received two or three doses contained antibodies against HPV16 and HPV18. The antibody titres in samples from women who received one dose were significantly lower than the samples obtained from women who received three doses [14].

6.4.5.3 Systematic review and meta-analysis on genital HPV prevalence in men, by sexual orientation

Genital type-specific human papillomavirus (HPV) infection in men is less well studied than in women. Few meta-analyses on male genital prevalence included type-specific data, or only focus on either MSM or men who have sex with women (MSW). Therefore, a more recent systematic review and meta-analysis on male genital HPV prevalence was conducted [15].

MEDLINE and Embase were searched for studies reporting on male genital HPV prevalence. Studies were included if: (1) the study population consisted of adolescent or adult men; (2) they assessed the genital type-specific HPV prevalence via any well-described genotyping methodology with samples taken from either the external genitals or urethra; (3) they were peer-reviewed with original data from randomised controlled trials, cohort studies, cross-sectional studies, or other studies that provide HPV prevalence; and (4) data collection occurred between 1 November 2011 and 25 October 2021. All data selection and extraction was done independently by two reviewers. Type-specific HPV prevalence and grouped HPV prevalence (any HPV and any hrHPV) summary estimates and 95% confidence intervals were calculated for external genital and urethral HPV separately. Subgroup analyses were conducted for MSW, MSM, and men without data on sexual orientation.

The most common genotypes were HPV-6 and HPV-16 for both external genital (HPV-6: 5.6%; HPV-16: 3.6%) and urethral HPV (HPV-6: 5.5%; HPV-16: 5.3%). For all type-specific and pooled estimates, high heterogeneity across the studies was observed. In all but one HPV type, no significant difference in pooled type-specific prevalence between MSW and MSM were observed. This differs for anal HPV, where MSM have a higher prevalence than MSW [15].

6.4.5.4 Screening of precancerous lesions and cervical cancer

Visioli *et al.* compared the participation rate of routine cervical cancer screening among vaccinated and unvaccinated women in Italy [17]. A total of 34,993 women, born in 1993-1995 were invited for cervical cancer screening between 2018 and 2020. Of these women, 13,006 (37.2%) participated in the screening. Among the women invited for screening, 51.0% were vaccinated, whilst among the women who participated in the screening, 60.6% were vaccinated. The adjusted odds ratio for participation in cancer screening was 1.80 (95% CI 1.72-1.89) in vaccinated versus unvaccinated women. Among unvaccinated women not participating in the screening, 25.8% was born in Italy [17].

6.4.5.5 Cost-effectiveness

Modelling the cost-effectiveness of various HPV vaccination strategies is a helpful tool in the decision-making process for possible future adaptations in the vaccination policy. Linertová *et al.* compared HPV vaccination strategies in an economic model, adapted for the Spanish healthcare system, to assess the cost-effectiveness of vaccination of boys [18]. Five strategies were compared including gender-neutral vaccination with either a 4-valent or 9-valent vaccine, girls-only vaccination with either a 4-valent or 9-valent vaccine, or no vaccination at all. The benefits in reducing the incidence of HPV-related diseases achieved by immunisation were measured by quality-adjusted life years (QALYs). The model showed that implementing a gender-neutral 9-valent vaccination strategy would be more effective than the girls-only 4-valent strategy which is closest to the current Spanish vaccination programme. When comparing the gender-neutral 9-valent strategy to the girls-only 9-valent strategy the ICER equalled €34,040/QALY, which exceeds the willingness-to-pay threshold in Spain of €25,000. Yet, the gender-neutral 9-valent vaccination strategy would become cost-effective by changing some of the key parameters, such as inclusion of oropharyngeal and penile cancer in the total of prevented cases of HPV-related disease or by substantially reducing the cost per dose (from €45 to €28) [18].

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* *RIVM publication.*

6.4.7 Other RIVM publications

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6.5 Measles

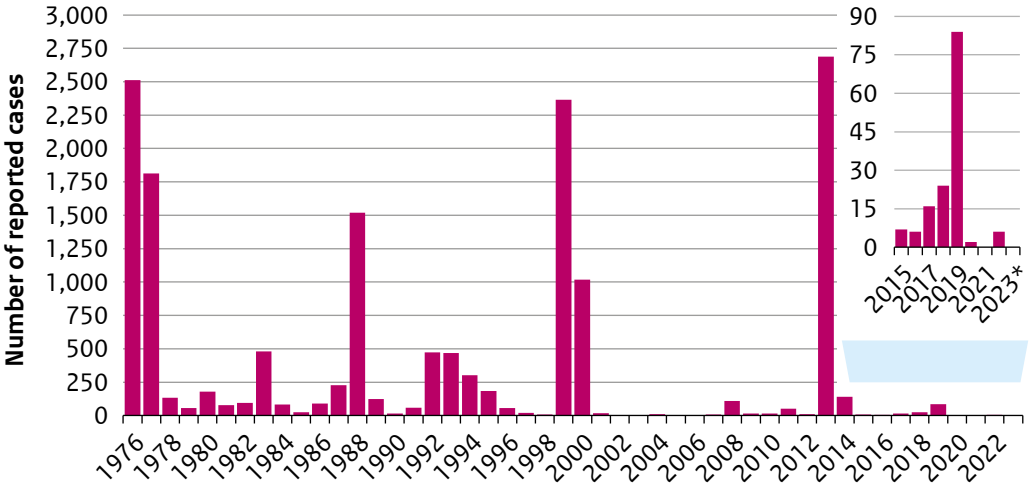
T. Woudenberg, R. Bodewes, W.L.M. Ruijs, R. van Binnendijk, N.Y. Rots, C.A.C.M. van Els, H.E. de Melker

6.5.1 Key points

- In 2022, six cases of measles were reported in the Netherlands.
- Early 2023, a girl deceased due to SSPE.

6.5.2 Tables and figures

Figure 6.5.1 Annual reported measles cases since 1976.



** Cases included up to and including 17 May 2023.*

6.5.3 Epidemiology

In 2022, six cases of measles were reported (Figure 6.5.1). Among these, one case was vaccinated twice (age 38 years old), and five were unvaccinated (0, 1, 5, 8, and 8 years old). Four of the cases were in men and two of the cases in women. Five out of six cases belonged to one cluster which occurred in November 2022. Four cases out of this cluster were within one family. After this cluster, no new infections of measles have been reported until 17 May 2023. In early 2023, a girl deceased due to subacute sclerosing panencephalitis (SSPE). SSPE is a rare degenerative disease of the central nervous system, causing progressive loss of cerebral function, paralysis, coma, and death [1]. It is the late sequelae of measles virus infection, is associated with viral persistence in brain tissue, and occurs years after a measles virus infection [2].

6.5.4 Pathogen

Measles virus genotype B3 was detected in the patients of the cluster and in the individual patient. The B3 sequences of the measles viruses detected in the 5 clustered cases were identical, but different from the B3 sequence detected in the individual patient and also different from B3 type infections detected in previous years in the Netherlands.

6.5.5 Research

6.5.5.1 'Early Measles Immunized' children (EMI) study

During the measles epidemic in 2013-2014, an additional mumps, measles and rubella (MMR-0) vaccination was offered to children between the ages of 6 and 12 months who live in an area with a vaccination coverage below 90% and with an increased risk of infection [3]. This early measles immunisation intends to provide direct protection against measles but comes with a more rapid loss of acquired antibodies assumed to be associated with reduced long-term protection. This has been specifically investigated in the Early Measles Immunized children (EMI) study, which focusses on the long-term effects of the early additional MMR-0 vaccination on the immune response following the regular MMR-1 vaccination at 14 months of age.
The immunogenicity analyses showed that children who had a measles vaccination before 12 months of age had lower measles-specific neutralising antibody concentrations in their blood in the longer term than children in the control group who had only a MMR-1 and no MMR-0. At the age of 4 years, 11.1% of children with a MMR-0 between 6 and 9 months of age were found to have antibody concentrations below the limit for clinical protection. Timepoint 7 years post-MMR1 samples were recently investigated, which showed that up to 68% of these children had neutralising antibody concentrations that dropped below this limit, while for children with a MMR-0 vaccination at the age of 9-12 months, this was 21%, and for children in the control group who had a MMR-1 dose at 14 months, this was 12% (preliminary data, unpublished).

6.5.5.2 Social clustering

In the Netherlands, the clustering of unvaccinated children at school is enhanced by a school system where parents are free to start and choose schools based on their own philosophy or conviction, resulting in a range of registered school identities. Characterising the variability in vaccination coverage between schools is essential to fully understand the risk of outbreaks. The aim of our study was to estimate the MMR vaccination coverages for all primary and secondary schools in the Netherlands and assess the variation in vaccination coverage in primary and secondary schools [4]. By combining postcode catchment areas of schools and school feeder data, each child in the Netherlands was characterised by residential postcode, primary and secondary school (referred to as school career). Postcode-level vaccination data were used to estimate vaccination coverages per school career. These were translated to coverages per school, stratified by school identity.
About half of the unvaccinated children are clustered into a small minority of schools with very low vaccination coverage. These are almost all schools with an Orthodox Protestant or Anthroposophical identity. This suggests that even at a national one-dose MMR coverage of 97.5%, thousands of children per cohort are not protected by herd immunity.

6.5.6 International developments

In 2022, 126 measles cases were reported in EU/EEA countries [5]. The number of reported cases doubled compared with 2021, when 61 cases of measles were reported to ECDC. In comparison with years before the COVID-19 pandemic this remains a small number, as in 2018 over 17,000 cases were reported and in 2019 more than 13,000 cases. Contrary to Europe, numbers of reported measles cases are rising in other continents compared to 2021, especially in the Eastern Mediterranean (from 26,100 cases in 2021 to 56,401 cases in 2022) and South-East Asia WHO regions (9389 in 2021 to 49,201 in 2022). Countries with most reported cases in 2022 were India (40,967), Nigeria (23,983), and Yemen (23,941) [6].

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* *RIVM publication.*

6.6 Meningococcal disease

A. Steens, G. den Hartog, W. Miellet, M.A. Davies, R. Mariman, L.J. Visser, W. Freudenburg-de Graaf, H.E. de Melker, N.M. van Sorge

6.6.1 Key points

- Mitigation measures aiming to control the COVID-19 pandemic coincided with a decline in invasive meningococcal disease (IMD). The decline reversed once all measures were lifted in March 2022: the incidence in 2022 was 0.47/100,000 (n=78). In the period January-April 2023, 59 IMD cases had already been diagnosed.
- IMD caused by the vaccine serogroups ACWY was uncommon in 2022-April 2023: IMD-C and IMD-Y were each diagnosed four times, IMD-W occurred twice and no IMD-A was diagnosed. None of the IMD-ACWY patients were reported to have been vaccinated with MenACWY.
- Serogroup B caused 88% of all IMD cases in 2022. The IMD-B incidence was 0.39/100,000 (n=68) in 2022, which is higher than it was during the COVID-19 years 2020-2021 but slightly lower than during the pre-COVID period (on average 0.43/100,000 in 2015-2019). In January-April 2023, 54 IMD-B cases had already been diagnosed.
- Four deaths were reported among IMD-B cases in 2022, and four deaths in 2023. Two in each year were aged <5 years.
- Overall, 71% of IMD-B isolates of 2022-January 2023 were predicted to be covered by 4CMenB and 89% by the MenB-fHbp vaccine. The coverage differed slightly by age group.

6.6.2 Tables and figures

Figure 6.6.1 Incidence of meningococcal disease by serogroup, 1992-2022.

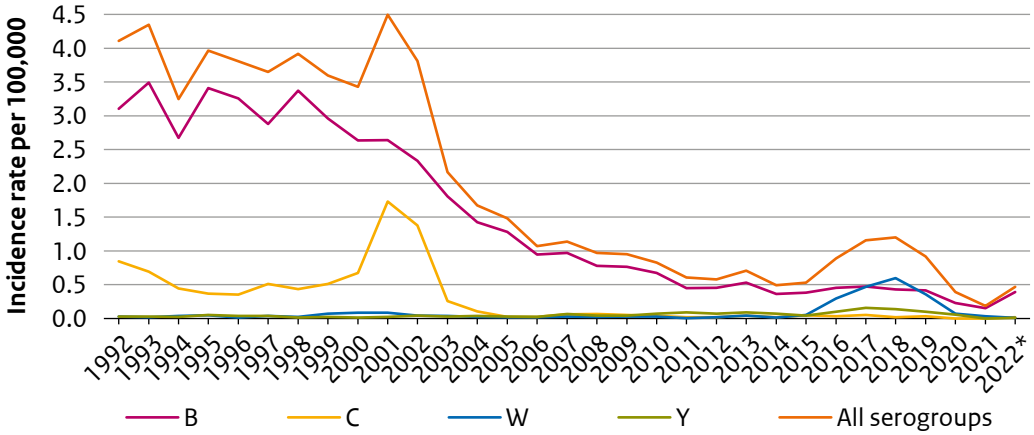
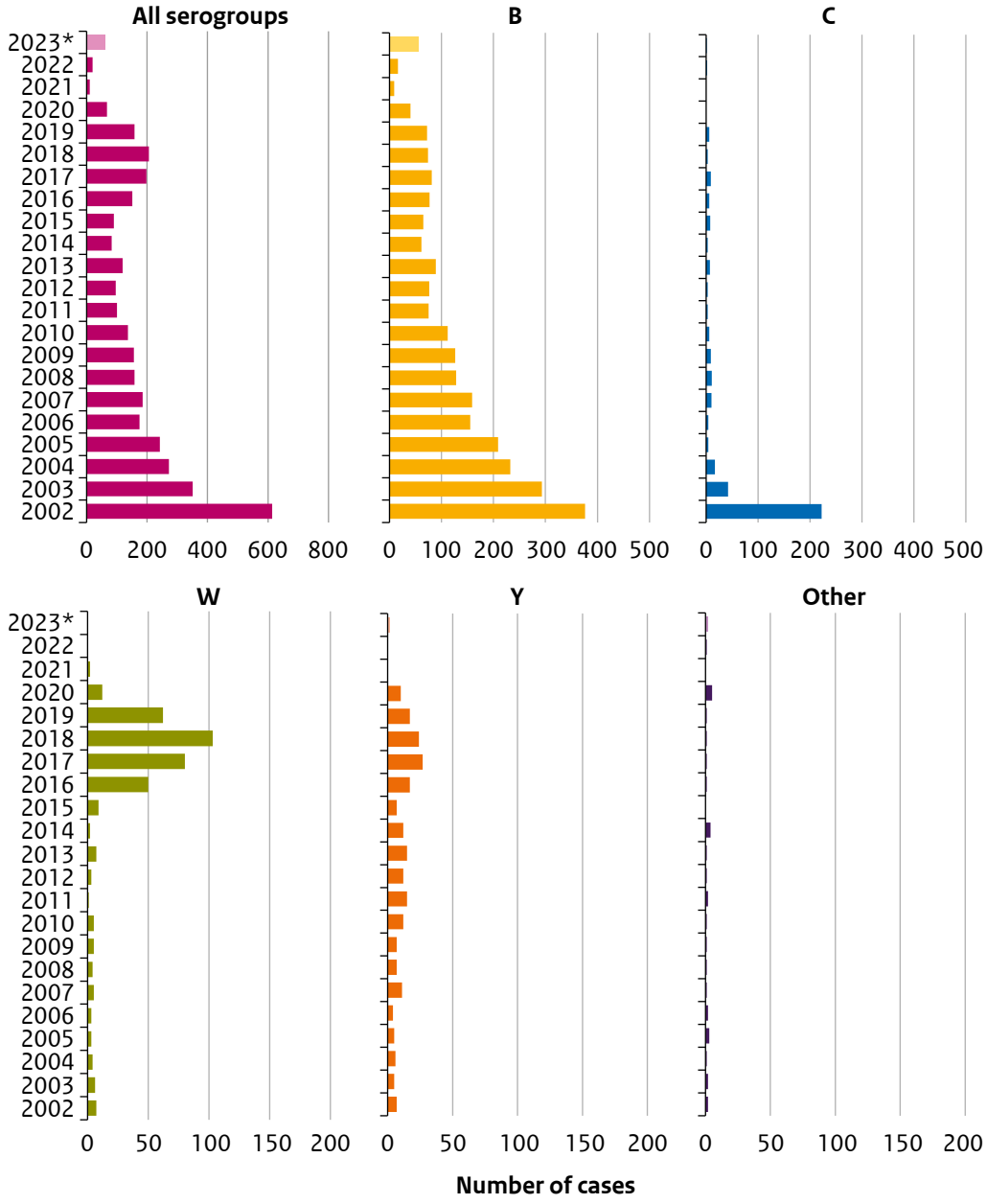
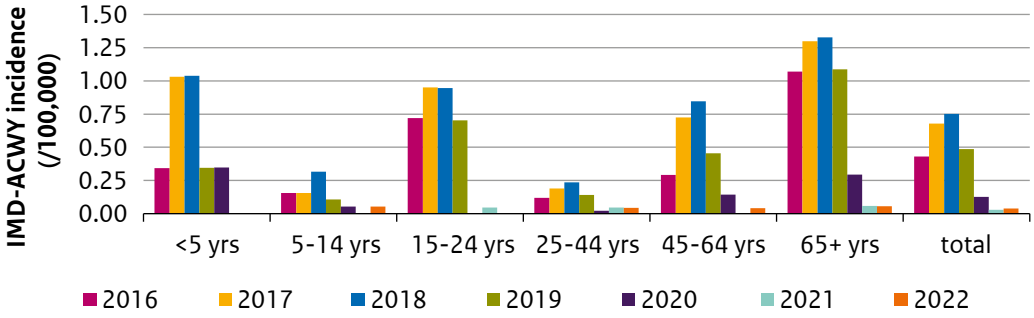


Figure 6.6.2 Number of cases of meningococcal disease by serogroup, 2002-2023*.



Note the different scales in the graphs.
** Up to and including April.*

Figure 6.6.3 Age-specific incidence of invasive meningococcal disease caused by serogroup A, C, W or Y by year, 2015-2022.



Note that since 2004, no IMD-A has been diagnosed in the Netherlands.

Figure 6.6.4 Age-specific incidence of meningococcal serogroup B disease by year, 2015-2022.

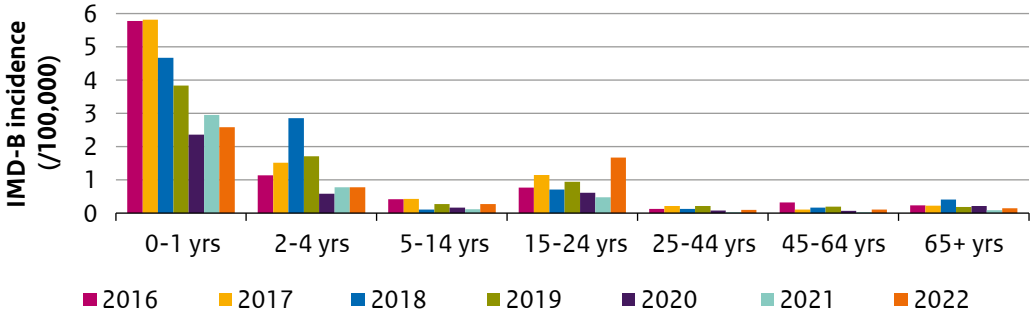
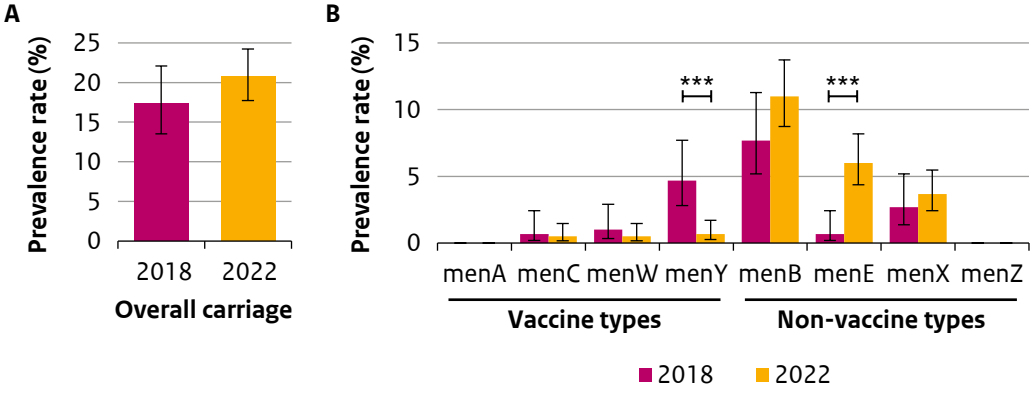


Figure 6.6.5 Overall meningococcal carriage and genogroup-specific prevalence rates among young adults, sampled in autumn 2018 and 2022.



6.6.3 Epidemiology

Invasive meningococcal disease (IMD) is defined as disease caused by *Neisseria meningitidis*, whereby the bacteria have invaded otherwise sterile sites. IMD has been notifiable by law since 1905, but enhanced surveillance has been in place since 2003 and covers all age groups [1]. Since that time, information on notified cases is linked to the information on meningococcal isolates that have been submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) for serogrouping.

6.6.3.1 Meningococcal disease

The incidence of invasive meningococcal disease (IMD) declined from 4.5 per 100,000 (n=719) in 2001 to 0.49 per 100,000 in 2014 (n=83), after which it increased again to 1.2 per 100,000 in 2018 (n=206). In May 2018, vaccination against serogroups A, C, W and Y (MenACWY) was introduced into the infant national immunisation programme (NIP) and in 2020, for 14-year-olds. Also, adolescents born between January 1st 2001 and December 31st 2005 (14-18 years old) were offered MenACWY vaccination. Next, in 2020 and 2021, transmission very likely decreased as a result of the mitigation measures in response to the COVID-19 pandemic. Together, this resulted in a sharp decrease in IMD incidence of 0.21 per 100,000 in 2021 (n=37; see Figure 6.6.1). After all mitigation measures were lifted in March 2022, IMD incidence increased to 0.47/100,000 (n=78 cases). In the first four months of 2023, 59 IMD cases have already occurred, which is slightly less than in the pre-COVID-19 years 2015-2019 (median of 70 cases within the first four months of the year). Serogroup B has been the most common cause of IMD; since MenACWY implementation and its accompanied decrease in incidence, IMD-ACWY has become rare, as are other serogroups (see Figure 6.6.2 and below).

6.6.3.2 Meningococcal disease caused by the vaccine-covered MenACWY serogroups

Overall, the incidence of IMD caused by the vaccine-preventable serogroups ACWY has been low in recent years, with 0.04/100,000 in 2022. As expected, the incidence was highest in older adults (65+: 0.06/100,000; Figure 6.6.3.), as younger age groups have been largely vaccinated with MenACWY (vaccine coverage 88.3% at 2 years old and 80.3% for adolescents [2]). The incidence in all age groups has decreased and has been low since the implementation of MenACWY and the COVID-19 pandemic. Of the IMD-ACWY cases, one older adult died of serogroup C. Among individuals who were vaccinated during the MenACWY catch-up campaign or through the NIP, only one vaccine failure has occurred; this IMD-W case was two years old without known underlying medical condition and occurred in 2019.

Looking at specific serogroups: following the increase in IMD-W incidence from 2015, the IMD-W incidence peaked at 0.59 per 100,000 in 2018 (n=102). Since then, incidence of IMD-W has decreased to 0.01 in 2022 as a result of the vaccination campaign as well as due to the COVID-19 mitigation measures (two cases; both over the vaccine-eligible age for the NIP). No IMD-W has been diagnosed in January-April 2023.

The IMD-Y cases peaked in 2017 for the first time in many years (incidence 0.16/100,000, n=27). In the following years, IMD-Y decreased to 0.10/100,000 pre-pandemic (in 2019) and to 0.01/100,000 (n=2) in 2022. In January-April 2023, two cases of IMD-Y were diagnosed (both older than the vaccine-eligible age for the NIP).

Vaccination against IMD-C at 14 months of age has been in place since 2002 and continuea to be covered by the MenACWY that has been in place in the NIP since 2018. Following the introduction of MenC vaccination, IMD-C incidence has decreased significantly from 1.7/100,000 (n=277) in 2001 to ≤0.05/100,000 in the last decade (on average, 6 cases pre-COVID-19 per year: in 2005-2019, see Figure 6.6.2). In 2022, three IMD-C cases were diagnosed: one case was between 5-10 years old, and two were over 50 years old. The child with IMD-C in 2022 had been sufficiently vaccinated through the NIP and thus was a vaccine failure. In January-April 2023, one older adult was diagnosed with IMD-C.

IMD-A has not been diagnosed since 2004.

6.6.3.3 Meningococcal disease caused by serogroup B

Meningococcal serogroup B has been the main serogroup to cause IMD in the Netherlands over many decades. The incidence of IMD-B has been declining steadily since the late nineties and stabilised around 0.45 per 100,000 between 2011 and 2019 (see Figure 6.6.1). Subsequently, the incidence decreased further in 2020 and 2021 to ~0.20/100,000, probably as a result of the COVID-19 mitigation measures. However, the number of IMD-B cases returned to pre-COVID levels in 2022 (0.39/100,000; n=68). In January-April 2023, 54 IMD-B cases have already been diagnosed. Pre-COVID (2015-2019), between 26 and 36 cases were diagnosed in those months. In 2022-April 2023, 89% of all IMD cases was IMD-B.

The 2022 incidence of IMD-B is highest among infants <2-year-olds (Figure 6.6.4) with 2.6 per 100,000, followed by adolescents (1.7 per 100,000 in 15-24-year-olds). While there has been a trend of decreasing IMD-B incidence in infants for years, the incidence in adolescents in 2022 was higher than in earlier years, both in men and women. This was especially the case in April, May and October, but on the basis of analyses of meningococcal finetypes (see below), no direct transmission between cases was suspected.

Since 2015, 27 out of the 549 (5%) IMD-B cases with information on survival died, including one unconfirmed case that had a direct epidemiological link with an IMD-B case and a clear IMD clinical picture. Four deaths were reported among IMD-B cases in 2022 (6%) and four in January-April 2023 (7%). In 2022 and January-April 2023, two of the cases each year were aged <5 years; for two additional IMD-B cases each year, survival status was unknown. Case fatality, i.e., the proportion that did not survive the IMD-B infection, among <5 year-olds was similar to the last five years: in that period, 1-2 children under 5 years of age died of IMD-B annually.

6.6.3.4 Disease caused by other meningococcal serogroups
In the period 2022-April 2023, four IMD cases were caused by a non-B and non-ACWY serogroup: three IMD-Z and an IMD-X (others in Figure 6.6.2). Two of the IMD-Z cases were adolescents, the other IMD-Z and the IMD-X cases were adults. No conjugate vaccine is available for these serogroups. The coverage of the (potentially cross-reactive) MenB vaccines was not determined.

6.6.4 Pathogen

6.6.4.1 Variability of finetypes
Within serogroups, the finetype is routinely determined on the basis of the sequence variation of two variable regions of PorA (VR1, VR2) and one variable region of the FetA protein (VR1). Finetype is used in surveillance to determine whether possible clusters are occurring, as isolates within an outbreak will generally have an identical finetype.

In 2022, 32 different finetypes were observed among 60 isolates with known finetype. The most commonly observed finetypes were P1.22,14:F5.5 (n=9), P1.22,9:F5-12 (n=7) and P1.22,14:F5-1 (n=5). Other finetypes were observed one to three times. In the January-April 2023 period, 27 different finetypes have already been observed, among 47 isolates with known finetype. The same finetypes as in 2022 were observed in the top 3, with respectively n=8, n=6 and n=4 isolates in those first 4 months of 2023.

6.6.4.2 Strain coverage meningococcal serotype B isolates
Recently, the predicted strain vaccine coverage, i.e., the proportion of IMD(-B) strains that match the MenB vaccine antigens, has been determined for isolates of 2022-January 2023. This theoretical coverage was determined for the multivalent 4CMenB using gMATS and the bivalent MenB-fHbp vaccine using MenDeVAR. We added half of the isolates with unpredictable results to the covered strains, as is standard practice when using gMATS. For almost all cases, at least one of the MenB vaccines (4CMenB or MenB-fHbp) would cover the isolate. Overall, 71% of IMD-B isolates were predicted to be covered by the 4CMenB and 89% by the MenB-fHbp vaccine. The proportion of cases that was predicted to be infected with a vaccine-covered strain differed per age group; 71% among those <5 years old, 75% for those aged 5-14 years and 67% for 15-24-year-olds for the 4CMenB vaccine, and, when calculated in the same way for the MenB-fHbp vaccine, 100% of IMD-B isolates were predicted to be covered for those aged 10-17 years and 94% for the 18-25-year-olds (the licensed age groups).

6.6.4.2.1 Investigation of serogroup B, finetype P1.22,9:F5-12
In the beginning of 2023, an increase of IMD-B caused by the relatively rare finetype P1.22,9:F5-12 was observed among adolescents/young adults. Although numbers were still low (5 up to and including March 2023), this was more than in earlier years (n=7 in entire 2022, in the years before on average n=2 or 3) and included 2 clustered cases and at least 2 others in the same geographical region. We therefore decided to determine the coverage of the finetype by the MenB vaccines, in order to be prepared when more (clustered) cases would occur. Overall, nine cases diagnosed in 2022-2023 were included in the analysis. All of them were found to

be infected with a covered strain, by either by MenB-fHbp (n=7) or by 4CMenB (n=2 cases); for the respective cases, coverage by the 'other MenB vaccine' appeared unpredictable. In case this finetype will cause more clustered cases and vaccination would be needed, MenB-fHbp might be more effective than 4CMenB, although, in such cases the strain coverage should be determined again.

6.6.5 Current/ongoing research at RIVM

6.6.5.1 Meningococcal carriage among students

Meningococcal carriage is an accepted endpoint in monitoring meningococcal vaccine effects. We assessed the impact of MenACWY vaccine implementation on meningococcal carriage and genogroup-specific prevalence in young adults (students of Hogeschool Utrecht) in the fall of 2022, four years after the introduction of the tetravalent vaccine in the Netherlands [3]. Genetic analysis of genogroups was used instead of phenotypical analysis of serogroups, as is standard practice in surveillance. Students had a median age of 20 years (range 16-30). As shown in Figure 6.6.5A, the overall carriage rate of genogroupable meningococci was not significantly different from a pre-MenACWY cohort investigated in 2018 (20.8% or 125 of 601 versus 17.4.% or 52 of 299 individuals, p=0.25). Of 125 carriers of genogroupable meningococci, 122 (97.6%) were positive for either vaccine-types MenC, MenW, MenY or genogroups MenB, MenE, MenX and MenZ, which are not targeted by the MenACWY vaccine. Figure 6.6.5B shows that, compared with a pre-vaccine-implementation cohort, there was 3.8-fold reduction ($p<0.001$) in vaccine-type carriage rates and 9.0-fold increase ($p<0.0001$) in non-vaccine type MenE prevalence. These findings suggest that MenACWY vaccination reduced circulation of vaccine-type meningococci. Although no conclusions can be drawn with this study design, the rise in MenE carriage may represent serogroup replacement, or could be caused by secular trends not related to the MenACWY vaccine introduction. Vaccine-induced replacement has not been described as being relevant following MenACWY vaccination, and MenE carriage has been found before in other (student) settings [4]. Considering low invasiveness of MenE meningococci, the rise in MenE carriage may not be a general public health concern, and no large increase in IMD-E incidence is expected.

6.6.5.2 Immunity against vaccine strains

Meningococci causing IMD have distinct genetic signatures, referred to as clonal complexes (CC) or sequence types, compared to non-invasive meningococci found in carriage studies. A well-known CC also associated with IMD in the Netherlands is CC11. Upon invasive infection, the complement system is the main line of defence against meningococci. In a project funded through the EpIg Men MarieCurie project (grant ID 835433), meningococci from IMD patients were compared with meningococci isolated from healthy individuals to investigate resistance to complement-mediated killing [5]. Isolates (n=56) with distinct serogroups, CC and clinical disease of the patients were selected. Most isolates from patients were much more resistant to complement-mediated killing compared to carrier isolates from healthy individuals (n=20). As antibodies enhance the ability of complement to kill meningococci, the ability of antibodies induced by MenACWY vaccination to promote complement-mediated killing was studied. Vaccine-induced antibodies effectively activated the complement system resulting in effective

killing of all carrier and invasive isolates, even against the most (complement-)resistant isolates from patients. This effect of vaccine-induced antibodies was observed using sera from adolescents as well as from adults aged 55-65 years. These data show that MenACWY vaccination induces protective antibodies to genetically distinct commensal and hyperinvasive meningococcal bacteria.

6.6.6 (Inter)national research

6.6.6.1 Severity of disease

The characteristics and outcomes of adult IMD cases with meningitis as a clinical picture, diagnosed between 2006-2021 in the Netherlands, have recently been published [6]. The study includes overlapping cases as the study of Middeldorp *et al.* [7] but focusses only on meningitis patients and looks at the characteristics of the complications and sequelae. The study included 442 IMD-meningitis episodes (37% of all IMD episodes). As with all IMD (see above), IMD-meningitis was mainly caused by serogroup B. Of the meningitis patients, 7% developed neurological complications and 19% had systemic complications during treatment; 4% died. Of the patients who survived, 31% developed sequelae, which is quite similar to what was found in IMD caused by any clinical picture, except for mild meningococcaemia, for which the percentage is lower [7]. Overall, 14% had suffered cognitive impairment and 14% later suffered hearing impairment; 7% had cranial nerve palsy.

6.6.6.2 Meningococcal carriage

(Persistence of) meningococcal carriage has been evaluated among 2744 university students in Sweden using throat samples [8]. Eighteen percent of the participants participated at least twice in the sample collections. The median age of the students was 23 years (range 16-59). Two percent reported a history of meningococcal vaccination. Overall, 9.1% (95% 8-10) carried meningococci, which is lower than recently found in Dutch students (see above). Age of ≤22 years, previous tonsillectomy, cigarette smoking, drinking alcohol, and attending parties, pubs and clubs was positively associated with carriage, while female gender and sharing a household with children aged 0–9 years were negatively associated with carriage. Capsule null locus, genogroup B and genogroup Y were most commonly isolated. In two students, persistent carriage for at least 12 months was observed.

6.6.6.3 Meningococcal B disease and vaccination

The Health Council of the Netherlands advised against current implementation of MenB vaccination into the NIP in 2022 [9]. The advice was based, among other considerations, on the relatively low incidence of IMD-B, the expected high costs to prevent one case of IMD-B and the reactogenicity of the vaccines. A cost-effectiveness analysis made for the Netherlands indeed estimated high costs per QALY gained (€131,940 in the base case) [10]. As there have been increases in IMD-B after lifting the COVID-mitigation measures in, among other countries, the UK, France [11, 12] and the Netherlands (see above), we remain extra vigilant.

The UK has implemented 4CMenB vaccination since 2015. The country has evaluated the programme with enhanced surveillance including data on morbidity and mortality of IMD-B in vaccinated and unvaccinated patients younger than 5 years [13]. 4CMenB has decreased the number of IMD-B cases in vaccinated individuals by 55%. However, among IMD-B cases, no difference was seen in the risk of intensive care admission, sequelae, or death of IMD-B between vaccinated and unvaccinated cases [13].

In Spain, 4CMenB is available for private purchase; it is advised to start MenB vaccination at 2 months of age. National data including all laboratory-confirmed IMD cases younger than 5 years from the October 2015-October 2019 period, was used to investigate the VE of 4CMenB in a matched case-control design (4 controls per case matched on date of birth and province) [14]. Overall, 306 IMD cases, of which 243 IMD-B, were included and 1,224 controls. 11% of the cases and 24% of the controls had received at least one 4CMenB dose. Of the IMD-B cases, 5% was fully vaccinated with 4CMenB, and 13% of their controls, leading to an overall VE of 71% (95%CI 45-85). Having received at least one dose resulted in a VE of 64% (41-78). Interestingly, the estimated VE against IMD-B was not different from the VE against IMD caused by non-B serogroups (following full vaccination: 92, 95%CI 28-99). The high VE against non-B disease can be explained by the dominance of serogroup W disease caused by a 4CMenB-covered-strain.

The impact of 4CMenB vaccination in the NIP in South Australia has been evaluated after three years [15]. The NIP consists of an infant programme (6 weeks, 4 and 12 months) and two adolescent doses in school year 10 (at approximately 15 years of age). The study consisted of a cohort and a case-control part that is based on IMD-B, gonorrhea and chlamydia notification data and on vaccination history from the Australian Immunisation Register. After 3 years, the IMD-B incidence had decreased by 63% (95%CI 29-81) in infants and by 79% (95%CI 33-93) among adolescents. No reduction was observed among children 4-6 years (120%, 95%CI 17-829); only part of these children were eligible for the catch-up campaign that was provided by school age year. Among infants, no IMD-B cases occurred after having received all three doses. Following two infant doses, the VE was estimated to be 91% (95%CI 7-99). Among adolescents, one vaccine failure was reported; the estimated VE was 89% (95%CI 0–99%).

(At least) two pentavalent meningococcal vaccines are being developed that cover serogroups A,B,C,W,Y. One combining the MenB-fHbp vaccine with a CRM197-conjugated MenACWY vaccine, and one combining the 4CMenB vaccine with the CRM197-conjugated MenACWY vaccine. In a recent phase-3 RCT, both vaccines have been shown to be non-inferior to the separate MenB and MenACWY vaccines in terms of safety, tolerability, and immunogenicity; the trials were performed in individuals aged 10-25 years [16, 17].

6.6.6.4 Factors related to and effects of interventions

To gain insight into factors affecting the decision-making process regarding MenACWY vaccination, a questionnaire-based study was performed in the Netherlands after the introduction of MenACWY into the NIP and its accompanied catch-up campaign [18]. The study focused on adolescents and their parents. Using random-forest analysis, the best predictors

of the vaccination decision were determined. The study showed that parents have a more prominent role in decision-making than adolescents and spend more time thinking about the decision. For parents, variables centring on the process of the decision, their attitude about MenACWY vaccination, trust in the vaccination, and ideas of important people around them were most predictive of the decision. For adolescents, the ideas of important people around them was most predictive, followed by the process of the decision and trust in the vaccination. They concluded that information about such a vaccination campaign might mainly be addressed to the parents and focus on stimulation of the dialogue about vaccination between parents and adolescents.

During the COVID-19 pandemic, the implemented mitigation measures led, among others, to a decline in IMD [19]. In the UK, the effect these measures and MenACWY vaccination had on the incidence of IMD was determined using an age-based mathematical susceptible-carrier-susceptible transmission model [20]. They included a VE against MenACWY carriage of 41% (97.5%CI: 38-44) from 2015 onwards and age-specific social mixing patterns from a pre-pandemic study and one performed during the COVID-19 pandemic. Altogether, the model predicted that the MenACWY implementation had already resulted in a substantial reduction of carriage, accelerated by the mitigation measured against COVID-19 and which is expected to lead to long-lasting reductions in MenACWY carriage and IMD-ACWY. Although the vaccine uptake had been reduced in the UK during the COVID-19 pandemic, the model predicted that the effect of the mitigation measures was larger than the effect of a decreased vaccine uptake for 'COVID-19 cohorts', even if reduced to 50% vaccine uptake.

In France, the impact of different interventions in response to an IMD-C outbreak in 2015-2016 among young adults was evaluated using a susceptible-carrier-susceptible transmission model [21]. During the outbreak, an effective reproductive number (Re) of 1.35 (95%CI 1.13-1.47) was estimated. For 1,000 MenC carriage episodes, it was estimated that 4.6 (1.8-12.2) would result in IMD-C. The model determined that chemoprophylaxis and vaccination of close contacts of IMD cases, as well as age-targeted vaccination had effectively stopped the outbreak. According to the model, case-based interventions alone, such as ring vaccination, would have been insufficient for outbreak control. The authors concluded that the selection of the most affected age groups for the age-targeted vaccination campaign had a critical impact on the effectiveness of the control measures; such selective vaccination campaign will have reached the most important age groups faster compared to when the campaign should reach a population.

6.6.7 Literature

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** RIVM publication.*

6.6.8 Other publications with RIVM authors

Ohm M, van Straalen JW, de Joode-Smink G, van Montfrans J, Bartels M, van Wildenbeest JG, *et al.* Meningococcal ACWY conjugate vaccine immunogenicity in adolescents with primary or secondary immune deficiencies, a prospective observational cohort study. Pediatr Rheumatol Online J. 2023;21(1):73.
Ohm M, van Straalen JW, Zijlstra M, de Joode-Smink G, Jasmijn Sellies A, Swart JF, *et al.* Meningococcal ACWY conjugate vaccine immunogenicity and safety in adolescents with juvenile idiopathic arthritis and inflammatory bowel disease: A prospective observational cohort study. Vaccine. 2023;41(25):3782-9.

6.7 Mumps

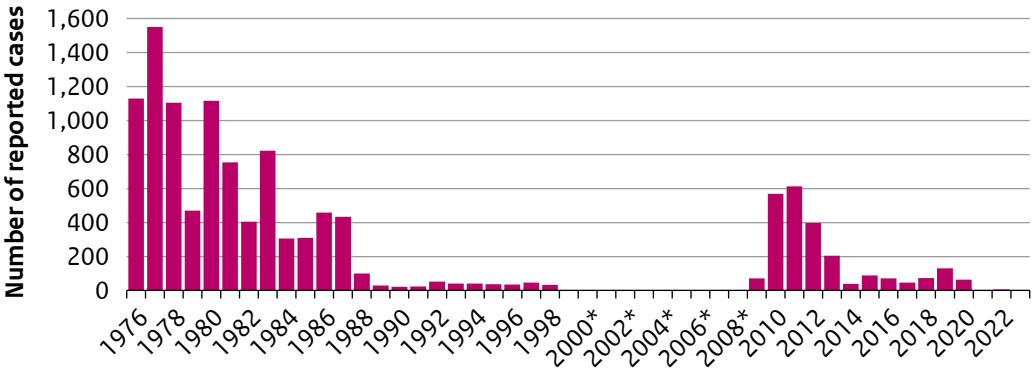
T. Woudenberg, R. Bodewes, P. Kaaijk, N.Y. Rots, C.A.C.M. van Els, W.L.M. Ruijs, H.E. de Melker

6.7.1 Key points

- In 2022, a total of seven cases were reported in the Netherlands.

6.7.2 Tables and figures

Figure 6.7.1 Number of notified mumps cases in 1976-2023*.



** Cases up to and including 9 May 2023.*

6.7.3 Epidemiology

In 2022, seven cases of mumps were reported (Figure 6.7.1). Among these, three were vaccinated, and three were unvaccinated. Vaccination status was unknown for one patient. Among those that were vaccinated, two cases had one registered vaccination, and one had two registered vaccinations. The average age was 38 years. Four of the cases concerned men and three of the cases concerned women. For four cases, the most likely country of infection was the Netherlands, the three other cases were most likely to have been infected outside of the Netherlands.

6.7.4 Pathogen

From 2009 to 2020, most mumps cases in the Netherlands were caused by infection with genotype G mumps viruses. From mumps cases reported in 2022, a genotype was obtained from two cases. Mumps virus genotype D and G were detected. The exact sequence of the mumps virus genotype G that was detected in the Netherlands in 2022 was different from the mumps virus genotype G viruses detected from 2009 to 2020. Also, the exact sequence of the mumps genotype D virus had not previously been detected in the Netherlands.

6.7.5 International developments

From ECDC, most recent annually reported cases from EU/EEA countries are from 2021, when 1,567 cases were reported [1]. This is the lowest number of annually reported cases of mumps since 2000. From 2008 to 2019, the annually reported number fluctuated around 15,000 cases. Given the reduced contact patterns during the COVID-19 pandemic years, and potentially reduced health care seeking behaviour, the decrease in annually reported cases is expected to be temporary, and an increase towards pre-pandemic levels could be expected in the years to come.

6.7.6 Literature

1. European Centre for Disease Prevention and Control, Surveillance Atlas of Infectious Diseases. 2023: Stockholm.

6.8 Pertussis

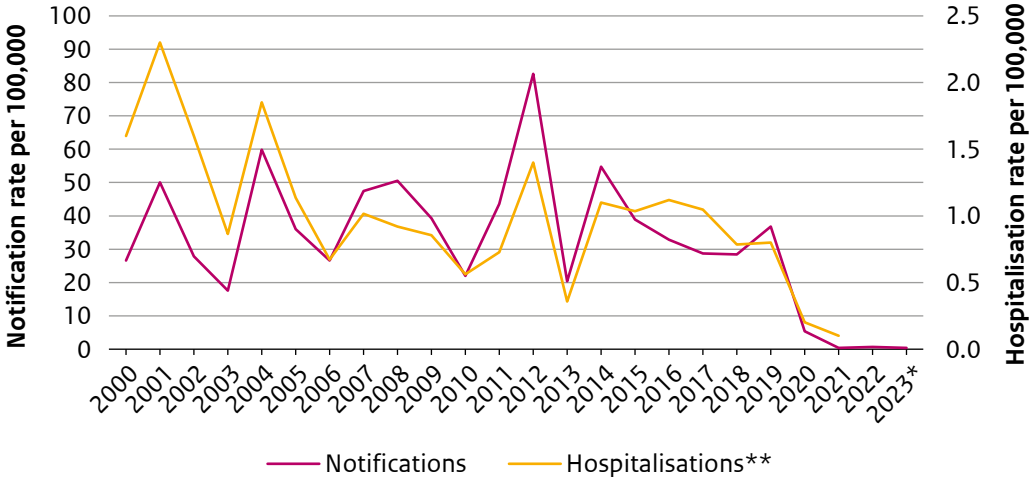
D.L. van Meijeren, R. Mariman, L. Visser, C.A.C.M. van Els, H.E. de Melker

6.8.1 Key points

- The reduction in the number of notifications that was observed after the introduction of the COVID-19 measures in March 2020 continued in 2022 and in the first four months of 2023 (end of observation period for this report). In 2022, the overall number of pertussis notifications and the incidence rate (IR) were 129 and 0.7 per 100,000, respectively, which are unprecedentedly low numbers compared with the past 25 years.
- Besides a reduction of circulation of *B. pertussis* due to the COVID-19 measures, other reasons, such as changed health care seeking behavior, might also have caused part of the decrease in the number of notifications.
- In 2022 and in the first four months of 2023, no infections with *B. pertussis* among 0- to 3-month-olds were reported, as was the case in 2021. Therefore, the vaccine effectiveness (VE) estimate of the maternal Tdap vaccination (74% (95% CI: -32 to 96%)) continues to be based on 8 cases reported between April 2020 and December 2020.

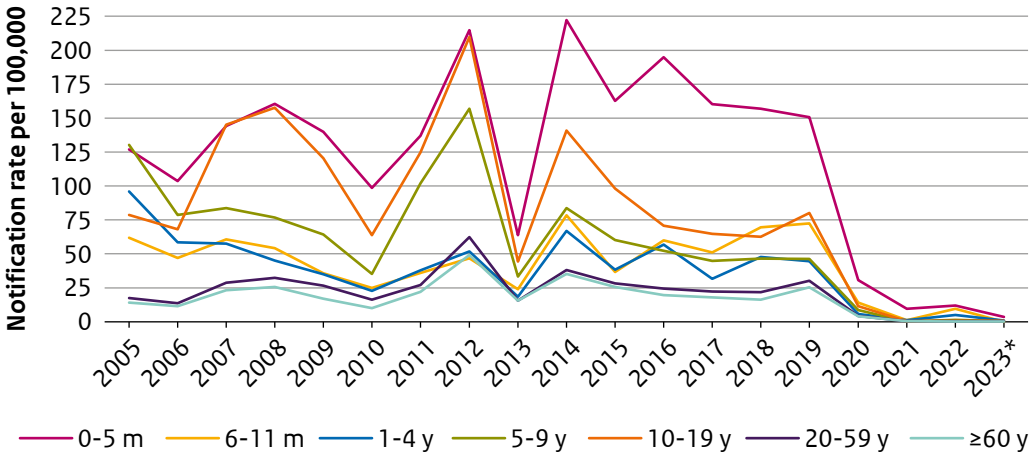
6.8.2 Tables and figures

Figure 6.8.1 Pertussis notifications (left Y-axis) and hospitalisations (right Y-axis) per 100,000 for 2000-2023*.



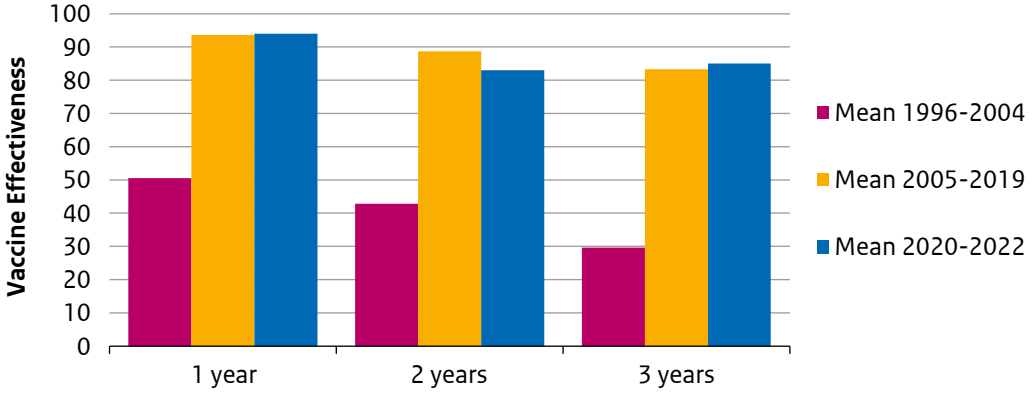
** For 2023, notifications are depicted for the period up to and including April 28, extrapolated to numbers for a whole year.*
*** No hospitalisation data from 2022 onwards is available yet.*
Source: Osiris and Statistics Netherlands.

Figure 6.8.2 Pertussis notifications per 100,000 per age category for 2005-2023*.



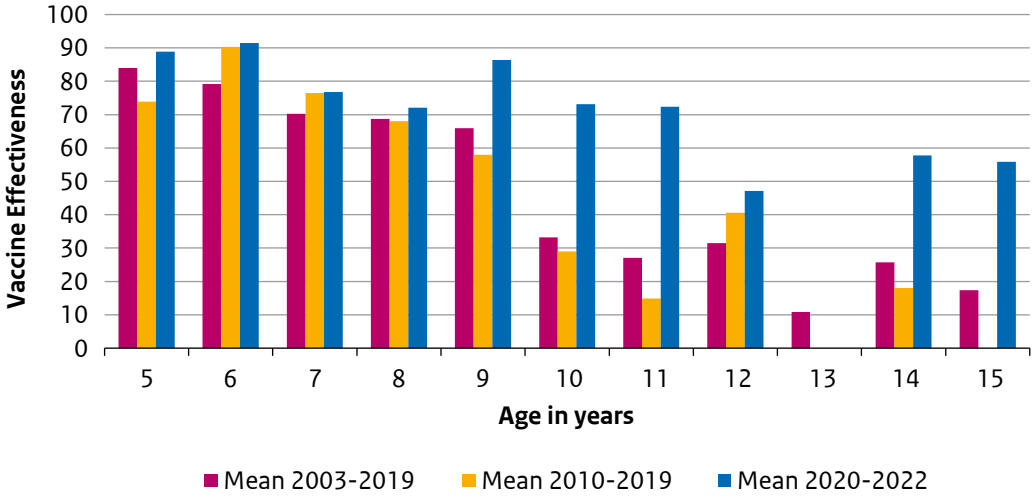
** For 2023, notifications are depicted for the period up to and including April 28, extrapolated to numbers for a whole year.*
Source: Osiris.

Figure 6.8.3 Vaccine effectiveness of primary pertussis vaccination, calculated with the screening method*, estimated for 1-, 2- and 3-year-olds during use of the whole-cell pertussis vaccine (mean 1996-2004) and during use of the acellular pertussis vaccine (mean 2005-2019, and 2020-2022 separately).



** A population coverage of 94% was used for 2017, and a coverage of 93% for 2018-2022. For all other years, a population coverage of 96% was used.*
Source: Osiris, National vaccination coverage report [1].

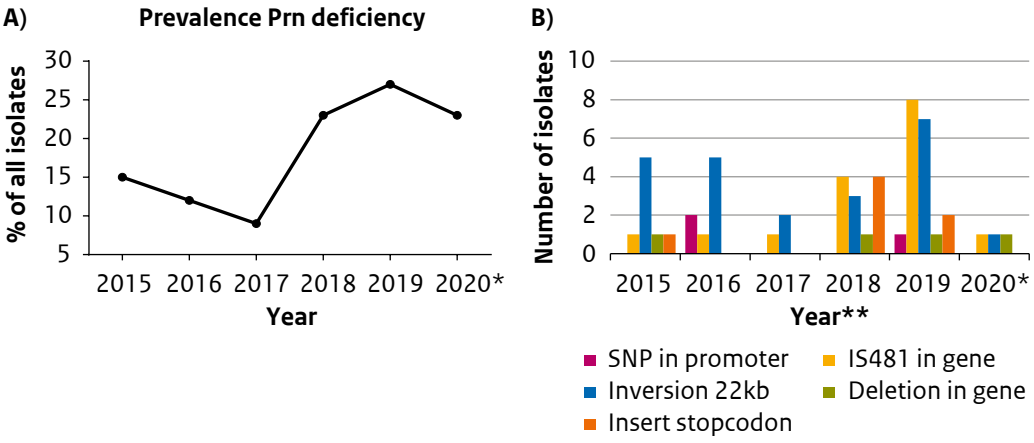
Figure 6.8.4 Vaccine effectiveness of the pre-school booster, calculated with the screening method*, estimated for 5- to 15-year-olds for the whole-cell pertussis priming cohorts (mean 2003-2019, birth years 1998-2004) and the acellular pertussis priming cohorts (mean 2010-2019 and 2020-2022 separately, birth years 2005 and later).



** For all separate birth cohorts, the registered population coverage of the booster vaccination was used, as retrieved from the National vaccination coverage report [1].*

Source: Osiris.

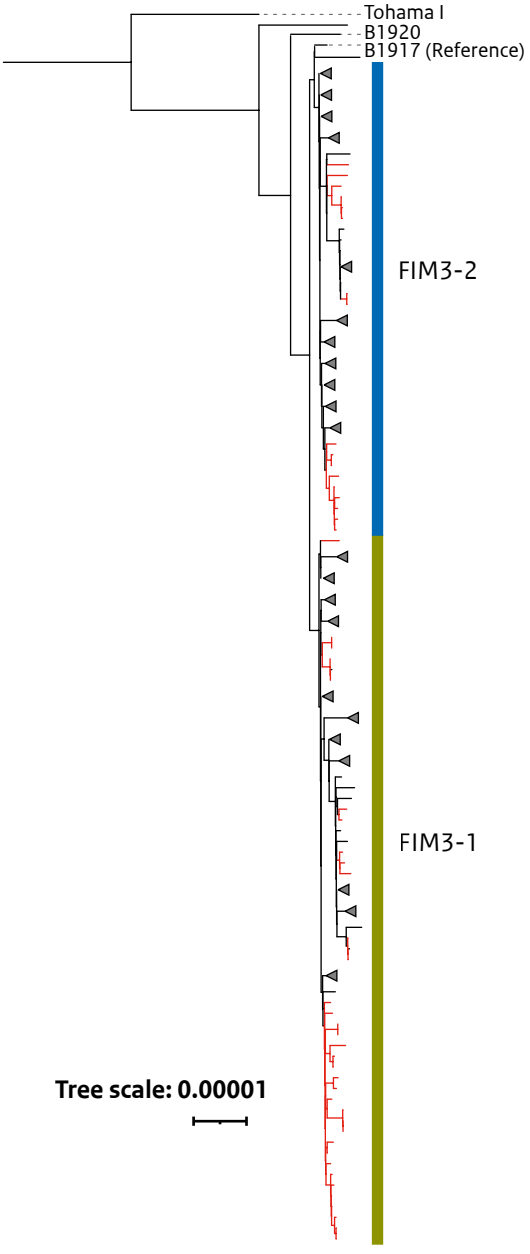
Figure 6.8.5 Prevalence (A) and molecular mechanism (B) of loss of pertactin (Prn) production in clinical isolates collected between 2015 and 2020**.



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

*** No isolates were available for 2021, 2022 and 2023.*

Figure 6.8.6 Genetic relationship between 271 clinical isolates obtained between 2015-2020, based on single nucleotide polymorphisms (SNPs) typing using "snippy", with core-genome alignment based on the B1917 strain used as input for a maximum likelihood phylogeny estimation. In 2021, 2022, and 2023 up to and including May, no isolates were sequenced.



6.8.3 Epidemiology

6.8.3.1 Disease

The decreasing trend in the number of notifications that was observed after the introduction of the COVID-19 measures in March 2020 has continued in 2022. In 2022, the overall number of pertussis notifications and the incidence rate (IR) were 129 and 0.7 per 100,000, respectively, which are unprecedentedly low numbers compared to the past 25 years (Figure 6.8.1). In the first four months of 2023, no increase in the number of pertussis notifications was observed. Besides a reduction of circulation of *B. pertussis* due to the COVID-19 measures, other reasons, such as changed health care seeking behavior, might also have caused part of the decrease in the number of notifications.

Compared to pre-pandemic years, the IR was low in all age categories in 2022. The IR was lowest in persons aged 60 years and over (0.3 per 100,000, n=13) and remained highest in 0- to 5-month-old infants (11.9 per 100,000, n=10) (Figure 6.8.2). However, for all these infants, *B. parapertussis* was the reported pathogen. With the exception of persons aged ≥60 years, the proportion of notifications due to *B. parapertussis* increased in 2022 compared to previous years in all age groups, although actual numbers are low. Recently, pathogen diagnosis by multiplex polymerase chain reaction has gained popularity for respiratory infections. This allows testing simultaneously for different pathogens, including *B. parapertussis*, which makes it likely that (co)-infections with *B. parapertussis* are more often found compared to previous years [2, 3]. Within the EUpertstrain network no increase of *B. parapertussis* cases was observed in 2022, with exception of France.

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

In 2022, no deaths due to a pertussis infection were reported, compared to one or two deaths each year between 2014-2020. No hospitalisation data for 2022 are available yet.

6.8.3.2 Vaccine effectiveness (VE)

In 2022 and the first four months of 2023 no infections with *B. pertussis* among 0- to 3-month-olds were reported. This was also the case in 2021. Therefore, the VE estimate of the maternal Tdap vaccination against infection with *B. pertussis* continues to be based on eight cases reported between April 2020 and December 2020. Three of these infants had received maternal Tdap vaccination. Using an estimated maternal vaccination coverage of 70% [2] VE was estimated at 74% (95% CI: -32 to 96%) with the screening method. The VE against infection with both *B. pertussis* or *B. parapertussis* among 0- to 3-month-olds was estimated at 57% (95% CI: -43 to 87%) with the same method and vaccination coverage. For this estimate, fourteen 0- to 3-month-old infants, notified with a *B. pertussis* or *B. parapertussis* infection in 2020, 2022 and 2023 were included. Seven of these cases had received maternal Tdap vaccination. The year 2021 was excluded, because it is very likely that all infected 0- to 3-month-old infants that were

reported during this year were based on a false positive infection with *B. parapertussis* [4, 5]. Since both VE estimates are based on a relatively low number of notifications, they might not be accurate.

Figure 6.8.3 shows the VE estimates of the infant series during the use of the whole-cell pertussis vaccine (mean 1996-2004) and the use of the acellular pertussis vaccine (mean 2005-2019, and 2020-2022 separately). Since the switch from the whole-cell pertussis (wP) vaccine to an infant combination vaccine with an acellular pertussis (aP) component in 2005, the VE estimate has been consistently high up to the booster vaccination given at 4 years of age. It should be noted that the VE estimates of the years 2020-2022 are based on a relatively low number of notifications compared to the 1996-2019 period, and that most of these notifications date from the first three months of 2020. A separate estimate for 2021 and 2022 could therefore not be made since this would lead to inaccurate VE estimates. Moreover, the VE estimates include notifications in which *B. parapertussis* was the reported pathogen. When these notifications would be excluded for the year 2022 (as in this year the proportion of *B. parapertussis* was 64%, versus 3% on average in 2005-2021), these VE estimates would be slightly higher, particularly for the 2-years-olds (89% versus 83%).

Following the booster dose at the age of 4, the VE estimate shows a decrease after ~5 years, i.e., when children reach the age of 10 (Figure 6.8.4). This is in agreement with the notification rates in these age groups as 10-to-19-year-olds have a higher IR compared to 5-to-9-year-olds (Figure 6.8.2). It should again be noted that the VE estimates of the years 2020-2022 are based on a relatively low number of notifications compared to the 2003-2019 period, and that most of these notifications date from the first three months of 2020. A separate estimate for 2021 and 2022 could therefore not be made since this would lead to inaccurate VE estimates. Moreover, the VE estimates include notifications in which *B. parapertussis* was the reported pathogen. When these notifications would be excluded for the year 2022 (as in this year the proportion of *B. parapertussis* was 53%, versus less than 1% on average in 2003-2021) these VE estimates would be slightly higher for the children aged 5-8 (87% versus 82%) and lower for the children aged 9 years or over (45% versus 56%).

The VE estimates discussed above were made by use of the screening method. This is a rather crude method to easily estimate a VE that can be used to monitor VE over time, but the estimates should not be interpreted as the 'true' VE. Appendix 1 provides an overview of the methods that can be used to estimate VE.

6.8.4 Pathogen

In the Netherlands, the NIP makes use of an acellular pertussis (aP) vaccine consisting of five pertussis antigens, i.e., fimbriae 2 and 3 (Fim2 and Fim3), pertussis toxin (PTx), filamentous hemagglutinin (FHA) and pertactin (Prn). The re-emergence of pertussis has been attributed to several factors, including bacterial strain adaptation due to vaccine pressure [6]. Hence, careful monitoring of bacterial expression of vaccine targets, in particular Prn, is essential. Therefore, Dutch medical microbiology laboratories are asked to submit their *B. pertussis*-suspected samples to RIVM. Confirmed *B. pertussis* strains are whole genome sequenced (WGS), and an

antigen expression validation assay is performed for the pertussis antigens PTx, Prn, and FHA. In 2021, 2022, and 2023 for the period up to and including May, no strains were received for strain surveillance, which is in line with the low number of pertussis notifications in this period. Despite the easing of COVID-19 control measures in the second half of 2022, no re-surge of pertussis was observed. Results of the strain surveillance for the years 2015-2020 can be found in Figure 6.8.5 and Figure 6.8.6.

Between 2010 and 2015, an emergence of *B. pertussis* isolates deficient in the vaccine component Prn was observed with a prevalence of 10-15% in 2015-2017. However, in 2018, a sharp increase was observed, with Prn deficiency in 24% (11/46) of clinical isolates. This alarming increase continued in 2019, with Prn deficiency in 27% of all isolates (19/71). In 2020, 21% (3/14) of all collected isolates were found to be Prn-deficient (Figure 6.8.5A). Sequence analysis from 2015-2020 showed that an inversion of ~22 Kb in the promotor region was the most frequently observed cause of Prn deficiency (n=23), followed by an insertion of the IS481 element in the prn gene (n=16), and insertion of a stop codon (n=7) as shown in Figure 6.8.5B.

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

Single nucleotide polymorphisms (SNPs) typing using "snippy", was used to infer genetic relationships between the isolates. Core-genome alignment based on the B1917 strain was used as input for a maximum likelihood phylogeny estimation as shown in Figure 6.8.6. As expected, most Dutch isolates closely match the B1917 global strain, while the Tohama I and B1920 strains are more distant. Only one isolate encoded the original pertussis toxin promotor (PtxP, allele 1), while all other isolates encode PtxP3, which is associated with higher levels of toxin [7]. The fimbriae 3 (fim 3) allele is a divisor for the dataset, with half the isolates containing the original allele (green highlighting) and the other half, containing the novel allele (alanine-to-glutamic acid mutation at position 87) [8], blue highlighting). This alternative fim3 allele is associated with pertussis re-emergence in the USA [9] and the mutation is located in an immunogenic epitope [10].

Branches highlighted in red indicate Prn-negative strains, determined phenotypically by Luminex analysis and confirmed by analysis of the WGS reads for mutation in the pertactin gene or promoter. Multiple introductions of Prn deficiency have been observed in the tree; seven separate introductions in isolates carrying the original Fim3 allele and at least three separate introductions in isolates carrying the alternative Fim3 allele. As a consequence, the chance of pertactin deficiency in isolates containing the original Fim3 allele is much higher (OR 4.4, Fisher's exact test p=7.55*10-6). Within this subsection of the tree, one fully pertactin-deficient branch can be noted, consisting of 24 strains isolated in all included years. Further expansion of this branch could be considered a potential concern, although the presence of the original Fim3 allele warrants coverage by vaccine-induced Fim3 antibodies. Among isolates with the novel Fim3 allele, a small pertactin-deficient subbranch was also observed, a total of nine strains, seven of which have been isolated in 2018-2020. These isolates carry the potential to evade both pertactin and Fim3 antibodies induced by acellular pertussis vaccines.

In summary, the pre-COVID-19 pandemic circulating *B. pertussis* strains are genetically homogenous and predominated by sequence type 2. We also see a trend towards more pertactin-deficient strains in later years. Since the pandemic, all epidemiologic evidence suggests little to no circulation of pertussis. When pertussis re-emerges and which genetic lineages will resurface, is unknown. The data presented here provides a good baseline of pre-pandemic pertussis, to which future (post-pandemic) circulating strains may be compared.

6.8.5 Research

6.8.5.1 Maternal pertussis vaccination

In the previous year, we described results of the PIMPI-study regarding levels of vaccine-induced IgG antibodies following maternal Tdap vaccination in preterm and full-term new-borns [4]. As part of the PIMPI study, socio-psychological predicting factors for attitude, intention and acceptance of maternal Tdap vaccination during the second trimester (between 20 and 24 weeks of gestation) of pregnancy were also investigated [11]. Before 20 weeks of pregnancy, participants completed an online questionnaire covering socio-demographics (age, country of birth, education level, gravidity, parity, whether or not her lastborn child participated in the NIP (if parity ≥1) and the affiliation to certain beliefs), behavioural determinants and beliefs that may underlie attitude and intention towards, and acceptance of Tdap vaccination. After completion, the vaccine was offered free of charge and administered by the antenatal care provider or at a youth health care centre.

Determinants that were most predictive for vaccine acceptance were (in order of magnitude) intention, attitude towards vaccination, belief of safety, risk perception of severity of side effects, moral responsibility, belief effectiveness and risk perception of susceptibility of side effects. In turn, intention was positively affected by attitude towards vaccination, belief of safety, belief of effectiveness, trust in NIP and healthcare professionals and moral responsibility. Negative determinants of intention were risk perception of susceptibility of side effects, risk perception of severity of side effects, decisional certainty and fear of vaccination. No differences in attitude or intention towards vaccination, or actual vaccine acceptance were found between nulliparous and multiparous women.

In another research that was part of the PIMPI-study [12], the reactogenicity and safety of the Tdap vaccination (Boostrix®) was studied among pregnant women who received the vaccination between 20.0/7 and 24.0/7w gestational age (GA) (early vaccinated). One week after Tdap vaccine administration, a questionnaire on local reactions and systemic adverse events (AEs) that occurred within one week after vaccination, was filled in. Also, information on perceived severity of the symptoms and the occurrence of similar systemic symptoms in the week prior to vaccination was obtained. The reactogenicity data was compared with pregnant women who received the vaccination between 30.0/7 and 33.07w GA (late vaccinated). Data on adverse pregnancy outcomes was compared with unvaccinated pregnant women that were registered in the Dutch Perinatal Registry (DPR) database by linkage based on date of birth of the mother, living area (4-digit postal code), and date of expected delivery.

67.5 % of all participants (488/723) notified at least one local reaction within the week following Tdap vaccination, of which pain at the injection site was recorded most often. Stiffness in muscles and/or joints, rash, headache, nausea, fatigue and itch are systemic AEs that were more frequently reported compared with the week before vaccination. The occurrence of local and/or systemic AEs did not differ between women that were vaccinated early versus late. Moreover, no significantly different risk ratios were observed for any of the adverse pregnancy outcomes studied; pregnancy duration shorter than 370/7 weeks, being small for gestational age, and the composite outcome, which consisted of severe congenital anomalies, perinatal mortality, low Apgar-score (i.e. < 7/10 at 5 min) or admission to a neonatal intensive care unit.

Maternal Tdap vaccination augments neonatal pertussis immunity by elevating serum IgG antibody levels to pertussis vaccine antigens PTx, Prn, and FHA in the mother, and – via transplacental transfer – also in the neonate. The initial concentration of passively acquired antibodies is known to be influenced by factors such as gestational age at vaccination and birthweight, but little was known about the rate of decay after birth. In an individual participant data meta-analysis, combining data from 10 studies in 9 countries including the Netherlands, it was found that maternal antibodies decay at different rates for the different Tdap antigens, with half-lives varying between 30 and 35 days for PTx, Prn, and FHA, and that decay rates were not modified by gestational age at vaccination, birthweight, or vaccine characteristics [13]. This knowledge can be utilised in mathematical models and to inform policy decisions on vaccination programmes.

6.8.6 International developments

In October 2012, the maternal pertussis vaccination was introduced in the UK. In a recently published study [14], several effects of the vaccination were evaluated. It was shown that extending the optimal timing of vaccination from 28-32 weeks to 20-32 weeks of pregnancy, from September 2016 onwards, resulted in a consistently higher coverage level. Approximately 40% of pregnant women received their vaccination ≥13 weeks before delivery from September 2016 onwards, compared to <5% before that time. The study also showed that the rates of laboratory-confirmed and hospitalised cases in infants <3 months of age remained at similar levels between 2013-2015 and 2017-2019 compared to 2009-2011, while in other age groups these rates increased.

The VEs against a laboratory-confirmed pertussis infection among infants <2 and <3 months of age were estimated to be 88% and 89%, respectively. GA during vaccination did not affect these VEs, with the exception of vaccination 0-6 days before or 1-41 days after pregnancy, which resulted in a substantially lower VE. The VEs against hospitalisation and death among infants <3 months of age were estimated to be 89% and 97%, respectively. VE of maternal vaccination during a prior pregnancy against a pertussis infection among infants aged <63 days, was estimated to be 44%, with a median interval of 2.5 years between pregnancies. In addition, the study showed that the estimated VE against a laboratory-confirmed pertussis infection in infants <3 months of age was lower for dT3aP-IPV (Repevax) compared to dTa5P-IPV (Boostrix-IPV), when mothers were vaccinated 7-55 days before pregnancy.

The potential blunting effect of the maternal pertussis vaccination on the primary course, was assessed among children who received ≥1 dose of their primary course and whose mothers were vaccinated ≥7 days prior to the birth. Since the VE of the maternal vaccination remained above zero up to and including the third dose, blunting was not demonstrated.

In the US, the maternal Tdap vaccination was introduced in 2011. Earlier, between 1992 and 1997, the US transitioned step-by-step from complete use of wP vaccines towards complete use of aP vaccines for childhood vaccinations. Therefore, currently, mothers who received either wP or aP vaccines during childhood, receive Tdap vaccination during pregnancy. Recently, it was studied whether geometric mean concentrations (GMCs) of pertussis-specific IgG antibodies in cord blood of infants born to Tdap-vaccinated women who were aP-primed themselves, differed from those born to Tdap-vaccinated women who were wP-primed. The study included mother-infant pairs of whom the mother was born in the US, delivery occurred ≥37 weeks of GA, residual umbilical cord blood was available for serologic testing, and maternal Tdap vaccine (Adacel®; Sanofi) was received between 27 and 36 weeks of gestation and ≥14 days before delivery. Infants born to women with human immunodeficiency virus or women with laboratory-confirmed syphilis were excluded [15].

Results showed that the maternal immune response and efficiency of transplacental anti-PT transfer were significantly affected by the type of vaccine the mother received during childhood, in favour of the wP vaccine. Moreover, the anti-PT and anti-FHA GMCs of infants born to aP-primed women were significantly lower compared to those born to wP-primed women (52% and 14%, respectively). The Netherlands makes use of another maternal Tdap vaccination (Boostrix®), with higher doses of PT and FHA compared to Adacel®. In addition, maternal Tdap vaccination is recommended from 22 weeks of pregnancy onwards. Nevertheless, these results might be important for the Netherlands too, since we shifted from wP-vaccines towards aP-vaccines for childhood vaccinations in 2005 [15].

The international Periscope consortium of pertussis experts from various universities, national institutes (including RIVM) and pharmaceutical companies and funded by the Horizon 2020/ Innovative Medicines Initiative (IMI)-2 programme (2016-2021; extension 2021-2022) entered its last project phase. The aim of the consortium is to identify biomarkers for protective immunity to *B. pertussis* and to understand the role of the primary vaccine type (acellular or whole-cell) on the duration of protection against pertussis. New whole blood assays were developed to accurately monitor cell types of the innate immune system in clinical studies [16] and the kinetics of T cells specific for *B. pertussis* antigens following Tdap vaccination [17]. Also, our Periscope studies indicated that individuals primed with whole-cell vaccine in their youth had stronger plasma cell responses to pertussis vaccine antigens following a Tdap booster vaccination than individuals primed with acellular vaccine [18]. Infant vaccination studies, addressing the impact of primary vaccine type (acellular or whole-cell) and maternal immunisation on the infants' immune response to *B. pertussis*, were the last Periscope clinical studies to be conducted and, being delayed by the pandemic, will continue to be analysed in the coming two years in support of the primary aims of the project.

6.8.7 Literature

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** RIVM publication.*

6.8.8 Other RIVM publications

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6.9 Pneumococcal disease

A. Afrian, W. Miellet, N.Y. Rots, L.J. Visser, A. Niessen, R. Mariman, P de Boer, W. Freudenburg-de Graaf, N.M. van Sorge, H.E. de Melker, A. Steens

6.9.1 Key points

- In 2021/2022 the incidence of invasive pneumococcal disease (IPD) was low (9.4/100,000), mainly due to the COVID-19 mitigation measures. However, after all measures were lifted in March 2022, the incidence increased again to 12.8/100,000 in 2022/2023. The increase was seen across all age groups. Note that the incidence is still slightly lower than pre-COVID-19 with an average of 15.0 per 100,000 per year in 2015-2019.
- In 2022/2023, the incidence in children <5 years of age increased to the highest level in more than a decade (8.6/100,000; n=75). The increase was mainly due to an increase in serotype 19A (44% of all cases) that is covered by PCV13/PCV15/PCV20 but not by PCV10. Serotype 19A is now the most common serotype for IPD patients <5 years.
- In the epidemiological year 2022/2023, four vaccine failures occurred among children. The vaccine effectiveness of at least two doses of PCV10 was estimated at 88% (95% CI: 67-96%) compared to no vaccination.
- The PCV13 serotypes that are not included in PCV10 (serotypes 3, 6A and 19A), together with the PCV13-associated serotype 6C (cross-protection of serotype 6A) caused 42% of all cases in 2022/2023. PCV15 serotypes + 6C caused 57% and PCV20 serotypes + 6C caused 80% of all cases.
- For individuals ≥65 years, 80% of IPD was caused by a serotype included in the 23-valent pneumococcal polysaccharide vaccine (PPV23). The newly licensed PCV15 and PCV20 (both including 6C) caused 57% and 77% of the cases, respectively.
- Since autumn 2020, PPV23 is being offered to individuals born in 1941-1947, since autumn 2021 to those born in 1948-1952, and since autumn 2022 to those born in 1953-1956. The estimated impact of PPV23 on vaccine type IPD in these age groups ranged between 43-57%, depending on the age groups and method used.

6.9.2 Tables and figures

Figure 6.9.1 Number of invasive pneumococcal disease (IPD) cases from June 2021 up to and including May 2022 (pink) and June 2022 up to and including May 2023 (yellow) reported by nine sentinel labs (covering ~28% of the Dutch population) by month compared to the pre-COVID 5-year moving average (2014/2015-2018/2019). Only IPD presented with positive blood or cerebrospinal fluid samples were included.

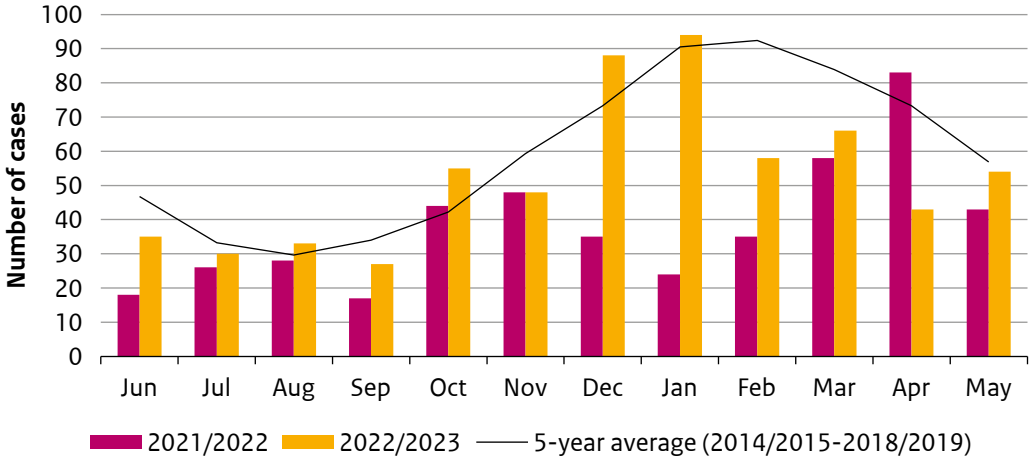

Figure 6.9.2 Incidence of invasive pneumococcal disease (IPD) in all ages by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes, PCV15 serotypes, PCV20 serotypes), as well as all serotype IPD, presented by epidemiological year (e.g. 04/05 = June 2004-May 2005). PCV7 was introduced in the childhood immunisation programme in June 2006 and PCV10 in May 2011. PPV23 was introduced in autumn 2020 for those born in 1941-1947, in autumn 2021 for those born in 1948-1952, and in autumn 2022 for those born in 1953-1956. Sentinel surveillance data have been used and are extrapolated to the Dutch population. Only IPD presented with positive blood or cerebrospinal fluid samples were included.

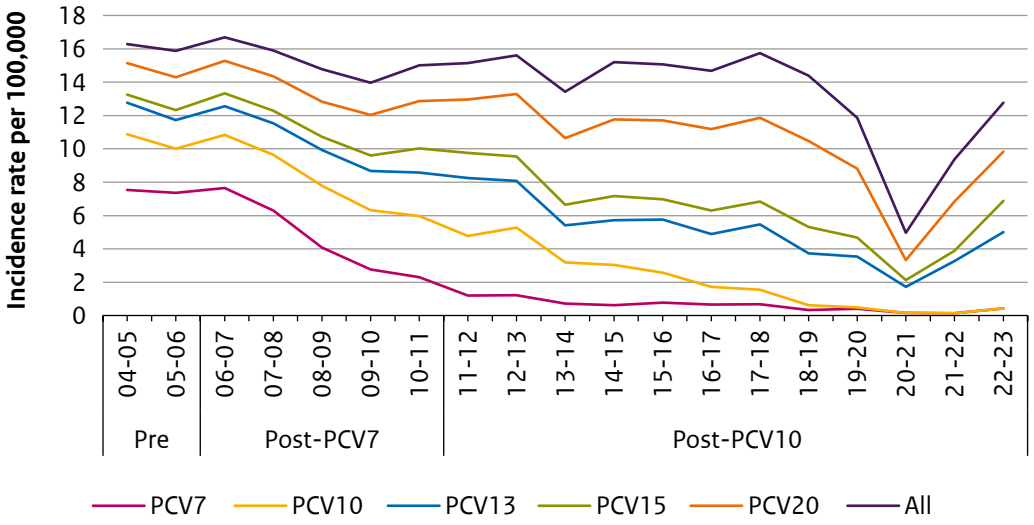

Figure 6.9.3 The percentage of cases in all age groups per top-ten serotype in the epidemiological years 2017-18 to 2022-23.
The selection is based on and sorted by the top 10 serotypes in 2022-2023 and with at least 10 cases in the last epidemiological year, namely: PCV13/15/20/PPV23-serotypes 19A and 3, PCV13-associated serotype 6C (cross-protection of serotype 6A in PCV13/15/20), PCV15/20/PPV23 serotypes 22F and 33F, PCV20/PPV23 serotypes 8 and 12F and PPV23 serotype 9N. Serotypes 15A and 23A are not covered by currently available vaccines.
Sentinel surveillance data has been used of IPD presented with positive blood or cerebrospinal fluid samples. The epidemiological year ranges from June to May.

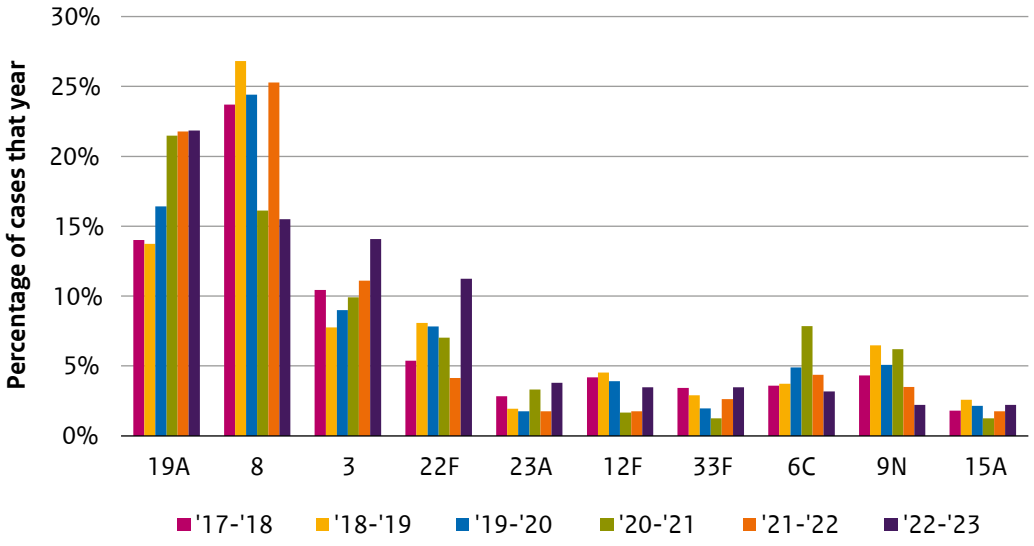

Figure 6.9.4 Incidence of IPD in children <5 years of age by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes, PCV15 serotypes, PCV20 serotypes), as well as all serotype IPD, presented by epidemiological year (e.g.,04/05 = June 2004-May 2005).
PCV7 was introduced in June 2006 and PCV10 in May 2011. From 2004-2005 to 2007-2008, sentinel surveillance data has been used and extrapolated to the Dutch population. From 2008-2009 onwards, data of national surveillance has been used of IPD presented with positive blood or cerebrospinal fluid samples.

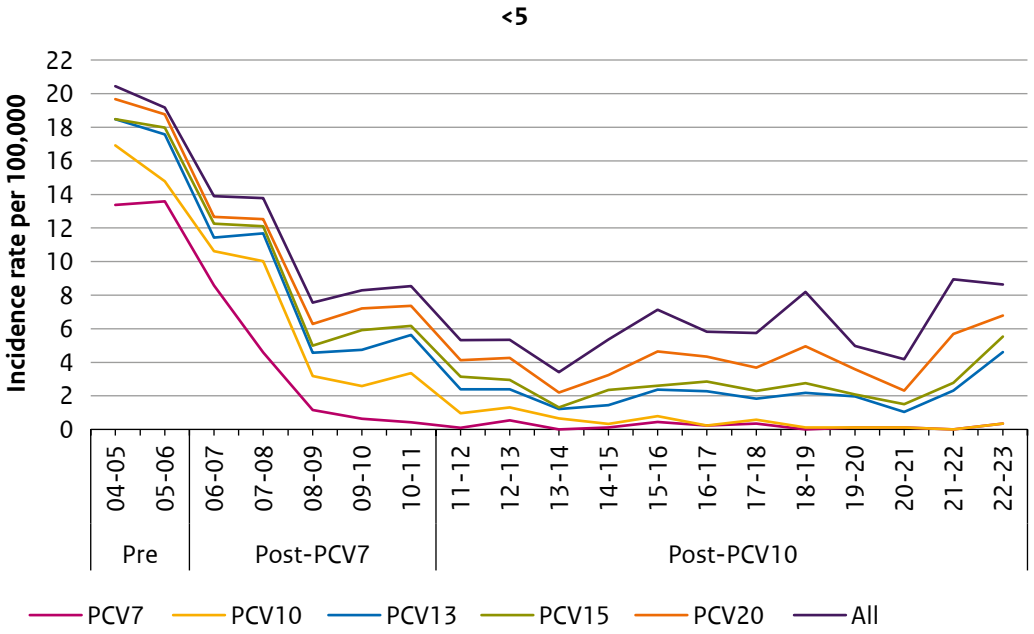

Figure 6.9.5 Incidence of IPD in persons 5-49 years of age by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes, PCV15 serotypes, PCV20 serotypes), as well as all serotype IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005).
Sentinel surveillance data has been used of IPD presented with positive blood or cerebrospinal fluid samples and is extrapolated to the Dutch population.

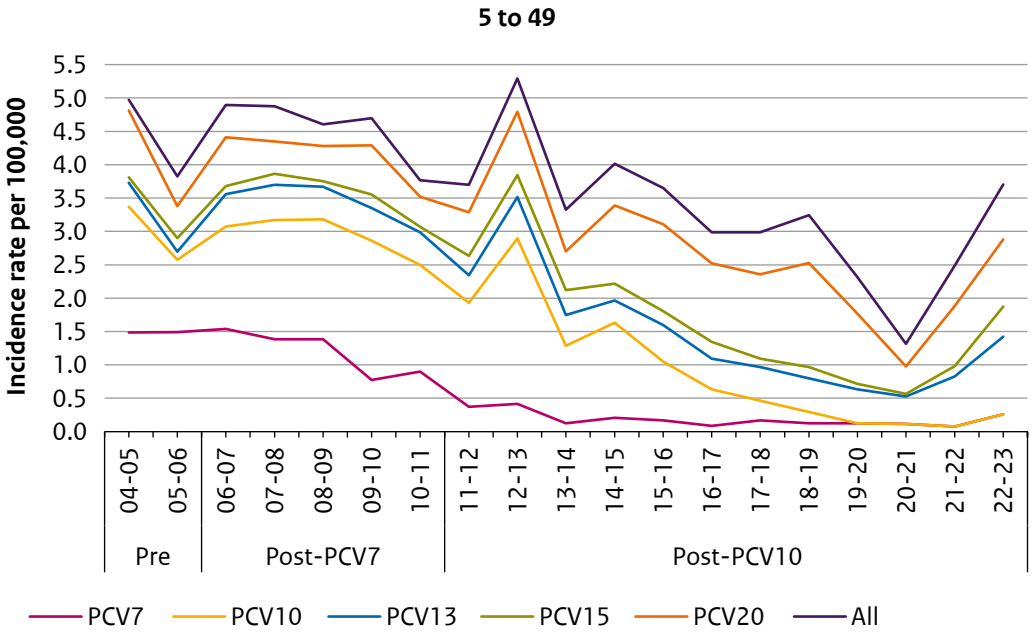

Figure 6.9.6 Incidence of IPD in persons 50-64 years of age by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes, PCV15 serotypes, PCV20 serotypes), as well as all serotype IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005). Sentinel surveillance data has been used of IPD presented with positive blood or cerebrospinal fluid samples and is extrapolated to the Dutch population.

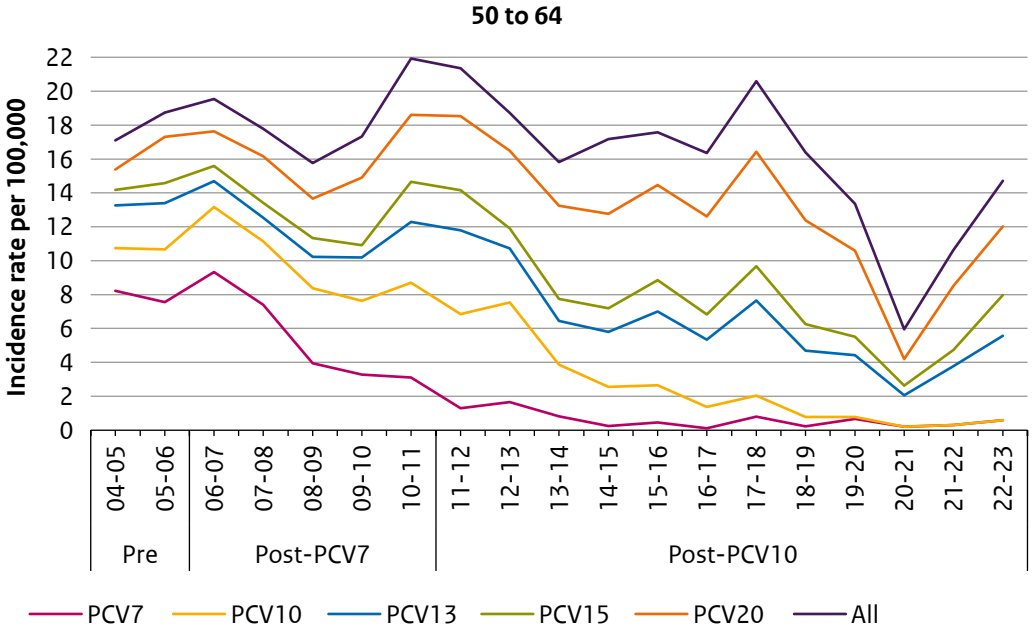

Figure 6.9.7 Incidence of IPD in persons aged 65 years or over, by vaccine serotype (PCV7 serotypes, PCV10 serotypes, PCV13 serotypes, PCV15 serotypes, PCV20 serotypes, PPV23 serotypes), as well as all serotype IPD, presented by epidemiological year (e.g., 04/05 = June 2004-May 2005).
PPV23 was introduced in autumn 2020 for those born in 1941-1947, in autumn 2021 for those born in 1948-1952, and in autumn 2022 for those born in 1953-1956. Sentinel surveillance data has been used of IPD presented with positive blood or cerebrospinal fluid samples and is extrapolated to the Dutch population.

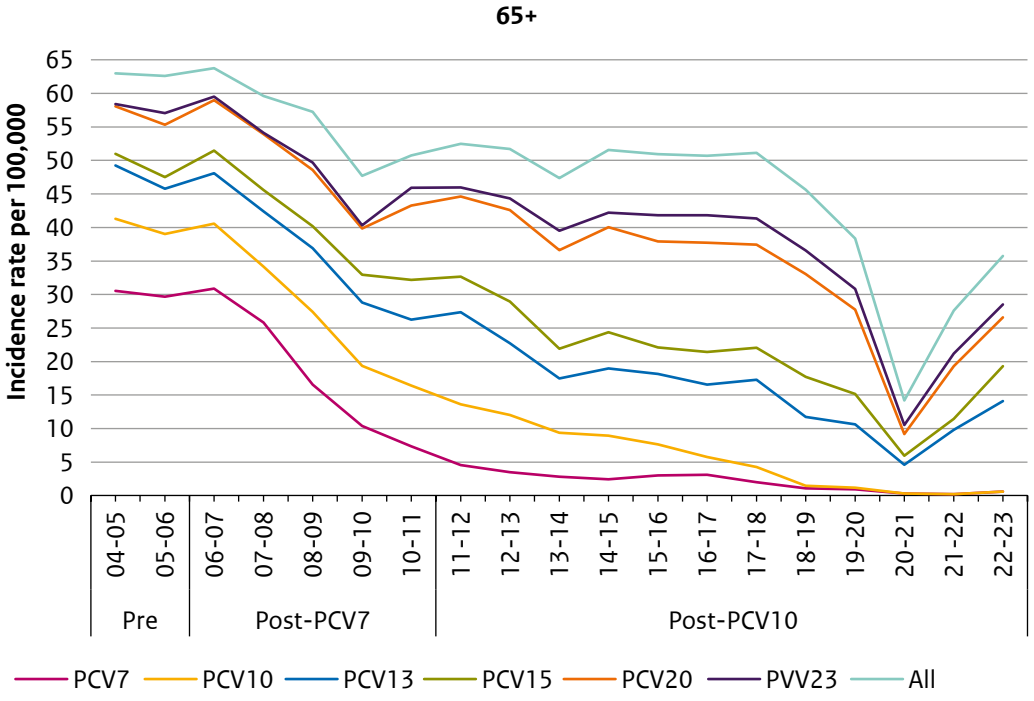

Figure 6.9.8 Distribution of IPD-causing serotypes in epidemiological year 2022/2023.
For children <5 years, data of the national surveillance system has been used. For other age groups, sentinel surveillance data has been used.
Only IPD presented with positive blood or cerebrospinal fluid samples are included. Note that no serotypes that are covered by PCV10 but not by PCV7 (PCV10-extra) were observed in this period.

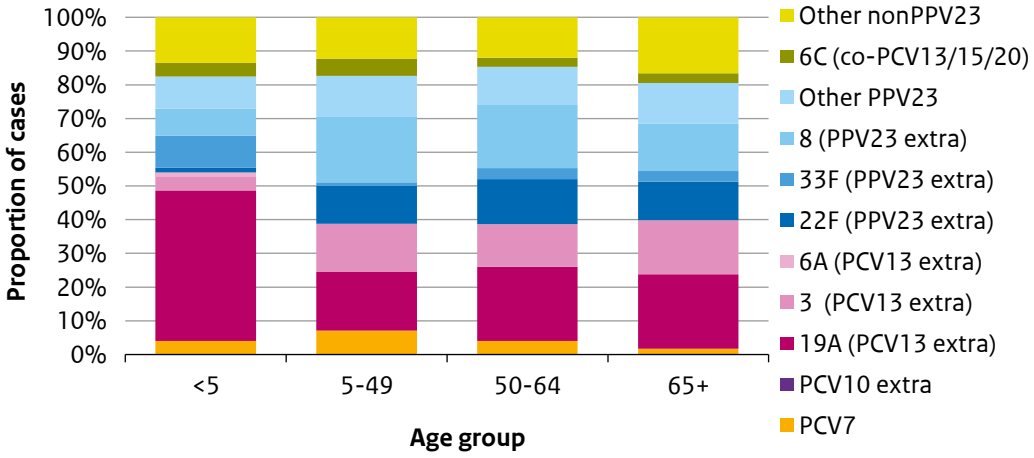

Figure 6.9.9 Number of pneumococcal serotypes isolated from colonies cultured from nasopharyngeal swabs from 330 24-month-old children.
Orange bars represent the serotypes most frequently found in IPD cases. The orange line indicates the cumulative percentage of all carried serotypes.

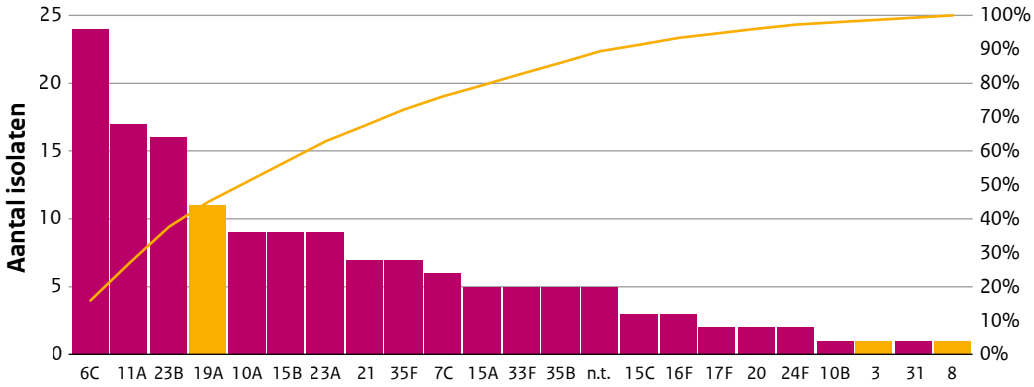

Figure 6.9.10 Culture based pneumococcal vaccine type-specific carriage prevalence in 24-month-old children for the different carriage surveillance studies.
The colours indicate the year/season when the various studies were performed.

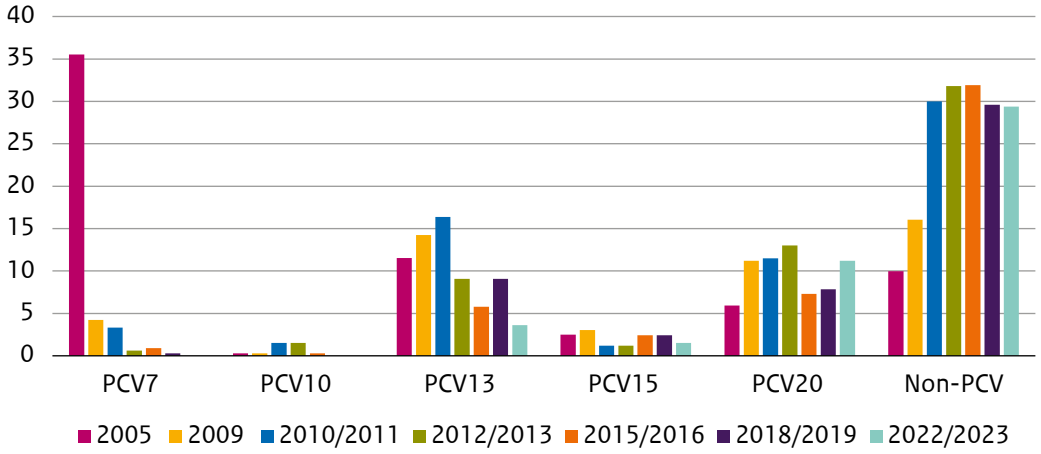

Figure 6.9.11 SNP-based pairwise distances between Dutch ST801 and ST15063 isolates. Pairwise SNP distances are determined using "snippy" and "snp-dists". Hierarchical clustering was performed on these pairwise distances using the default settings of the R package "pheatmap". Isolates are placed in identical order along the horizontal and vertical axes, the diagonal thus represents a to-self comparison. SNP distances are indicated by a colour scale (red to blue, representing low to high number of SNPs). STs are represented at the top and left of the distance matrix by coloured boxes (ST801 in green and ST15063 in pink). The resulting hierarchical clustering is visualised by the tree indicated at the top and left of the figure next to the ST.

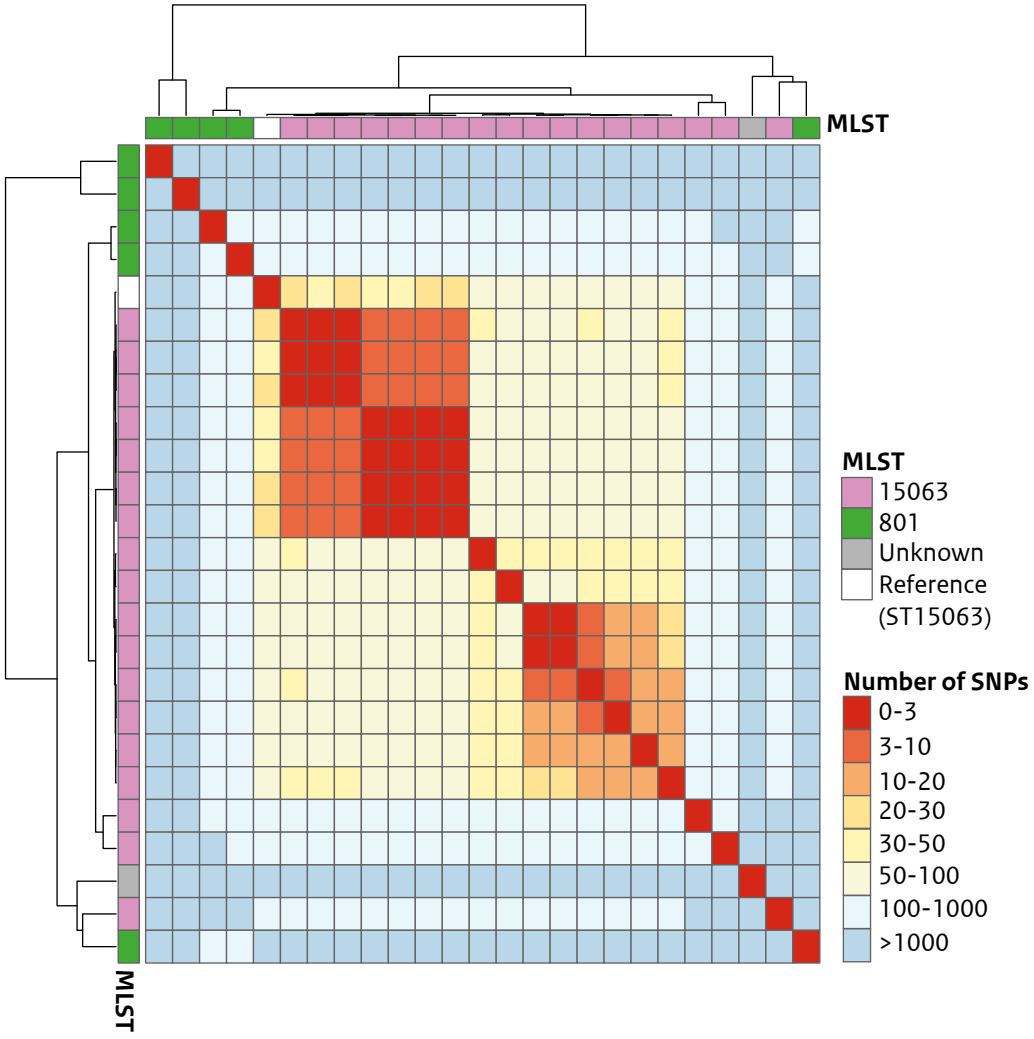

Figure 6.9.12 Phylogeny of Dutch, Norwegian, Finnish and UK serotype 4 isolates. Comparison with the reference genome (the first Dutch ST15063 strain) and the core genome of the dataset was determined using "snippy". Core genome alignment was used as input for maximum likelihood estimations using "IQ-TREE". A GTR+F+I+I+R2 model best fit the dataset, determined by IQ-TREE Modelfinder, and was used to construct the tree. Each isolate is coloured according to the country it was isolated in and labelled with its respective ST. The scalebar represents the number of substitutions per site.

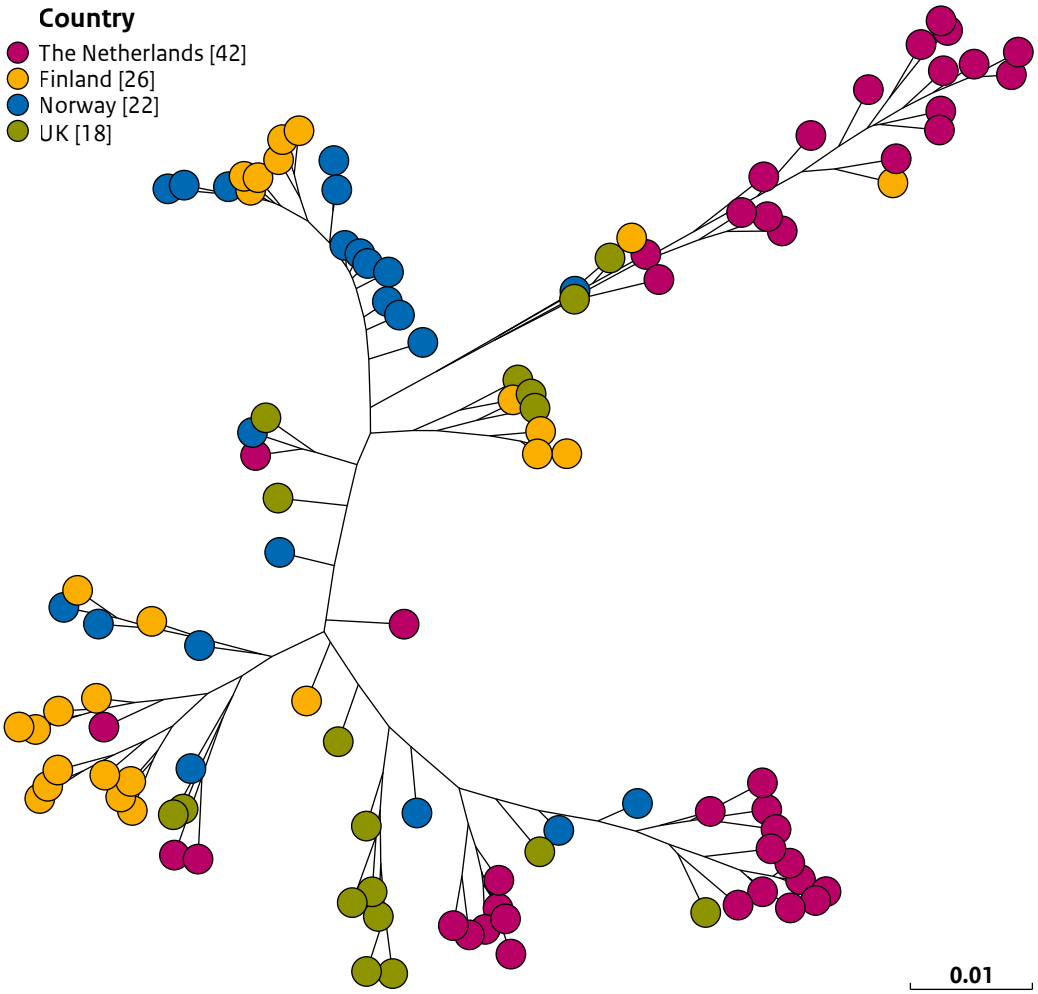

Table 6.9.1 Serotypes included in the various pneumococcal vaccines (current and those in development).

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

 # Note that PCV7 is no longer on the market, and that PCV10 is licenced for children but not for adults. PCV21 is not available on the market yet, but is being investigated in a phase 3-randomised clinical trial.

** indicates cross-protection. PCV10 protects against 6A through cross-protection from the 6B antigen. PCV13, PCV15 and PCV20 protect against 6C through cross-protection of the 6A antigen. Note that PCV21 defines 6A/C and 15B/C as one serotype each. Furthermore, note that PPV23 covers the A subtype of serotype 20. Which serotype 20 subtype PCV21 will include is not yet described.*

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 before the diagnosis – based on nationwide surveillance data up to and including May 2023.

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
2022	189	19F	PCV7	4	None
2022	149	23F	PCV7	4	Immunological underlying illness
2022	50	14	PCV10	3	Chronic disease: chromosome abnormality, bladder problems, trachae cannula
2022	61	14	Other: sinflorix	3	Other: congenital nephrotic syndrome, Kidney transplant in 2018
2022	38	23F	PCV10	3	None

6.9.3 Epidemiology

Since December 2008, invasive pneumococcal disease (IPD) is notifiable for children born in or after 2006, and since April 2021, for individuals aged 60 years and over. Isolates of persons with IPD in these age groups are submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) for serotyping and are linked to notification data [1]. Additionally, since 2004, nine sentinel laboratories, which covered about 25% of the population up to 2020, when they extended to 28%, submit all IPD isolates (from blood or cerebrospinal fluid; CSF) to NRLBM. Furthermore, since 2006, all laboratories submit isolates of children under 5 years suffering from IPD. Since 2017, all clinical laboratories have been requested to send IPD isolates of all age groups to NRLBM of their own accord. However, the national coverage for the entire population has not yet been evaluated. To be able to determine long-term time trends for the <5-year-olds, national data is used, and for all other age groups the sentinel data is used. In this report, IPD cases presented by positive blood or CSFsamples are included in the analysis of trends over time.

Note that infant vaccination with a 7-valent conjugated pneumococcal vaccine (Prevenar-7, PCV7) was introduced into the national immunisation programme (NIP) in 2006, and was replaced by a 10-valent vaccine (PCV-10) in 2011. PPV23 has been recommended for 60-79 year-olds; vaccine implementation started in autumn 2020 for individuals born in 1941-1947 and is being rolled out by cohort. In autumn 2021, individuals born in 1948-1952 were offered PPV23, and in autumn 2022 individuals born in 1953-1956.

6.9.3.1 Overall

While the overall IPD incidence has been quite stable since 2004/2005, with an average incidence of 15.0 per 100,000 (range: 13.4 to 16.7 per 100,000) per epidemiological year (June to May), the incidence in epidemiological years 2020/2021 and 2021/2022 decreased to 5.0 and 9,4 per 100,000, respectively, probably as a result of the COVID-19 mitigation measures. After lifting all measures in March 2022, the monthly number of cases was closer to the average as seen before the pandemic (Figure 6.9.1), and the incidence increased again to 12.8 per 100,000 in epidemiological year 2022-2023 (Figure 6.9.2).

The distribution of IPD-causing serotypes has been changing since PCV7 introduction and has continued to change after the switch to PCV10 in May 2011 (Figure 6.9.3). The 10 most common serotypes in 2022/2023 were: 19A (22% of all cases), 8 (16%), 3 (14%), 22F (11%), 23A (4%), 12F (3%), 33F (3%), 6C (3%), 9N (2%), and 15A (2%). Of these, only serotype 23A and 15A are not covered by currently available vaccines (Table 6.9.1). Altogether, in 2022/2023, PCV10 serotypes represented 3% of all IPD cases, PCV13+6C 42%, PCV15+6C 57%, PCV20+6C 80%, and PPV23 81%.

6.9.3.2 Children <5 years of age (Figure 6.9.4)

In the epidemiological year 2022/2023, 75 IPD cases with a positive blood or CSF sample were reported in children <5 years of age, resulting in an incidence of 8.6 per 100,000. Out of these 75, 30 patients (40%) had sepsis, 5 (7%) had meningitis and 12 (16%) had pneumonia. Other clinical pictures among this age group were bacteraemia and pleural empyema. In addition to these 75 cases, there were 11 IPD cases <5 years for which pneumococci were isolated from

other normally-sterile places, were identified on the basis of PCR on CSF or isolation-location was unknown. After the switch to PCV10 in 2011, the incidence in this age group decreased substantially and stabilised around 2015/2016 at an incidence 16% lower than the incidence before PCV10 introduction (Figure 6.9.4). Although the incidence in the first COVID-19 year (2020-2021) was lower than in previous years, probably related to the COVID-19 mitigation measures, the incidence among children <5 years in 2021/2022 and 2022/2023 were the highest in more than a decade. This increase was mainly due to an increase in IPD caused by non-PCV10 serotypes (8.3/100,000 in 2022/2023 versus 4.1/100,000 in 2020/2021; especially 19A (33 cases) and 33F (7 cases)). Only three cases caused by PCV10 serotypes were observed. Out of the 75 cases aged <5 years in 2022/2023, 33 (44%) were caused by serotype 19A, the most common serotype seen in 2022/2023 in this age group and which is covered by the higher-valent PCVs but not by PCV10 (Figure 6.9.8). Fourteen of these serotype 19A cases caused IPD in children younger than 1 year of age. Other common serotypes in this age group were serotype 33F (7 cases) and serotype 8 (n=6, Figure 6.9.8). Serotype 33F is not included in the currently available childhood vaccines but is included in PCV15 and PCV20, serotype 8 is covered by PCV20. Overall, 57% of cases <5 years in 2022/2023 were caused by PVC13+serotype 6C (PCV13/15/20-associated), 68% by a PCV15+6C serotype and 83% by a PCV20+6C serotype. PCV15 has recently been licensed for use in children and is among the vaccines that the Health Council of the Netherlands recently advised for childhood vaccination [2]. PCV20 is expected to be licensed for use in children in 2023.

6.9.3.2.1 IPD mortality among children <5 years

From 2014 up to and including May 2022, 535 IPD cases among children younger than 5 years were reported nationally. For 401 cases (75%), the mortality status was known. Out of the 401 patients, 29 (7%) died. These 29 patients were all infected with non-VT serotypes (serotypes 8 (n=7), 15C (n=4), 19A (n=4), 10A (n=3), 12F (n=2), 3 (n=2), 6C (n=2), 22F, 23A, 24F, 31, 33F). The 26 patients that died were <2 years of age and 8 of them had known comorbidities. In the epidemiological year 2022/2023, 3 patients died (infected with 33F, 8 and 15C), all <2 years of age.

6.9.3.3 Persons aged 5-49 years (Figure 6.9.5)

In the epidemiological year 2022/2023, 99 IPD cases were reported by the nine sentinel laboratories (covering about 28% of the Dutch population) in persons aged 5-49 years, resulting in an incidence of 3.7 per 100,000 per year. The incidence in this age group has decreased slightly over time since the introduction of PCV7. After an even sharper decrease in the incidence in 2019/2020 and 2020/2021 as a result of the COVID-19 mitigation measures, after all measures were lifted in March 2022, incidence increased again to pre-COVID levels in 2022/2023 (Figure 6.9.5). The IPD incidence due to serotypes included in PCV10 in 2022/2023 was 0.3 per 100,000, which is slightly higher than in 2021/2022 (0.1 per 100,000), but substantially lower compared to the incidence before the introduction of childhood vaccination in 2006 (3.0 per 100,000).

The incidence caused by serotypes not included in PCV10 has been rising from 1.2 per 100,000 in 2020/2021 to 2.4 per 100,000 in 2021/2022; this non-PCV10 incidence was 3.4 per 100,000 in 2022/2023. In 2022/2023, the most common serotypes were serotype 8 (covered by PPV23 and PCV20; 19 cases), serotype 19A (covered by PCV13/15/20 and PPV23; 17 cases), serotype 3 (covered by PCV13/15/20 and PPV23; 14 cases), and serotype 22F (covered by PCV15/20 and PPV23; 11 cases) (Figure 6.9.8).

6.9.3.4 Persons aged 50-64 years (Figure 6.9.6)

In the epidemiological year 2022/2023, the 9 sentinel laboratories reported 153 IPD cases in individuals aged 50-64 years, resulting in an incidence of 14.7 per 100,000. This was lower than reported in 2018/2019 (pre-COVID-19; 16.4 per 100,000), but higher than in the COVID years 2020/2021 and 2021/2022 (Figure 6.9.6). Before the COVID-19 pandemic, the incidence in this age group fluctuated around 18 per 100,000 annually, with a decrease after PCV7 introduction in children in 2006 and a further decrease after the switch to PCV10 in the NIP in 2011. Since the epidemiological year 2018-2019, IPD caused by PCV10 serotypes has become very rare in this age group; in 2022/2023, the incidence of IPD for these serotypes was only 0.6 per 100,000. Because of serotype replacement resulting from childhood vaccination with PCV7 and subsequently PCV10, the IPD incidence caused by serotypes not included in PCV10 has been increasing from 14.1 in 2010/2011 to 15.6 per 100,000 in 2018/2019 (Figure 6.9.6). The incidence was 10.3 per 100,000 in 2021/2022 and further increased to 14.1 per 100,000 in 2022/2023. In 2022/2023, the most common serotypes among those aged 50-64 years were serotype 19A (covered by PCV13/15/20 and PPV23; 33 cases), serotype 8 (covered by PPV23 and PCV20; 28 cases), serotype 22F (covered by PCV15/20 and PPV23; 20 cases), and serotype 3 (covered by PCV13/15/20 and PPV23; 19 cases) (Figure 6.9.8).

6.9.3.5 Persons aged 65 years or over (Figure 6.9.7)

During the epidemiological year 2022/2023, the sentinel laboratories sent 352 isolates of IPD patients aged 65 years and over to NRLBM, representing an incidence of 35.7 per 100,000. Of these 352 cases, 136 patients (39%) had sepsis, 83 (24%) suffered from pneumonia and 5 (1%) had meningitis.

The incidence decreased after PCV7 introduction in children and has remained stable since the switch to PCV10 at around 20 cases per 100,000 inhabitants per year up to the COVID-19 pandemic. As in other age groups, the incidence decreased during the COVID-19 pandemic, presumably as a result of the mitigation measures, when the corresponding absence of influenza led to fewer numbers of secondary bacterial infections (see paragraph 6.9.5.5). The introduction of PPV23 vaccination for older adults also affected the incidence in those aged 65 years and older (see paragraph 6.9.4.1).

IPD caused by PCV10 serotypes was rare in 2022/2023 (incidence 0.6 per 100,000), but non-PCV10 IPD increased to 35.1 per 100,000 in 2022/2023, compared to 27.4 per 100,000 in 2021/2022. Note that the (non-PCV10 and all-type) IPD incidence was still only about half compared to recent pre-COVID years (Figure 6.9.7). Of all IPD cases in this age group, 80% was caused by a serotype included in PPV23, PCV13+6C covered 42%, PCV15+6C covered 57%

and PCV20+6C covered 77%. In 2022/2023, the most common serotypes were 19A (covered by PCV13/15/20 and PPV23; 77 cases), 3 (covered by PCV13/15/20 and PPV23; 56 cases), and 8 (PPV23 serotype; 49 cases) (Figure 6.9.8).

Nationwide, 1,286 isolates were sent in to NRLBM in 2022/2023; 1,162 (90%) of those had an Osiris notification that could be linked to the laboratory record. Of all notifications in Osiris of cases aged 65 years and over in that period (n=1162 during the time since the question was asked for all cases), information on comorbidity was available for 1,066 patients (92%), of whom 75% had a reported comorbidity. 26% of the notified patients was reported to be vaccinated (8% missing data). Of the patients who were reported to be vaccinated, 78% was reported to have at least one comorbidity. For unvaccinated patients, this was 71%. According to Osiris, 66 (6%) of the patients died as a result of the infection. No conclusion can be drawn regarding the effectiveness of vaccination in case of underlying medical conditions, as prevalence data on those conditions for the population under surveillance is needed for such an analysis and vaccination might more often be accepted by those who have underlying medical conditions.

6.9.3.6 Vaccine failure after childhood vaccination

Since the introduction of PCV7, 53 cases of vaccine type IPD have been reported among vaccine-eligible children born after 1 April 2006 and aged 2 months and over, and since 2020, aged 3 months and over. In 2020, the standard schedule of the NIP changed from 2, 4, 11 months to 3, 5, 11 months. Of the children born after April 2006 and aged 2 months and over, 29 children (55%) were vaccinated with at least 2 doses (with the second dose given at least 2 weeks before diagnosis), and therefore were considered vaccine failures (Table 6.9.2). Since the change of the standard schedule in 2020, no vaccine failure has occurred among that eligible group. Overall, serotype 19F was the most common serotype among vaccine failure cases (n=8, 28%), a serotype that has been described in relation to vaccine failure in other settings, too [3]. There were four vaccine failure cases in 2022/2023 (two cases of serotype 23F and 14 each). Three of them had a known underlying medical risk condition.

6.9.3.7 Vaccine effectiveness (VE) of childhood vaccination against IPD

The VE of PCV10 was calculated using the indirect cohort (or Broome) method, in which the odds of vaccination in patients infected with a vaccine serotype (VT cases) is compared to the odds of vaccination in patients infected with a non-PCV10 serotype (non-VT cases). The analysis was focused on PCV10. We include here all reported IPD patients for the period from June 2011 up to and including May 2023, who had a known serotype and vaccination status and were aged 3 months or over. Patients were assumed to be correctly vaccinated if vaccination according to age occurred at least 20 days before arrival of the isolate in the reference laboratory (i.e., 14 days pre-disease onset, considering the median time between sampling and the arrival of the isolate). Those who obtained one dose were excluded from the analysis.

Out of the 21 PCV10-type IPD patients, 14 were vaccinated with at least 2 doses (67%), as were 404 out of the 432 non-PCV10 IPD patients (94%). This resulted in a VE of 88% (95% CI: 67-96%) for at least two doses of PCV10 compared to no vaccination, in the 2022-May 2023 period.

6.9.4 Current/ongoing research at RIVM

6.9.4.1 Impact and VE of PPV23 in older adults

In October 2020, PPV23 vaccination was offered to all 73- to 79-year-olds (born in 1941-1947), and in October 2021 all 68- to 73-year-olds (born 1948-1952) were eligible for vaccination. We estimated the impact of the adult pneumococcal vaccination programme and the direct VE of PPV23 against VT-IPD using surveillance data from October 2020 up to and including September 2022 [3]. The impact was calculated by modelling the incidence of PPV23 serotype (VT)-IPD by age and vaccine eligibility. The impact was defined as one minus the incidence rate ratio for being eligible for vaccination. Separate models were fit for season 2020/2021 and 2021/2022. The impact for those born in 1941-1947 was 40% (95% credibility interval (CrI): 18-59%) in the first year following vaccination and 30% (95%CrI 5-50) in the second year following vaccination. The impact for those born in 1948-1952 was 40% (95% CrI: 22-56%) after the first year. The combined impact of the vaccination programme until October 2022 was 35% (95%CrI: 16-51%).

Preliminary estimates for the VE against VT-IPD among vaccinated older adults was obtained with the same model, using an instrumental variable method. Since we expected the notification data to be incomplete, thus overestimating the VE-estimates, we defined a lower-limit for the VE by extrapolating the notification data on the basis of the NRLBM surveillance data. The VE among vaccinated 73-79 year olds in 2020 ranged between 47% (95%CrI: 30-59) and 59% (95%CrI: 41-70) in the first year following vaccination and between 46% (95%CrI: 14-61) and 50% (95%CrI: 19-66) in the second year. The VE among 68-73-year olds vaccinated in 2021 ranged between 54% (95%CrI: 39-64) and 58% (95%CrI: 43-68) in the first year following vaccination. The estimated number of prevented cases among vaccinated individuals was 31 (95% CrI 14 – 48) in the first year of the vaccination programme, and 110 (95% CrI 38-173) in the second year of the vaccination programme. The VE was also estimated using the indirect cohort method. Since IPD-notification and reporting of vaccination was incomplete [1] in the first year of the vaccination programme, this method was only used on the notification data in the second year after implementation. Between November 2021 and September 2022, there were 300 IPD-cases who had been eligible for vaccination and had complete data on vaccination status and serotype. The VE against VT-IPD for those aged 73-79 at vaccination was 57% (95% confidence interval (CI): 12-80) in the second year following vaccination. The VE for those aged 68-73 at vaccination was 51% (95%CI: -1-77) in the first year following vaccination.

6.9.4.2 Cost-effectiveness analysis of vaccination of older adults

The higher-valent PCVs (PCV15 and PCV20) have become or will soon be available for use in adults and children, and a 21-valent PCV21, containing 8 serotypes not covered by PPV23 or PCV20, is under development for use in adults. We used a static health economic decision model to investigate the cost-effectiveness of vaccination of older adults (60+ years) with PPV23, PCV15, PCV20 and PCV21 [4]. In the model, we considered potential indirect effects of moving from PCV10 to PCV13, PCV15 or PCV20 in children. We therefore assumed an 80% reduction in the incidence of IPD caused by childhood vaccine serotypes, which was fully offset

due to replacement by IPD caused by non-childhood vaccine serotypes. We did not consider side effects in the model, even though these can cause losses [5] as they were assumed nondifferent between vaccinations.

Of the currently available vaccines, vaccination with PCV20 was economically the most attractive vaccination strategy for older adults, if PCV10, PCV13 or PCV15 was used in children. The impact of future PCV21 on the burden of pneumococcal disease in older adults was projected slightly higher than PCV20, but its vaccine price is still unknown. The assumed indirect effects of the childhood vaccine worsened the cost-effectiveness of PCV15, PCV20 and PPV23 in older adults compared to no vaccination, with the size of impact depending on the extent of overlap in serotypes covered by the childhood and adult vaccine. With a switch to PCV20 in children, repeated PPV23 became economically more attractive than PCV20 for older adults vaccinated three years or more after that switch. The cost-effectiveness of PCV21 in older adults was minorly affected by a switch to higher-valent vaccines in children due to different range of serotypes covered than the childhood vaccine.

Besides being useful to the advice of the Health Council on pneumococcal vaccination of older adults [6], the study also demonstrated the importance of combining childhood and adult vaccination programmes in a combined economic evaluation [4].

6.9.4.3 Pneumococcal carriage

Since the introduction of pneumococcal vaccination into our NIP, changes in serotype-specific pneumococcal nasopharyngeal carriage in vaccinated children and their unvaccinated parents have been monitored every 3-4 years in the OKIDOKI studies as a way to monitor the national pneumococcal vaccination programme. During the 2022-2023 season the carriage study was repeated to monitor currently carried pneumococcal serotypes and thereby to estimate the preventive potential of the novel more-valent PCVs. In addition, the effect of the COVID-19 mitigation measures on carriage of respiratory pathogens was explored. In total, 330 children aged 24 months and one of their parents were enrolled in the study. Nasopharyngeal and saliva samples were collected from the children, while oropharyngeal (OP) samples were collected from the parents.

In the 2022-2023 season (OKIDOKI6), the total nasopharyngeal culture-based carriage in 24-month-old children was 46%, which is comparable to previous post pneumococcal vaccination carriage surveillance studies data except for 2010-2011 (OKIDOKI2, 64%) and 2012-2013 (OKIDOKI3, 57%). The most prevalent serotypes in OKIDOKI6 were 6C, 11A, 23B and 19A (Figure 6.9.9). In contradiction to the earlier studies, no PCV7 and PCV10 serotypes were detected (Figure 6.9.10). Of the PCV13-specific serotypes, 19A was isolated in 3% of the carriers and serotype 3 in 1%. PCV15 serotypes that are not covered by PCV13 (33F and 22F) were isolated in 1% and 0% of the carriers (22F was not detected). PCV20-serotypes together were carried by 23% of the children. With 6%, the proportion of children that reported respiratory tract infections and/or acute otitis media symptoms was significantly lower than during the previous OKIDOKI studies (21-35%).

Potential interferences between SARS-CoV-2 and pneumococcal carriage were assessed in the SARSLIVA study [7], with Kaplan-Meier estimator and time-dependent Cox regression models, whichever was allowed according to power. The study took place between October 2020 and January 2021, during the second COVID-19 wave and prior to COVID-19 vaccine implementation in the Netherlands. SARS-CoV-2, pneumococcus and overall bacterial (16S) abundances were quantitatively detected in saliva collected from 176 adults and 98 children of 80 households. Ten saliva samples were collected per person over a 42-day period. Shortly after SARS-CoV-2 detection of one household member and commencement of stay-at-home measures, elevated rates of pneumococcal carriage were observed among children and adults. Living with a young child (≤5 years) in the household (Hazard ratio [HR] 4.2, 95%CI, 2.28 – 7.81) and quantified SARS-CoV-2 presence (HR 0.91, 95% CI, 0.83 – 0.98) were both independently associated with an increased risk of pneumococcal colonisation in the Cox regression analysis. Moreover, SARS-CoV-2-infected individuals displayed elevated pneumococcal and overall 16S abundances. Pneumococcal carriage was also associated with delayed clearance of SARS-CoV-2 infection (HR 0.90, 95%CI, 0.82 – 0.99, measured in the index case). In household contacts, pneumococcal carriage was associated with a subsequently increased risk of SARS-CoV-2 infection in the Kaplan-Meier analysis (cumulative hazard rate 2.5, 95%CI 1.2 – 3.9). Collectively, these results suggest that SARS-CoV-2 infection exacerbates pneumococcal carriage and vice versa. Home isolation accelerated pneumococcal transmission independently from the viral infection.

6.9.4.4 Investigation of an increase in serotype 4 IPD

In a comparison of national data and data from the sentinel labs, it became clear that IPD caused by serotype 4 had increased compared to earlier years, mainly in non-sentinel labs. Because the patients fitted a similar profile, mostly men of working age and over often living in coastal regions, we started an investigation to the increase 1) using whole genome sequencing, and 2) making an effort to interview patients.

All serotype 4 isolates from 2019 (a pre-COVID-19 reference year; n=8) and 2022 (n=32; up to December 2022) were whole-genome sequenced. The majority of the sequenced isolates belonged to ST15063 (n = 18), a single locus variant (SLV) from ST801 that was first reported in a Norwegian shipyard outbreak in 2019 [8]. The second most common ST was ST205 (n= 10), which has been a known dominant ST amongst serotype 4 strains. We focused our attention on the ST801 and ST15063 strains in the genetic analysis, and on the ST15063 cases in the epidemiological investigation.

Single Nucleotide Polymorphisms (SNPs) can be used to track evolutionary trajectories, determine relatedness of strains and thus detect outbreaks. We therefore reconstructed the full genome of the first ST15063 strain identified in the Netherlands, isolated in 2019, and used this as a reference genome. We subsequently found that 15 other ST15063 strains were relatively similar (<100 SNPs difference, green/yellow boxes in Figure 6.9.11). Within this group, there were two clusters of strains extremely similar (<10, dark red cluster top left, and <23 SNPs, red/orange cluster bottom right in Figure 6.9.11), and in there, some near-identical strains (0-3 SNPs) for which direct transmission could theoretically have occurred (see below).

Four remaining strains, three of ST15063, were unrelated to the dominant circulating strain(s). These differed by 800-2,000 SNPs from other ST15083 strains. Similarly, the ST801 strains were quite diverse, with a SNP distance of 1,900-2,500.

Next, we placed the sequenced Dutch isolates in an international context. To do so, we selected all isolates related to the published shipyard outbreaks of Norway, Finland, and the UK [8]. The Dutch isolates are indicated in orange in the tree (Figure 6.9.12). The isolates located at the top right are a distant branch, representing predominantly ST205 isolates. The large spread-out branches on the left of the tree represent ST801, which was the outbreak strain in 2019 in Norwegian and Finnish shipyards. Five Dutch ST801 strains cluster in this part of the tree. The Dutch ST801 strains do not cluster together, which is consistent with the large number of SNPs (1900-2500 SNPs) between them. The ST15063 branch is located on the bottom right of the tree, with the two clusters of Dutch isolates split from each other by two Norwegian and two UK strains (Figure 6.9.12). It was already reported that ST15063 strains from different countries differ by a low number of SNPs (e.g. 17 SNPs between a Norwegian and UK isolate), indicating that this ST is quite stable [8]. Further evidence for this is that, in the international tree, the 15 Dutch strains that differ by a maximum of 100 SNPs are split by two Norwegian and two UK strains. Overall, this international analysis confirms the presence of two smaller clusters (<10 SNPs and <23 SNPs) in the Netherlands for which genetic analysis cannot rule out direct transmission events. However, knowing that the ST is quite stable, without epidemiological evidence, the genetic data is insufficient to confirm direct transmission events.

Both Dutch clusters contain isolates from geographically distant locations within the Netherlands and the cluster furthest right in Figure 6.9.12 contains data of several years. Interview data was only available for those aged 60 years or over (n=4) and did not indicate an epidemiological link or overlapping profile. Although we were unsuccessful in collecting interview data for patients <60 years, on the basis of the genetic investigation and the available epi-data from the NRLBM we assume the increase in serotype 4-ST15063 not to be due to an outbreak, but possibly due to an introduction of a successful clone along the coast (potentially related to the shipyard outbreaks), with a slow spread across the country.

In the January-May 2023 period, 25 cases of IPD-serotype 4 have already been reported nationally, of which 6 in sentinel laboratories; all through 2022, 38 IPD-serotype 4 cases were observed, of which 6 in sentinel laboratories. In 2023, 76% is aged between 20-66 years ('working age'), but note that serotype 4 is covered by PCV10 and PPV23, which may explain (part) of the age-related pattern. 72% is male. The patients live scattered across the country.

6.9.5 (Inter)national developments

6.9.5.1 Vaccination of children

In autumn 2022, the Health Council of the Netherlands advised moving the pneumococcal booster in the NIP from 11 months to 12 months, together with a proposed change in the age of the co-administered hexavalent DTaP-IPV-Hib-HepB booster [9]. This advice was drawn up following the evaluation of the NIP in order to further optimise the programme [10].

The recent registration of PCV15 for children in the EU [11] has opened possibilities for enhanced vaccination. The Health Council of the Netherlands published an advice on the kind of vaccine to use in the NIP of children [2]; they recommend using PCV13 or PCV15 instead of PCV10 because of the larger coverage. A similar advice was given in among others Germany and the US, where PCV13 and PCV15 are made interchangeable for all recommendations for children [12, 13]. As the registration of PCV20 for use in children is expected at the end of 2023, the Health Council of the Netherlands has planned to provide another advice for the kind of vaccine to be used in the NIP in 2024 [14]. The registration of PCV15 for children was partly based on the phase-3 randomised clinical trial (RCT) performed in Denmark, Finland, Italy, and Norway, which used a 2+1 schedule with vaccinations at 3, 5 and 12 months [15]. In that study, PCV15 was compared to PCV13; DTPa-IPV/Hib was administered concomitantly. About 600 children were included in each arm. Adverse events were collected the 14 days post-vaccination, and serotype-specific IgG was measured 30 days post-primary, pre-booster and 30 days post-booster. Using the cut off of ≥0.35µg/mL, PCV15 was found non-inferior to PCV13 for the 13 shared serotypes.PCV15 was superior for added serotypes 22F and 33F.

In the PREVIX_COMBO RCT performed among Australian First Nations children, participants received different primary vaccination schedules (3x PCV10, or 3x PCV13 (both at 2, 4, 6 months), or 3x PCV10 + 1xPCV13 at 1, 2, 4, 6 months) [16]. Participants were subsequently invited to participate in the PREVIX_BOOST RCT, where either a PCV10 or a PCV13 booster was received [17]. About 125 children were included in each group. Children were randomised within each primary vaccination group. Immunogenicity of the PCV13 serotypes was assessed at 6 months post-booster, as well as otitis media, nasopharyngeal carriage, hearing loss, and developmental milestones. They found that all groups met the cut off of a geometric means concentration of ≥0.35µg/mL for 11 of 13 serotypes. However, the seroprevalence, i.e., the proportion of children above the threshold, was below 70% for 7 (for PCV10) or 4 (PCV13) serotypes. Of the PCV10 serotypes, this was for six serotypes in the PCV10 booster group. The PCV13 booster group had significantly higher seroprevalences six months post-booster for five out of ten shared serotypes; titres against PCV13-serotype 19A were nondifferent between any primary plus booster comparison. Otherwise, they found that if priming included PCV13, there were no differences between groups receiving the PCV10 or PCV13 booster. No differences were observed in the prevalence of otitis media, nasopharyngeal carriage, hearing loss, and developmental milestones.

6.9.5.2 Adult vaccination

The registration in Europe of PCV15 and PCV20 for use in adults [11, 18] has opened possibilities for enhanced vaccination. RIVM summarised recent literature and the epidemiological situation among older adults in the Netherlands for the Health Council of the Netherlands [19]. Furthermore, RIVM performed a cost-effectiveness analysis for vaccination of older adults, in which different scenarios for adults vaccination and childhood vaccination were incorporated (see above; [4]). That information was used, among others, by the Health Council of the Netherlands for their advice on vaccination in the national programme for pneumococcal vaccination in adults (NPPV). They have now advised a single PCV20 to be used at 60 years of age, instead of the current PPV23 with revaccination every five years [6]. Furthermore, a catch-up campaign is advised for all individuals aged 60 years or over that have not received a PPV23 in the last 5 years. The advice regarding those who have recently been vaccinated with PPV23 is that they are to be offered vaccination with PCV20 (or the PCV advised at the time) five years after PPV23. The Ministry of Health, Welfare and Sport still needs to decide whether or not the advice will be implemented.

For the use of PCV15 or PCV20 in older adults, several cost-effectiveness analyses have been performed. Studies focused on England [20], Denmark [21] and Italy [22] (all funded by Pfizer, the manufacturer of PCV20), as well as on Japan [23] and the US5 (both independent). All concluded that PCV20 is cost-saving compared to PCV13+PPV23. Otherwise, PCV20 was estimated to be economically more favourable than PCV15, PCV15+PPV23 or PCV20+PPV23. None of the studies included both indirect protection and serotype replacement from childhood vaccination.

A 21-valent pneumococcal conjugate vaccine (PCV21, called V116) is being developed for adults to be used in countries that include pneumococcal vaccination in their NIP. PCV21 was tested in a phase-1-2 randomised clinical trial (RCT) in the US [24], including vaccine-naïve, healthy adults with or without chronic medical conditions assessed as stable, aged 18–49 years (phase 1; n=30 per group) or aged 50 years or over (phase 2; approximately n=250 per group). Two different doses of PCV21 (2 µg pneumococcal polysaccharide per serotype per 0.5 ml or 4 µg per 1.0 ml) were compared to PPV23 in phase 1, and the highest dose (4 µg/1.0 ml) was compared with PPV23 in phase 2. Safety was determined by analysing injection-site adverse events and solicited systemic adverse events up to day five following vaccination, and serious adverse events up to six months following vaccination. Immunogenicity was assessed using serotype-specific opsonophagocytic antibody geometric mean titres (OPA-GMT) ratios at 30 days following vaccination. No vaccine-related serious adverse events or deaths were observed during the study period. Of those aged 18–49 years, 73% and 77% of participants receiving PCV21 in, respectively, the lower or higher dose perceived injection site pain, compared to 57% of the participants receiving PPV23. Among the 50+ participants in phase 2, this was 46% of PCV21 vaccinees and 38% of PPV23 vaccinees. Fatigue was the most frequently reported solicited systemic adverse event (27%, 27% and 14% in 18–49-year-olds and 19% and 12% in 50+-year-olds; order of groups as above). Immunogenicity data showed non-inferiority of PCV21 to PPV23 for the 12 shared serotypes, and superiority for the 9 unique serotypes, both in 18–49 year olds and in the 50+ participants. In the phase-1 study

in 18–49-year-olds, the OPA-GMT responses were generally numerically higher for the higher dose PCV21 than for the lower dose; for the higher dose PCV21, the lower bound of the 95%CI of the GMT ratio was more than 0.5 for the common serotypes and more than 1.0 for the unique serotypes. In phase 2 in 50+-year-olds, the lower bound of the 95%CI of the GMT ratio was more than 0.33 for the common serotypes and more than 1.0 for the unique serotypes. Cross-protection of PCV21 to serotype 6C and 15B was observed, although for serotype 6C, the proportion of participants that seroconverted (around 55%) was slightly lower than for other serotypes, but this was higher than for PPV23 (around 30%). PCV21 with 4 µg pneumococcal polysaccharide per serotype per 1.0 ml is currently investigated in a phase-3 RCT. A phase-1 study using PCV21 versus PPV23 in Japanese adults ≥20 years [25] showed comparable results concerning side effects (safety profile not different from PPV23, no serious event or deaths) and immunogenicity (comparable for shared serotypes, PCV21 higher for its unique serotypes) as found in the studies described above.

The impact of pneumococcal vaccination (and vaccination against influenza or shingles) on the risk of cardiovascular events in older adults (≥65 years) has been reviewed [26]. A meta-analysis of 15 studies and a separate other study reported a significantly, though modest (~6-7%) lower risk of cardiovascular disease after PPV23. Vaccination against pneumococci and influenza (dual vaccination) was associated with lower risks of some cardiovascular events (stroke, congestive heart failure, ischemic heart disease, and myocardial infarction).

6.9.5.3 Pneumococcal carriage in children

Carriage studies among children aged between 13-18 months (in 2014/15 and 2017/19) and 6-12 months (2017/20) were performed in the UK, where PCV13 is used in the NIP [27]. Carriage prevalence had remained stable during the study samples at ~50%. The non-PCV13 serotypes 15B/C, 23B, 21, 10A, and 11A were most commonly carried. Interestingly, in the recent Dutch carriage study (see paragraph 6.9.4.3), these were also among the eight most-frequently carried serotypes despite the fact that we use PCV10. Serotypes 15B/C, 10A and 11A are covered by PCV20. In the Netherlands, PCV13 serotypes 19A and cross-reacting serotype 6C were otherwise among the most frequently carried serotypes, while in the UK, these were uncommon. Still, despite prolonged PCV13 vaccination, serotype 19A as well as serotype 3 and 19F were still found among children.

In 2020, the UK changed their NIP schedule from a 2+1 to a 1+1 schedule (at 3 and 12 months). While IPD surveillance data has shown good effectiveness against disease (discussed in last year's report), carriage data of the 1+1 era has now become available [28]. Six months after the booster, the carriage prevalence was 65% for the 2+1 group and 54% for the 1+1 group. At the time of booster, this was very similar (63% and 51%, respectively). Importantly, vaccine-type carriage (including cross-reacting 6C) was similar between groups (5% and 3% for 2+1 and 1+1 groups at time of booster and 2% and 1%, respectively, 6 months after the booster). While there had been slightly more non-vaccine type carriage at booster time for the 2+1 groups (60%) than for the 1+1 group (45%), no statistical difference was observed after 6 months (62% and 54%, respectively). These results suggest that 1+1 prevents carriage similarly to 2+1, and one may therefore expect herd protection to other age groups.

The UK results were comparable to (preliminary) data from Vietnam [29], South Africa [30] and India [31]; in South Africa and India, PCV10 (Synflorix) and PCV13 were compared for the two schedules, though, with earlier boosters (9 months) than in the UK (12 months). PCV10 and PCV13 were nondifferent from each other for both schedules in South Africa, while in India, no difference between schedules was observed for PCV13, but for PCV10, in none of the schedules vaccine-type carriage was decreased in the second year (prevalence ~15%, control 22%, which were all slightly higher than ~7% at baseline).

A review summarised the effect of PCV7, PCV10 and PCV13 on the density of pneumococcal carriage in children <5 years of age [32]. Out of the 1,941 studies published between 2000 and 2021 that were reviewed, 10 were included; most were performed in non-Western settings. The review found no consensus in the effect of vaccination on the density of pneumococcal carriage; by comparing unvaccinated and vaccinated children, some studies found no differences, some found increased density and others decreased density in vaccinees. The inconsistent results included density of vaccine type and non-vaccine type carriage. Factors that might have affected the results include different laboratory techniques in the various studies and sampling during (respiratory) symptomatic or asymptomatic periods. If results concerning the density of pneumococcal carriage are being used, critical review and standardisation of the methods is needed.

6.9.5.4 Geographical spread of pneumococci over time

The analysis of serotype 4 IPD (see paragraph 6.9.4.5) could indicate introduction of ST15063 along the coast and subsequent spread through the Netherlands. The speed of such clonal spread was determined for a multidrug-resistant serotype 24F clone in France [33]. Whole genome sequencing of 229 carriage serotype 24F isolates and 190 IPD serotype 24F isolates of individuals <18 years in the period 2003-2018 was performed. Results were combined with data from the Global Pneumococcal Sequencing project database and among others, spatiotemporal analysis was performed. The multi-drug lineage GPSC10 drove the increase in 24F in France; it took the lineage three to five years to spread across the country.

6.9.5.5 Infections/conditions preceding or coinciding with IPD

A sustained decrease in IPD incidence, among other respiratory infections, was observed when containment measures were in place because of the COVID-19 pandemic [34]. After lifting the non-pharmaceutical interventions, the IPD incidence increased again. The abnormal dynamics provided an opportunity to determine correlations between different viruses and pneumococcal disease. An Israelian study investigated the attribution of so-called pneumococcal disease-associated viruses (respiratory syncytial virus [RSV], human metapneumovirus [hMPV], influenza viruses, and parainfluenza viruses [PIV]) to community-acquired alveolar pneumonia (CAAP; n= 918 in 2020-2021), non-CAAP lower respiratory infections (n=9346), pneumococcal bacteraemic pneumonia (n=64) and non-pneumonia-IPD (n=185) among children <5 years old [35]. Virus detection was performed from hospitalised children as well as children without respiratory infection that visited a paediatric emergency room. Pneumococcal carriage was determined in children coming for immunisations. Pneumococcal disease outcome data was obtained from active prospective surveillance

systems. They modelled the proportion of each clinical endpoint that was attributable to each virus over time. They observed that during the lockdowns, the so-called pneumococcal-disease associated viruses disappeared among children; rhinovirus (RhV) and adenovirus (AdV) as well as pneumococcal carriage remained present during the lockdowns. After society opened up, the pneumococcal disease-associated viruses sequentially returned, with PIV emerging first followed by hMPV, RSV and influenza, each a few months later. They estimated that 82% of CAAP cases at <5 years old could be attributed to the common respiratory viruses, mostly to RSV (49%), followed by hMPV (13%), PIV (11%) and influenza (7%). There was a trend of lower viral contributions in older age groups. For children <1 year old, 62% of CAAP could be attributed to RSV. Non-pneumonia IPD was not associated with any of the viruses, while RVP was also estimated to be the main contributor for non-CAAP (21%) and IPD pneumonia (18%). RhV and AdV were not associated with the pneumococcal outcomes. Together, these results may indicate that RSV prevention may have additional public health benefits by preventing pneumococcal disease.

A temporal association between an RSV outbreak and IPD in children was also found in Quebec, Canada [36]. The study included data of the 2013-2022 period (n=7712 IPD cases) and used quasi-Poisson regression models to determine the fraction of the increase in IPD that was attributed to different viruses in 2021-2022. They estimated that the fraction of IPD among <5-year-olds attributed to RSV was 77% (95%CI [33-100]). No such association was found in other age groups. In ≥65-year-olds, IPD was temporally associated with influenza and parainfluenza 3.

In several countries, it is recommended to perform immunological investigations in children with IPD in order to rule out or detect immunodeficiencies. In UK, this recommendation was evaluated by determining the proportion of children with IPD in whom an immunological disorder was found [37]. Retrospective collection of medical records was done for patients presenting in the January 2015-November 2020 period. Out of the 68 included children with IPD, immunological investigations were performed for 51%; of those not investigated, four had died and four had other explanations for the infection. Out of 51, four children (8%) had abnormal findings that were judged to be medically relevant. This proportion is similar to the 10% that was found before the recommendation was made. In the Netherlands, no such national recommendation is in place, although further investigation of vaccine failure IPD in children does occur, depending on the hospital.

6.9.5.6 Mortality

It has been unclear whether IPD increases long-term mortality, or whether increased mortality after IPD is the result of predisposing medical conditions that both increased the risk for IPD and for death. A recent Canadian study indicated that IPD increased the risk for short, intermediate, and long-term mortality, independent of age, sex, or concurrent conditions [38]. Adult IPD patients diagnosed between 1999-2019 in Alberta were matched with age- and sex-matched controls, which were, where possible, hospitalised within ±3 months of the diagnosis of IPD in the matched case. Based on the Discharge abstract database, the National ambulatory care reporting system, the Ambulatory care classification system and the Physician claim data,

ICD-9/10 codes were used to define comorbidities in the 5-year period pre-hospitalisation or pre-pseudo-diagnosis. Using Cox proportional hazard modelling, mortality in cases and controls was compared, taking into account Elixhauser comorbidity categories. The adjusted Hazard ratio (aHR) for 30-day mortality was 3.8 (95%CI 3.3–4.3), although the aHR decreased over time, with aHR 2.9 (2.3-3.6) in 2014-2019. The aHRT for all-cause mortality after 90 days among those having survived the 90 days post-IPD/hospitalisation was 1.4 (1.3–1.5). Increased long-term mortality was seen among those with or without comorbidity and in all age groups except for those over 75 years.

6.9.6 Literature

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** RIVM publication.*

6.9.7 Other RIVM publications

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6.10 Poliomyelitis

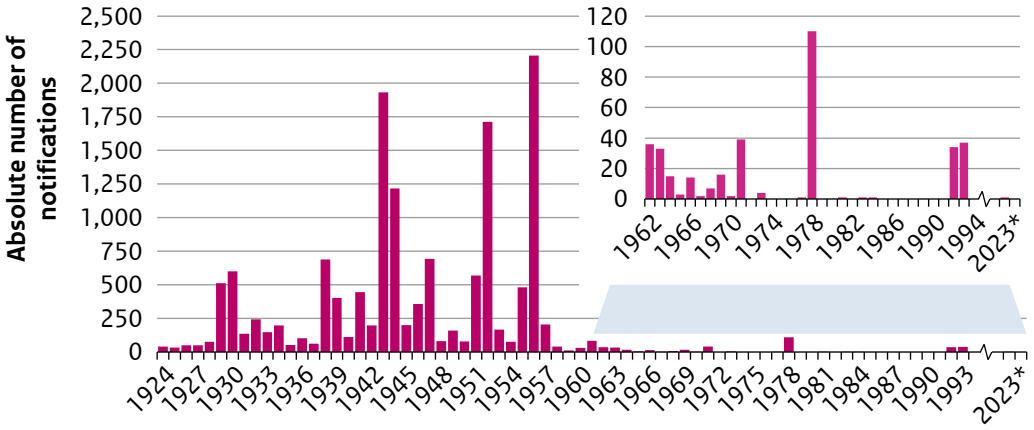
D.L. van Meijeren, K.S.M. Benschop, H.E. de Melker, E. Duizer

6.10.1 Key points

- One case of asymptomatic poliovirus infection was reported in the Netherlands in 2022. This concerned an employee of a vaccine producer located at Utrecht Science Park in Bilthoven, who showed no signs of illness since he was fully vaccinated against poliovirus.
- One Sabin 1-Sabin 3 recombinant poliovirus was found in the clinical enterovirus surveillance in 2022.
- Enterovirus (EV) surveillance in the Netherlands shows that the percentage of EV-positive stool samples where poliovirus was excluded, decreased from 60% in 2015 to 48% in 2022.
- Environmental surveillance activities performed in the Netherlands in 2022 have again documented the absence of poliovirus circulation in the country.
- In 2022-2023, the WHO classified two countries – Afghanistan and Pakistan – as polio-endemic countries.
- Export of a WPV1 strain from this endemic region to Southern Africa resulted in a WPV1 outbreak in Malawi and Mozambique with 1 and 8 AFP cases, respectively, in 2021 and 2022.
- The global number of circulating vaccine-derived poliovirus type 2 (cVDPV2) cases remained at a similar level in 2022 compared to 2021 (673 and 683, respectively).
- The WHO clearly defined four outbreak areas that, together, accounted for almost nine tenths of the cVDPV2 cases in 2022: eastern DR of Congo, northern Nigeria, south-central Somalia and northern Yemen.
- Between February 2022 and February 2023, poliovirus was detected in sewage in London (UK) and New York State (US). The strains were related to each other as well as to strains found in Jerusalem (Israel) sewage. Additionally, in July 2022, a VDPV2 case in an unvaccinated person was confirmed in New York State.

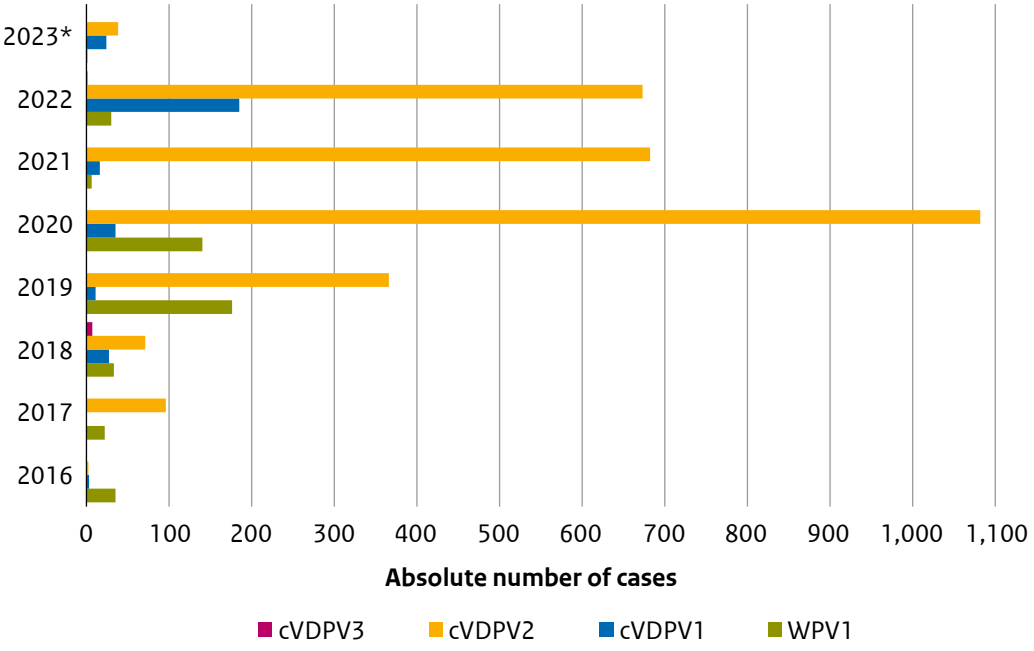
6.10.2 Tables and figures

Figure 6.10.1 Notifications of poliomyelitis (AFP cases) in the Netherlands from 1924-1994 and zoomed in on 1960-2023* (right-hand part).



** For 2023, notifications up to and including June are entered.*

Figure 6.10.2 Total number of global polio cases 2016-2023* as reported to WHO HQ [1, 2].



** For 2023, data for the period up to and including 2 May is reported.*

6.10.3 Epidemiology and pathogen

6.10.3.1 Epidemiology
One case of asymptomatic wild-type poliovirus infection was reported in the Netherlands in 2022 (Figure 6.10.1). This concerned an employee of a vaccine producer located at Utrecht Science Park in Bilthoven (USPB). The Saukett strain (wild poliovirus type 3 (WPV3) strain) was first detected by routine wastewater surveillance at poliovirus facilities in the Netherlands in a sample from November 15, 2022. Follow-up investigation yielded one employee still shedding the virus. The employee showed no signs of illness because he was fully vaccinated against polio, just like all employees of the vaccine producer. He was kept in isolation until three consecutive faecal samples were tested negative for poliovirus. No contacts of the employee got infected with WPV3.

In October 2022, a child who was recently vaccinated with bivalent oral polio (bOPV) in Moldavia, was found to be secreting a Sabin 1-Sabin 3 recombinant virus. The child did not show signs of acute flaccid paralysis (AFP). These two findings did not change the polio-free status of the Netherlands or the World Health Organization (WHO) region Europe.

In 2023, up to and including June, no cases of poliomyelitis were reported in the Netherlands.

6.10.3.2 Polio-free status
In 2002, the European WHO region was declared wild poliovirus (WPV)-free. Until all six WHO regions have been declared WPV-free, establishing and/or maintaining high vaccination coverage and performing high-sensitive surveillance of polio cases are key. For countries with a strong healthcare system, high levels of sanitation, and a long period of non-endemicity, including the Netherlands, other surveillance strategies, including enterovirus and environmental surveillance, are also approved [3].

6.10.3.3 Enterovirus surveillance
For the year 2022, nationwide coverage of enterovirus (EV) surveillance was obtained as complete data from all 33 virological diagnostic laboratories was received. In total, 13,720 stool samples were tested for the presence of EV in order to exclude poliovirus. Stool sampling yielded 1,209 EV positives, resulting in an average EV positivity rate of 8.8% [4]. According to the Global Polio Laboratory Network, an effective enterovirus surveillance system detects between 5 and 25% of enteroviruses in all stool samples tested annually [3].
Exclusion of poliovirus presence on the basis of EV surveillance can be defined at two levels: the percentage of stool samples for which the presence of poliovirus is excluded and the percentage of EV-positive samples for which the presence of poliovirus is excluded. Poliovirus in EV-positive samples is excluded by the detection of non-polio EVs through sample sequencing.

In 93% (12,821/13,720) of the total stool samples analysed in 2022, poliovirus was shown to be absent. The percentage of poliovirus excluded in EV-positive stool samples was 48% (585/1209). One Sabin 1-Sabin 3 recombinant poliovirus was found in the clinical enterovirus surveillance in 2022 (see chapter 6.10.3.1) [5].

Over the years, the percentage of EV-positive stool samples where poliovirus was excluded decreased from 60% in 2015 to 48% in 2022 [5]. In 2020, the percentage was lowest (30%) due to the fact that less sequencing was performed on the EV-positive samples compared to other years [5] and because priorities in the laboratories had shifted to COVID-19 control. Whereas it is mandatory to send in stool samples for poliovirus testing when polio is suspected, it is highly recommended but not mandatory to send in EV-positive stool samples in non-AFP cases for sequencing [5]. In 2022, 541 EV-positive stool samples failed to be sent in for typing, and 82 EV-positive stool samples were un-typable. A further reduction of the percentage of EV-positive stool samples for which poliovirus is not excluded may be achieved only if poliovirus exclusion on all EV-positive stool samples is mandatory or if laboratories are offered financial compensation for contributing to the EV surveillance.

6.10.3.4 Environmental surveillance

Environmental surveillance for poliovirus has been in place in the Netherlands since 1997 and, in combination with the system for enterovirus surveillance, has provided clear documentation for the absence of poliovirus circulation in the country over the years. In May 2022, a Sabin like type 3 (SL3) vaccine virus without mutations in VP1, was isolated from one Bible Belt sample. The enteroviruses detected through environmental surveillance in the Bible Belt were strongly related, and often identical, to the viruses detected in the Netherlands by EV surveillance [4].

Following the report on an ongoing circulating vaccine-derived poliovirus type 2 (cVDPV2) outbreak in London-New York-Jerusalem in the orthodox Jewish community, RIVM analysed wastewater samples from Amsterdam Buitenveldert for September-October 2022 (4 wastewater samples) and no polioviruses were detected.

Ukraine experienced a cVDPV2 outbreak at the end of 2021 [1]. In March and April 2022, there was an increased influx of refugees from Ukraine into the Netherlands. Most Ukrainian refugees were housed across the country and only one refugee centre was monitored by our sensitive environmental surveillance. No polioviruses were detected [4].

All areas with a polio vaccination coverage <90% (n=25) were monitored by performing a poliovirus polymerase chain reaction (PCR) test on the ribonucleic acid (RNA) extracted for the national wastewater surveillance for SARS-CoV-2. These samples were not concentrated and catchment populations per sewage treatment plant (i.e. per sample) were larger than in our environmental surveillance in the Bible Belt. This method is less sensitive by an order of 200 to 2000 but it covered the entire Bible Belt population. In 2022 (between 25 March and 31 December) 951 samples from 25 sewage treatment plants were screened by the Sabin-poliovirus detection: no poliovirus (PV) was detected while > 95% of the samples was positive for enterovirus. Environmental surveillance activities performed in the Netherlands in 2022 have again documented the absence of poliovirus circulation in the country in combination with the system for EV surveillance.

6.10.4 Research

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

The NPL participates in the validation of new poliovirus strains (S19 strains), including type 2, that can be applied outside of the fourth edition of the Global Action Plan (GAPIV) containment for the poliovirus neutralisation assay. In April 2023, the NPL has implemented the poliovirus neutralisation assay using S19 strains in their routine diagnostics. Environmental surveillance as supplemental surveillance in addition to acute flaccid paralysis surveillance, is mandatory for countries that will be using novel oral polio vaccine type 2 (nOPV2) under the current Emergency Use Listing (EUL) [5]. The NPL analysed sewage samples from Tajikistan following an optimised algorithm for the period from April 2021 up to and including March 2022. Eight weeks after the last of two vaccination rounds using nOPV2, the last cVDPV2 was detected in the environmental surveillance in Tajikistan. After the last and third vaccination round with nOPV2, the nOPV2 strains were isolated from the sewage system for another nine weeks. None of the isolated strains showed the characteristic mutations known to correlate to reversion to pathogenicity. Between March 2021 and March 2023, over 600 million doses of nOPV2 were given in 28 countries. Sequencing of all nOPV2 strains is obligatory under the current EUL. This sequence was scheduled to be performed by centers for disease control and Prevention (CDC) (USA) and the National Institute for Biological Standards and Control (NIBSC) (UK) but due to the enormous number of nOPV2 strains isolated, the GSLs of Institute Pasteur in Paris and RIVM participated in this activity. Even though the novel oral polio vaccine type 2 (nOPV2) strain is safer than Sabin 2, up to March 2023, two emergences of nOPV2 vaccine derived polioviruses (VDPV) have caused AFP cases.

6.10.5 International developments

In 2022-2023, the WHO classified only two countries – Afghanistan and Pakistan – as polio-endemic countries (endemic countries have never stopped the transmission of indigenous wild poliovirus) [6]. However, export of a WPV1 strain from this endemic region to Southern Africa resulted in a WPV1 outbreak in Malawi and Mozambique with 1 and 8 AFP cases, respectively, in 2021 and 2022 [7-9]. The African WHO region was declared wild-type polio free in 2020 after no WPV cases have been notified in Nigeria since 2016 [10]. Both in Malawi and Mozambique, the last endemic WPV cases were reported in 1992. The current WPV1 cases do not affect the polio-free status of the African region, since the virus strain originated from Pakistan [6].

In Afghanistan and Pakistan, a combined total of 23 WPV1 cases were notified in 2022 and 2023 for the period up to and including 2 May [7]. This is an increase compared to 2021, when only 5 cases were reported but yet a substantial decrease compared with 2020, when a total of 140 cases was reported. Moreover, the environmental surveillance continued detecting low levels of WPV1 in both countries in 2022 and 2023 up to and including 2 May [6, 7]. In environmental surveillance, no WPV1 was detected in countries other than Afghanistan or Pakistan in

the same period [7]. Both countries reported no cVDPV2 cases in 2022 and 2023 up to and including 2 May [11].

The global number of cVDPV2 cases remained at a similar level in 2022 compared to 2021 (673 versus 683, respectively, Figure 6.10.2) [11]. These cases were reported by twenty, mainly African, countries. More than half (n=360) of the cases occurred in the Democratic Republic of Congo (DR of Congo), where only 28 cases were reported in 2021 [11]. Moreover, 162 cases were reported by Yemen, causing the number of cases in this country to more than double compared to 2021 (n=66) [11]. The WHO clearly defined four outbreak areas that together accounted for almost nine tenths of the cVDPV2 cases in 2022: eastern DR of Congo, northern Nigeria, south-central Somalia and northern Yemen [6]. Insufficient quality and timeliness of outbreak response, lack of outbreak response with type 2 containing vaccines and disruption in delivery of essential immunisation services, resulting in a persistently high proportion and concentration of zero-dose children and communities, result in the intensity of transmission in these areas [6]. Moreover, cVDPV2 outbreaks are mainly the result of the use of monovalent type 2 oral polio vaccine (mOPV2) in areas with previous cVDPV2 outbreaks where the required >80% vaccination coverage could not be reached. To stop these outbreaks, the nOPV2 continues to be administered through the WHO Emergency Use Listing Procedure. This procedure ensures that countries meet a pre-defined set of criteria to be eligible to use nOPV2. At the end of October 2022, 39 countries at high risk of cVDPV2 had met these criteria and by the end of March 2023, more than 600 million doses were administered in 28 of these countries [6].

In June 2022, the UK Health Security Agency reported the detection of several related VDPV2 strains in the sewage of the London Beckton Sewage Treatment Plant (STP) between February and June 2022 [12]. Multiple detections from different but related strains suggest that local spread of the virus has occurred, mainly in areas in London with some of the lowest vaccination rates, and that multiple people have been infected. In response to the detection, sewage surveillance has been expanded, health care professionals were alerted to be aware of patients with symptoms of polio, and the UK's Joint Committee on Vaccination and Immunisation (JCVI) advised that all children between 1 and 9 years of age living in London boroughs should be offered an IPV booster dose [13]. The last detection was reported in November 2022. No associated cases of paralysis have been reported in the UK up to and including 2 May 2023 [11].

On 21 July 2022, the New York State Department of Health (NYSDOH) confirmed a VDPV2 polio case in Rockland County in an unvaccinated person [14]. As of the 9 May 2023, 101/3060 samples collected as part of the New York sewage surveillance (implemented for COVID-19 surveillance) had tested positive for poliovirus Type 2, of which the last detection was reported in February 2023 [15]. 94/101 positive samples were genetically linked to the virus responsible for both the Rockland case and the strains detected in the London sewage [15, 16]. cVDPV2 strains with a common ancestor as the strains found in New York State and London, were detected in an AFP case and the sewage system of Jerusalem (Israel) and in a wastewater sample from the city of Montreal, Canada [16].

6.10.6 Literature

1. World Health Organization (WHO). Global Polio Eradication Initiative: Global Circulating Vaccine-derived Poliovirus (cVDPD). Geneva2023 [updated 2 May 2023; cited 9 May 2023]. Available from: https://polioeradication.org/wp-content/uploads/2023/05/weekly-polio-analyses-cVDPV-20230502.pdf.
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3. World Health Organization Europe and Centers For Disease Control And Prevention. Enterovirus surveillance guidelines. 2015 [cited 14 July 2021]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0020/272810/EnterovirusSurveillanceGuidelines.pdf.
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6. World Health Organization (WHO). Poliomyelitis eradication - Report by the Director-General. Geneva: WHO; 2022 16 December 2022.
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15. New York State Department of Health. Poliovirus Wastewater Surveillance Report. Albany: New York State Department of Health. 15 May 2023.

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* *RIVM publication.*

6.10.7 Other RIVM publications

Helfferich J, de Lange MMA, Benschop KSM, Jacobs BC, van Leer-Buter CC, Meijer A, *et al.* Epidemiology of acute flaccid myelitis in children in the Netherlands, 2014 to 2019. Euro Surveill. 2023;27(42).

Duizer E, Ruijs W, Hintaran P, Hafkamp M, Veer Mvd, Wierik Mt. Wild poliovirus type 3 (WPV3)-shedding event following detection in environmental surveillance of poliovirus essential facilities, the Netherlands, November 2022 to January 2023. Eurosurveillance. 2023;8(5).

Van Vliet H, Houwaart E, Rümke HC. Onzekerheden bij invoering nieuwe vaccinaties - Polio- en covid-vaccinatie vergeleken. Nederlands Tijdschrift voor Geneeskunde. 2022;166(D6902).

6.11 Rubella

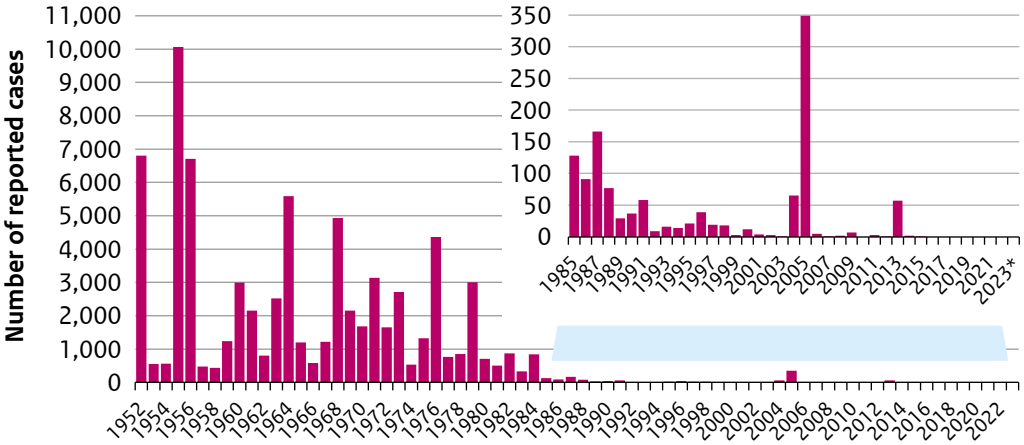
T. Woudenberg, R. Bodewes, W.L.M. Ruijs, R. van Binnendijk, N.Y. Rots, C.A.C.M. van Els, H.E. de Melker

6.11.1 Key points

- In 2022 and in the first four months of 2023, no rubella cases were reported.

6.11.2 Figures

Figure 6.11.1 Annually reported rubella cases since 1952.
* Cases up to and including 9 May 2023.



6.11.3 Epidemiology

Since 2015, no new cases of rubella were reported in the Netherlands.

6.11.4 International developments

The number of reported cases from EU/EEA countries remains below levels observed prior to the COVID-19 pandemic. In 2021 and 2022, 62 and 171 cases were reported, respectively, whereas in 2018, 558 cases of rubella were reported, and in 2019, 384 cases. Regarding the progress towards rubella elimination, the WHO Europe reports that incidence declined by >99%, from 234.9 cases per 1 million population (206,359 cases) in 2005 to 0.67 cases per 1 million population (620 cases) by 2019 [1]. The occurrence of congenital rubella syndrome also declined from 16 cases in 2005 to 8 cases in 2019 in the WHO European region.

6.11.5 Literature

1. O'Connor P, *et al.* Progress Toward Rubella Elimination – World Health Organization European Region, 2005–2019. Morbidity and Mortality Weekly Report, 2021. 70(23): p. 833.

6.12 Tetanus

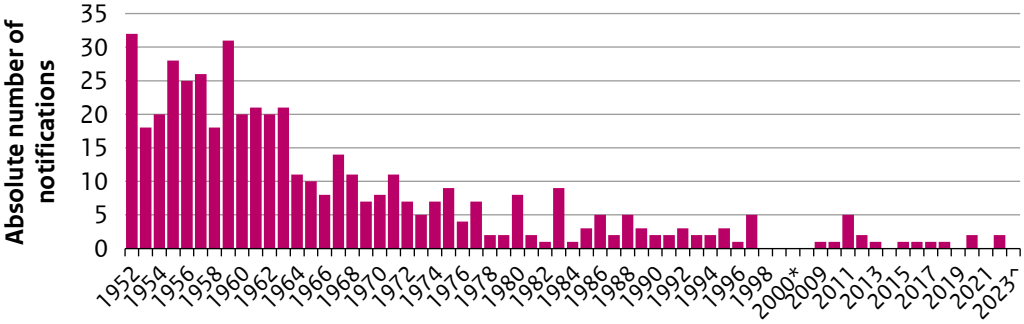
D.L. van Meijeren, D.W. Notermans, H.E. de Melker

6.12.1 Key points

- In 2022, two women died because of a tetanus infection in the Netherlands.
- Both women were elderly and therefore not eligible for childhood tetanus vaccination.
- In 2023, up to and including April, no tetanus cases were reported in the Netherlands.

6.12.2 Tables and figures

Figure 6.12.1 Reported cases of tetanus in the Netherlands by year, 1952-2023^.



** Between 1999 and 2009, tetanus was not notifiable.*
^ For 2023, notifications for the period up to and including April were included.

6.12.3 Pathogen

The diagnosis of tetanus is usually made on clinical recognition; laboratory diagnosis is not often made. *Clostridium tetani* is rarely isolated from suspected patients, and in 2022 and 2023, up to and including April, no isolates were received at RIVM for the tetanospasmin gene PCR. Serological diagnosis is not possible, as infection does not lead to a detectable antibody response; the presence of a protective antibody level in a blood sample taken before immunoglobulins are given, will make a tetanus diagnosis unlikely.

6.12.4 Epidemiology

In 2022, two tetanus cases were reported in the Netherlands. Both patients were aged >80 years and therefore not eligible for childhood tetanus vaccination. Both patients died, with tetanus being reported as the primary or secondary cause of death.

The first case concerned a woman who had probably received one tetanus vaccination later in life. She suffered deep injuries after an accident on the street, after which she consulted

the emergency department. Incomplete tetanus post- exposure prophylaxis (T-PEP) was administered; the woman received a tetanus vaccination, but no tetanus immunoglobulin (TIG) [1]. More than a week later, painful muscle contractions of the jaw and neck muscles developed, leading to jaw clenching and stiffness of the neck. The disease progressed with spasms of limbs and an opisthotonos. Subsequently, high-dose tetanus immunoglobulin (TIG) was administered as treatment. She died a few weeks after initial presentation of the disease. No *C. tetani* was cultured out of the wound.

The second case concerned a woman who probably did not receive any tetanus vaccination later in life. She suffered small wounds on her hands during gardening, for which she did not consult any doctor. Subsequently, characteristics of a tetanus infection presented, by which the diagnosis was made. No *C. tetani* was cultured out of the wounds. Details about the disease course or treatment are unknown. Four weeks after presentation of the disease characteristics, the woman died.

6.12.5 Literature

1.* Dutch National Institute for Public Health and the Environment (RIVM). Richtlijnen en Draaiboeken - Tetanus Bilthoven: Dutch National Institute for Public Health and the Environment (RIVM); 2023 [updated 14 April 2023].

** RIVM publication.*

6.12.6 Other RIVM publications

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7
Immunisation programme in the Dutch Caribbean islands

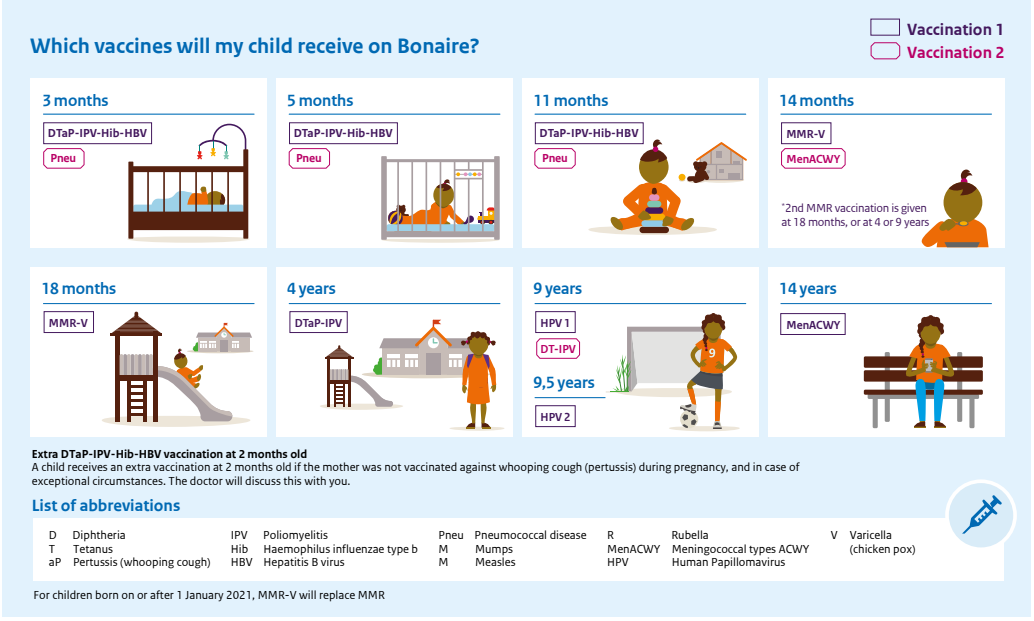
A.J.M. Pluijmaekers, A.A.A. Maxwell, E.A. van Lier, J.F. van Slobbe, T. Gordon, E. Lista-de Weever, P.H. Voskuil, J. Hubert

7.1 Key points

- In general, vaccination coverage in the Dutch overseas territories, including the Caribbean Netherlands (Bonaire, St. Eustatius, and Saba), is high.
- Recent and upcoming changes to the immunisation schedules in the Dutch overseas territories include the maternal pertussis vaccination (in Bonaire and Sint Eustatius) and consequent changes to the corresponding childhood vaccinations, VZV vaccination (Bonaire and Saba), MenACWY vaccination for all children (Bonaire), and HPV vaccination for boys (Bonaire and Saba).
- Additionally, Bonaire's Youth Healthcare will change the basis of its records to the municipal personal records database to improve the reach of the Youth Healthcare services, including the NIP, and the reporting accuracy of vaccination coverage.
- In 2022, one case of invasive pneumococcal disease was reported on St. Maarten. No other diseases covered by the NIP were reported in the Caribbean Netherlands.

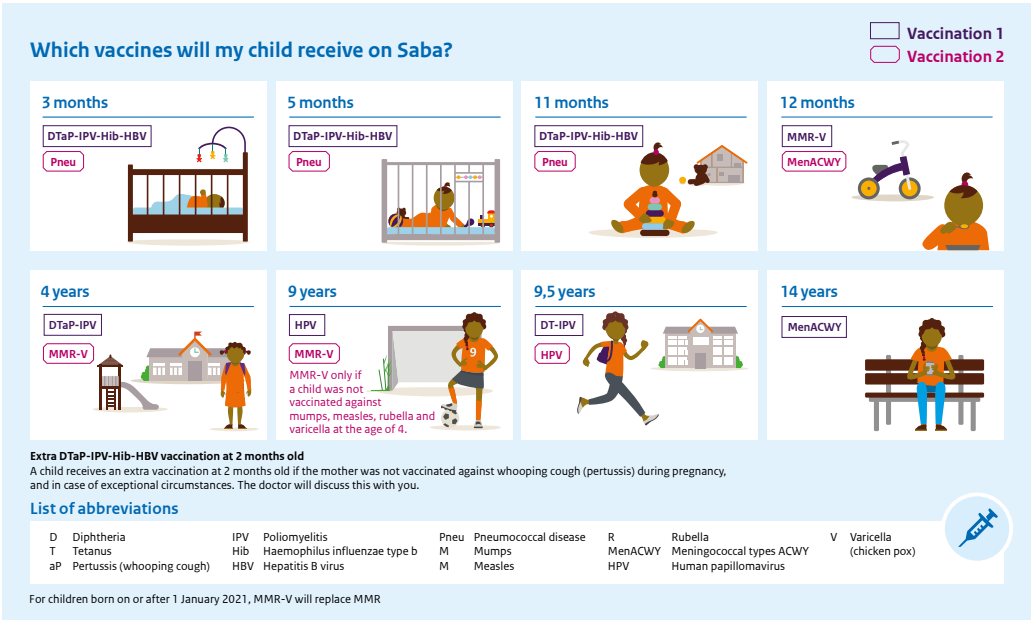
7.2 Tables and figures

Figure 7.1 Immunisation schedule for Bonaire.



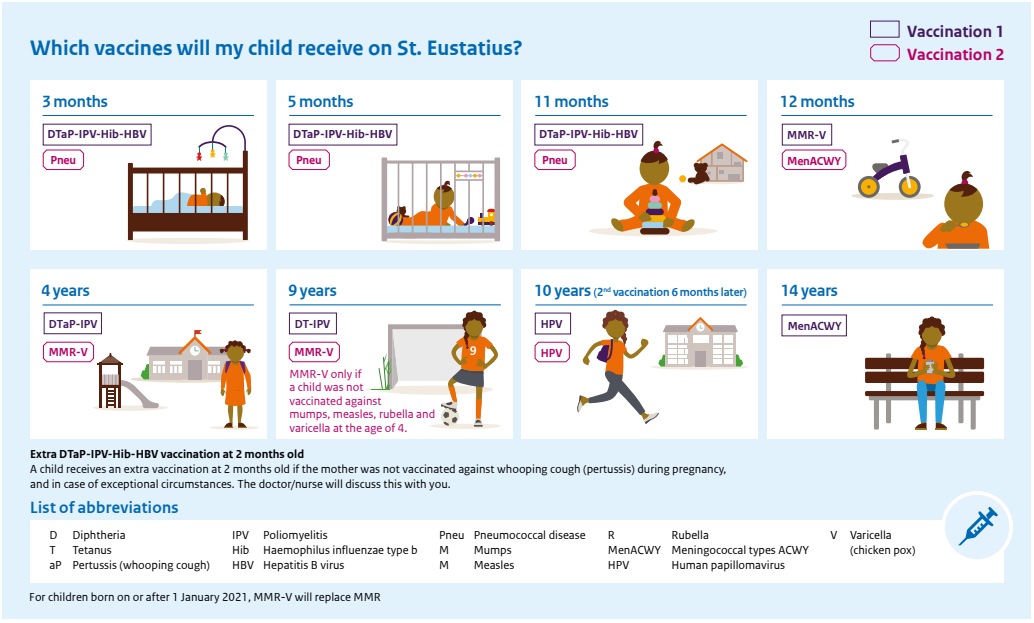
Source: https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-bonaire-english

Figure 7.2 Immunisation schedule for Saba.



Source: https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-saba-english

Figure 7.3 Immunisation schedule for St. Eustatius.



Source: https://rijksvaccinatieprogramma.nl/documenten/vaccination-schedule-st-eustatius-english

Table 7.1 Immunisation schedule for Curaçao.

Age	Vaccination 1	Vaccination 2	Vaccination 3
2 months (7-9 weeks)	DTaP-Hib-HBV 1	Polio 1 (IPV)	
3.5 months	DTaP-Hib-HBV 2	Polio 2 (IPV)	Pneu 1 (10-valent)
5.5 months	DTaP-Hib-HBV 3	Polio 3 (bOPV)	Pneu 2 (10-valent)
>12 months	MMR 1		Pneu 3 (13-valent)
15 months	DTaP-Hib-HBV 4	Polio 4 (bOPV)	MMR 2
4/5 years	DT 1 (paediatric)	Polio 5 (bOPV)	
9/10 years	dT 2 (adult)	HPV 1	
9.5/10.5 years	HPV 2		

Table 7.2 Immunisation schedule for Aruba.

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

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

Table 7.3 Immunisation schedule for St. Maarten.

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

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

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

		Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Newborns (2 years of age)							
Number in cohort 2020		*1,022*	*237*	*	*16*	59	*379*
Dta(P)-IPV-Hib(-HBV)	Number	856	216	*	16	40	353
	%	83.8%	91.1%	*	100%	67.8%	93.1%
HBV	Number	957	n/a	n/a	n/a	n/a	355
	%	93.6%	n/a	n/a	n/a	n/a	93.7%
Polio	Number	n/a	n/a	*	n/a	n/a	n/a
	%	n/a	n/a	*	n/a	n/a	n/a
Pneu	Number	901	213	*	16	40	326
	%	88.2%	89.9%	*	100%	67.8%	86.0%
MMR1	Number	922	216	*	16	37	343
	%	90.2%	91.1%	*	100%	62.7%	90.5%
MMR2	Number	n/a	133	*	n/a	n/a	n/a
	%	n/a	56.1% [g]	*	n/a	n/a	n/a
MenACWY	Number	n/a	212	n/a	16	37	n/a
	%	n/a	89.5%	n/a	100%	62.7%	n/a

		Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Toddlers (5 years of age)							
Number in cohort 2017		*1,296*	*268*	*	*25*	*34*	*
DTaP-IPV	Number	864	152	*	25	10	*
	%	66.7% [d]	56.7%	*	100%	29.4%	*
MMR2	Number	837	n/a	n/a	25	10	*
	%	64.6% [d]	n/a	n/a	100%	29.4%	*
Schoolchildren (10 years of age)							
Number in cohort 2012		*1,434*	*266*	*	*18*	*36*	*
DT-IPV	Number	1,151	145	*	16	26	*
	%	80.3% [e]	54.5%	*	88.9% [c]	72.2%	*
MMR2	Number	1,365	165	n/a	17	n/a	*
	%	95.2% [e]	62.0%	n/a	94.4% [c]	n/a	*
Adolescent girls (10 years of age)							
Number in cohort 2012		*688*	*152*	*n/a*	*<10*	*22*	*
HPV	Number	411	25	n/a	<10	12	*
	%	59.7% [f]	16.4%	n/a	100% [c]	54.5%	*
Adolescents (15 years of age)							
Number in cohort 2007		*n/a*	*n/a*	*n/a*	*<10*	*46*	*n/a*
MenACWY	Number	n/a	n/a	n/a	<10	3	n/a
	%	n/a	n/a	n/a	62.5% [c]	6.5% [h]	n/a

* *Not reported in time/ due to circumstances, reporting was nog possible.*

[a] *The registration systems in Caribbean Netherlands are not linked to the national population register. As a result, immigration and emigration cannot be monitored as precisely as in the European Netherlands The figures in this table provide the closest possible approximation.*

[b] *Vaccination status at 2 years of age: DTaP-IPV/MMR = basic immunity, Hib/HBV/PCV/MenC = completed; at the age of 5 years: DT(aP)-IPV = revaccinated; at the age of 10 years: DTaP/MMR/HPV = full participation; at the age of 15: MenACWY = full participation.*

[c] *Interim vaccination coverage: the vaccination is linked to school year, not birth year. In 2023, vaccination will be offered to part of these children.*

[d] *On Aruba, catch-up vaccinations are being offered at schools in the second year of pre-school education (at the age of 5-6).*

[e] *On Aruba, the DT(aP)-IPV is provided in year 7 of regular education, regardless of age, and at the age of 10 years in special education. These figures relate to the schoolyear 2021-2022. From cohort 2008 onwards, the age for MMR2 has been brought forward to the age of 4. As a result, the percentage of vaccinees for this group of schoolchildren was much higher than that of DT(aP)-IPV.*

[f] *On Aruba, HPV vaccination is given to girls in year 8, regardless of age. These figures relate to schoolyear 2021-2022, rather than cohort 2012, at age 10.*

[g] *As from 2019, Bonaire has moved its MMR2 vaccination up from 9 years to 18 months.*

[h] *Started as from November 2022.*

7.3 Immunisation schedules

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

7.3.1 Recent and upcoming changes to Bonaire's immunisation schedule

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

Additionally, from 1 March 2022, VZV vaccination is being offered to all children aged 14 and 18 months (born on or after 1 January 2021). This addition consisted of replacing the previously offered MMR vaccine by the MMR-V vaccine. Once the existing supply of MMR vaccine has been depleted, children who are due for a follow-up dose of an MMR-containing vaccine will be offered an MMR-V vaccine, even if they previously received an MMR vaccine.

From June 2022 onwards, the MenACWY vaccine is offered to adolescents aged 14 years (born in 2008), supplemented with a catch-up campaign for all adolescents aged 15 to 18 (born in 2004 to 2007). Lastly, apart from offering HPV vaccination to girls, in 2023, the HPV vaccination will also be offered to boys who turn 9.

7.3.1.1 Other upcoming changes to Bonaire's childhood vaccination programme

On Bonaire, there is currently no connection between the youth healthcare services (Sentro Akseso, SA) and the municipal personal records database. As a result, not all children living on Bonaire are known to the SA, which makes determining the actual vaccination coverage a challenge; children born on Bonaire have all been registered at the SA, but many children that migrated to Bonaire have not, because this needs to be done manually. Migrants are often unaware of this requirement or even of the existence of youth healthcare services, and if they are aware, they are often unable to take time off work to arrange these things.

The Youth Healthcare services on Bonaire aim to improve this situation substantially. Authorisation to connect to the municipal personal records database has been requested and is expected to be granted and put into effect by the end of 2023. It is very likely that including these children will cause a paradoxical decrease in vaccination coverage of timely administered vaccines, while the true vaccination coverage will in effect increase.

7.3.2 Recent and upcoming changes to Saba's immunisation schedule

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

Additionally, since 1 April 2022, boys born on or after 1 January 2013 are being invited for HPV vaccination alongside girls in the year in which they turn 9. A catch-up campaign was run for boys born from 2004 to 2012.

In 2024, Saba will start offering rotavirus vaccination to new-borns.

7.3.3 Recent and upcoming changes to St. Eustatius' immunisation schedule

Since February 2022, pregnant women on St. Eustatius are being notified of the possibility to receive a maternal pertussis vaccination.

7.3.4 Recent and upcoming changes to Curaçao's immunisation schedule

Recent changes to Curaçao's immunisation schedule include the change of their second polio vaccination from bOPV to an IPV, the change of their 3rd pneumococcal vaccination from 10-valent to the 13-valent vaccine, and the addition of HPV vaccination at 9/10 years.

7.4 Vaccination coverage

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

7.5 Epidemiology of diseases included in the NIP

Surveillance data in the Dutch Caribbean Islands has been available from 2017 onwards for Bonaire and Saba, and since 2021 for St. Maarten. In those six years, there have been two pertussis cases in Bonaire in 2017, and one in 2018. Additionally, in 2022 one case of invasive pneumococcal disease was reported on St. Maarten. No other diseases covered by the NIP were reported in the Caribbean Netherlands.

8
Potential NIP target diseases

8.1 Hepatitis A

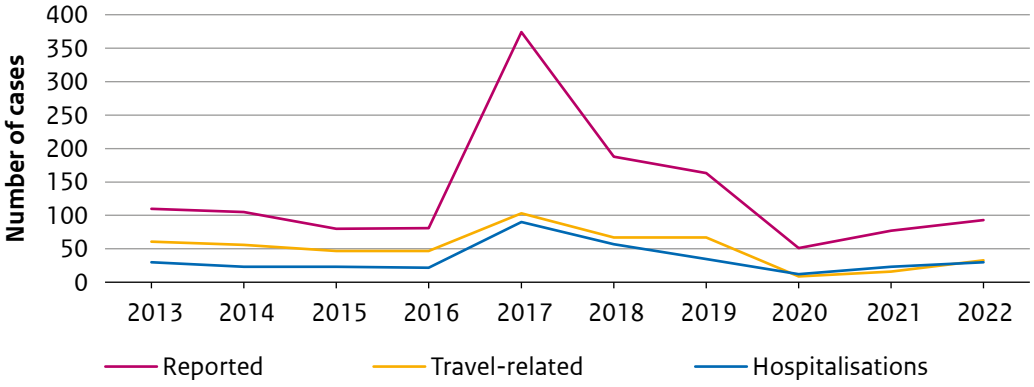
I.H.M. Friesema, H. Vennema

8.1.1 Key points

- In 2022, 93 hepatitis A-cases were reported, corresponding to 0.5 cases per 100,000 population. This is higher than in 2020 (n=51) or 2021 (n=77), but lower than in the last year pre-COVID-19 (2019: n=163).
- Infections were mainly seen in the 20-49 years age group.
- 30 patients (32%) were hospitalised compared to 21-30% in 2013-2021.
- The percentage of travel-related cases (35%) was almost back to pre-COVID-19 levels (2013-2019; mean: 41%).

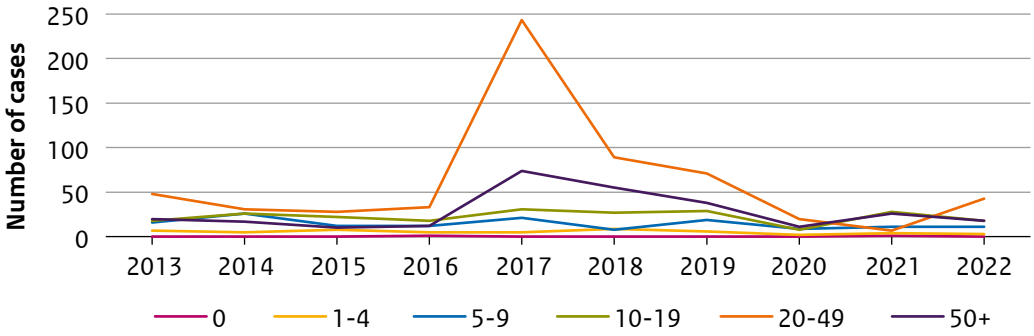
8.1.2 Tables and figures

Figure 8.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2013-2022.



Source: Osiris

Figure 8.1.2 Age distribution of hepatitis A-cases, 2013-2022.



Source: Osiris

8.1.3 Epidemiology

In 2022, 93 hepatitis A-cases were reported, corresponding to 0.5 cases per 100,000 population. This is the second year in which numbers have increased since 2020 (n=50 cases; Figure 8.1.1/Appendix 2). The two main transmission routes for hepatitis A are travel and person-to-person contact. Both were limited due to the measures taken since mid-March 2020 to control COVID-19. This explains why the number of cases was lower in 2020 and, to a lesser extent, in 2021. In 2022, the number of cases is comparable to the annual numbers before 2017. The peak in 2017 was caused by a large, international, hepatitis A outbreak resulting in 243 cases in the Netherlands. Two thirds of these cases concerned men who have sex with men (MSM) [1]. The outbreak lagged in 2018, both nationwide and internationally [2]. The age distribution over the years 2013-2022 is presented in Figure 8.1.2. Infections were mainly seen in the 20- to 49-year-olds. The 2021 shift towards more cases in the 10-19 years and 50+ years age groups did not continue into 2022. In total, 30 patients were hospitalised (32%), which is slightly higher than the hospitalisation percentages in the previous years (2013-2021: 21-30%; mean: 26%). The last case reported to die from hepatitis A dates back to 2007.

In 2022, the proportion of travel-related cases was 35%, which is almost back to pre-COVID-19 levels (2013-2019; mean: 41%), compared to 2020 (18%) and 2021 (21%). Most travel-related cases had been in Asia (11/33 cases) or Africa (11/33 cases), followed by Europe (n=10) and 1 in Central America. Countries mentioned most were India and Morocco (both four times), other countries were mentioned once or twice.

Based on the notifications, 11 epidemiologically linked clusters with a total of 25 cases in 2022 and another cluster with 1 case in 2021 and 1 in 2022 could be deduced. Four clusters occurred within one household, three occurred within families not living together and/or friends or acquaintances; one cluster had both secondary cases within the household and a child and employee at the day-care centre. In one cluster, the first case was part of a MSM cluster abroad and then infected one other MSM and two friends in the Netherlands. The cases of the remaining three clusters got infected abroad.

8.1.4 Pathogen

Hepatitis A virus (HAV)-specific IgM-positive samples can be sent to IDS of RIVM for typing as part of the molecular surveillance of this virus. In 2022, samples were submitted for virus typing for 68 out of 93 reported cases (73%). This percentage is lower than in the last five years, when it invariably exceeded 80%. Of these samples, 66 (97%) were found positive by PCR and made available for sequence analysis. Samples from the remaining cases were not submitted for various reasons; sometimes because the Municipal Health Service already identified the source. In these cases, it is still worthwhile to sequence a sample because the same strain may show up somewhere else where no clear source is indicated.

In 2022, RIVM tested a total of 231 serum and faecal samples of 215 unique persons. HAV RNA was detected in 67 samples (19%) and 64 of these reported cases could be typed, which resulted in 35 unique sequences. In addition, four cases that were positive for hepatitis A could not be linked to any reported case. A total of 44 cases could be assigned to clusters of two or more cases. These concerned fourteen molecular clusters varying between one and six cases in the Netherlands in 2022. Some molecular clusters involved cases from previous years or from other countries. The largest cluster (six cases) was in a school that refused cooperation with the GGD to contain the outbreak with vaccination and advice. The second largest cluster (five cases) was most likely foodborne, but no source was identified. All clusters, except the school outbreak, were contained by contact tracing and vaccination. Transmission occurred mostly within households. The school outbreak was monitored by sewage sampling in the neighbourhood. Hepatitis A virus was detected in sewage at several locations and time points before and after the first reported cases. Typing of hepatitis A in sewage samples demonstrated that the detected virus was from the outbreak. The index case of this outbreak visited Somalia and was diagnosed with hepatitis A in October 2022. The last positive sewage sample containing the outbreak strain was detected on 8 February 2023.

8.1.5 Research

A protocol has now been validated for whole genome sequencing (WGS) analysis of HAV types I.A and I.B. The main advantage is the 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. Moreover, it allows clear distinction of closely related but nonidentical strains that are thought to belong to an outbreak. An overlapping amplicon protocol, similar to the protocol employed for SARS-CoV-2 sequencing analysis, was designed for HAV. The protocol was used to determine more than 150 genome sequences from historic samples and will soon be implemented as the routine typing method.

8.1.6 International developments

Changes in occurrence and outbreaks of hepatitis A in Europe have been reviewed [3]. In the past two decades, the age of the cases has increased, while a change in populations at risk is seen. Overall, a shift in cases was reported from travellers and children to other risk groups, such as MSM and adults, although cases are still seen throughout the general population.

Cost-effectiveness of hepatitis A vaccination was summarised in a systematic review by several characteristics, such as income level [4]. On the basis of 43 published studies, the authors concluded that universal vaccination among children was more likely to be cost-effective than a no-vaccine strategy. This was especially true in middle-income countries. Universal vaccination among adults in middle- and high-income countries was less likely to be cost-effective. Cost-effectiveness of vaccination of specific risk groups increased in proportion to the risk of acquiring the infection. However, cost-effectiveness depends on many parameters and factors that differ between countries, limiting the transferability of results from one country to another. For Spain Valcárcel-Nazco *et al.* [5] concluded that, due to the low endemicity, the health outcomes with or without vaccination will be practically the same, making vaccination not cost-effective.

In the past two decades, several countries have introduced universal vaccination against hepatitis A virus using one- and two-dose schedules. Andani *et al.* [6] have reviewed the results of these vaccination strategies, using 33 articles and one conference abstract. Both schedules led to significant decreases in hepatitis A incidence. The largest declines were seen in children aged 14 years or under but were also observed in the other age groups. The impact of a two-dose schedule has been demonstrated via significant decreases in incidence and burden, and through protective antibody levels for more than 14 years. The evidence of long-term (more than six years) effects of a one-dose schedule is still limited, as these studies have not reached longer follow-up periods yet.

In Argentina, the long-term humoral and cellular immune memory response was assessed in a group of 81 individuals who received one dose between 11.7 and 14 years ago at the age of 12 months [7]. Out of the 54 individuals with antibody concentrations below 10 mIU/ml in 2015, 13 now had levels sufficiently high to be considered protective. All received a booster vaccination, resulting in an increased titre in 12 out of the 13 individuals with protective levels (one was lost to follow-up), and in 36 out of the 41 of the remaining individuals having an adequate response to the booster; 4 remained unprotected and 1 was lost to follow-up. Out of the 27 individuals included who had a protective level in 2015, 25 had still protective levels and in 2 the level had waned at the start of the present study (so that they received the booster). The presence of HAV-specific memory T cells was tested in 21 individuals with and in 26 individuals without protective antibody levels. No significant difference in CD4+ and CD8+ T cell responses or median frequencies were seen between the subjects with and without protective antibody levels.

A follow-up study in Brazil was performed after 6-7 years after vaccination with one dose (VaqtaTM) at the age of 12 months [8]. A total of 109 (46%) of the initial 236 children could be included in the present study, although 2 had to be excluded due to having insufficient volume of blood available. Anti-HAV IgG was detected in 70 children, and in another 12 children, effector T cells produced IFN-y in cellular immune response assays, resulting in an actual immunity against hepatitis A virus of 77% (82/107).

8.1.7 Literature

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* *RIVM publication.*

8.2 Respiratory Syncytial Virus

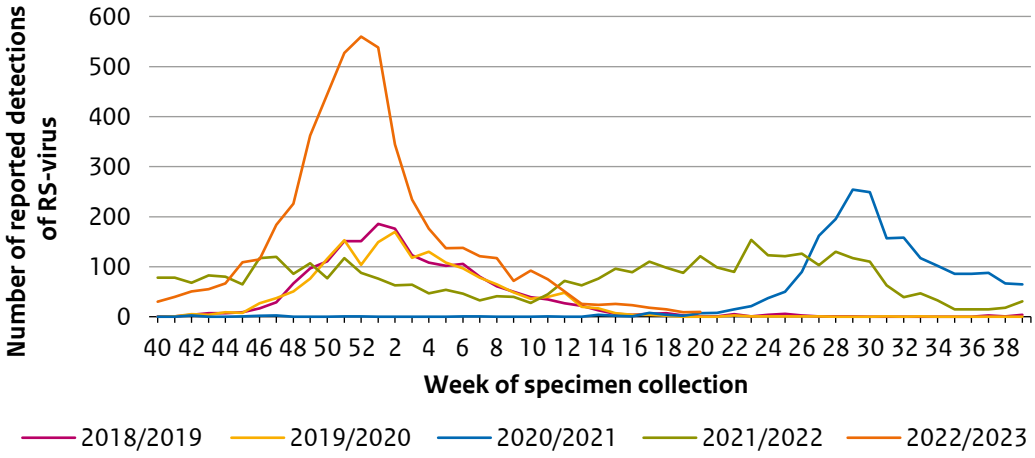
A.C. Teirlinck, P.B. van Kasteren, M. van Boven, M. Knol, H. de Melker, A. Meijer

8.2.1 Key points

- At the end of the summer of 2022, the number of RSV detections reported in the virological laboratory surveillance started to decrease, after more than a year of increased circulation in the Netherlands. Detections increased again by the end of September of 2022. While the absolute numbers of RSV detections were much higher than in previous seasons, the timing of the peak (week 52 of 2022) was within the range of the timing in pre-pandemic seasons. Since testing practices have probably changed since the COVID-19 pandemic, the number of RSV diagnoses and subsequent outcomes on onset and duration of the RSV season should be interpreted with caution. After a sharp drop in detections from weeks 2-5 of 2023, the number of detections gradually decreased further and has been at a low level from April 2023 until the end of the reporting period (21 May 2023).
- The number of children <2 years of age that were hospitalised in 2022/2023 with RSV-bronchiolitis followed a similar trend in time as the virological detections. However, in the winter 2022/2023, the peak number of hospitalisations (n=100) in these 33 hospitals was lower than during the summer peak of 2021 (n=163).
- The percentage of samples collected by sentinel GPs from patients with acute respiratory infections (ARI) that were positive for RSV peaked in week 46 of 2022 (18/73 = 25% of samples positive) and gradually declined until no RSV was detected anymore in week 17 of 2023.
- RSV-B was dominant during the entire season of 2022/2023, in all age groups.
- The percentage of RSV-positive ARI specimens collected by the GPs was highest in children in the age 0-1 years, where 32% of the sampled children of 0-1 years was positive for RSV, followed by age group 2-4 years (13%) and >65 years (11%). The percentage was lowest in the age group 5-64 years (range 4-8%).

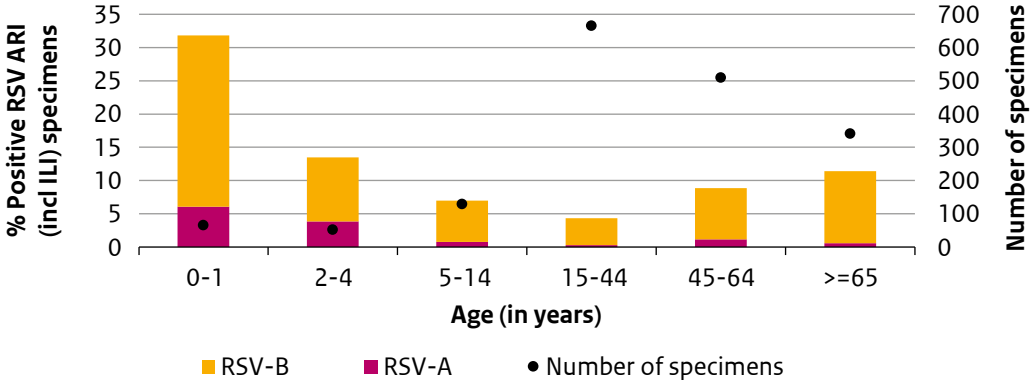
8.2.2 Figures

Figure 8.2.1 Number of RSV diagnoses in the virological laboratory surveillance for the 2018/2019-2022/2023 period, reported on a weekly basis.



Source: virological laboratory surveillance, NWKV (Dutch Working Group for Clinical Virology of the Dutch Society for Medical Microbiology (NVMM).

Figure 8.2.2 Percentage of RSV-A- and RSV-B-positive specimens from patients with ILI and other ARI, and the number of tested specimens, sentinel influenza surveillance during the respiratory season of 2022/2023 (week 40 of 2022 up to and including week 20 of 2023), displayed for six age groups.



ARI = acute respiratory infection, ILI = influenza-like illness.
Source: Nivel Primary Care Database, RIVM.

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], causing outbreaks in elderly care facilities [3]. RSV is subdivided in RSV-A and RSV-B, mainly on the basis of the variation in the attachment protein, the G-protein.

Between June 2021 and August 2022, RSV circulated continuously in the Netherlands. The number of RSV detections reported in the virological laboratory surveillance only started decreasing by the end of the summer of 2022, albeit briefly. The number of RSV detections increased again by the end of September of 2022. While the absolute numbers of RSV detections were much higher than in previous seasons, the timing of the peak (week 52 of 2022) was within the range of the timing in pre-pandemic seasons, see Figure 8.2.1. Since testing practices have probably changed since the COVID-19 pandemic, the number of RSV diagnoses and subsequent outcomes on onset and duration of the RSV season should be interpreted with caution. After a sharp drop in detections from week 2-5 of 2023, the number of detections gradually decreased further and have been at a low level since April 2023.

In the period from week 40/2022 up to week 20/2023, the percentage of samples collected by sentinel GPs from patients with acute respiratory infections (ARI) that were positive for RSV peaked in week 46 of 2022 (18/73 = 25% of samples positive) and gradually declined until no further RSV was detected in week 17 of 2023. RSV-B was dominant during the entire season of 2022/2023, in all age groups, see Figure 8.2.2. The percentage of RSV-positive ARI specimens collected by the GPs was highest in children in the age 0-1 years, where 32% was positive for RSV, followed by age group 2-4 years (13%) and >65 years (11%). The percentage was lowest in the age group 5-64 years (range 4 – 8%).

Since early May 2021, the Wilhelmina Children's Hospital (WKZ) of UMC Utrecht registers the number of (RSV-)bronchiolitis admissions of children <2 years old in 42 hospitals in the Netherlands on a weekly basis. This data is collected and analysed in the context of the SPREAD-study, which aims to compare characteristics of children who are admitted during earlier winter epidemics with characteristics of children who have been admitted since the summer of 2021, and is also used for modelling purposes. RIVM uses the aggregated data for RSV surveillance. The number of children <2 years of age who were hospitalised in 2022/2023 with RSV-bronchiolitis followed a similar trend in time as the virological detections. In the winter of 2022/2023, the peak number of hospitalisations (n=100) in the 33 hospitals that have reported data over the entire period was lower than during the summer peak of 2021 (n=163).

For these results and for further information and data on epidemiology in the Netherlands, please refer to the annual report 'Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2022/2023', and the RIVM website on RSV surveillance (only available in Dutch).

8.2.4 Research

RIVM is a partner in the PROMISE project (subtopic and work package lead), funded by the Innovative Medicines Initiative Joint Undertaking, under grant agreements 101034339, receiving support from the European Union's Horizon 2020 Research and Innovation Programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The project aims to advance scientific knowledge on RSV to inform public health strategies and support the development and introduction of novel immunisation tools and therapeutics in Europe. Furthermore, PROMISE aims to prepare for the introduction of vaccines and monoclonal antibodies that are currently entering the market or are expected to do so soon, among others by developing an EU-wide surveillance network on RSV.

RIVM is also partner (subtopic and work package lead) in the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking INNO4VAC. Funded under grant agreement No 101007799, this Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. This consortium aims to harness advances in the fields of immunology, big data and artificial intelligence, 3D tissue models and human infection models to accelerate and support the development of new vaccines. Within this consortium, RIVM is specifically involved in the development of *in vitro* differentiated epithelial models to study infection with and immunological protection from RSV and influenza virus, aiming to reduce the need for animal models in preclinical testing. The project is due to run from September 2021 to February 2027.

8.2.5 International developments

Several immunisation strategies are currently in (late-stage) clinical development, an up-to-date overview of which can be accessed via the Path website. Furthermore, a recent complete overview is provided by Mazur *et al.* [4]. See also chapter 10 of this report on products in clinical development. The Dutch Ministry of Health, Welfare and Sport asked the Health Council of the Netherlands to issue advice on immunisation products to prevent RSV in new-born babies and infants. To support this advice, RIVM gathered background information for the Health Council (see this report).

In October 2022, a novel monoclonal antibody (nirsevimab/Beyfortus, AstraZeneca/Sanofi) for the prevention of RSV disease in infants was approved for marketing by EMA. Similar to palivizumab (AstraZeneca), the main mechanism of action of nirsevimab is to prevent entry of RSV into host target cells by binding to the viral fusion (F) protein, i.e. virus neutralisation. Two important improvements compared to palivizumab are nirsevimab's increased potency for neutralisation and extended *in vivo* half-life [5]. In a phase-3 clinical study including 3012 late preterm (>35 weeks' gestation) and term infants (2009 in the nirsevimab and 1003 in the placebo group), nirsevimab was found to have an efficacy of 76.4% (95% CI 62.3 to 85.2) against medically attended RSV-associated lower respiratory tract infection through 150 days post administration and 76.8% (95% CI 49.4 to 89.4) against hospitalisation for the same condition during the same period [6].

An alternative strategy for the prevention of RSV disease in infants is maternal vaccination, whereby antibodies produced by the mother are transferred to the unborn child via the placenta. A phase-3 randomised placebo-controlled trial (MATISSE, NCT04424316, Pfizer, 2020-2022) assessed the safety and efficacy of a stabilised prefusion F protein subunit vaccine in 6975 infants (3495 in the vaccine and 3480 in the placebo group) in 18 countries, including 194 (2.6%) maternal participants from the Netherlands [7]. An interim analysis showed an efficacy against medically attended RSV-associated lower respiratory tract infection throughout 150 days after birth of 52.5% (97.58% CI 28.7-68.9%) and against medically attended severe RSV-associated lower respiratory tract infection throughout 150 days after birth of 70.9% (97.58% CI 44.5-85.9%). Since one of the two pre-specified success criteria for efficacy was met with these results (i.e. a lower bound of the confidence interval >20% for all timepoints assessed), the data monitoring committee recommended stopping the efficacy trial. In July 2023, EMA recommended a marketing authorisation in the EU for the Pfizer vaccine (Abrysvo), and in August 2023 the FDA also approved this vaccine.

In contrast, several phase-3 studies (NCT04605159, NCT04980391, NCT05169905, all GSK) assessing maternal vaccination with another RSV prefusion F protein subunit vaccine were recently stopped due to safety concerns as increased numbers of preterm births and neonatal deaths were observed in the vaccinated arm as compared to the placebo arm [8, 9]. The mechanism(s) underlying this observation remains unclear and development of this vaccine candidate for use for maternal vaccination has been discontinued. In response to the GSK trial results, concerns were raised by some scientists regarding a potential minor imbalance in preterm births between the vaccine and placebo arms in the Pfizer phase-3 MATISSE study as well [7, 8]. The prescribing information for Abrysvo includes a warning about this imbalance.

Notably, two prefusion F subunit vaccines (GSK and Pfizer) showed efficacy against RSV disease in older adults (≥60 years of age) in phase-3 trials without apparent safety concerns [10, 11]. In April 2023, EMA recommended a marketing authorisation for the GSK vaccine (Arexvy) for the protection of older adults. In addition to maternal vaccination, the above-mentioned EMA and FDA approvals for Abrysvo (Pfizer) also include its use for vaccination of older adults (≥60 years of age). Lastly, Moderna has announced positive results with an mRNA-based RSV vaccine (mRNA-1345) in older adults, but no peer-reviewed data is available yet.

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** RIVM publication.*

8.2.7 Other RIVM Publications

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8.3 Rotavirus

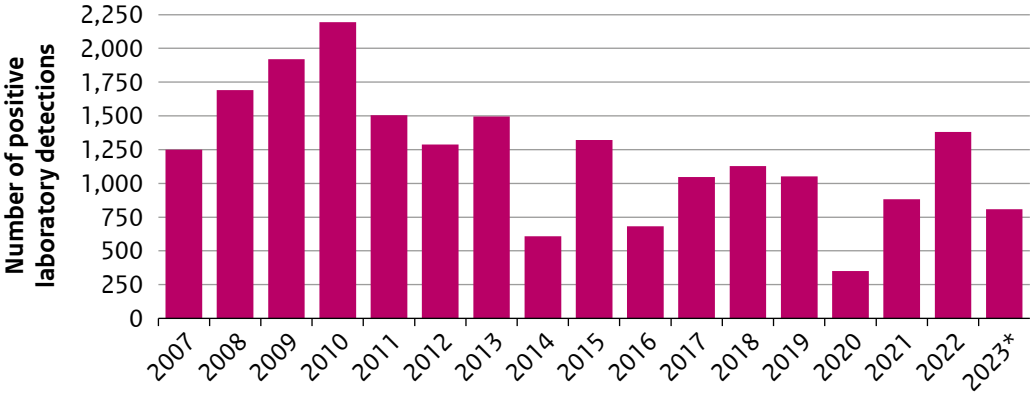
R. Pijnacker, E.A. van Lier, H. Vennema, M. Hooiveld, H.E. de Melker

8.3.1 Key points

- The 2022 rotavirus season had an early start, probably due to an increase in the number of susceptible children due to COVID-19 control measures.
- This resulted in more rotavirus detections in 2022 (n=1391) compared to 2016-2019, with an average of 981 detections (range: 682-1054)
- In contrast to previous years, the most prevalent genotype in 2022 was G3P8 (74%).
- In the Netherlands, universal rotavirus vaccination will be added to the NIP in 2024.

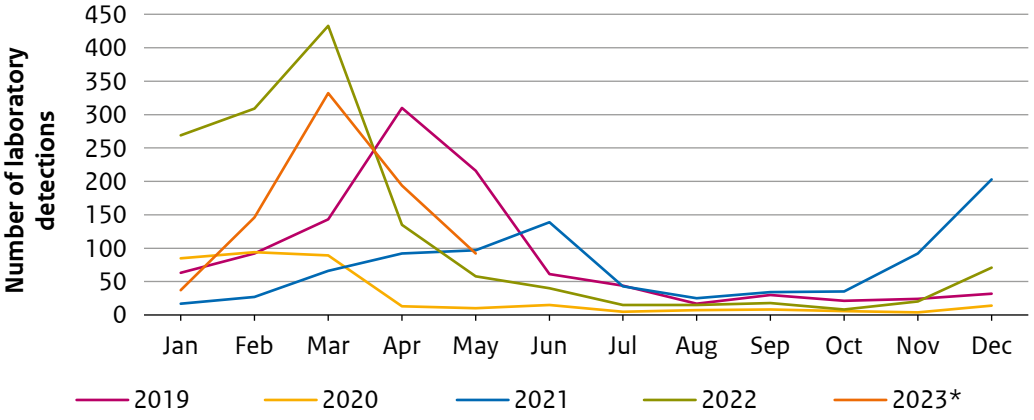
8.3.2 Tables and figures

Figure 8.3.1 Number of reported laboratory rotavirus detections per year in the Netherlands, 2007-2023.



** Data available until week 22.*

Figure 8.3.2 Number of reported laboratory rotavirus detections per month in the Netherlands, 2019-2023.



** Data available until week 22.*

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 in the Netherlands, 2014-2022.

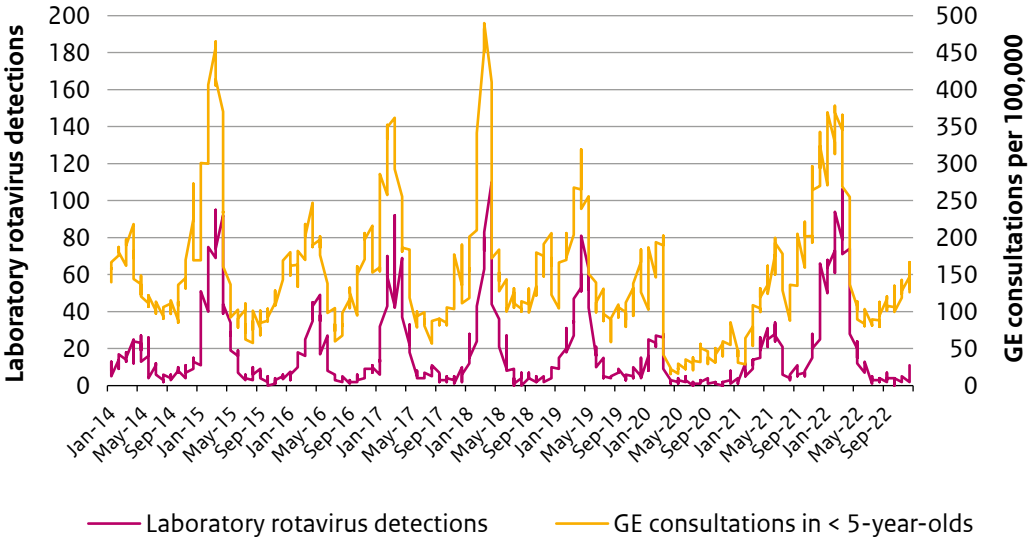


Table 8.3.1 Number of rotavirus samples typed per year and identified genotypes the Netherlands, 2018-2022.

Type	2018	2019	2020	2021	2022	Total
G12P8	1.1%	0.6%	0.0%	1.1%	5.7%	**19**
G1P8	3.9%	6.7%	1.1%	7.3%	8.0%	**118**
G2P4	3.4%	7.3%	2.8%	6.1%	2.3%	**124**
G3P8	31.3%	22.3%	1.7%	10.6%	73.9%	**265**
G4P8	1.7%	0.0%	0.0%	0.0%	0.0%	**178**
G9P8	33.5%	21.2%	6.1%	16.2%	9.1%	**306**
G9P4	16.2%	13.4%	0.6%	0.6%	0.0%	**64**
Other	8.9%	9.5%	0.0%	0.0%	1.1%	**131**
Total	**179**	**145**	**22**	**75**	**88**	**1,205**

8.3.3 Epidemiology

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

8.3.3.1 Laboratory detections

In 2022, 1,391 rotavirus detections were reported, which is more than in 2020 (n=350), when the number of rotavirus infections was at an all-time low due to COVID-19 control measures (Figure 8.3.1), and in 2021 (n=870). However, the 2022 season already started in October 2021, instead of its usual start in February (Figure 8.3.2), which is believed to be the result of an increase in the number of children susceptible to rotavirus due to the absence of a rotavirus season in 2020 and a mild season in 2021. As a result, the annual number of rotavirus detections was higher in 2022 than it had been in 2016-2019, when it averaged 981 detections (range: 682-1,054).

8.3.3.2 Consultations in primary care

Nivel Primary Care Database provided data on all-cause gastroenteritis (GE) in children under the age of 5 years consulting their general practitioner [2]. GE was defined as a diagnosis of presumed gastrointestinal infection (ICPC code D73). In 2022, 8,851 all-cause GE consultations were reported per 100,000 children under 5 years of age (on average 171 per 100,000 per week) (Figure 8.3.3). This was comparable to 2021 (8,237 per 100,000) and 2016-2019 (range: 7,915-9,840 per 100,000). It was higher than in 2020, which was a year with an abnormally low number of GE consultations (3,449 per 100,00). Consultations in 2021 had no pronounced seasonal pattern, with an early start of the 2022 rotavirus season in October 2021, which is reflected by an increase in the number of GE consultations in October 2021, on top of the increase of consultation from week 31 onwards following the norovirus season.

8.3.4 Rotavirus genotypes

IDS/RIVM receives faecal samples throughout the year from the Working Group Clinical Virology laboratories for rotavirus genotyping. The results per calendar year are presented in Table 8.3.1. In 2022, G3P8 was the most prevalent genotype (65/88, 74%), which was a continuation of what was found in November and December 2021, when the unusually early 2022 rotavirus seasons started. The prevalence of this genotype was higher than in previous years (2021 = 26%, 2020=14%; 2019=28%; 2018=31%), where G9P8 was most prevalent.

8.3.5 (Inter)national developments

As of January 2022, 114 countries worldwide have introduced rotavirus vaccination in their national immunisation programmes [1]. Although 70% of sub-Saharan Africa have introduced rotavirus vaccines, more than half of all rotavirus deaths occur in African countries due to the high disease burden in this region [2]. The World Health Organization (WHO) prequalified four available rotavirus vaccines, namely ROTASILL®, ROTAVAC®, Rotarix®, and RotaTeq®. Only Rotarix® and RotaTeq® are licensed for use in Europe. In the Netherlands, universal rotavirus vaccination will be added to the NIP in 2024 [3]. A 2-dose schedule will be used because Rotarix® has come out of the vaccine procurement tender [4].

8.3.6 Literature

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8.4 Varicella zoster virus (VZV) infection

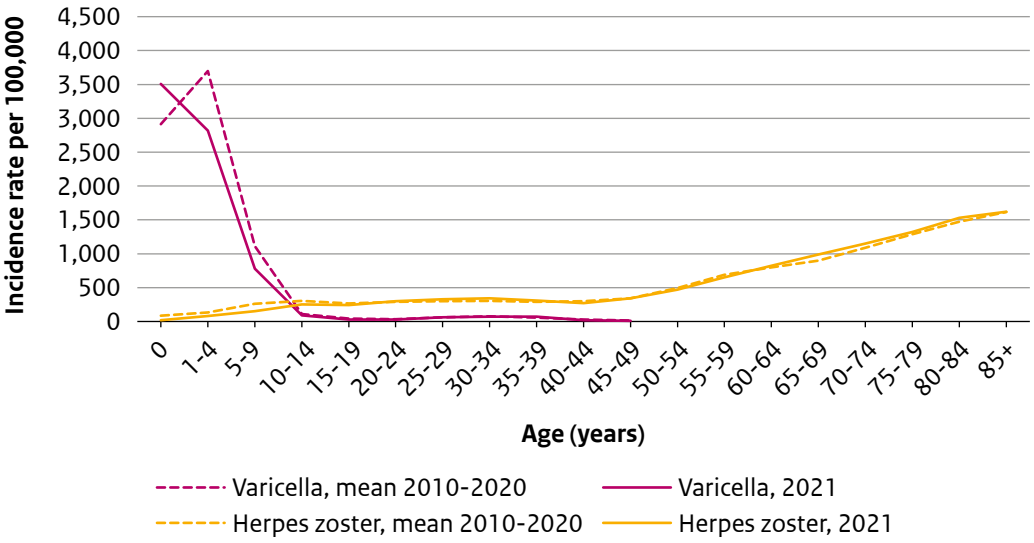
C. van Roekel, E.A. van Lier, J.W. Vanhommerig, C. Kampshoff, H.E. de Melker

8.4.1 Key points

- The epidemiology of herpes zoster (incidence of GP consultations, hospitalisations and deaths) in the Netherlands did not change in 2021 and was comparable to that in previous years; GPs recorded about 94,000 herpes zoster episodes (540 episodes per 100,000 population).
- For varicella, the incidence of GP consultations and hospitalisations in 2021 was still lower than before 2020, but somewhat higher than in 2020; GPs recorded about 33,000 varicella episodes (190 episodes per 100,000 population). This is probably linked to the COVID-19 measures, which also have limited transmission of VZV.
- Preliminary data showed an increase in varicella in the Netherlands since the beginning of 2022 also affecting older children between 5 and 15 years of age (higher risk of complications), which may be a catch-up effect following the corona years.

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 2021 versus mean 2010–2020 by age group [3].



Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and therefore not included; data for 2010–2011 recalculated according using more precise method (see Table 8.4.1).
Source: Nivel

Table 8.4.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on Nivel-Primary Care Database (PCD) (rounded to nearest 10) [3].

Syndrome	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Varicella	250	280	270	250	240	280	260	300	130	190
Herpes zoster	510	510	530	530	530	530	540	550	530	540

According to a more precise method for estimating morbidity rates used by Nivel from 2012 onwards [1], the incidence of HZ is higher than reported previously.
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), 2010–2021* [4].

Syndrome	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Varicella	1.9	1.7	1.5	1.7	1.9	1.8	2.0	2.0	1.7	1.9	0.9	1.1*
Herpes zoster	2.1	2.2	2.1	2.1	2.7	2.9	2.8	2.8	3.0	3.1	3.0	2.9*

In 2006/2007, a number of hospitals ceased registration, causing an underestimation of hospital admissions from 2006 until 2014 (see Appendix 1).
Admissions for a single day have been excluded.
The number of admissions may be higher than the number of hospitalised patients reported here because some patients have been admitted more than once within the same year.
From 2015 onwards, number of admissions were rounded off to the nearest 5. Corrected for non-participating hospitals. Data retrieved from Dutch Hospital Data/Statistics Netherlands; this may have resulted in a trend break compared to previous years.
** Data for 2021 are preliminary.*
Source: DHD, CBS

Table 8.4.3 Absolute number of deaths with varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) as primary cause of death, 2011-2022* [2].

Syndrome	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Varicella	1	2	1	2	2	4	3	2	3	2	4	9*
Herpes zoster	20	21	21	26	33	27	33	36	32	43	37	38*

** Data for 2022 are preliminary.*
Source: CBS

8.4.3 Epidemiology

In 2021, general practitioners (GP) recorded about 33,000 varicella zoster virus (VZV) and 94,000 herpes zoster (HZ) episodes (190 and 540 episodes per 100,000 population, respectively). The incidence of GP consultations due to varicella episodes per 100,000 population was highest in children under 5 years of age, whereas the incidence of GP consultations due to HZ episodes was highest in those aged 50 years and over (Figure 8.4.1).

The epidemiology of HZ (incidence of GP consultations, hospitalisations, and deaths) in the Netherlands in 2021 was similar to previous years (Tables 8.4.1, 8.4.2, and 8.4.3). However, for varicella, the incidence of GP consultations and hospitalisations in 2021 was still lower than before 2020 but somewhat higher than in 2020. This is probably linked to the COVID-19 measures, which have limited transmission of VZV, too. As a result of lack of immune stimulation due to reduced circulation, preliminary data shows an increase in varicella in the Netherlands since the beginning of 2022, also affecting older children between 5 and 15 years of age (who have a higher risk of complications), which may be a catch-up effect after the corona years [5].

Mahamud *et al.* found that national death certificate data tends to overestimate the number of deaths in which HZ is the underlying or contributing cause of death [6]. 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 2021 and 2021, we would expect 4 deaths (range 2–7) in both years, instead of the 37 and 38 deaths reported in 2021 and 2022 respectively (Table 8.4.3).

8.4.4 International developments

8.4.4.1 Varicella

8.4.4.1.1 Epidemiology

The seroprevalence of VZV in Italy in 2019 and 2020 was 92% in males and 93% in females and increased with age [7]. Leung *et al.* describe the changing epidemiology of varicella outbreaks in the United States during the varicella vaccination programme. A varicella outbreak was defined as ≥5 varicella cases withing 1 setting and ≥1 incubation period. Between 1995 and 2019, outbreak size declined from a median of 15 to 7 cases per outbreak and outbreak duration declined from a median of 45 to 30 days [8]. In Australia, there was a reduction of 92% in the incidence of congenital varicella syndrome and a reduction of 91% in the incidence of neonatal varicella infection, after the introduction of universal varicella vaccination [9].

8.4.4.1.2 Vaccine effectiveness

A systematic review of reviews on the clinical efficacy/effectiveness of varicella vaccination strategies was performed by Ahern *et al.* The quality of included reviews was mostly low, however, the available evidence suggested that two-dose vaccination strategies are more effective in preventing varicella of any severity, whereas the effectiveness of one-dose and two-dose strategies was equally high in preventing moderate to severe varicella [10].

Several studies report on varicella vaccine effectiveness (VE) in the United States, where from 1995, a one-dose vaccination strategy was implemented, which was changed to a two-dose strategy in 2007 [11-15]. One-dose vaccination coverage among children aged 19-35 months is at least 90%. In 2020, two-dose coverage was 86-100% among children aged 7 years at 6 sentinel sites and two-dose school entry requirements were implemented in 88% of states [11]. One-dose VE against varicella of any severity was 82-85% and VE against severe varicella was 100%. VE waned over time, resulting in a VE of 97% against any severity varicella in the first year after vaccination and a VE of 84% in the second year after vaccination. The annual rate of breakthrough infection also increased significantly in the course of time since vaccination. There was a 71-90% decrease of incidence, hospitalisation and mortality of varicella. Two-dose VE against varicella of any severity was 92-98%, with no difference in VE or association in breakthrough infection in five years post-vaccination [14]. During the two-dose program, there was a >97% decline in incidence of varicella, with the highest declines among children and adolescents [12]. Hospitalisation and mortality due to varicella declined by 94% and 97% among persons <50 years. The greatest declines were seen in people <20 years [15]. In young people born in the vaccine era, HZ incidence was reduced, likely as a consequence of the introduction of universal varicella vaccination [13]. Pillsbury *et al.* compared the performance of one- and two-dose vaccination with Varivax and with Varilrix, on the basis of long-term clinical trial data. It was estimated that one dose of Varivax was more likely (90% versus 62%) to provide permanent protection against breakthrugh varicella (modelled on a data span of 10 years), but two-dose VE was similar for Varivax and Varilrix [16].

8.4.4.1.3 Cost-effectiveness

Anderson *et al.* carried out a systematic review of economic evaluations of varicella vaccination programmes. They included 79 studies, most of which focused on universal childhood vaccination. A key issue among these studies was the effect of varicella vaccination on HZ incidence. Most studies of universal childhood vaccination reported an increase in overall costs to healthcare services but a favourable outcome from a societal perspective [17]. A cost-effectiveness analysis of universal varicella vaccination in Slovenia was performed by Burgess *et al.* [18]. Varicella incidence was estimated at 1228 per 100,000 population. All two-dose universal vaccination strategies studied were cost-effective compared to no vaccination, with a predicted reduction in varicella incidence of 77-85% [18]. In Portugal, a prospective study of the loss of health-related quality of life (HRQoL) in children and their families was conducted. Among 109 families with children with varicella, the mean loss of HRQoL per child was 2 days and the mean loss per primary caretaker was 1.3 days [19]. Sharomi *et al.* modelled the impact of exogenous boosting and universal varicella vaccination on the incidence of varicella and HZ in England and Wales. It was estimated that over 50 years, universal one- or two-dose vaccination would reduce varicella incidence by 70-92% and mortality by 16-41%. It was projected that HZ incidence would rise a little by 22 years after vaccination introduction but would decrease afterwards to levels below pre-vaccination rates. Universal vaccination strategies were cost-effective [20]. The health and economic impact of the 25-year universal varicella vaccination programme of the US was reviewed by Zhou *et al.* It was estimated that among persons aged 0-49 years, more than 91 million varicella cases, 238,000 hospitalisations and almost 2000 deaths were prevented, which led to a societal saving of 23.4 billion dollars [21].

8.4.4.1.4 Other

Grose *et al.* report on the association of stroke following varicella infection in children. This is a known rare complication, with a risk of 1:15,000–1:26,000. The most common interval between the varicella infection and stroke is one month, followed by two months and three months [22]. Zhu *et al.* investigated the association between multiple sclerosis (MS) and varicella infection. By performing a two-sample Mendelian randomisation analysis on genome data of over 100,000 varicella cases and 15,000 controls, evidence of a significant association between genetically predicted varicella infection and risk of MS was found (OR 35.3, 95%CI 23.0-54.2), indicating a possible causal effect of varicella on MS [23]. Looking at the review by Khallafallah *et al.*, reporting 285 cases with coinfection of mpox and varicella, varicella may also be a risk factor of mpox infection in children [24].

8.4.4.2 Herpes zoster

8.4.4.2.1 Epidemiology

Among Spanish adults aged ≥50 years with HZ presenting in primary care, the incidence rate of HZ was 4.9/1,000 person-years. Incidence increased with age and the proportion of patients developing post-herpetic neuralgia (PHN) also increased with age, the latter reaching 10% in adults aged 80 years and older [25]. From 2016 to 2019, there were 27,642 HZ-related hospitalisations in Spain. The hospitalisation rate was 17.7, the mortality rate was 1.4 and the case fatality rate was 7% (all per 100,000 inhabitants). The majority of hospitalisations was related to elderly people: 90% in people aged >50 years and 46% in people >80 years. Risk factors for hospitalisation were age, female sex, use of immunosuppression and other underlying chronic conditions. Over the last 20 years, the HZ-associated hospitalisation rate increased significantly [26]. This increase in hospitalisation rate was confirmed by Risco Risco *et al.*, who described the epidemiology of HZ-related hospitalisations in Spain from 1998-2018. Annual mean hospitalisation rate was 6.8 per 100,000 population [27].

The global trends of varicella and herpes zoster (VHZ) burden in 204 territories and countries from 1990-2019 were estimated by Zhang *et al.* Worldwide, in 2019, there were approximately 0.9 million disability-adjusted life years (DALYs) due to VHZ, with a VHZ incidence of 84 million. In people <20 years of age, incidence and DALYs decreased from 1990-2019. In contrast, the incidence and DALYs in people aged >50 years significantly increased. The greatest number of incident cases was found in South Asia, East Asia and Western Sub-Saharan Africa [28].

8.4.4.2.2 Vaccine efficacy/effectiveness

The efficacy of recombinant zoster vaccine (RZV) in reducing the duration of clinically significant pain, HZ-associated pain medication use, and duration of use was investigated in participants with breakthrough HZ of the ZOE-50, ZOE-70 and ZOE-HSCT trials. In the ZOE-70 study, RZV significantly reduced the use of pain medication by 40%, and the duration of pain medication use by 50%. In the ZOE-HSCT study, RSV significantly reduced the duration of clinically significant pain by 39% [29]. Marra *et al.* reviewed effectiveness studies of zoster vaccine live (ZVL) and RZV with a follow-up of approximately ten years. VE against HZ was 46% for ZVL; for RZV this ranged between 70-85% [30]. Mbinta *et al.* conducted a

nation-wide retrospective matched cohort study in Australia to assess the effectiveness of ZVL. In adults aged ≥45 years, VE against community HZ was 30% (95%CI 25-34), VE against hospitalised HZ was 54% (95%CI 36-68) and VE against hospitalised PHN was 58% (95%CI 41-70) [31]. Strezova *et al.* analysed the long-term efficacy of RZV against HZ in participants of the ZOE-50 and ZOE-70 studies who received at least one dose. Ten years after vaccination, RZV efficacy was 73% (95%CI 47-88) [32]. The efficacy of RZV in adults with chronic diseases and immunocompromising conditions was high, ranging from 85% in patients with respiratory disorders to 97% in patients with coronary heart disease [33]. A review by Xia *et al.*, summarising the results of both RCTs and cohort studies, showed that, compared to placebo, VE of RZV was 60% (95%CI 49-69) in immunocompromised adults, where ZVL was not significantly different from placebo [34].

8.4.4.2.3 Cost-effectiveness

Balan *et al.* investigated the economic burden of HZ in the Latin America and Caribbean region. Direct costs per patient, based on visits to doctors, transportation, days in the hospital, nursing, medication schedules and physical therapy ranged from $100-$4178 per country. Indirect costs, ranging between $511-$1956, were based on days missed at work for the patient or relative and on impaired labour capacity. Direct and indirect costs were much higher for patients with PHN [35].

Nishimwe *et al.* used the Markov model to estimate the cost-effectiveness of RZV vaccination of adults aged ≥65 years in Switzerland. They estimated that vaccination with RZV, at a coverage of 30% for the first dose, would avoid almost 39,000 cases of HZ, 7,760 cases of PHN and 4,775 other complication cases over the remaining lifetime. RZV vaccination would yield almost 1700 quality-adjusted life-years (QALYs) and prevent CHF 49 million in direct medical costs, with an ICER of CHF 29,656 per QALY gained. Eight people need to be vaccinated to prevent one HZ case [36].

The Markov model was also used in the Netherlands, estimating cost-effectiveness of RZV vaccination in a high-risk cohort (based on comorbidity) and the overall cohort of 70-year-old people. At a coverage of 75%, RZV vaccination is estimated to prevent 2011 HZ cases and 152 PHN cases over a 20-year horizon. The ICER per QALY gained was €38,428 for the high-risk cohort and €59,261 for the overall cohort. The probability of being cost-effective of vaccinating high-risk groups was 75.5% at a willingness to pay threshold of €50,000 per QALY [37].

Giannelos *et al.* reviewed the available evidence of the past five years on cost-effectiveness of RZV vaccination against HZ. In fifteen out of eighteen included studies, RZV vaccination was cost-effective [38].

8.4.4.2.4 COVID-19 association

Several studies assessed the association between COVID-19 infection, COVID-19 vaccination and HZ. To date, a causal relationship has not been established. Akpandak *et al.* assessed the risk of HZ in a risk interval of 30 days after COVID-19 vaccination or up to the date of the second dose, compared to the risk of HZ in a control interval remote from COVID-19

vaccination. Over two million recipients of either BNT162b2, mRNA-1273 or Ad26.COV2.S were included, 1451 of whom were diagnosed with HZ. COVID-19 vaccination was not associated with increased risk of HZ [39]. In a systematic review of studies that evaluated active human herpesvirus (among whom VZV) infection in COVID-19 patients, no difference was found in the prevalence of VZV infections in COVID-19 patients and non-COVID-19 controls [40]. In contrast to these findings, Chen *et al.* estimated the risk of HZ in a propensity-matched cohort study of 2.4 million patients and found that during a 1-year follow-up period, the risk of HZ was significantly higher in COVID-19 patients (hazard ratio (HR) 1.59, 95%CI 1.49-1.69), compared to patients without COVID-19 [41]. Tabet *et al.* conducted a retrospective cohort study in France among children aged 0-18 years with signs of HZ. Twenty-five patients were included, of whom five had a suspected COVID-19 infection prior to HZ. There were no differences between the HZ patients with and without COVID-19 infection [42]. Yuk Fai Wan *et al.* evaluated the effect of inactivated virus (CoronaVac) and BNT162b2 COVID-19 vaccination of the risk of HZ-related hospitalisation in Hong Kong. They identified 16 CoronaVac recipients and 27 BNT162b2 recipients, who were diagnosed with HZ within 28 days of vaccination. CoronaVac was associated with a higher risk of HZ within 14 days after the first dose (incidence risk ratio (IRR) 2.67, 95%CI 1.08-6.59). A significantly higher risk of HZ after BNT162b2 was found after the first dose up to 14 days after the second dose, with IRRs ranging between 5.14 – 5.82 [43].

8.4.4.2.5 Other associations

HZ infection and varicella/HZ vaccination have been linked to other diseases as well. Chen *et al.* investigated the association between HZ and psoriasis in a nationwide retrospective cohort study in Taiwan. Between 1999-2013, 26,623 patients with HZ were selected and a matched control group of patients without HZ was established during the same time period. The adjusted HR for psoriasis was 1.66 (95%CI 1.31-2.13), suggesting an increased risk of psoriasis in patients diagnosed with HZ [44].

Curhan *et al.* investigated the longitudinal association of HZ and long-term risk of cardiovascular disease (stroke or coronary heart disease) [45]. In almost 204,000 participants of three large cohort studies, they found that the multivariable-adjusted HRs for stroke and coronary heart disease after diagnosis of HZ were significantly elevated. Further evidence of the association between HZ and risk of stroke is provided in the review of Grose *et al.*, summarising relevant clinical evidence. They also reviewed the neuropathogenesis of stroke after HZ and propose that this is similar to stroke after varicella [22]. Horev *et al.* retrospectively investigated the risk of major adverse cardiac and cerebrovascular events (MACCE) in a large cohort of 20,965 HZ patients and a matched cohort group. The adjusted HR for incidence of MACCE after HZ was 1.19 (95%CI 110-1.39) during the first year of follow-up up to 4.4 years of follow-up, but was no longer significantly elevated after five years of follow-up [46]. In a retrospective case-control study of over 2 million patients who received care at the Veterans Affairs facility, Parameswaran *et al.* found that the odds of developing a stroke in patients with a history of HZ were 1.93 (95%CI 1.6-2.4) within the first 30 days following HZ infection. A protective effect from vaccination was seen, with an OR of 0.57 (95%CI 0.46-0.72) for RZV and an OR of 0.77 (95%CI 0.65-0.91) for ZVL [47]. These results are corroborated by the review on vasculopathy and HZ by Yawn *et al.* [48]. Parameswaran *et al.* also investigated risk of myocardial infarction following

HZ infection in a cohort of almost 2.2 million patients at the Veterans Affairs facility. Among patients with a history of HZ, myocardial infarction within 30 days occurred in 0.34%, versus 0.28% among the control cohort. Patients with a HZ infection were 1.35 times more likely to develop a myocardial infarction within 30 days post-infection, but vaccination with RZV had a protective effect (OR for myocardial infarction 0.82, 95%CI 0.72-0.92) [49].

Another known association is the risk of HZ in patients with (auto)immune disorders and patients receiving immunosuppressants, such as patients with rheumatoid arthritis (RA). Dlamini *et al.* investigated the association between RA and HZ in a matched cohort study of almost 20,000 RA patients and almost 40,000 control patients in Taiwan. The incidence rate ratio was higher in RA patients than in controls (1.74, 95%CI 1.65-1.84). In a matched subgroup of patients with severe RA, prednisolone use (compared with non-use) was associated with a higher incident odds of HZ (OR 1.48, 95%CI 1.08-2.03) and this further increased with prolonged prednisolone use (OR 2.16, 95%CI 1.46-3.19) [50]. Real-world evidence that HZ risk is also increased in patients with chronic inflammatory diseases treated with JAK inhibitors is summarised in the review by Galloway *et al.* [51]. Gialouri *et al.* reviewed studies indicating that the risk of HZ is higher for the JAK inhibitor tofacitinib than for baricitinib and updacitinib [52]. Singer *et al.* conducted a retrospective cohort study among 67,750 RA patients and 11,401,743 controls. The overall incidence rate of HZ was higher in the RA cohort than in the control cohort: 21.5 versus 7.6 per 1000 person-years and the adjusted incidence rate ratio for HZ was 1.93 (95%CI 1.87-1.99). Higher age, corticosteroid use and JAK inhibitor use were associated with higher incidence rates of HZ [53].

The association between Sjögren's syndrome (SS) and a history of HZ was investigated in a nationwide case-control study in Taiwan. The risk of SS was associated with a history of HZ, with an adjusted OR of 1.9 (95%CI 1.7-2.1) [54].

Diabetes is considered a risk factor for HZ. On the basis of a retrospective cohort analysis in the US, patients with type 2 diabetes are almost twice as likely to develop HZ (adjusted incidence rate ratio 1.84, 95%CI 1.82-1.85) [55]. Patients with diabetes who use metformin are at lower risk for HZ and PHN, with adjusted HRs of 0.70 (95%CI 0.66-0.75) and 0.51 (95%CI 0.39-0.68) [56].

In a cohort study of patients with COPD and a control group of patients without COPD, the adjusted incidence rate of HZ was 2.8 (95%CI 2.7-2.9) for patients with COPD, suggesting that COPD is also a risk factor for HZ [57]. Wang *et al.* investigated the risk of HZ in patients with pulmonary tuberculosis (TB) in a cohort of almost 31,000 TB patients, matched 1:1 to patients without TB. The adjusted HR for HZ in patients with TB was 1.23 (95%CI 1.16-1.30) [58].

Eyting *et al.* investigated the association between HZ vaccination and dementia. People in Wales were naturally randomised, on the basis of date of birth, for vaccination with Zostavax or no vaccination. There were no other differences between the two groups. Among the vaccinated people, the probability of a new dementia diagnosis over a follow-up period of 7 years was reduced by 3.5 percentage points (95%CI 0.6-7.1), which corresponds to a relative reduction of almost 20% in the occurrence of dementia. The protective effects were stronger in women than in men [59].

8.4.5 Literature

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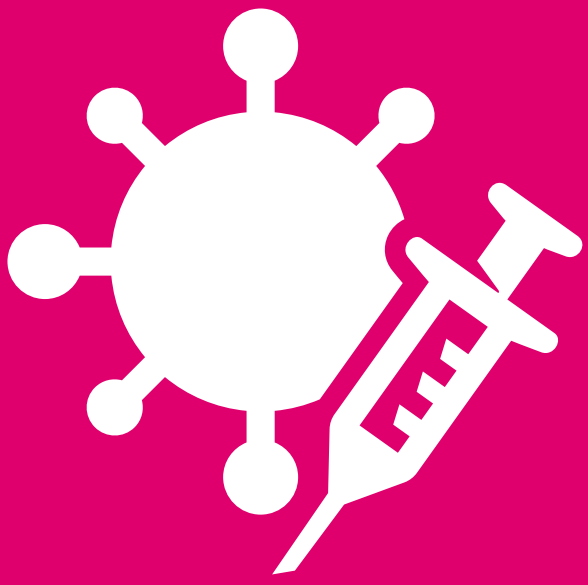
** RIVM publication.*

9
COVID-19



9.1 The COVID-19 epidemiological situation in the Kingdom of the Netherlands

F. Jongenotter, D.S.F. Berry

9.1.1 Key points

SARS-CoV-2 surveillance in the Netherlands

- A description of last winter's epidemiological developments in the Netherlands (week 21 2022 until week 20 2023) can be found in this year's Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2022/2023.

SARS-CoV-2 surveillance in the Dutch Caribbean

- The first SARS-CoV-2-positive cases were detected on Aruba and Curaçao in March 2020.
- Throughout 2022, the governments of Curaçao and Sint Maarten discontinued covering the cost of public SARS-CoV-2 testing, after which the number of SARS-CoV-2 tests and positive cases declined. Due to different COVID-19 policies, testing rates remained higher on Aruba than on other Dutch Caribbean islands, although they declined in comparison to previous years.
- In April 2023, Saba and Sint Eustatius reported an increase in cases, although COVID-19-related deaths remained low, whilst there were several COVID-19-related hospital visits on Saba.

9.1.2 Tables and figures

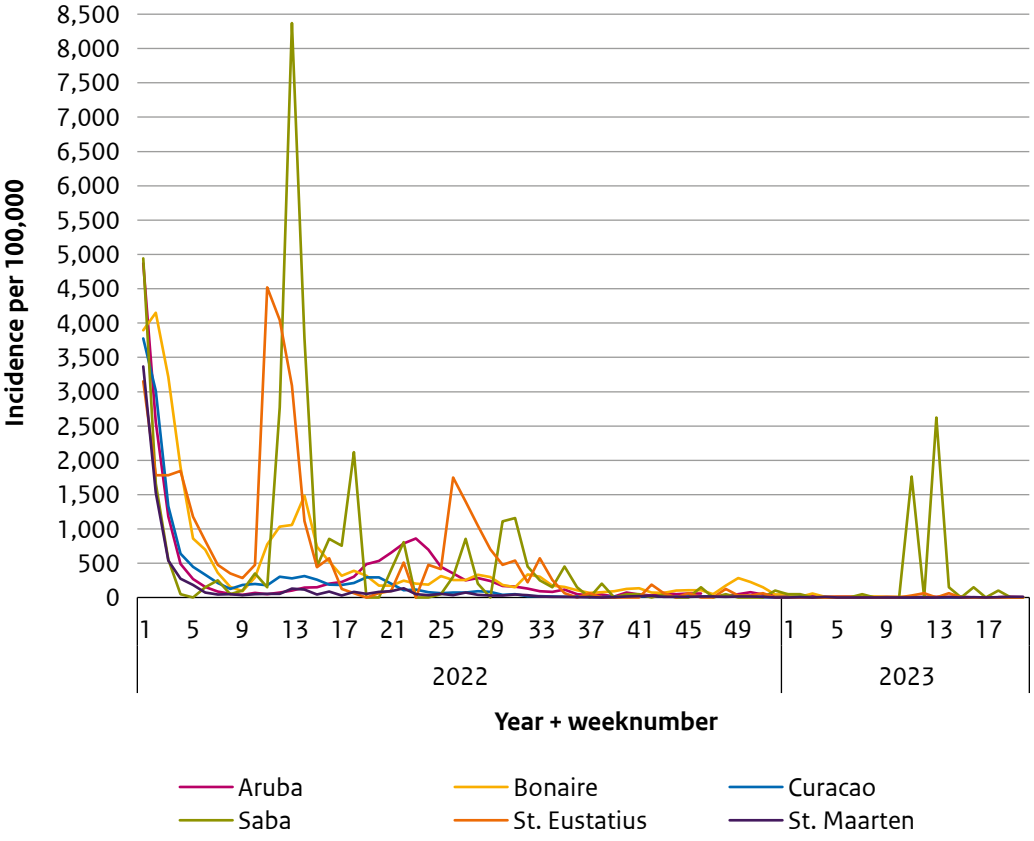
Table 9.1.1 Cumulative numbers of SARS-CoV-2 infections and COVID-19-related hospital admissions and deaths in the Dutch Caribbean, from 1 February 2020 up until 22 May 2023.

Island	Population size[1] (in 2022)	Confirmed SARS-CoV-2 cases	COVID-19-related hospital admissions	COVID-19-related deaths
Aruba	120,605	44,194	1,721	289
Bonaire	22,575	9,861	152	33
Curaçao	161,671	45,806	1,219	301
St. Maarten	62,350	11,047	427	92
St. Eustatius	3,142*	1,219	22	6
Saba	1,983	837	14	2

1 *For the CAS Islands, the population size includes the estimated number of undocumented persons residing on the islands.*

* *In 2021 instead of 2022 (population data were not available at the time of writing).*

Figure 9.1.1 Incidence per 100,000 persons in the Dutch Caribbean, 1 January 2022 - 22 May 2023 (week 20).



Please note that the testing policy on St. Maarten and Curaçao changed in the course of the reporting period. Consequently, after 26 April (week 17) 2022, and 4 June (week 22) 2022, respectively, their trends are not comparable to the previous period.

9.1.3 SARS-CoV-2 surveillance in the Netherlands

For an overview of the developments of COVID-19 epidemiology and SARS-CoV-2 pathogen surveillance, please see chapters 9.1 and 9.7 in the NIP surveillance reports that were published in 2021 (see this link, up to 26 September 2021) and 2022 (see this link, from January 2021 up to and including May 2022). A description of last winter's epidemiological developments in the Netherlands (week 21 2022 until week 20 2023) can be found in this Surveillance of acute respiratory infections in the Netherlands: winter 2022/2023. SARS-CoV-2, influenza virus, RSV and other respiratory viruses (see this link). As that report does not include any results from the Dutch Caribbean, these epidemiological updates are presented here.

9.1.4 SARS-CoV-2 surveillance in the Dutch Caribbean

For an overview of the COVID-19 epidemiology and SARS-CoV-2 pathogen surveillance in the Dutch Caribbean between January 2021 and May 2022, please see Chapters 9.1.5 and 9.7 in the NIP surveillance report that was published in 2022 (see this link). An overview of developments until week 20 of 2023 can be found in Table 9.1.1 and Figure 9.1.1.

Between late December 2021 and February 2022, the Dutch Caribbean islands reported considerable numbers of SARS-CoV-2-positive tests due to the spread of the less severe Omicron-variant. COVID-19-related hospitalisations and deaths remained low throughout this wave. On Aruba, the number of newly detected cases remained high until June 2022, partially due to an elaborate testing policy as compared to other Dutch Caribbean islands at the time. After June 2022, the number of newly detected cases declined on the island. As from 27 April 2022, the government of Sint Maarten no longer covered the cost of public SARS-CoV-2 testing. Similarly, the government of Curaçao no longer covered the cost of public SARS-CoV-2 testing as from 5 June 2022. No major outbreak has been reported by these islands since, although cases may have gone undetected as a result of the changed testing policies.

Up to 1 July 2023, the BES Islands carried out source and contact tracing efforts as well as free community testing. Since 1 July 2023, SARS-CoV-2 is no longer an A-status notifiable disease (see this link). Public interest in SARS-CoV-2 testing has declined on all islands, and no major outbreak has been reported on Bonaire since early 2022. Saba and Sint Eustatius reported a slight increase in cases in July 2022, driven by an increased number of persons getting tested for SARS-CoV-2 as well as summer carnival festivities. Sint Eustatius reported a small increase in cases in April 2023 as a result of increased SARS-CoV-2 testing due to an Influenza outbreak on the island. Saba reported a large number of newly detected SARS-CoV-2 cases in April 2023, of which several patients sought care at the Saba Cares facility. The increase in cases was largely driven by confirmations of SARS-CoV-2-positive self-tests. Mass gatherings due to local elections may have been a contributing factor. No measures were implemented during these outbreaks.

SARS-CoV-2 whole genomic sequencing (WGS) for the Dutch Caribbean islands by the RIVM-IDS laboratory has continued to date, as WGS remains an important source for monitoring SARS-CoV-2 and which variants are emerging or prevalent. Since early 2022, most of the SARS-CoV-2 variants circulating in the Dutch Caribbean have been in the Omicron lineage: sub-variants BA.1 through BA.5. In 2022 and 2023, the HERA 1 project provided training to local laboratory staff on Aruba and Curaçao as well as technical assistance for conducting local WGS. The project was completed in March 2023.

9.2 COVID-19 vaccination strategy in the Netherlands

A.J.M. Pluijmaekers, S.J. Lanooij, A.A.A. Maxwell, B.A. Smagge

9.2.1 Key points

- The primary aim of the COVID-19 vaccination programme in the Netherlands is to prevent serious illness and death from SARS-CoV-2 infections.
- At the beginning of 2022, the first booster campaign was still running. During this campaign, booster vaccinations were offered to everyone aged 12 years and over.
- There were two new vaccination campaigns in 2022: the repeat vaccination (second booster) for adults aged 60 years and over and healthcare workers, and the repeat vaccination in the autumn round available to everyone aged 12 years or over.
- In both campaigns starting in 2022, only persons who were at risk of becoming severely ill or dying from SARS-CoV-2 and healthcare workers were targeted for vaccination.
- In the Caribbean part of the Netherlands there were also two new vaccination campaigns in 2022 (repeat vaccination and autumn round).

9.2.2 Tables

Table 9.2.1 Overview of all Health Council (HC) and Outbreak Management Team Vaccinations (OMT-V) recommendations regarding SARS-CoV-2 vaccination in the Netherlands, for the period 1 January 2022 up to and including April 2023. For an overview of the earlier recommendations, please see Table 9.2.1 in last year's report (see this link) and the complete list of recommendations on the Health Council's website.

Date	Links	Title
19/01/22	NL	Actualisatie advies vaccinatie van 5- tot en met 11-jarigen tegen COVID-19
04/02/22	NL	Boostervaccinatie van adolescenten tegen COVID-19
18/02/22	NL, EN	Second booster vaccination against COVID-19
25/03/22	NL, EN	Application framework for revaccination against COVID-19
25/03/22	NL	Vervolgadvies tweede boostervaccinatie tegen COVID-19
07/04/22	NL	Inzet Moderna-vaccin bij kinderen van 6 tot en met 11 jaar
26/07/22	NL	Advies n.a.v. 1e OMT-V
05/10/22	NL	Vaccinatie tegen COVID-19 met het Novavax-vaccin bij adolescenten
05/10/22	NL	Revaccinatie tegen COVID-19 met het Novavax-vaccin bij volwassenen
15/11/22	NL, EN	COVID-19 vaccination of children aged 6 months to 6 years
10/01/23	NL, EN	COVID-19 vaccination of children aged 5 to 11 and the use of bivalent vaccines
24/02/23	NL	Advies n.a.v. 2e OMT-V COVID-19
29/03/23	NL	BCG-vaccinatie en COVID-19; vervolgadvies
28/06/23	NL, EN	Routine vaccination programme against COVID-19
29/06/23	NL	Revaccinatie tegen COVID-19 met het HIPRA-vaccin

Table 9.2.2 Overview of additions to the COVID-19 vaccination programme from 1 January 2022 up to and including April 2023. The table shows all specified target groups and the dates from which they either were vaccinated, and/or could make an appointment for vaccination. Most, but not all, links lead to the corresponding news update in English. For an overview of the implementation of the vaccination campaign before 1 January 2022, please see table 9.3.2 in last year's report (see this link).

Date	Group
Nov 25, 2021 – Jan 4, 2022	Booster vaccinations offered to all adults born before or in the years 1939 – 2003, in ascending order of birthyear***
Dec 2	Booster vaccination offered to: • Persons with Down syndrome, who live at home • Immobile persons* living at home
Dec 10	Booster vaccination offered to all healthcare and social welfare personnel who come in close contact with patients or clients, and have not yet been invited through the route for the general population
Dec 18	Primary vaccination for minors belonging to medical risk groups, that are at least 5 years old; persons born between 2010 and 2016
Jan 18, 2022	Primary vaccination for all minors born between or in 2010 – 2016, who are at least 5 years old
Feb 26	Additional vaccination for vulnerable groups, three months after their most recent vaccination: • Persons aged 70 or older • Immunocompromised adults • Adults with Down syndrome
Mar 11	Novavax vaccine available for persons who cannot be vaccinated with, or are hesitant to be vaccinated with, an mRNA- or vector-vaccine
Mar 23	Janssen vaccine as booster vaccination for adults who: • Could not be vaccinated with an mRNA-vaccine because of medical reasons • Did not want to receive an mRNA-vaccine as a booster
Apr 19	Additional vaccination for immunocompromised adults, three months after their most recent vaccination
July 18	Reminders sent out for booster and additional vaccinations
Sep 13	Additional vaccination for all persons aged 12 and over, three months after their most recent vaccination, in order of: • Persons aged 60 or older, starting with oldest age groups • Healthcare personnel who come in close contact with patients or clients • Persons aged 59 or younger who are at risk for severe COVID-19 • All persons aged 12 and over

Date	Group
Oct 24	Start of repeat vaccinations with a bivalent vaccine as part of the autumn round for all persons aged 12 years and over, starting with the oldest age groups. (No personal invites were sent out.)
Nov 1	Reminders sent to all persons aged 60 and over who had not received their primary vaccinations. (As this was based on registered information, it could also be that these persons were vaccinated but had not given consent for registration of their vaccination.)
Jan 16, 2023	Start of primary vaccination for children aged 6 months to 5 years with high medical risk for severe disease and death due to a SARS-CoV-2 infection
Feb 27	Start of repeat vaccination for children aged 5 to 12 with high medical risk of severy disease and death due to a SARS-CoV-2 infection

** 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.*

Table 9.2.3 Characteristics of the COVID-19 vaccines that were used in the Netherlands for the primary series, week 1, 2022-week 17, 2023.

Vaccine	Type	Offered to ages (years)	Dose	Doses, intervals (min-max) [1]
BioNTech/Pfizer Comirnaty® [2]	mRNA, monovalent (WT [3])	12+	30 µg	2 doses, 3 (3-6) weeks
BioNTech/Pfizer Comirnaty® [2]	mRNA, monovalent (WT)	5-11	10 µg	2 doses, 8 (8-12) weeks [4]
BioNTech/Pfizer Comirnaty® [2]	mRNA, monovalent (WT)	0.5-4	3 µg	3 doses, 1st 3 (3-4) weeks, 2nd >8 weeks
Moderna Spikevax®	mRNA, monovalent (WT)	12+ [5]	100 µg	2 doses, 4 (3-6) weeks
Janssen Jcovden® [6]	Recombinant vector, monovalent (WT)	18+	8.92 $\log_{10}$ Inf. U	1 dose
Novavax Nuvaxovid® [7,8]	Protein subunit, monovalent (WT)	12+	50 µg	2 doses, 3 weeks

1 *The primary series has been completed once someone has received the required number of doses. People who were infected with SARS-CoV-2 prior to their first vaccination only need one dose to complete their primary series.*

2 *Comirnaty® (BioNTech/Pfizer) was also used in the Caribbean part of the Netherlands for the primary series across all eligible age groups.*

3 *WT = Wild Type, the original SARS-CoV-2 variant.*

4 *Medical high-risk groups: 4 (4-8) weeks.*

5 *In practice, however, Spikevax Original/Omicron® has been used for individuals aged 45 years and over since the end of 2021, due to an increased risk for myocarditis and pericarditis in adolescents and young adults following vaccination with Spikevax (Original/Omicron)®, compared to Comirnaty (Original/Omicron)®, as decided by EMA.*

6 *Decision dated 24 December 2021 to make Jcovden® available as a booster to individuals aged 18 years and over in case of a contraindication to mRNA vaccines as well as to special groups. Available (within limits) at own request since 23 March 2022.*

7 *Limited availability, at own request.*

8 *Since 11 March 2022, Nuvaxovid® has been available to individuals aged 18 years and over in case of a contraindication to mRNA vaccines, to special groups, and at own request. For adolescents aged 12-17 years, this has only applied since October 2022.*

Table 9.2.4 Characteristics of the COVID-19 vaccines that were used in the Netherlands for the booster and repeat vaccinations, excluding the autumn round for repeat vaccination, week 1, 2022-week 17, 2023.

Vaccine	Type	Offered to ages (years)	Dose	Interval after last dose
BioNTech/Pfizer Comirnaty® [1]	mRNA, monovalent (WT [2])	12+	30 µg	6 months (3 months (12 weeks) minimum) [3]
Moderna Spikevax®	mRNA, monovalent (WT)	12+ [4]	50 µg	6 months (3 months (12 weeks) minimum) [3]
Janssen Jcovden® [5]	Recombinant vector, monovalent (WT)	18+	8.92 $\log_{10}$ Inf. U	6 months (3 months (12 weeks) minimum) [3]
Novavax Nuvaxovid® [6,7]	Protein subunit, monovalent (WT)	12+	5 µg	6 months (3 months (12 weeks) minimum) [3]

[1] *Comirnaty® (BioNTech/Pfizer) was used in the Caribbean part of the Netherlands for the booster series across all eligible age groups.*

[2] *WT = Wild Type, the original SARS-CoV-2 variant.*

[3] *In practice, only the bivalent Comirnaty (Original/Omicron)® vaccine aimed against Omicron variant BA.1 has been used during 2022.*

[4] *In practice, however, Spikevax Original/Omicron® has been used since the end of 2021 for persons aged 45 years and over, ue to an increased risk for myocarditis and pericarditis in adolescents and young adults following vaccination with Spikevax (Original/Omicron)®, compared to Comirnaty (Original/Omicron)®, as decided by EMA.*

[5] *Decision dated 24 December 2021 to make Jcovden® vailable as a booster to individuals aged 18 years and over in case of a contraindication to mRNA vaccines as well as to special groups. Available (within limits) at own request since 23 March 2022.*

[6] *Limited availability, at own request.*

[7] *Since 11 March 2022, Nuvaxovid® has been available to individuals aged 18 years and over in case of a contraindication to mRNA vaccines, to special groups, and at own request. For adolescents aged 12-17 years, this has only applied since October 2022.*

Table 9.2.5 Characteristics of the COVID-19 vaccines that were used in the Netherlands for the repeat vaccinations within the autumn round, week 38, 2022 – week 17, 2023.

Vaccine	Type	Offered to ages (years)	Dose	Interval after last dose
BioNTech/Pfizer Comirnaty Original/Omicron® [1]	mRNA, bivalent (WT [2] + BA.1 or BA.4-5 [3])	12+	15+15 µg	6 months (3 months (12 weeks) minimum) [4]
BioNTech/Pfizer Comirnaty Original/Omicron® [1]	mRNA, bivalent (WT + BA.1 or BA.4-5)	5-11	5+5 µg	6 months (3 months (12 weeks) minimum) [4]
Moderna Spikevax Original/Omicron®	mRNA, bivalent (WT + BA.1)	12+ [5]	25+25 µg	6 months (3 months (12 weeks) minimum) [4]
Janssen Jcovden® [6]	Recombinant vector, monovalent (WT)	18+	8.92 $\log_{10}$ Inf. U	6 months (3 months (12 weeks) minimum) [4]
Novavax Nuvaxovid® [6]	Protein subunit, monovalent (WT)	18+	5 µg	6 months (3 months (12 weeks) minimum) [4]

[1] *Comirnaty® (BioNTech/Pfizer) bivalent vaccines were also used in the Caribbean part of the Netherlands for the booster series. In 2022, only the BA.1 bivalent vaccine was used for eligible groups aged 12 years and over. In 2023, both the bivalent BA.1 and BA.4-5 were used across all eligible age groups.*

[2] *WT = Wild Type, the original SARS-CoV-2 variant.*

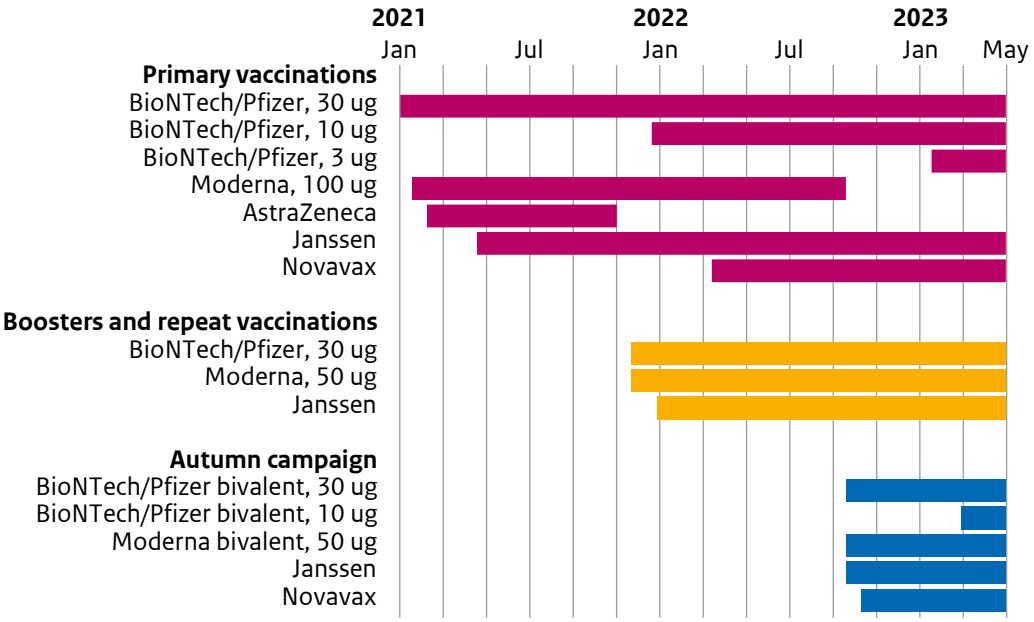
[3] *In practice, only the bivalent Comirnaty (Original/Omicron)® vaccine aimed against Omicron variant BA.1 was used during 2022.*

[4] *Moreover, a three-month interval applies following a SARS-CoV-2 infection.*

[5] *In practice, however, Spikevax Original/Omicron® has only been used for persons aged 45 years and over since the end of 2021, due to an increased risk for myocarditis and pericarditis in adolescents and young adults following vaccination with Spikevax (Original/Omicron)®, compared to Comirnaty (Original/Omicron)®, as decided by EMA.*

[6] *In case of a contraindication for mRNA vaccines, for special groups and at own request, Jcovden® and Nuvaxovid® are (limitedly) available to persons aged 18 years and over. In principle, a bivalent mRNA vaccine (Comirnaty Original/Omicron® or Spikevax Original/Omicron®) is used for the repeat vaccination in the autumn round.*

Figure 9.2.1 Timeline of the COVID-19 vaccines that were used in the Netherlands, week 1, 2021 up to and including week 17, 2023.
Different doses of BioNTech/Pfizer were used for different age groups. For people aged 12 years and over, 30 µg was used. For children aged 5-11 years, 10 µg was used and for children under the age of 5 years, 3 µg was used. For Moderna, for the booster and repeat vaccinations, half a dose was used compared to the dose for the primary series.



9.2.3 Vaccination campaign

The SARS-CoV-2 vaccination campaign in the Netherlands is informed by advice offered by the Health Council (HC) and the Outbreak Management Team Vaccination (OMT-V). As with non-COVID-19-related HC advice, the Minister of Health, Welfare and Sport (HWS) decides if and/or to what degree the HC recommendations are translated into policy. Thus, there may be differences between the HC recommendations and the actual vaccination campaign.

We refer to last year's report for a full overview of the vaccination campaign before 2022. The HC and OMT-V recommendations that were published from 1 January 2022 to 30 April 2023 can be found in Table 9.2.1, and the resulting changes in or amendments to the vaccination campaign can be found in Table 9.2.2. An overview of the various COVID-19 vaccines and their characteristics are shown in Tables 9.2.3, 9.2.4, and 9.2.5, while Figure 9.2.1 shows when these vaccines were in use as part of the vaccination strategy.

9.2.3.1 Vaccination strategy

From February 2022 to April 2023, persons who are at risk of becoming severely ill or dying from SARS-CoV-2 and healthcare workers were invited for a repeat vaccination. The general population is also eligible for a repeat vaccination, but this group was not actively invited.

Up to week 17, 2023, the Netherlands used eight different COVID-19 vaccines, which have all been approved by the European Medicines Agency (EMA), see Figure 9.2.1.

The recommended number of doses to complete the primary series is two doses, except for the Janssen vaccine for which one dose is considered sufficient. Individuals below the age of 80 years who have been infected with SARS-CoV-2 equally only require one dose to complete their primary series. On the other hand, immunocompromised people aged 12 years and over are advised to receive a third dose to complete their primary series, as two doses have been shown to provide inadequate protection for this group.

9.2.3.2 Primary vaccination

In spite of EMA approval of the Novavax vaccine (Nuvaxovid®), on 23 December 2021, the HC advised to continue preferentially vaccinating unvaccinated people with the mRNA vaccines. These vaccines had proven to be effective against both the Delta variant and the increasingly dominant Omicron variant. While the HC concluded that limited data was available about the effectiveness of the Novavax vaccine against these two variants, it did indicate that this peptide vaccine was of value for people who did not want to receive an mRNA vaccine. From 11 March 2022 onwards, people with a contraindication for use of mRNA vaccines, or people who would rather not receive an mRNA vaccine, could make an appointment to be vaccinated with the Novavax vaccine.

9.2.3.3 Booster vaccination

The booster campaign started on 18 November 2021. Most boosters were given in 2022. Following this campaign, additional COVID-19 vaccine doses were called 'repeat vaccinations'.

9.2.3.4 First repeat vaccination

On 18 February 2022, the HC advised offering a repeat vaccination (second booster) with an interval of at least three months to people over 70 years of age, people residing in care facilities, adults with Down syndrome, and adults with a severe immune disorder. This recommendation was made because the improved protection against SARS-CoV-2 these vulnerable groups had gained following their booster was thought to have waned after three months. Invitations for the repeat vaccination were sent out as from 26 February 2022. On 25 March, the group that was eligible for repeat vaccinations due to age was expanded to include everyone aged 60 to 69 years. They could make appointments for the repeat vaccinations from 26 March onwards while invitations to do so were being mailed.

The same two recommendations indicated that people who were not part of these vulnerable groups would receive limited health gains from a repeat vaccination in the Omicron era. However, on 25 March, the HC did point out the value of being able to quickly offer repeat

vaccinations to specific target populations, if the epidemiological situation indicated this to be of value. To this end, the HC provided a framework to quickly determine at which moment certain groups should become eligible for booster vaccination.

9.2.3.5 Repeat vaccination autumn 2022

On 24 July 2022, the OMT-V advised to only invite people with a high medical risk for a repeat vaccination with a bivalent vaccine in the autumn of 2022.
The Minister of HWS decided to offer a repeat vaccination with a bivalent vaccine to all adults and children aged 12 years and over. The autumn round started on 19 September 2022.

Following EMA approval of the HIPRA vaccine, on 29 June 2023, the HC advised to make HIPRA limitedly available for revaccination for people with a contra-indication for mRNA vaccines. Pregnant women with a contra-indication for mRNA vaccines are advised to opt for Novavax instead of HIPRA. The Minister of HWS did not decide on the use of HIPRA until week 17, 2023.

9.2.3.6 Repeat vaccination spring round 2023

On 24 February 2023, the OMT-V advised that a new vaccination campaign during the spring of 2023 was not needed. Only people with a high medical risk are eligible for revaccination during spring. They should be advised by their own healthcare providers.

9.2.3.7 Primary vaccination for children

Children aged 5-11 years who were not part of a risk group for severe COVID-19 illness, were invited for their primary vaccination series starting 18 January 2022. On 19 January 2022, the earlier HC advice to vaccinate all children aged 5 years and over was continued after it was re-evaluated in the light of the Omicron variant, which causes less severe disease. Vaccination was still found to provide protection against severe and mild illness due to Omicron, and while Multisystem Inflammatory Syndrome in Children (MIS-C) might occur less often after an Omicron infection, incidence was still estimated at a total of 100 cases (instead of 150), posing a substantial health risk. Children who had already had COVID-19, as evidenced by a PCR test, were already protected against MIS-C, and would thus not need to be vaccinated.

On 24 February 2022, the Moderna vaccine was approved by EMA for use in children aged 6 to 11 years. Still, on 7 April 2022, the HC recommended to continue using the lower-dose BioNTech/Pfizer vaccine in children because availability of this vaccine was good and it conferred good protection, while effectiveness and safety data on the Moderna vaccine were limited.

On 10 January 2023, the HC advised to only vaccinate children from 5 to 11 years with a high medical risk rather than all children. On 23 February 2023, only children from 5 to 11 years with a high medical risk of severe disease and death due to a SARS-CoV-2 infection were eligible for the primary vaccination. Children who were not part of a risk group were no longer eligible.

On 19 October 2022, the EMA approved the use of Moderna end BioNTech/Pfizer vaccine for children from 6 months to 4 years in a lower dose. In the Netherlands, only the BioNtech/Pfizer vaccine is used for this group.

On 15 November 2022, the HC advised vaccinating children from 6 months to 6 years who were part of a risk-group for severe COVID-19. They were invited for their primary vaccination series as from 16 January 2023.

9.2.3.8 Booster vaccination for children

On 4 February 2022, the HC advised not to offer booster vaccinations to adolescents aged 12-17 years, as data showed its health gains were limited, especially in relation to the decreased severity of COVID-19 due to the Omicron variant, even in high-risk adolescents. The HC stated that up to that time vaccinated adolescents were adequately protected against severe illness and/or MIS-C due to an Omicron infection, and the effect on viral spread was expected to be minimal, whereas receiving another vaccination carried the rare yet possible risk of myocarditis. Furthermore, EMA had not yet approved a vaccine to be used as a booster for adolescents, which would mean this specific use would be off-label. However, the HC did recommend tailoring to specific adolescents with severe immune disorders and adolescents who wanted to receive a booster to protect vulnerable family members.

9.2.3.9 Repeat vaccination autumn round for children

On 10 January 2023, the HC advised offering repeat vaccinations to children aged 5-11 years with a high medical risk for severe disease and death due to a SARS-CoV-2 infection. There is no preference for the use of a bivalent or a monovalent vaccine. On 19 January, the Minister of HWS decided to offer repeat vaccinations with bivalent vaccines to this group.

9.2.4 Overview of changes to vaccination programme from January 2022 to June 2023

From January 2022 to June 2023, there were two vaccination campaigns: the repeat vaccination for elderly people, healthcare workers and medical risk groups and the repeat vaccination in the autumn round for the general population aged 12 years and over with bivalent vaccines.

Children aged 5-11 years are no longer eligible for vaccination, unless they have a high medical risk for severe disease and death. In that case, they are also eligible for a repeat vaccination with a bivalent vaccine. Children aged 0.5-4 years are eligible for the primary series when they have a high medical risk for severe disease. In June 2023, the Minister of Health, Welfare and Sport decided to implement a structural COVID-19 vaccination campaign, preferably in the autumn, for people aged 60 years and over and for adults and children with a medical risk for severe disease and death.

9.2.5 COVID-19 vaccination in the Dutch Caribbean

The vaccination strategy determined for the Dutch mainland, also applies to the oversees Dutch municipalities (Bonaire, Saba, and Sint Eustatius) and the CAS countries (Aruba, Curacao, and Sint Maarten).

In 2022 and 2023, RIVM continued to distribute the COVID-19 vaccines to the CAS and BES islands. The islands handled the storage of the COVID-19 vaccines and were responsible for the implementation of the vaccination strategy and registration of the administered COVID-19 vaccine doses. This resulted in small differences in the vaccination strategy per island, mainly

in the start dates for the various (booster) campaigns and the order in which target groups were vaccinated. Overall, the eligibility for the primary series, booster vaccination, and repeat vaccination was similar to the European Netherlands.

9.2.5.1 Primary vaccination in the Dutch Caribbean

From January 2022 to April 2023, the Comirnaty® (BioNTech/Pfizer) vaccine was mainly used for the primary series on all islands. In January 2022, a small number of Janssen Jcovden® doses were given on Aruba to those who specifically requested it for their primary series, and children aged 5-11 years, irrespective of their risk for severe COVID-19, were invited to receive their primary series with the 10-µg dose of the Comirnaty® (BioNTech/Pfizer) vaccine on all islands. Following the HC decision to only vaccinate high risk groups aged 5-11 years at the beginning of 2023, all islands adapted their vaccination strategies accordingly. Additionally, children aged 0.5-4 years with a high risk for developing severe COVID-19 were invited as from January 2023 to receive the 3 µg dose of the Comirnaty® (BioNTech/Pfizer) vaccine.

9.2.5.2 Booster vaccination in the Dutch Caribbean

The first booster campaign began in November 2021, starting with the oldest age groups on all islands. At the beginning of 2022, all individuals over 18 years were invited to receive their first booster shot with the monovalent Comirnaty® (BioNTech/Pfizer) vaccine. In the following months, adolescents aged 12-17 years were also invited to receive their booster with the monovalent Comirnaty® (BioNTech/Pfizer) vaccine.

9.2.5.3 First repeat vaccination in the Dutch Caribbean

The repeat vaccination campaign (second booster) started in April 2022 on all islands with the Comirnaty® (BioNTech/Pfizer) vaccine, beginning with the oldest age groups (60+) and healthcare workers.

9.2.5.4 Repeat vaccination during the autumn round in the Dutch Caribbean

As of October 2022, all individuals aged 12 years or over were eligible for a repeat vaccination on the islands with the bivalent Comirnaty® (BioNTech/Pfizer) BA.1 vaccine. Additionally, citizens over 60 years and high-risk groups aged 18-59 years were invited to receive their third booster.

9.3 COVID-19 vaccination coverage

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

9.3.1 Key points

- The national COVID-19 vaccination coverage declined with each consecutive vaccination round. This is also the case in the Caribbean part of the Kingdom of the Netherlands.
- The national COVID-19 vaccination coverage was higher among older age groups than among younger age groups.
- At the municipal level, a pattern is observed with lower coverage in the Bible Belt and in the north of the Netherlands than in the south. This pattern was observed in all vaccination rounds. In the Caribbean part of the Kingdom of the Netherlands, the vaccination coverage was highest on Saba for the primary vaccination series, as well as for the 2022 autumn repeat vaccination round.
- In collaboration with Statistics Netherlands (CBS), RIVM conducts ongoing research into determinants of intention for vaccination and vaccination uptake.

9.3.2 Tables and figures

Table 9.3.1 Registered vaccination coverage of the completed primary series, booster, repeat vaccination and the 2022 autumn round repeat vaccination for birth years 2010 and before, 2004 and before and 1962 and before, up to and including week 21, 2023[1-4].

		Coverage			
Age group (years)	Birth cohort	Completed primary	Booster	Repeat vaccination	Autumn round
12+	2010 or before	80.2%	57.7%	n/a	26.9%
18+	2004 or before	82.1%	62.1%	n/a	28.9%
60+	1962 or before	93.1%	84.9%	52.1%	60.9%

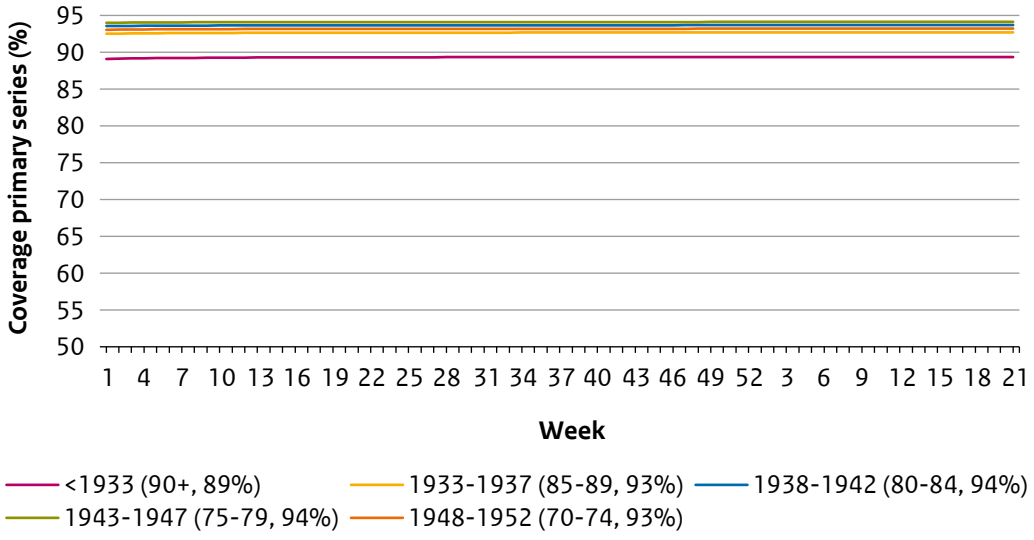
[1] *Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) database supplemented with GGD vaccination data that is not registered in CIMS. In addition, the number of vaccine doses administered by organisations other than the GGD were calculated using assumptions based on the GGD data (CIMS+ method). People who died or emigrated were excluded. Denominator: People who were registered in the Personal Records Database (BRP) [1], as of 3 April 2023.*

[2] *Persons who were infected with SARS-CoV-2 prior to their first vaccination only needed one vaccine dose to complete their primary series.*

[3] *'Coverage of the completed primary series' refers to the part of the Dutch population that completed their primary series (one dose of Jcovden®, one dose after a SARS-CoV-2 infection, two doses of Comirnaty®, Spikevax®, Vaxzevria® or Nuvaxovid®). 'Coverage of the booster' refers to the part of the Dutch population that received a booster (first vaccination after completing the primary series) between November 2021 and 19 September 2022. 'Coverage of the repeat vaccination' refers to the part of the Dutch population that received a vaccination after the booster before 19 September 2022. 'Coverage of the autumn round repeat vaccination' refers to the part of the Dutch population that received an additional vaccination after the primary series from 19 September 2022 onwards.*

[4] *When age was unknown, persons were only included in the numerator of the birth cohort 2010 and before and not in the numerator of the birth cohorts 2004 and before or 1962 and before.*

Figure 9.3.1 (continues on the next page) Coverage of the completed primary series of COVID-19 vaccination, stratified by birth year, for week 1, 2022 up to and including week 21, 2023[1-7].



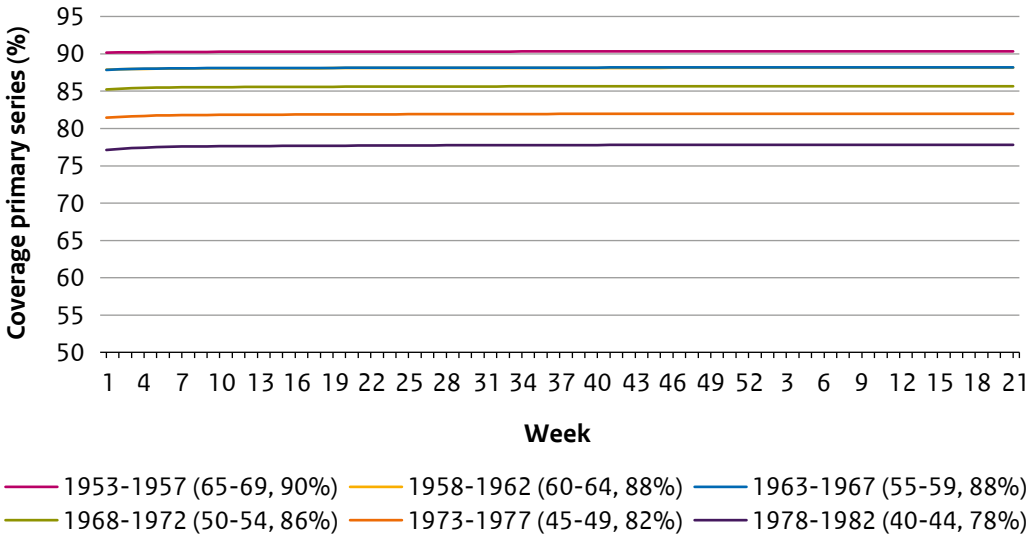
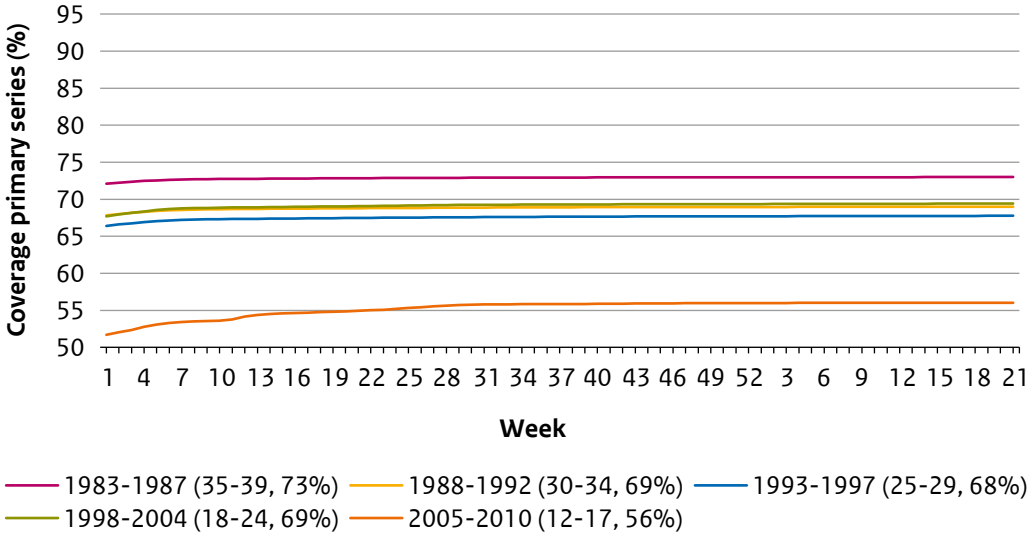


Figure 9.3.1 (continued) Coverage of the completed primary series of COVID-19 vaccination, stratified by birth year, for week 1, 2022 up to and including week 21, 2023[1-7].



1 *Week numbers are calendar weeks (ISO 8610); week 1, 2022 = 3-9 January 2022, etc.*

2 *Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) database supplemented with GGD vaccination data that is not registered in CIMS (CIMS/CoronIT method). Denominator: People who were registered in the Personal Records Database (BRP) [1], as of 3 April 2023.*

3 *People born between 1956 and 1960 were mainly vaccinated by their GP with Vaxzevria®. Vaccinations performed by GPs were based on vaccinations registered in CIMS. From 15 March until 23 March and from 3 April until 5 April 2021, Vaxzevria® was temporarily not administered.*

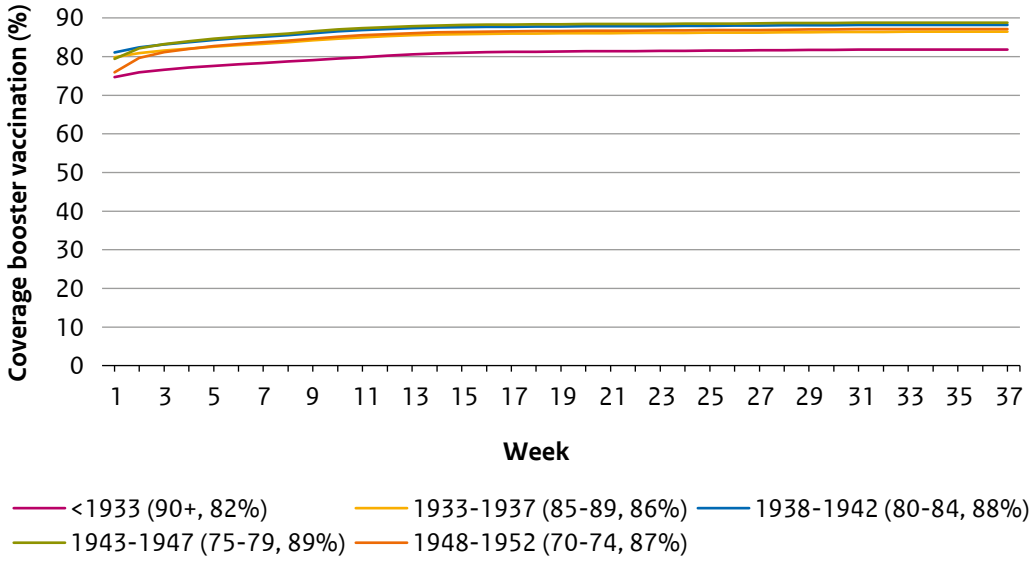
4 *'Coverage of the completed primary series' refers to the part of the Dutch population that completed their primary series (one dose of Jcovden®, one dose after a SARS-CoV-2 infection, two doses of Comirnaty®, Spikevax®, Vaxzevria®, Nuvaxovid®).*

5 *On 23 February 2023, eligibility for the primary vaccination series was limited from all children aged between 5 and 11 years to only children with high medical risk in this age group. The size of this medical risk group is not known to RIVM. Therefore, this group is not included in the figure.*

6 *From 16 January 2023 onwards, children with high medical risk aged between 6 months and 4 years have been eligible for the primary vaccination series. Due to traceability, only the total number of administered vaccinations is reported to RIVM. The size of this medical risk group is not known to RIVM either. Therefore, this group is not included in the figure.*

7 *This figure includes vaccinations administered to people who were still living in the Netherlands in week 21 of 2023. Persons who died or emigrated were retrospectively filtered from this data.*

Figure 9.3.2 (continues on the next page) Coverage of the booster COVID-19 vaccination, stratified by birth year, for week 1, 2022 up to and including week 37, 2022[1-3].



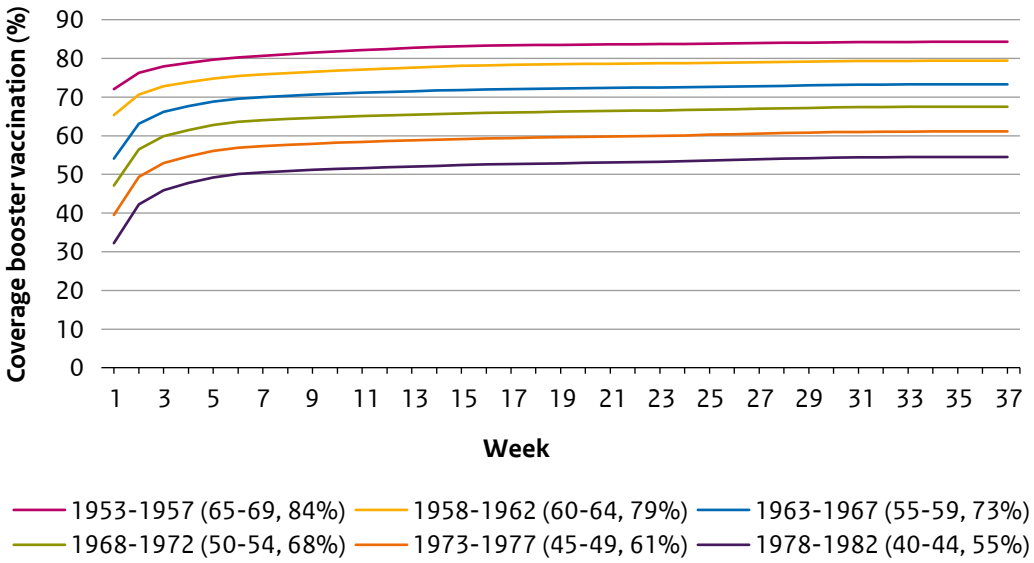
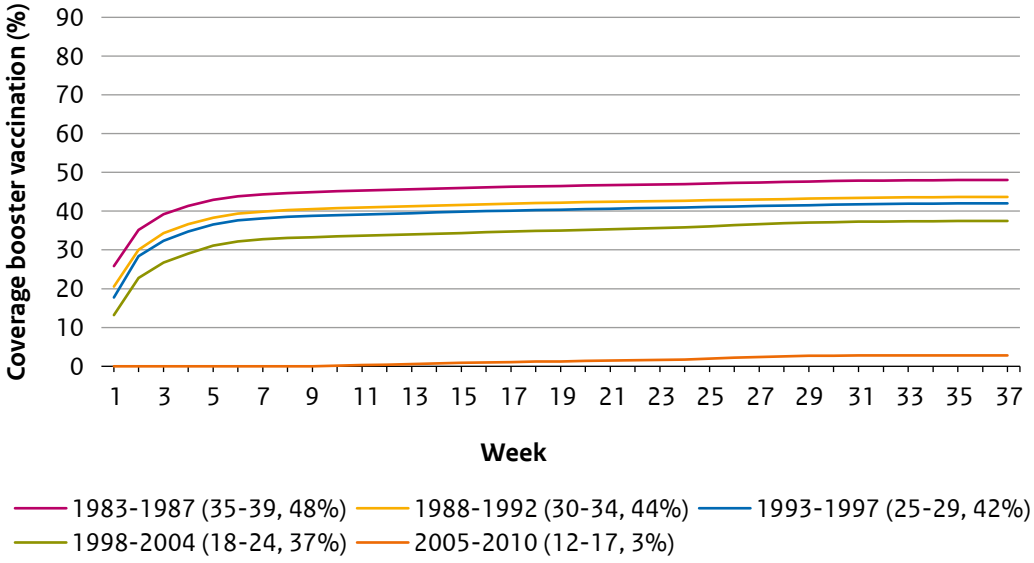


Figure 9.3.2 (continued) Coverage of the booster COVID-19 vaccination, stratified by birth year, for week 1, 2022 up to and including week 37, 2022[1-3].

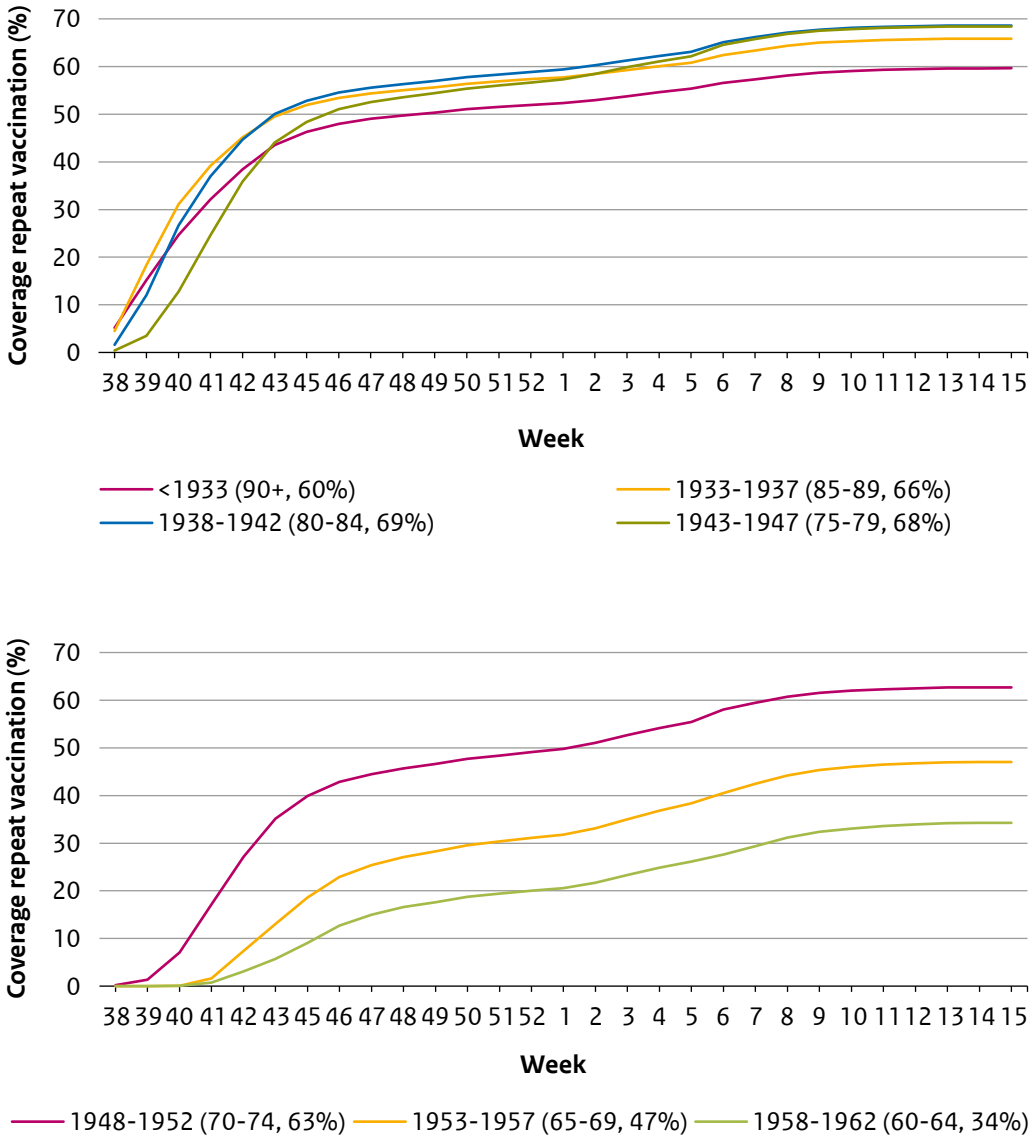


1 *Week numbers are calendar weeks (ISO 8610); week 1, 2022 = 3-9 January 2022, etc.*

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

3 *This figure includes vaccinations administered to people who were still living in the Netherlands in week 37 of 2022. Persons who died or emigrated were retrospectively filtered from this data.*

Figure 9.3.3 Coverage of the 2022 repeat COVID-19 vaccination, stratified by birth year, for week 9, 2022 up to and including week 37, 2022[1-3].

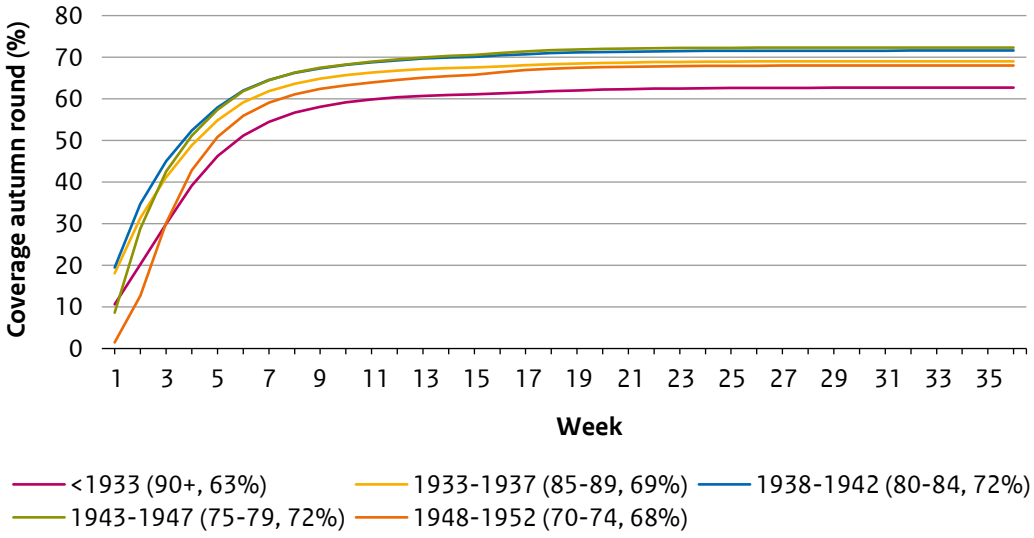


[1] *Week numbers are calendar weeks (ISO 8610); week 1, 2022 = 3-9 January 2022, etc.*

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

[3] *This figure includes vaccinations administered to people who were still living in the Netherlands in week 37 of 2022. Persons who died or emigrated were retrospectively filtered from this data.*

Figure 9.3.4 (continues on the next page) Coverage of the 2022 autumn repeat COVID-19 vaccination round, stratified by birth year, for week 38, 2022 up to and including week 21, 2023[1-4].



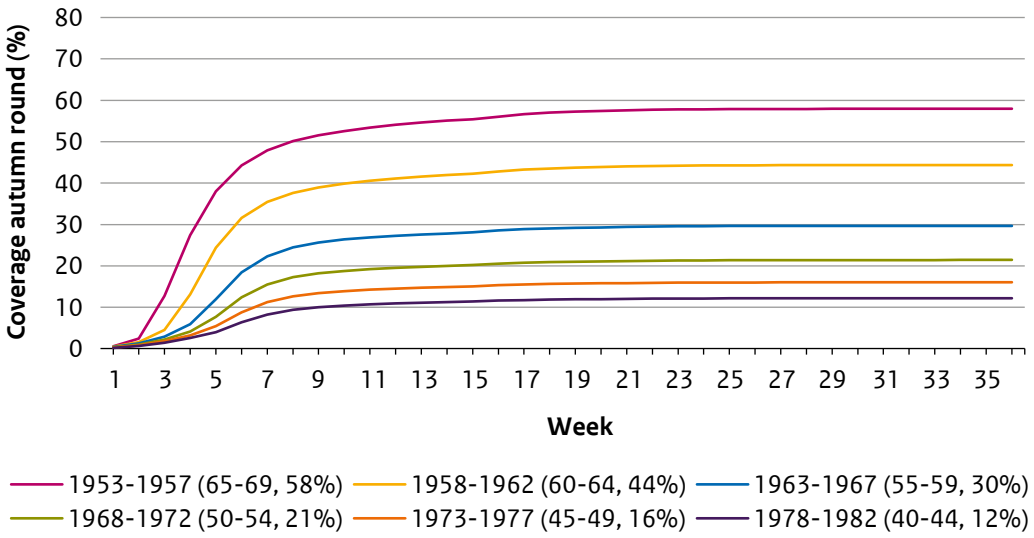
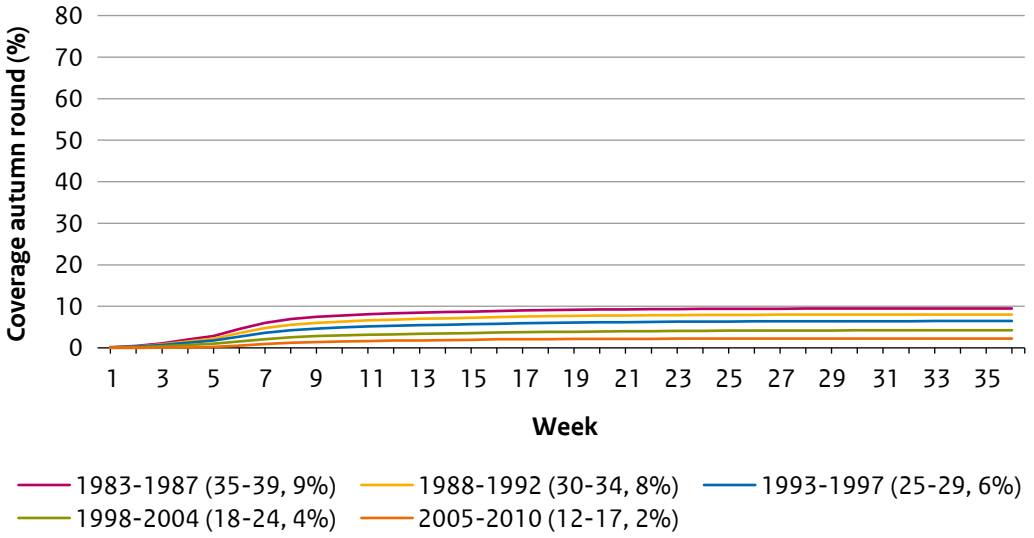


Figure 9.3.4 (continued) Coverage of the 2022 autumn repeat COVID-19 vaccination round, stratified by birth year, for week 38, 2022 up to and including week 21, 2023[1-4].



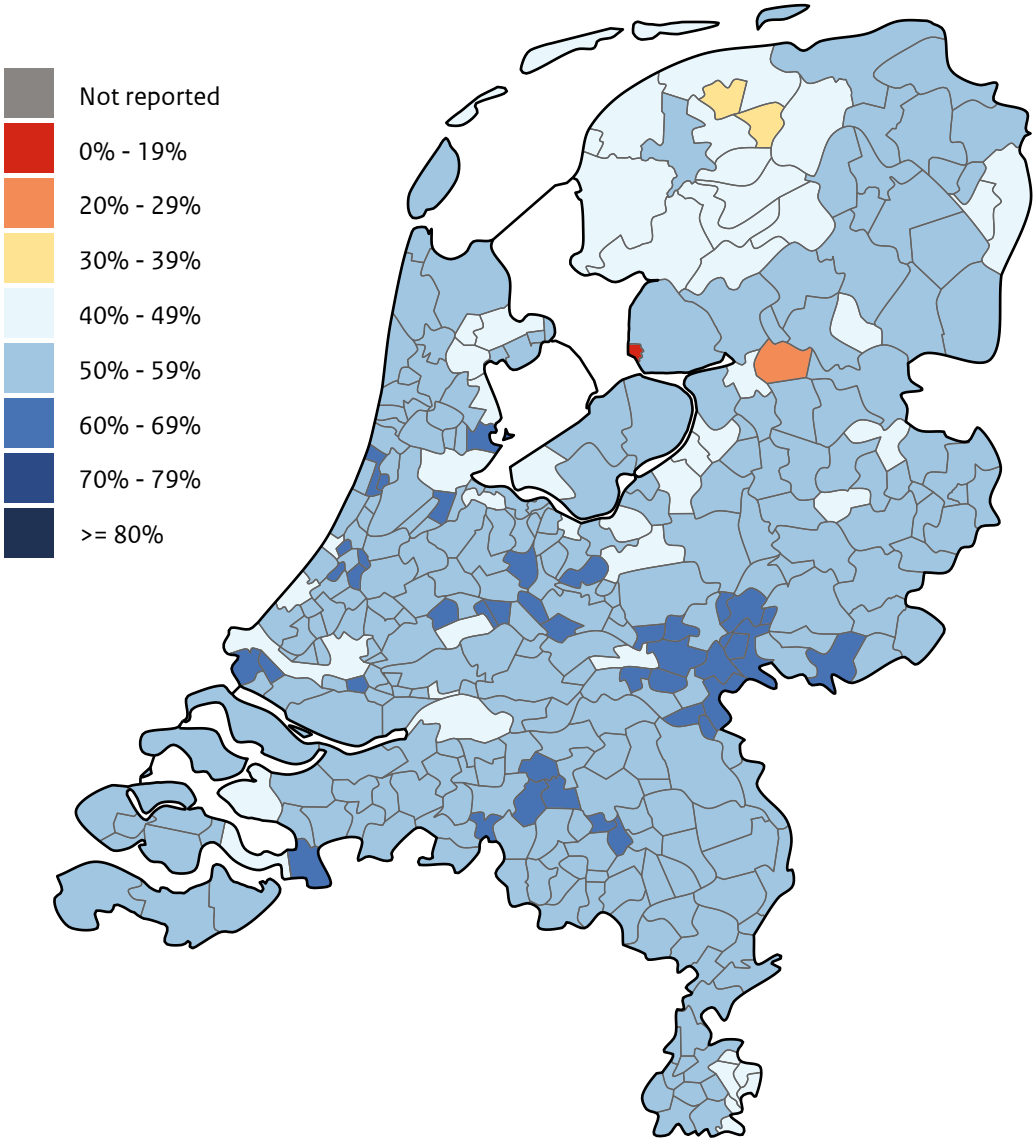
1 *Week numbers are calendar weeks (ISO 8610); week 1, 2022 = 3-9 January 2022, etc.*

2 *Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) database supplemented with GGD vaccination data that is not registered in CIMS (CIMS/CoronIT method). Denominator: People who were registered in the Personal Records Database (BRP) [1], as of 3 April 2023.*

3 *On 22 February 2023, the repeat vaccination of the 2022 autumn round also became available for children with high medical risk, aged between 5 and 11 years, who have completed the primary series. The size of this medical risk group is not known to the RIVM. Therefore, this group is not included in the figure.*

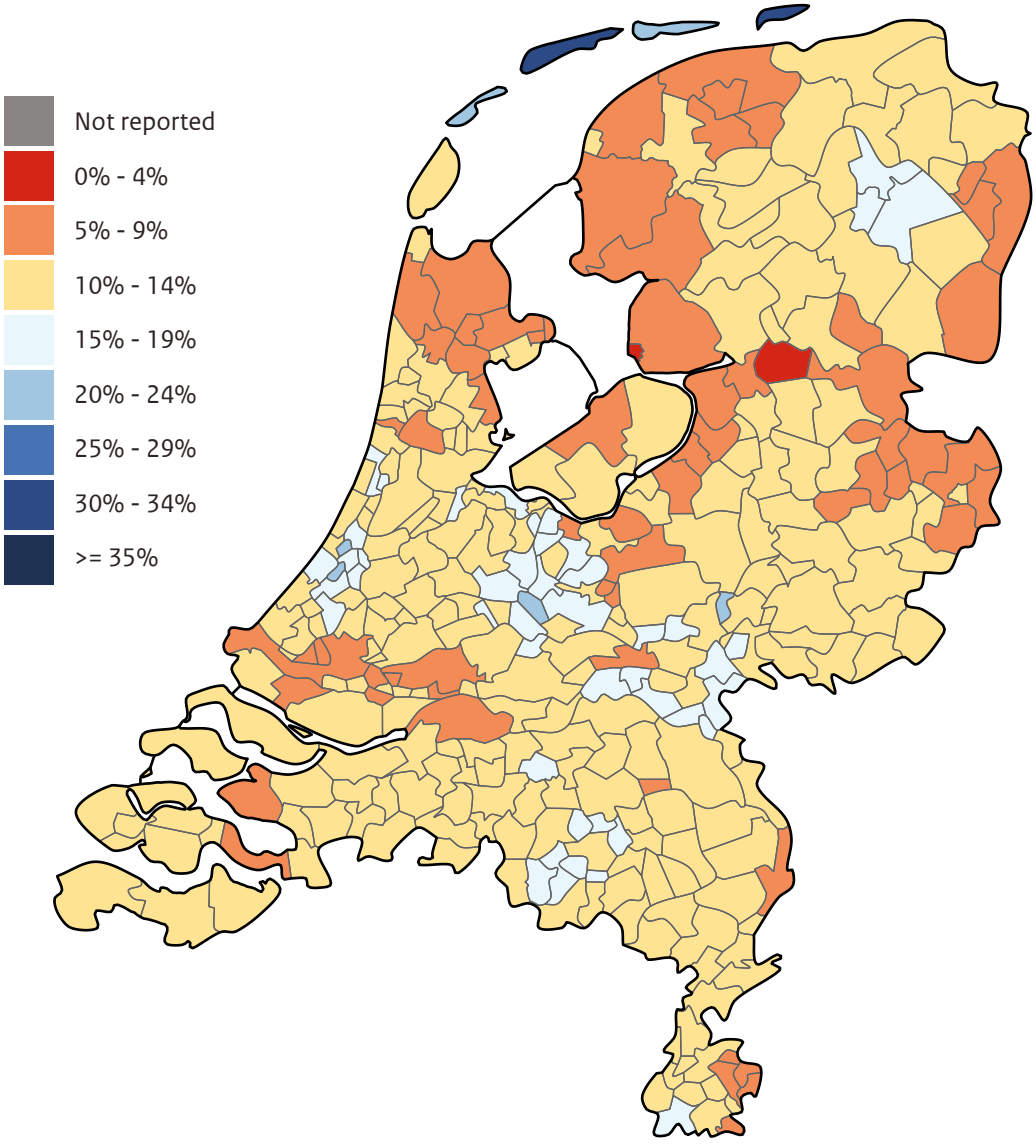
4 *This figure includes vaccinations administered to people who were still living in the Netherlands in week 21 of 2023. Persons who died or emigrated were retrospectively filtered from this data.*

Figure 9.3.5 Coverage of the 2022 repeat COVID-19 vaccination per municipality, birth years 1962 and before, for week 9, 2022 up to and including week 37, 2022[1].



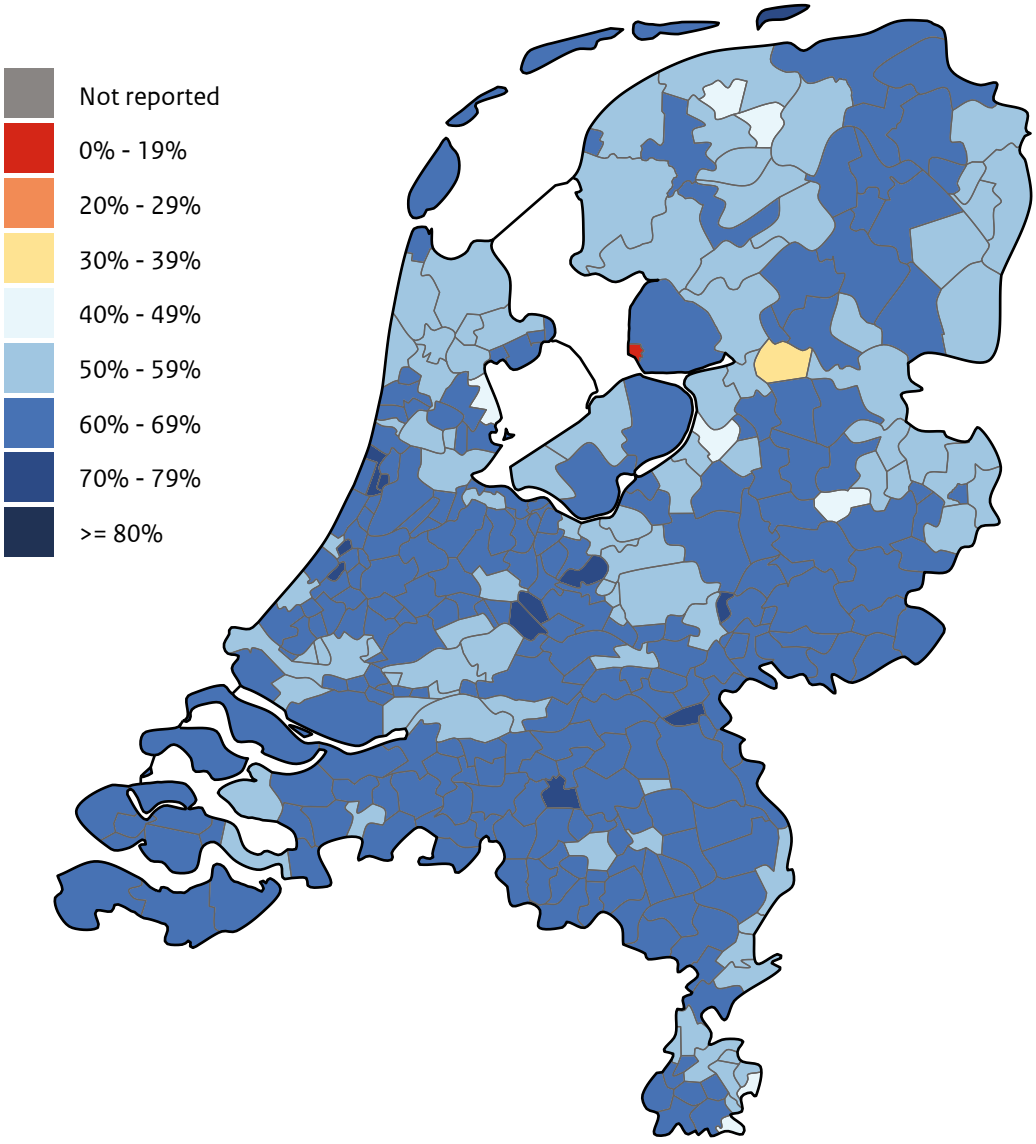
[1] *Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) database supplemented with GGD vaccination data that is not registered in CIMS (CIMS/CoronIT method). Denominator: People who were registered in the Personal Records Database (BRP) [1], as of 6 July 2022.*

Figure 9.3.6 Coverage of the 2022 autumn repeat COVID-19 vaccination round per municipality, birth years 1963-2010, for week 38, 2022 up to and including week 21, 2023[1].



[1] *Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) database supplemented with GGD vaccination data that is not registered in CIMS (CIMS/CoronIT method). Denominator: People who were registered in the Personal Records Database (BRP) [1], as of 3 April 2023.*

Figure 9.3.7 Coverage of the 2022 autumn repeat COVID-19 vaccination round, birth years 1962 and before, for week 38, 2022 up to and including week 21, 2023[1].



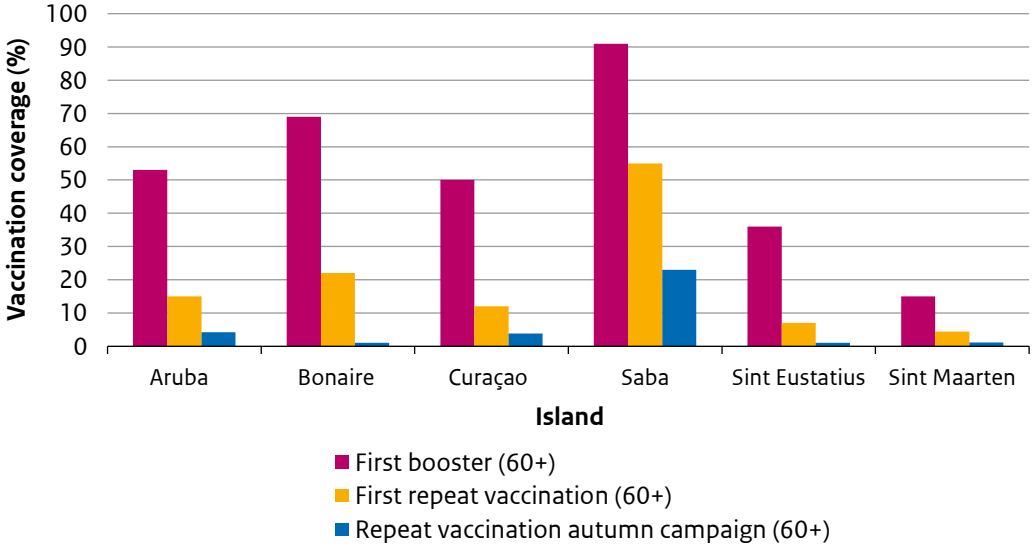
[1] *Data sources: Numerator: COVID-19 vaccination Information Monitoring System (CIMS) database supplemented with GGD vaccination data that is not registered in CIMS (CIMS/CoronIT method). Denominator: People who were registered in the Personal Records Database (BRP) [1], as of 3 April 2023.*

Table 9.3.2 Vaccination coverage of the completed primary series, first booster vaccination, first repeat vaccination (second booster), and the 2022 autumn round repeat vaccination campaign in the Caribbean part of the Kingdom of the Netherlands per age group, up to and including week 21, 2023[1].

	Primary series		Booster		Repeat	Autumn campaign	
Island	12+	60+	12+	60+	60+	12+	60+
Aruba	79%	83%	34%	53%	15%	<5%	10%
Bonaire	82%	94%	41%	69%	22%	11%	22%
Curaçao	72%	78%	31%	50%	12%	<5%	7%
Saba	93%	>95%	66%	91%	55%	16%	31%
Sint Eustatius	60%	55%	29%	36%	7%	<5%	<5%
Sint Maarten	47%	37%	16%	15%	<5%	<5%	<5%

1 *Data sources: DVG (Aruba), OLB-PG (Bonaire), UO G&Gz (Curacao), Public Entity Saba (Saba), Public Entity Sint Eustatius (Sint Eustatius), CPS (Sint Maarten).*

Figure 9.3.8 Vaccination coverage for the repeat vaccinations of the booster (1st booster), repeat vaccination (2nd booster), and 2nd repeat vaccination (3rd booster) per island in the Caribbean part of the Kingdom of the Netherlands, up to and including week 21, 2023[1].



1 *Data sources: DVG (Aruba), OLB-PG (Bonaire), UO G&Gz (Curacao), Public Entity Saba (Saba), Public Entity Sint Eustatius (Sint Eustatius), CPS (Sint Maarten).*

9.3.3 Methods

The data reported in this chapter is based on the COVID-19 vaccination Information and Monitoring System (CIMS) database, which is supplemented with data from the Municipal Health Services (GGD) that is not registered in CIMS due to lack of consent by the vaccinee. The CIMS database is linked to the Personal Records Database (BRP) [1]. This way, people who have emigrated or died are excluded from the numerator (daily) and the denominator (quarterly). To calculate the vaccination coverage, two different methods are used. Firstly, for the vaccination coverage by municipality and by smaller age groups, vaccinations administered by the GGD that are not registered in CIMS are added to the CIMS database (CIMS/CoronIT method). Secondly, for the vaccination coverage by age group at the national level, the CIMS+ method is used. In this method, the CIMS data is supplemented with vaccinations administered by the GGD that are not registered in CIMS, as well as with an estimate of the number of vaccinations that are not registered in CIMS and administered by other organisations than the GGD. This calculation is based on assumptions derived from anonymous and complete GGD data. The CIMS+ method also takes into account that a single vaccination following a COVID-19 infection counts as a completed primary vaccination series. A more detailed description of these calculation methods can be found in the 2021 report 'COVID-19 Vaccination Coverage' [2].

It should be noted that this chapter reports the COVID-19 vaccination coverage, which is not synonymous with the actual immunity reached in the population. In chapters 9.4 and 9.5, further information on the COVID-19 vaccine effectiveness and SARS-CoV-2 seroepidemiology in the Netherlands is provided.

All results in this report refer to the European part of the Kingdom of the Netherlands, unless otherwise mentioned.

9.3.3.1 Methods for the Caribbean part of the Kingdom of the Netherlands

To monitor the vaccination campaigns on the CAS (Curaçao, Aruba and Sint Maarten) and BES (Bonaire, Sint Eustatius and Saba) islands, each island kept a register of the total number of weekly administered vaccinations, and these were shared with RIVM. At the start of the primary vaccination campaign, the frequency of data sharing was weekly, but since 2022, this has been scaled back to monthly reporting. Vaccine registers contain anonymous aggregated data stratified into select age groups (0-4, 5-11, 12-17, 18-59, 60+ years) per vaccine dose. Population data was updated once a year and was received from the public health departments to ensure consistent reporting. People who were not registered citizens on the CAS islands were also included in the vaccine registrations and included in the calculations for the vaccine coverage on the islands. It should be noted that the residential status of vaccinated persons could not always be included in the vaccine registrations. Therefore, for some islands, the vaccination rates may therefore be slightly under- or overrepresented. Additionally, it was not always possible to filter out non-active individuals (due to emigration or death), and the data could not be corrected for vaccinated individuals who immigrated to the islands.

9.3.4 Vaccination coverage

In week 21, 2023, coverage of the completed primary series was 71.2% for persons aged 12 years and over, 73.1% for persons aged 18 years and over and 87.6% for persons aged 60 years and over (Table 9.3.1). Coverage of the primary series increased only slightly between the start of 2022 and week 21 of 2023 (Figure 9.3.1), because those aged 12 years and over had already been invited for the primary series in 2021. Compared to the vaccination coverage of the primary series, coverage decreased with each consecutive booster/repeat vaccination round (Table 9.3.1). The vaccination strategy also differed per vaccination round (see chapter 9.2). In week 21, 2023, the vaccination coverage of the 2022 autumn repeat vaccination round was 26.6% for persons aged 12 years and over, 28.6% for persons aged 18 years and over and 60.2% for persons aged 60 years and over.

9.3.4.1 Among children below 12 years of age

For children under 12 years of age (not included in Table 9.3.1, and Figures 9.3.1 to 9.3.7), the vaccination strategy differed from the other age groups and varied over time (see chapter 9.2). For children aged between 5 and 11, eligibility for the primary vaccination series was limited from all children in this age group to children with high medical risk only on 23 February 2023. On this date, vaccination coverage was 3%. Subsequently, a total of 66 first vaccinations were administered between 23 February and week 21, 2023. For children with high medical risk aged between 6 months and 4 years, vaccination with the primary series has been indicated since 16 January 2023. and 40 first vaccinations were administered between this date and week 21, 2023. It is not possible to calculate the vaccination coverage in these high medical risk groups because the size of these groups is not known to the RIVM.

9.3.4.2 By age

For all four vaccination rounds (primary vaccination series, booster, repeat vaccination, 2022 autumn round repeat vaccination), the vaccination coverage was higher in older age groups than in younger age groups (Table 9.3.1, and Figures 9.3.1 to 9.3.4). Older age groups were specifically targeted by the vaccination campaigns and usually invited for COVID-19 vaccination first, except for the primary series where healthcare workers were invited earlier. Research done by the RIVM Corona Behaviour Unit showed that willingness of vaccination during the 2022 autumn round was lower among younger age groups, people with a lower education level, people who do not belong to a medical risk group and people who recently had a SARS-CoV-2 infection [3].

9.3.4.3 By municipality

Figures 9.3.5 to 9.3.7 show the vaccination coverage of the repeat vaccination (vaccination campaign during spring 2022) and the 2022 autumn repeat vaccination round by municipality. People living in an asylum seekers' centre, homeless people and seafarers are not included in the vaccination coverage, because only people registered in the Personal Records Database (BRP) [1] are included in the numerator and denominator.

For the repeat vaccination (Figure 9.3.5), the vaccination coverage among people aged 60 years and over was between 40 and 49% in most municipalities. In general, coverage in the northern part of the Netherlands was lower compared to the southern part. A lower vaccination coverage was also observed in the 'Bible Belt', where a larger proportion of people reject vaccination in general, on religious grounds.

Regarding the 2022 autumn repeat vaccination round, the highest vaccination coverage by municipality among persons aged 12 to 59 years (Figure 9.3.6) is found on the Wadden Islands, and coverage is between 10 and 14% in the majority of municipalities. In the 'Bible Belt' and in larger cities, coverage is lower. In general, vaccination coverage is also lower in the north than in the south of the Netherlands. Among individuals aged 60 years and over, a similar pattern of vaccination coverage at the municipality level is observed for the 2022 autumn round (Figure 9.3.7), but overall, coverage is considerably higher than in the 12 to 59 age group. Among individuals aged 60 years and over, vaccination coverage is also relatively low in municipalities along the border between the Netherlands and Germany. This may be explained by people receiving their vaccination in Germany instead of in the Netherlands. These vaccinations are not registered in the Netherlands and, therefore, they are not included in the numerator.

The vaccination coverage of the primary vaccination series and booster vaccination at the municipality level showed quite similar patterns to the repeat vaccination and the 2022 autumn round repeat vaccination, as shown in the regular vaccination coverage reports (primary vaccination series) [4] and the 2021 National Immunisation Programme report [5].

9.3.4.4 Vaccination coverage in the Caribbean part of the Kingdom of the Netherlands

Vaccination coverage among the Dutch Caribbean islands, including non-registered populations on the CAS islands, was highest on Saba for the completed primary vaccination series. As of 2023, 93% of people aged 12 years or over had completed the primary series on Saba (Table 9.3.2). On the remaining islands, the vaccination coverage of the completed primary series ranged between 47% on Sint Maarten and 82% on Bonaire among people aged 12 years or over. The vaccination coverage for the booster was higher than for the subsequent repeat vaccinations in the population aged 60 or over on all islands (Figure 9.3.8). The coverage for the first booster ranged between 91% on Saba and 15% on Sint Maarten, and the coverage for the repeat vaccination ranged between 55% on Saba and <5% on Sint Maarten. During the 2022 autumn repeat vaccination campaign, vaccination coverage for people aged 60 years and over ranged between 31% on Saba and <5% on Sint Maarten and Sint Eustatius (Table 9.3.2).

In general, the vaccination coverage for the repeat vaccinations is lower on all islands (besides Saba), when compared to the vaccination coverage of the primary series on the islands. This is a similar trend to the European part of the Netherlands. This indicates a probable decrease in the willingness in the region to receive additional doses of the COVID-19 vaccine after the primary series despite local efforts to inform target populations.

9.3.5 Determinants for vaccination

RIVM is involved in research into both determinants for the intention for COVID-19 vaccination and determinants for getting vaccinated. Research output for the intention to vaccinate can be found in [3]. Here, the preliminary results of the effect of mobile vaccination units on uptake can also be found. Research output for determinants of vaccination includes a manuscript regarding an ecological analysis at municipal level [6]. Together with Statistics Netherlands (CBS), determinants were also studied at an individual level, both for the uptake of at least one COVID-19 vaccination [7] and for the 2022 autumn repeat vaccination round [8]. The results from this research so far suggest that, apart from age, personal income, socio-economic position, non-Western migration background and political preference are important determinants for vaccination.

9.3.6 Literature

1. Government of the Netherlands. Personal Records Database (BRP) 2022. Available from: https://www.government.nl/topics/personal-data/personal-records-database-brp.
2.* Valk A, *et al.* Vaccinatiegraad COVID-19 vaccinatie Nederland, 2021. RIVM; 2022. Report No.: 2022-0055.
3.* RIVM Corona Gedragsunit. Vaccinatiebereidheid zomer/najaar 2022. Available from: Publicaties Corona Gedragsunit | RIVM.
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5.* Pluijmaekers AJM, de Melker HE. The National Immunisation Programme in the Netherlands. Surveillance and developments in 2021-2022. RIVM; 2022. Report No.: 2022-0042.
6. Labuschagne LJE, *et al.* Neighbourhood sociodemographic factors and COVID-19 vaccine uptake in the Netherlands: an ecological analysis. *BMC Public Health*, accepted or publication.
7. Pijpers J, *et al.* Determinants COVID-19 vaccine uptake in the Netherlands: A nationwide registry-based study. *Vaccines*, accepted for publication.
8. van Roekel C, *et al.* Determinants of COVID-19 booster uptake in the Netherlands, autumn 2022: how well were those at risk for severe disease reached? Submitted for publication.

** RIVM publication.*

9.4 COVID-19 vaccine effectiveness

M.J. Knol, B. de Gier, A. Huiberts, C. Hoeve, S. van Iersel, N. Neppelenbroek, A. Valk, S. de Bruijn, A. Niessen, S. van den Hof, H.E. de Melker, S.J.M. Hahné

9.4.1 Key points

- RIVM uses both vaccine coverage and surveillance data and dedicated studies to monitor vaccine effectiveness (VE) against SARS-CoV-2 infection and transmission, and against severe COVID-19.
- In the February–April 2023 period, the risk of hospitalisation in persons aged 60 years or over who received a bivalent (Omicron BA.1) booster vaccination was 43% lower than in persons who received at least one COVID-19 vaccination, but not a bivalent vaccination. For ICU admission, this was 36%. Since October 2022, the relative risk reduction after bivalent booster vaccination decreased over time.
- VE against COVID-19 mortality estimated between January 2021 and January 2022 was >90% for all age groups shortly after the primary series, and >85% in all age groups shortly after first booster vaccination.
- Between 26 September and 19 December 2022, relative effectiveness of bivalent (Omicron BA.1) booster vaccination against self-reported Omicron SARS-CoV-2 infection was 31% in 18-59-year-olds and 14% in 60-85-year-olds, based on data from the VASCO study.
- Hybrid immunity gave better protection against new Omicron infections than only vaccine-induced or infection-induced immunity. By March 2023, 82% of vaccinated VASCO participants had experienced at least one SARS-CoV-2 infection, i.e. had acquired hybrid immunity.
- In contrast to some other studies, data from two prospective cohort studies by RIVM (LongCOVID and VASCO) did not find evidence of any effect of booster vaccination compared to primary vaccination or no vaccination against long-term symptoms or fatigue after SARS-CoV-2 infection.

9.4.2 Tables and Figures

Figure 9.4.1 Seven-day moving average of the incidence of COVID-19 hospitalisations per 100,000 person days, by vaccination status and age group in the period from July 2022 to June 2023.

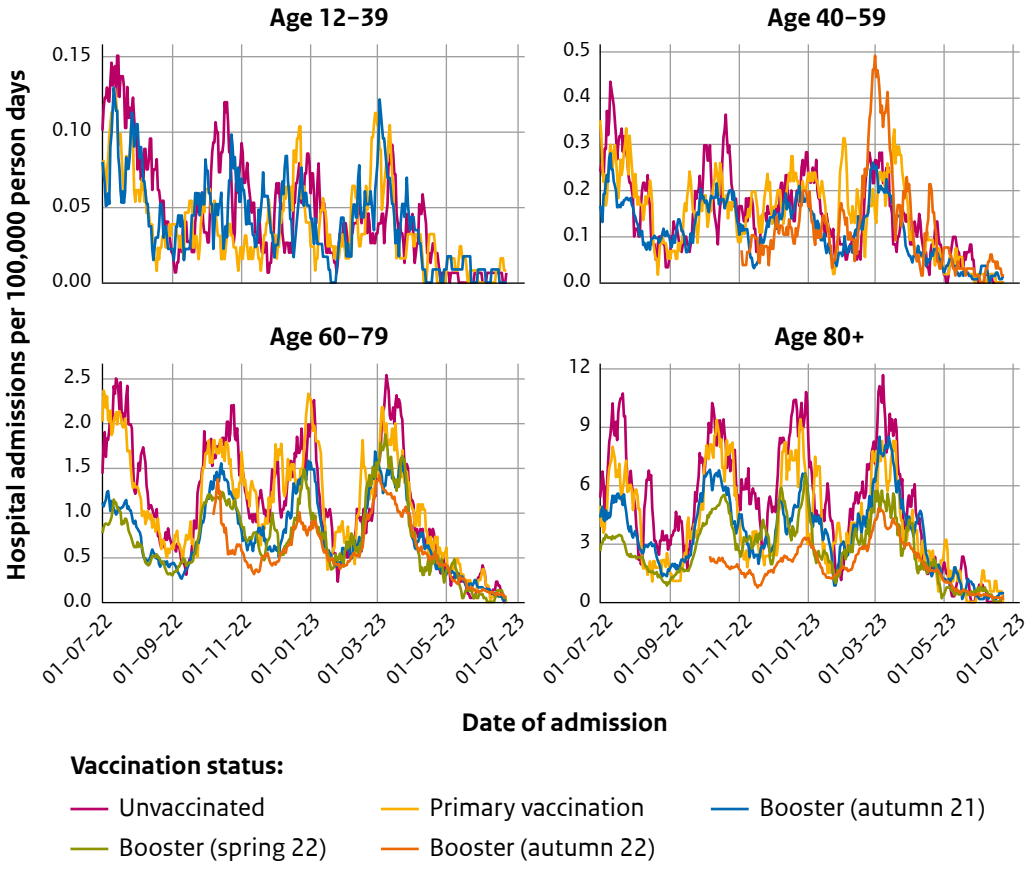
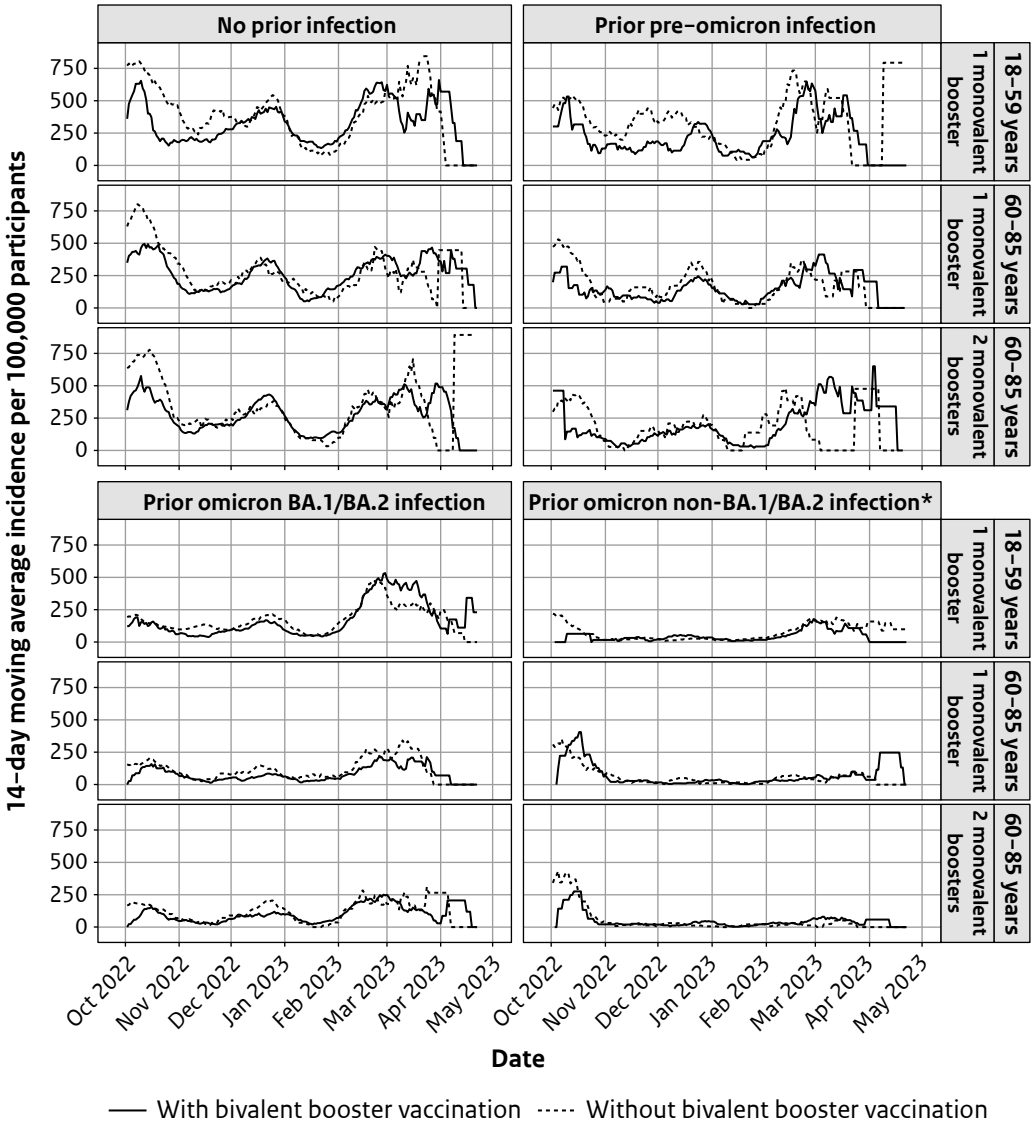
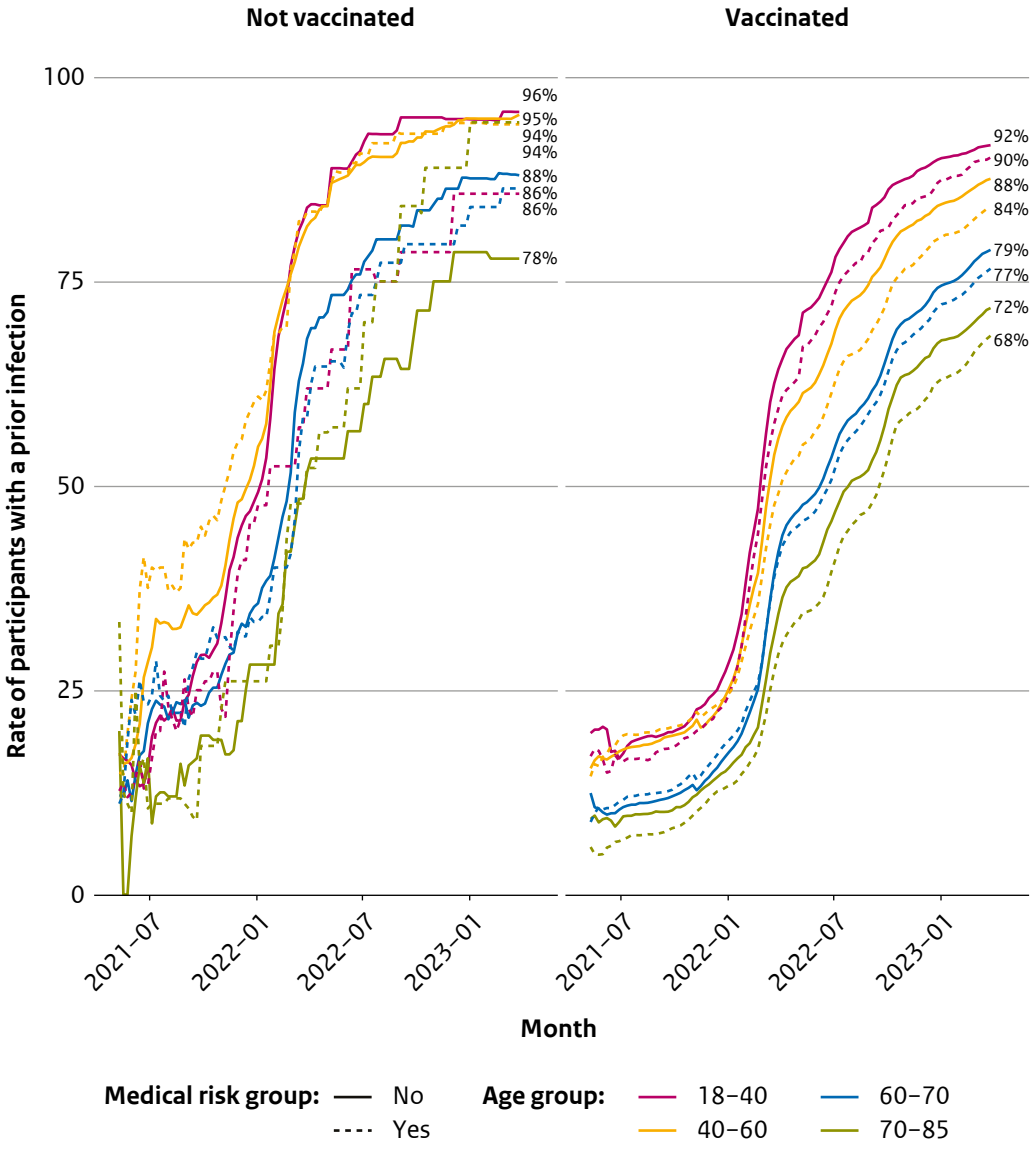


Figure 9.4.2 Fourteen-day moving average of the incidence of SARS-CoV-2 infections per 100,000 VASCO participants, 26 September 2022-30 April 2023.



BA.4, BA.5, BQ.1, XBB, XBF [1]

Figure 9.4.3 Cumulative incidence of SARS-CoV-2 infection among VASCO participants, based on self-reported positive tests or serological evidence of infection by vaccination status, age group and medical risk group, May 2021-March 2023.



9.4.3 Vaccine effectiveness against hospital admission

9.4.3.1 Hospital register data (NICE)

The effectiveness of COVID-19 vaccines against hospital and intensive care unit (ICU) admission is monitored on a monthly basis by enriching the hospital register data (NICE) with data from the central COVID-19 vaccination Information and Monitoring System (CIMS). The association between vaccination status and hospital admission is estimated by means of negative binomial regression adjusted for age and calendar time, yielding relative risks (RR). Vaccine effectiveness (VE) is expressed as (1-RR) * 100%. Due to the increasing importance of infection-induced and hybrid immunity in the risk of severe outcomes in current SARS-CoV-2 infections, VE estimates have increasingly been confounded by previous infections. In other words, the differences in hospitalisations between unvaccinated and vaccinated persons has, over time, become less indicative of the effects of vaccination alone. Therefore, since August 2022, we no longer report VE estimates in reports on COVID-19 hospitalisations by vaccination status. Instead, we present relative risk differences (RRD) to quantify the differences in disease burden between groups with different vaccination statuses. The reports describing RRD in different periods can be found online [2]. Figure 9.4.1describes the incidence of COVID-19 hospitalization in persons with a different vaccination status by age group in the period July 2022 to June 2023.

During the period of June 2022-July 2022 (when Omicron BA.5 variant dominated), persons who received the first booster had a 51% lower risk for hospitalisation than persons who received the full primary series vaccination only (RRD -51% (95% CI -56;-46)) [3]. Persons aged 60 years and over who received a second booster had a 25% lower risk for hospitalisation than persons who received the first booster only (RRD -25% (95% CI -32;-18)). In the period of July 2022-September 2022, the RRD had decreased slightly to a 47% (RRD -47, 95% CI -53;-39) lower risk for hospitalisation for persons who received the first booster, and a 22% (RRD -22, 95% BI -30;-12) lower risk for hospitalisation for persons aged 60+ years who received a second booster [4].

On 19 September 2022, the autumn vaccination campaign started in the Netherlands. People aged 12 years and over were offered a booster vaccination with a bivalent vaccine targeting the Omicron BA.1 strain and the original SARS-CoV-2 strain. People aged 60 years and over, and people with a medical risk condition were actively invited (see paragraph 9.2.4.1). Since 19 September 2022, we have described the RRD for a bivalent booster vaccination compared to receipt of at least one COVID-19 vaccination, which is not a bivalent vaccination. In the period of October-November 2022, the RRD for persons aged 60 years and over was -63% (95% CI -68; -58) against hospitalisation and -55% (95 CI -76; -14) against ICU admission [5]. Over time, the RRD slowly decreased. In the March-May 2023 period, the RRD for persons aged 60 years and over was -42% (95% CI -46; -37) against hospitalisation and -45% (95% CI -61; -22) against ICU admission [5]. In the age group of 40-59 years, the RRD also decreased over time and in the March-May 2023 period, it was lower than in persons aged 60 years and over (16% (95% CI -14 – 55) against hospitalisation and -12% (95% CI -65 – 122) against ICU admission). The RRD for persons aged 40-59 years might be underestimated because the group that received a bivalent booster vaccination in the autumn round is more likely to have an underlying condition than the group that did not receive a bivalent booster vaccination [6].

9.4.3.2 VECTOR study

In a test-negative case-control study, detailed information was collected from patients hospitalised with respiratory symptoms in nine hospitals [7]. VE against hospitalisation was assessed, adjusting for underlying comorbidities. In addition, VE was assessed in several subgroups. Data was collected from both the Alpha-dominant period (1 March to 5 July 2021) and the Delta-dominant period (1 October 2021 to 29 January 2022). A total of 1211 patients was included in the study, of whom 614 were admitted during the Alpha-dominant period (335 COVID-19 cases and 277 controls) and 612 during the Delta-dominant period (365 COVID-19 cases and 234 controls). VE was calculated by means of multivariable logistic regression adjusted for calendar week, sex, age, comorbidity, and nursing home residency. The VE during the Delta period was 78% for primary vaccination (95% CI 65-86) and 89% for booster vaccination (95% CI 69-96). During the Delta period, VE for primary vaccination decreased from 76% (95% CI 22-93) at 3-6 months after vaccination to 62% (95%CI 32-78) at 6-9 months after vaccination. VE was lower in patients aged >60 years, and in patients with malignancy, chronic cardiac condition and immune deficiency.

9.4.3.3 Averted hospitalisations by vaccination

From 6 January 2021 to 30 August 2022, an estimated 98,170 hospitalisations were averted by COVID-19 vaccination [8]. Of these, 90,753 were averted in the subperiod from 2 August 2021 to 30 August 2022, when all adults had the opportunity to at least complete their primary series. These estimates represent 57.0% and 67.9%, respectively, of all estimated hospital admissions. The estimates are made for different age groups using calendar-time-specific vaccine effectiveness (VE) estimates and vaccine coverage by vaccination campaign (primary series, first booster and second booster). The estimated number of averted hospitalisations was highest for the age group of 70-79 years, both absolutely (32,483, of which 30,268 in the subperiod) and relative to observed hospitalisations (63.5% from the beginning of the vaccination campaign and 73.3% in the subperiod). The lowest numbers were observed for the age group of 12-49 years: 7607 (37.3%) estimated averted hospitalisations, of which 7255 (49.9%) in the second study period. Furthermore, the largest number of hospitalisations was averted during the Delta period, both in absolute (57,395) and relative (72.3%) terms. COVID-19 vaccination prevented a considerable burden of morbidity by reducing the number of COVID-19 hospitalisations.

9.4.4 Vaccine effectiveness against death

Previously, we described preliminary results from a population-wide linkage study on COVID-19 vaccine effectiveness against death [9]. We updated these analyses with an adjustment for a medical risk group, which resulted in higher VE estimates. 'Medical risk group' was defined as either high-risk, as defined by the Health Council of the Netherlands, on the basis of conditions associated with high risk for severe COVID-19; intermediate-risk, defined as eligibility for influenza vaccination in the Netherlands due to a chronic condition; and low-risk, defined as not meeting the criteria for high or intermediate-risk. In the study period of January 2021-January 2022, VE against death from COVID-19 was estimated by means of Cox proportional hazards regression with calendar time as the underlying time scale, vaccination status as time-dependent exposure, and unvaccinated person-time as reference. All analyses were stratified on the basis of long-term care use and age group. Sex, year of birth, medical risk group and country

of origin were included as covariates in the models. Two months after completion of the primary series, VE against COVID-19 mortality was >90% for all age groups. Subsequently, VE gradually decreased to around 80% at 7-8 months' post-primary series for most groups, and around 60% for elderly receiving a high level of long-term care and for people aged 90+ years. Following a first booster dose, the VE increased to >85% in all groups.

9.4.5 Vaccine effectiveness against mild disease / infection

9.4.5.1 VAccine Study COvid-19 (VASCO)

VE against self-reported positive SARS-CoV-2 test during the period of 12 July 2021-6 June 2022, when the Delta and Omicron variants were dominant, was estimated by means of Cox proportional hazard models with vaccination status as time-varying exposure and calendar time as underlying timescale [10]. Estimates were adjusted for age, sex, educational level, and medical risk condition. Participants who reported a prior SARS-CoV-2 infection or showed serological evidence of previous infection were excluded from the analysis. A total of 37,170 VASCO participants with a mean age of 57 years and a median follow-up time of 28 weeks were included in the analysis. Adjusted VE in the Delta period decreased from 80% (95%CI 69-87) <6 weeks after completing the primary series to 71% (95%CI 65-77) at 18-23 weeks after completion of the primary series and increased to 96% (95%CI 86-99) at <6 weeks after booster vaccination. In the Omicron period, these estimates were 46% (95%CI 22-63), 25% (95%CI 8-39) and 57% (95%CI 52-62), respectively; VE decreased to 31% (95%CI 17-44) at 18-23 weeks after booster vaccination. For participants of ≥60 years, the VE against Omicron infection within 6 weeks after the second booster vaccination was 50% (95% CI 34-62). In a sensitivity analysis restricted to participants with a high intention to test in case of symptoms (n=26,520, median age = 61), VE estimates showed a similar pattern, although VE estimates for Omicron infection were 5-17 percentage points higher in this specific population. VE estimates against Omicron infection stratified by vaccine product were generally higher for Spikevax as the primary series and lower for Vaxzevria and Jcovden compared to Comirnaty. VE estimates for Spikevax as a booster were generally higher compared to Comirnaty as a booster, irrespective of the vaccine product of the primary series. Despite large confidence intervals, VE against Omicron infection appeared lower among participants with a medical risk condition than among participants without, which is visible both in younger and older individuals.

We restricted our analysis on VE against Delta and Omicron infection in 37,170 VASCO participants to symptomatic infections only, reducing the number of infections from ~13,000 to ~9000. The analysis showed slightly higher VE estimates for both the Delta and Omicron period compared to when all reported infections were included. VE of the primary series against Delta symptomatic infection decreased from 85% (74-91) within 6 weeks after primary series to 77% (70-82) at 18-23 weeks after the primary series. VE within 6 weeks after the primary series against Omicron symptomatic infection was 57% (25-75) and decreased to 29% (6-47) at 18-23 weeks after the primary series. VE increased to 59% (52-65) at <6 weeks after booster vaccination and decreased to 41% (24-54) at 18-23 weeks.

We analysed the protective effect of previous infections, vaccinations and hybrid immunity (i.e., at least one vaccination and at least one previous infection) on Omicron infection, between 10 January 2022 and 1 September 2022, among 43,257 participants of the VASCO cohort [11]. Of 20,418 SARS-CoV-2 infections in the study period, 89.2% was reported by the participant as a positive test, and 10.8% was detected only by seroconversion or 4-fold increase in Nucleoprotein-antibodies, based on 6-monthly serum samples. Cox proportional hazard models were used with SARS-CoV-2 infections and COVID-19 vaccinations as time-varying exposures, calendar time as underlying time scale and adjustment for age, sex, medical risk condition and educational level. We found a relative reduction of 71-85% in Omicron infection in weeks 4-10 post-last event with hybrid immunity compared to vaccine-induced immunity, for participants with 2, 3 or 4 prior immunising events (vaccination or previous infection). Differences in risk of infection were partly explained by differences in anti-Spike RBD (S) antibody concentration: differences in S-antibody concentrations showed a similar pattern to differences in risk of infection, although with smaller differences between vaccine-induced and hybrid immunity for antibody concentrations than for risk of infection. Compared to the lowest quartile, participants in subsequent quartiles of S-antibody concentrations had 19%, 35% and 71% reduced risk of infection, respectively. Among participants with hybrid immunity with one previous pre-Omicron infection, there was no relevant difference in risk of Omicron infection by sequence of vaccination(s) and infection. Regardless of the type of previous immunising events, additional events increased the protection against infection, but not above the level of the first weeks after the previous event. In conclusion, our results show that hybrid immunity is more protective against infection with Omicron than vaccine-induced immunity, up to at least 30 weeks after the last immunising event. Among participants with hybrid immunity, the sequence and number of immunising events were not found to be of importance, and its protective effect was partly explained by circulating S-antibodies. In our population with a high level of immunity, additional immunising events reduced risk of infection with Omicron variants only temporarily.

Effectiveness of bivalent original/Omicron BA.1 vaccination relative to receiving the primary vaccination series and one or two monovalent booster vaccinations against self-reported Omicron SARS-CoV-2 infection was estimated by means of Cox proportional hazard models with calendar time as the underlying timescale and bivalent vaccination as the time-varying exposure [12]. Estimates were adjusted for age group, sex, education level, presence of a medical risk condition, and infection history. 32,542 VASCO participants were included in the analysis. Between 26 September and 19 December 2022, relative effectiveness against self-reported Omicron SARS-CoV-2 infection was 31% (95% CI: 18-42) in 18-59-year-olds and 14% (95% CI: 3-24) in 60-85-year-olds. In both age groups, relative protection from a prior Omicron infection with or without bivalent vaccination was substantially higher (80-83%). When extending the study period up to 30 April 2023, relative effectiveness against self-reported SARS-CoV-2 infection was 19% (95% CI: 12-26) in 18-59-year-olds and 10% (95% CI: 3-16) in 60-85-year-olds. VE decreased over time since bivalent vaccination, explaining the lower VE in the extended study period. No differences in VE were observed between those with and without a medical risk condition in 18-59-year-olds (18% vs 19%) and 60–85-year-olds (10% vs 9%). Incidence was lowest among participants with a prior Omicron BA.5, BQ.1 or XBB

infection (Figure 9.4.2). Protection against a self-reported Omicron SARS-CoV-2 or a prior Omicron BA.5, BQ.1, or XBB infection (since June 2022) with or without bivalent vaccination was high in both 18-59-year-olds (89-91%) and in 60-85-year-olds (83-88%).

Because of the importance of hybrid immunity (i.e. immunity through vaccination and infection) in the protection against new infection, we assessed the cumulative SARS-CoV-2 infection incidence among VASCO participants on the basis self-reported positive SARS-CoV-2 tests and serological evidence of infection (antibodies against the nucleoprotein) by age and medical risk group. By March 2023, 82% of the vaccinated participants and 93% of the unvaccinated participants had experienced at least one SARS-CoV-2 infection (Figure 9.4.3). By 27 March 2023, the cumulative infection incidence was lower in older age groups (for participants aged 40-60 years OR: 0.65 95%CI: 0.58-0.73; for participants aged 60-70 years OR: 0.38 95%CI: 0.34-0.42; for participants aged 70-85 years OR 0.25 95%CI: 0.22-0.28 compared to participants aged 18-40 years) and was lower among participants with medical risk conditions (OR: 0.85 95%CI: 0.80-0.90).

9.4.5.2 Long-term care facilities

Persons living in long-term care facilities (LTCFs) are not tested in community testing facilities and are generally not hospitalised when having COVID-19. Therefore, they are not well represented in surveillance data monitoring VE. Data was collected on SARS-CoV-2 outbreaks to estimate disease severity and VE in collaboration with GGD Twente and the SNIV (Surveillance Netwerk Infectieziekten Verpleeghuizen) network. Twenty-eight outbreaks in LTCF were included with onset date of the first case between January and March 2022 (Omicron period). A total of 333 residents were exposed in these 28 outbreaks, and 183 SARS-CoV-2 infections (attack rate 55%) were reported. Among 183 residents with an infection, 13 (7%) needed oxygen and 3 (2%) died. For VE analyses, data from 21 outbreaks was included where vaccination status of all residents was known. Of 258 exposed residents, 97% was vaccinated, of whom 14% only received the primary series and 86% received the primary series and a booster vaccination. The attack rate among unvaccinated residents was 83% (5/6); this was 42% (15/36) among residents with only primary vaccination, and 59% (127/216) among residents with a booster vaccination. This resulted in a crude VE of 50% (95% CI 15-70) for primary vaccination only and 29% (95% CI –3-52) for booster vaccination. VE against severe disease (need of oxygen or death) could not be calculated because of low numbers. Compared with a similar analysis during the Delta period [13], severity of infection was clearly lower during the Omicron period despite a similarly high attack rate.

9.4.6 Vaccine effectiveness against transmission in case of infection

Following infection, VASCO participants were invited to complete a questionnaire on infections in their household. With this data, we can determine the transmission rate of SARS-CoV-2 in the household and the effects of vaccination on transmission. If the participant was the first infected case in the household, we followed the household members for infections from the second day after the index case date until fourteen days after. Only household members that were known to have done a (self-)test were included in the analysis. Using logistic regression, we estimated the VE against transmission, adjusting for age of the index case and household

members, calendar week, vaccination status of the contact and household size. Generalised estimating equations were used to control for dependencies within the household. Questionnaires submitted before 14 March 2023 were included. Analyses were stratified by Delta- and Omicron-dominant periods. Overall, 4387 index cases and 5198 contacts were included in the analysis. The median age was 61 (IQR: 51-65) for index cases and 58 (IQR: 37-66) for household members. During the Delta period, the VE of primary vaccination against transmission was 64% (95% CI: 15% to 84%); VE of booster vaccination in the Delta-dominant period was very uncertain due to low numbers. In the Omicron period, VE against transmission was higher with each additional dose, although the differences were small and the confidence intervals were wide: 49% (95% CI: -4% to 75%) for the primary series, 64% (95% CI: 32% to 81%) for the first booster, 67% (95% CI: 35% to 84%) for the second booster and 70% (95% CI: 33% to 86%) for the third booster.

9.4.7 Vaccine effectiveness against long COVID

9.4.7.1 LongCOVID study

The RIVM LongCOVID-study investigated the effect of vaccination prior to Omicron SARS-CoV-2 infection on symptom prevalence and severity in adult COVID-19 cases three months after infection [14]. Omicron cases were defined as such if they enrolled within seven days of a positive test between 3 January 2022 and 31 May 2022. During this period, at least 85% of detected SARS-CoV-2 in the Dutch pathogen surveillance concerned the BA.1 and BA.2 Omicron variant. There were too few unvaccinated or partially vaccinated cases in the cohort to analyse the difference between vaccination and no vaccination. Therefore, the added value of a booster vaccination was assessed, by comparing cases with only a complete primary vaccination course (n = 2970) to cases that had received a booster (n = 853), using permutation tests with stratification for the possible confounders age, sex, level of education and number of comorbidities. Severe fatigue (21.0% versus 23.1%) and severe dyspnea (10.9% versus 13.2%) seemed less prevalent in cases with a booster three months after their Omicron infection than in cases with a primary course, but the differences were not significant. Additionally, the prevalence of at least one possible post-COVID condition-related symptom (i.e. fatigue, dyspnea, problems with a busy environment and with memory or brainfog) was comparable between boostered cases (27.4%) and primary course cases (28.8%). There are other studies, however, that did find a lower number of symptoms in boostered cases three to six months following infection compared to cases with two vaccination doses, though evidence for a protective effect of an additional dose is not conclusive.

9.4.7.2 VAccine Study COvid-19 (VASCO)

Fatigue is one of the most commonly reported and debilitating long-term symptoms that can occur after SARS-CoV-2 infection. In VASCO, fatigue was measured at inclusion and every three months during follow-up by means of the Checklist Individual Strength (CIS; range 8-56, norm population average of 23). We assessed the prevalence and course of long-term fatigue after a SARS-CoV-2 infection by age, sex, SARS-CoV-2 variant and vaccination status. We included participants with a first positive SARS-CoV-2 test during the period from May 2021 to April 2023 and at least one CIS measurement 14-90 days pre-infection and 0-300 days post-infection.

Absolute differences between latest pre-infection and each post-infection CIS score were calculated. (Differences in) CIS scores and probability of severe fatigue (CIS score ≥35) were estimated as a function of time from positive tests (spline, 30 knots) on the basis of generalised additive models. A total of 23,849 participants (mean age 56.2) were included, with 22,699 pre-infection and 45,667 post-infection CIS questionnaires. The majority of the reported positive tests were attributed to Omicron (94.9%). Estimated within-person increase in CIS score at 3, 6 and 9 months post-Delta infection was 3.1 (0.8-1.5), 3.1 (0.8-5.4) and 2.7 (0.0-5.4), respectively. For Omicron infections, this was 0.8 (0.1-0.5), 0.1 (-0.3-0.4) and 0.4 (0.0-0.8). No significant differences were observed in changes in CIS score post-infection by sex and age group. Increase in CIS-score at 3, 6 and 9 months post-infection was 0.6 (-0.7-1.8), -0.1 (-1.4-1.2) and -0.4 (-1.7-0.9) for unvaccinated participants, 0.7 (0.1-1.4), 0.0 (-0.7-0.8), and 0.2 (-0.7-1.0) for primary vaccinated participants, and 0.9 (0.6-1.2), 0.1 (-0.3-0.5) and 0.5 (0.0-0.9) for boostered participants, respectively. For Delta infections, the proportion of severely fatigued was 16% (11-22%) pre-infection, and 24% (20-28%), 26% (20-33%), and 23% (16-31%) at 3, 6 and 9 months post-infection, respectively. For Omicron infections, the estimated proportions were 16% (15-18%), and 19% (18-20%), 18% (17-19%), and 20% (19-22%). In conclusion, participants with a Delta infection had a higher increase in fatigue scores at 3 and 6 months post-infection compared to participants with an Omicron infection. In contrast to some other studies, we did not find evidence of an effect of prior vaccination on long-term fatigue at 3 to 9 months post-infection.

9.4.8 International research

Several online resources are available that provide collections and/or summaries of international literature on COVID-19, including the effectiveness of COVID-19 vaccination. Examples are LitCovid (containing articles from PubMed, categorised by research topic) [15], EPPIcentre (a living map of research articles on COVID-19) [16] and the COVID-19 rapid reviews conducted by the UK Health Security Agency (UKSHA) [17]. To monitor VE estimates in the grey, preprint, and published literature, RIVM uses results of an ongoing systematic search by the International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health and the World Health Organization. They publish updated summary tables with the findings of COVID-19 vaccine effectiveness and impact studies on a weekly basis [18]. In addition, RIVM performs a weekly search in Embase.

9.4.8.1 Vaccine effectiveness against severe disease

International studies show that receiving a fourth monovalent COVID-19 vaccine dose restores the effectiveness against hospitalisation during the Omicron predominant period [17, 19-28]. In November 2022, the UKHSA reported a VE of 59% at 2-4 weeks after receiving a fourth dose, compared to receiving a third dose at least 6 months before [29]. The VE decreased over time to 19% after 15 weeks and to 11% after 20+ weeks.

The first results on VE of a bivalent booster were available from December 2022 and indicated an increased protective effect for severe disease [24, 30-36]. For example, a Scandinavian retrospective study (country combined) among persons aged 50 years and over who had received three monovalent COVID-19 vaccines showed a VE against hospitalisation of the

BA.4/5 bivalent booster of 81% (95%CI 69,5%-91,5%) and of the BA.1 bivalent booster of 74% (95% CI 68,6%-79,4%)[32]. Other studies reported lower VE estimates in the 50%-69% range [30, 31, 33]. Waning of the effectiveness was shown 10+ weeks after receiving the bivalent booster [37]. A paper by the CDC indicated that the relative effectiveness of the bivalent booster is higher when the period between receiving the last monovalent booster and receiving the bivalent booster is longer [38]: they reported a VE against hospitalisation of the bivalent BA.4/BA.5 booster in persons aged 65 years and over with at least 2 monovalent vaccines of 73%, 78% and 83% compared to persons who received their last monovalent vaccine ≥2 months, 6-11 months, and ≥12 months ago, respectively.

VE against COVID-19 mortality was high after the primary series (>90%, although lower in the highest age groups) [39-41], but waning was seen over time [40-44]. VE after booster vaccination was estimated to be around 90% [45, 46]. In a study by the WHO, a total of 469,186 deaths were estimated to be directly averted by COVID-19 vaccination in persons aged 60 years and over between December 2020 and November 2021 in 33 European countries, which was 51% of the expected deaths, although impact ranged highly between countries [47].

9.4.8.2 Vaccine effectiveness against mild disease / infection

Previously, we mentioned that the VE against infection with the Omicron BA.1 and BA.2 variant appeared to be lower compared to previous variants and that the protection waned over time [9]. Similar results are found for the VE against infection with the Omicron BA.4 and BA.5 variant [37]. On 6 April 2023, the UK HSA reported consensus estimates of relative VE against BA.4, BA.5, BQ.1 and CH1.1 Omicron infection for a booster dose compared to 6+ months since the last dose (at least two doses). They found that 0-1 month after a monovalent or bivalent booster dose, VE estimates against infection were around 30% (95% CI 20 – 40) [37]. After 2-3 months, the VE estimates decreased to around 20% (95% CI 10 – 30), and after 4-6 months, to approximately 10% (95% CI 0 – 20). The estimates were not stratified according to monovalent or bivalent vaccine.

International literature shows the BA.4/BA.5 bivalent vaccine to be associated with a lower risk of infection than in people who have not received a BA.4/BA.5 bivalent vaccine, although it is a small difference. The VE against infection for the BA.4/BA.5 bivalent vaccine ranged between 8% and 29% 7 days or more after bivalent booster vaccination [48-51]. The dominant variants in circulation in the referenced studies were BA.4/BA.5, and BQ and XBB subvariants.

9.4.8.3 Vaccine effectiveness against transmission

There have been several studies on the VE against transmission during the Omicron period. The VE against Omicron transmission to household contacts for a booster dose has been reported by a few studies. The VE estimates from 2 European studies vary between 1% and 12% [52, 53]. Both studies used contract tracing data and excluded history of COVID-19 in their data-analysis. The results of the study from Norway [53] should be interpreted with caution, as they were not able to adjust for age or for time since vaccination. A study from South Korea estimated the VE of a booster vaccination compared to unvaccinated cases against Omicron-transmission at 78% [54]. Results from studies investigating VE against Omicron transmission

to close contacts in a non-household setting for a booster dose range from 24% to 44% [52, 55-57]. Available data indicates a small, but significant effect of a booster vaccination against Omicron transmission. In their COVID-19 vaccine surveillance report from January 2023, the UKHSA stated that there is insufficient data for a consensus VE estimate against transmission for a booster dose [31].

9.4.8.4 Vaccine effectiveness against long COVID

Most studies that assessed the effect of vaccination (two doses) prior to infection showed that vaccinated cases were less likely to develop symptoms of long COVID than unvaccinated cases [58]. Studies before 2022 were generally retrospectively designed, while later studies were more often prospective. All studies were very heterogeneous in terms of study size (varying between max. 1000 to >10,000) and definition of long COVID. Published papers on the effect of booster vaccination on long COVID in the Omicron period report varying results. For example, a recently published preprint suggests that the booster vaccination was associated with fewer and less persistent symptoms, compared to primary vaccination and no vaccination [59], while another paper reports no difference in the prevalence of long COVID symptoms with respect to the number of received vaccines during the Omicron period [60].

9.4.9 Literature

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* *RIVM publication.*

9.5 Seroepidemiology of SARS-CoV-2 in the Netherlands

E.R.A. Vos, M.K. Verheul, C.E. Hoeve, C.C.E. van Hagen, J. Kaczorowska, D. Wong, M.I. Hofstee, R.S. van Binnendijk, F.R.M. van der Klis, M.J. Knol, G. den Hartog, H.E. de Melker

9.5.1 Key points

- Overall infection-induced seroprevalence in the Dutch population (as estimated from the nationwide PIENTER Corona (PICO) serosurveillance study) rose from 26% in November 2021 (during Delta) to 62% in March 2022 (following the emergence of Omicron). A relatively rapid increase in infections was observed in those aged <60 years (including the very youngest), and this was also reflected by large proportions of breakthrough infections among the vaccinated. At the same time, the total seroprevalence (i.e. including vaccine-induced antibodies) increased from 87% to 96%, and remained high all year.
- As control measures were eased in 2022, infection rates between regions and groups became comparable. Overall infection-induced seroprevalence increased to 74% in June 2022, with the steepest rise observed in persons >40 years, and to 86% in November 2022, with relatively similar increases among adults. At this point in time, the majority of the population had acquired hybrid immunity, while only some minor proportions of the oldest age groups had not been infected.
- In the PICO study in June 2022, 93% was positive for respiratory mucosal spike S1 IgG, while 24% was positive for IgA. Children aged <12 years (mostly unvaccinated) had the lowest prevalence and concentrations. Participants with a known history of infection had a significantly higher prevalence and levels of mucosal anti-S1 IgG and especially IgA, compared to those without evidence of infection. Higher levels of mucosal anti-S1 IgG, and especially IgA, reduced the probability of infection within the next six months.
- Nearly all participants in the nationwide Vaccine Study Corona (VASCO) were anti-S1 IgG seropositive following the primary series and first booster, and all were seropositive following the second booster. The early response to the primary series varied significantly between vaccine products, with the highest anti-S1 IgG concentrations evident in Spikevax recipients as well as in those participants with a previous infection, while concentrations were lower in the age group of 60-85 years and in the medical risk group for both Comirnaty and Spikevax. Differences in early response of anti-S1 IgG between vaccine products nearly diminished following the first, and completely diminished following the second booster.
- Furthermore, following the primary series with Vaxzevria, S1-specific antibodies waned faster among those in the medical risk group. Waning was faster in the older age group following a primary series with Comirnaty, and slower in the same age group following a primary series with Spikevax. Waning was slower in the age group of 60-85 years following the first booster and was not affected by medical risk following the first or second booster.

9.5.2 Tables and figures

Figure 9.5.1 Number of participants in the PIENTER Corona (PICO) study after the final sampling (in the sixth study round, November 2021), by municipality.

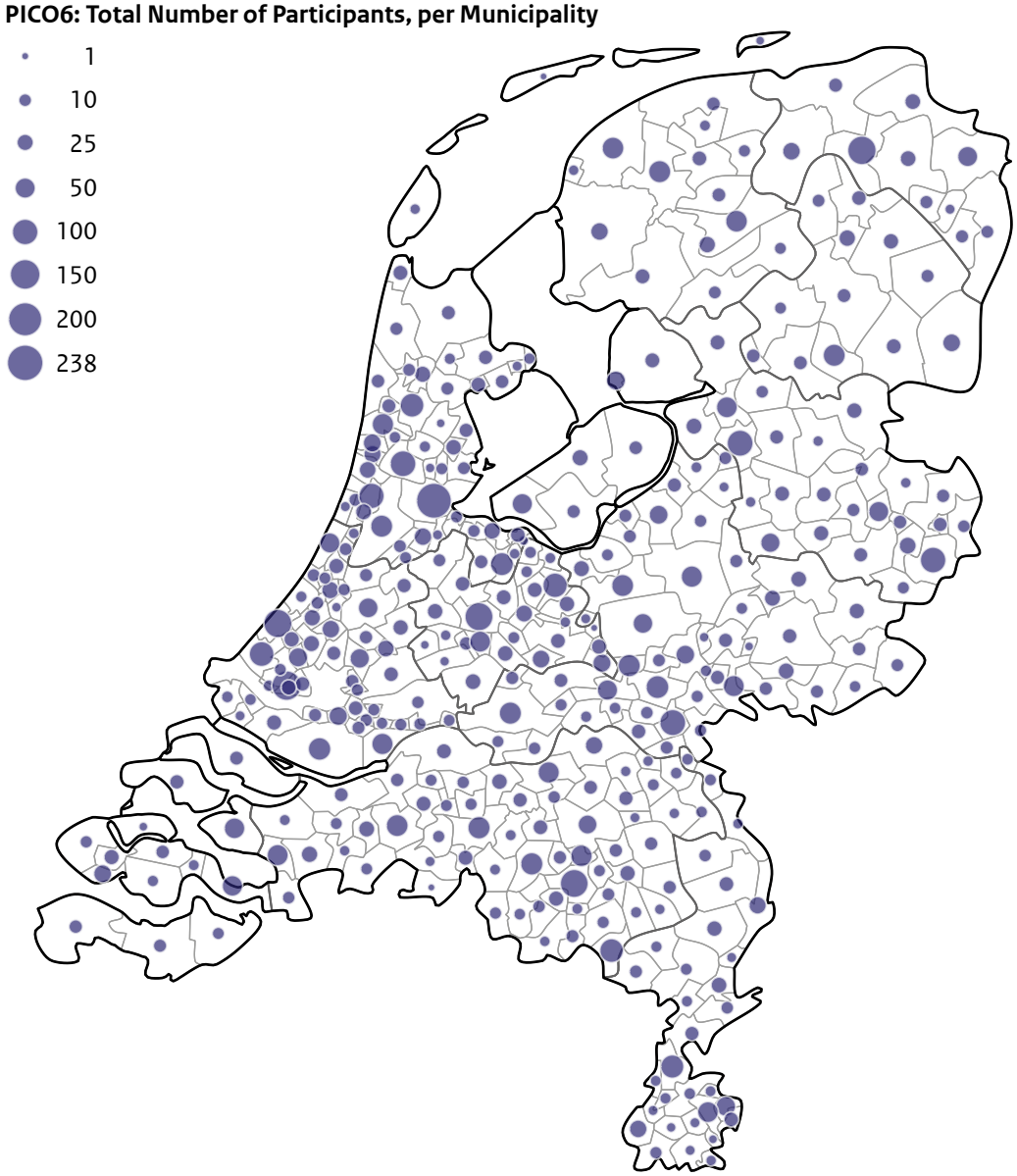


Figure 9.5.2 (continues on the next page) Weighted SARS-CoV-2 infection-induced (dashed lines) and total (i.e. infection and/or vaccination) (solid lines) seroprevalence (with 95% confidence intervals) in the general population of the Netherlands in 2021 (A) and 2022 (B) (following the PIENTER Corona study rounds 4 to 9), by age (years).

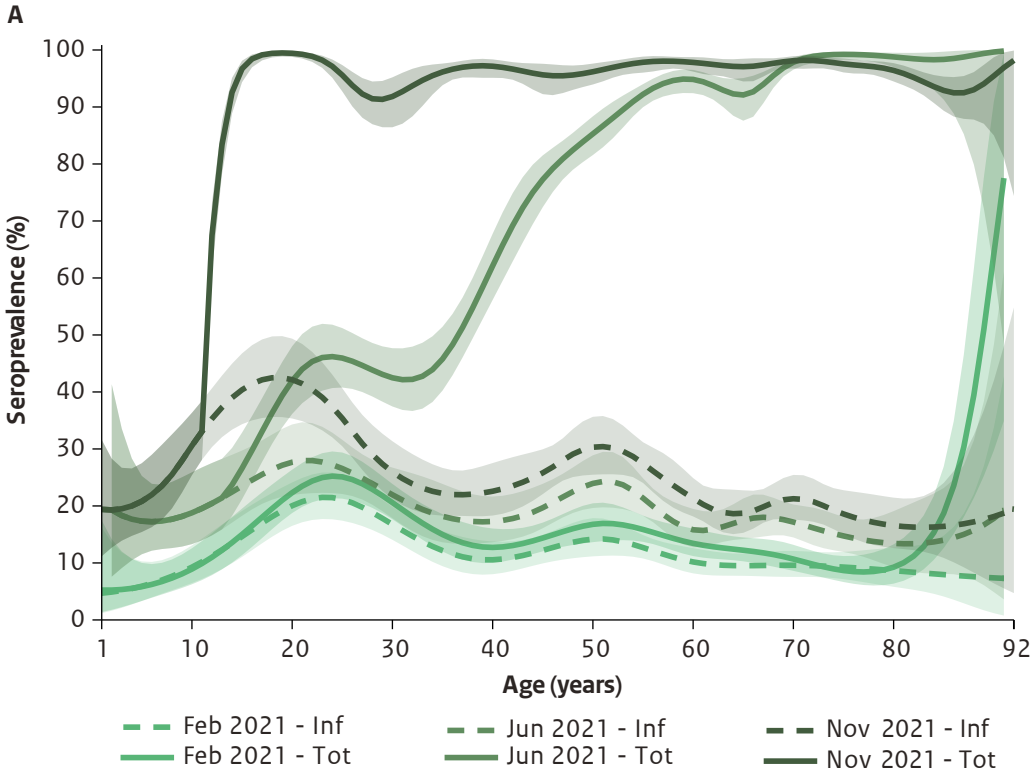


Figure 9.5.2 (continued) Weighted SARS-CoV-2 infection-induced (dashed lines) and total (i.e. infection and/or vaccination) (solid lines) seroprevalence (with 95% confidence intervals) in the general population of the Netherlands in 2021 (A) and 2022 (B) (following the PIENTER Corona study rounds 4 to 9), by age (years).

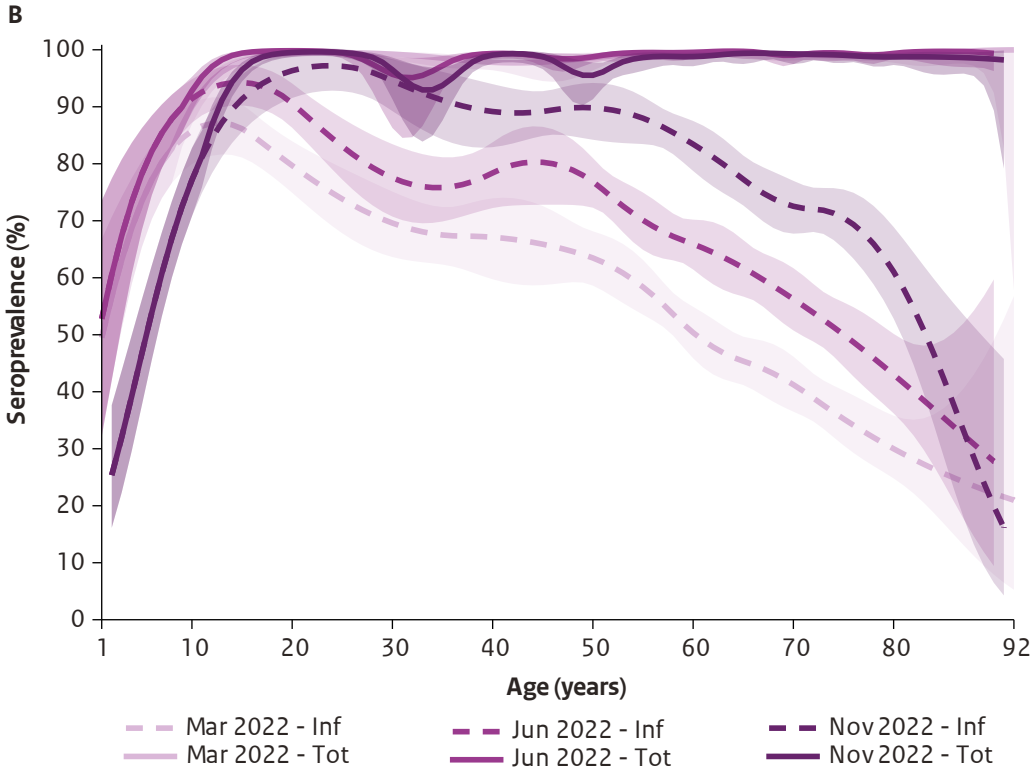


Figure 9.5.3 SARS-CoV-2 mucosal anti-S1 IgG (A) and IgA (B) prevalence (with 95% confidence intervals (CI)) in a subset of randomly-selected (age-stratified) PIENTER Corona participants, in June 2022 (study round 8), by age (years) and infection status. SARS-CoV-2 mucosal anti-S1 IgG (C) and IgA (D) concentration (in binding antibody units (BAU) and arbitrary units (AU) per mL, respectively) (with 95% CIs), by age and infection status. The horizontal dashed lines (in C and D) represent the cut-offs for seropositivity.

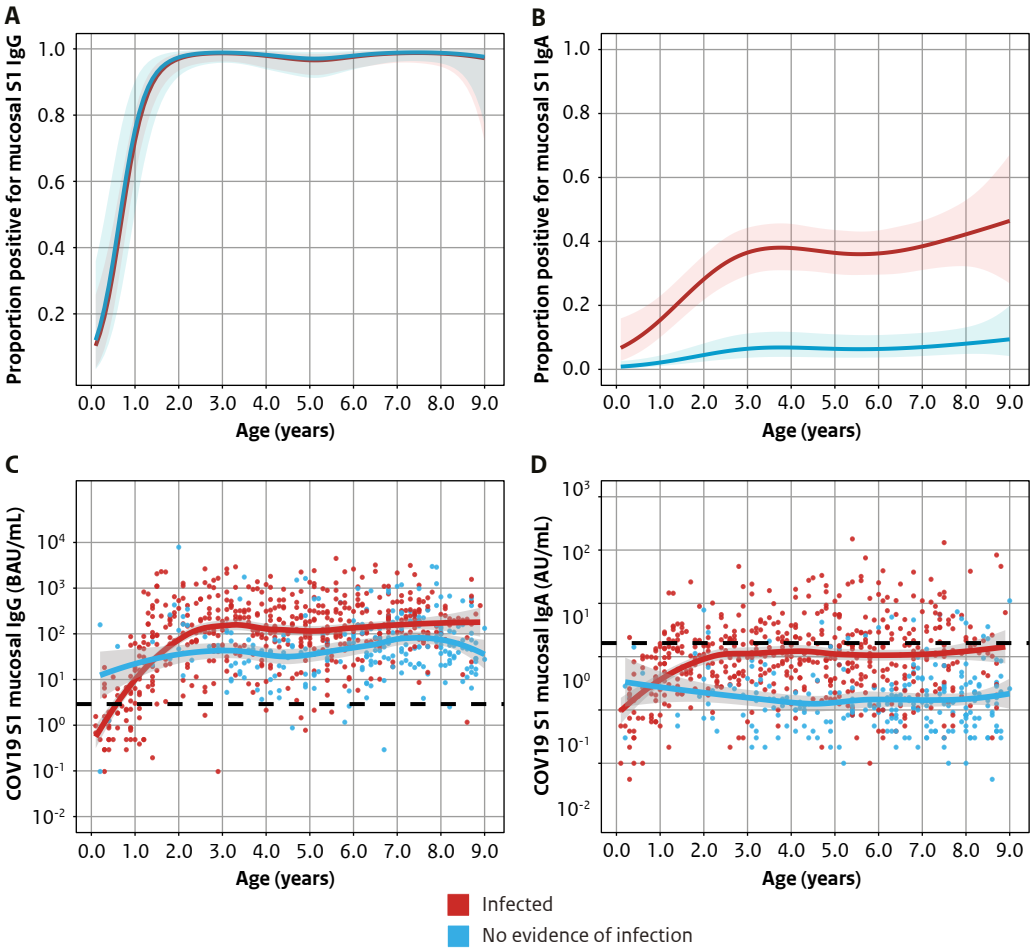


Figure 9.5.4 Predictors of future SARS-CoV-2 infection following analyses in the PIENTER Corona study (rounds 8 and 9). A. Importance of mucosal antibody levels and other predictors of infection within six months after the mucosal sample collection, following random forest analysis (highest most important, lowest less important). Influence of mucosal anti-S1 IgG (B) and IgA (C) concentration (in binding antibody units (BAU) and arbitrary units (AU) per mL, respectively) on the probability of infection within six months after the mucosal sample collection, following a simple quasibinomial model with mucosal antibody levels as the only predictor. The probability values (depicted by the scatterplot of the graph) (with 95% confidence intervals) were obtained by running the random forest model on the test dataset.

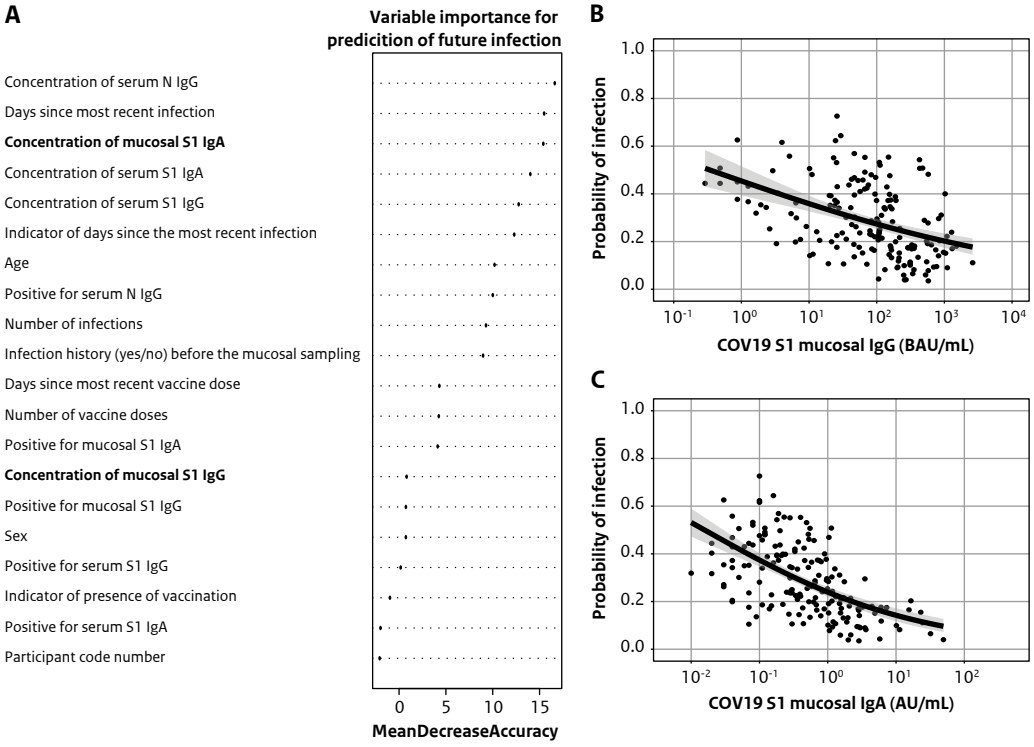


Figure 9.5.5 Measured Ig levels in the Vaccine Study Corona (VASCO) 14 to 42 days following vaccine administration, by vaccine product, dose, prior infection status, age group and medical risk group*. Black lines represent geometric mean concentrations and 95% confidence intervals. The dashed red lines represent the cut-off for seropositivity. Groups with <5 observations were excluded.

* Including absence of spleen, diabetes, cardiovascular disease, immune disorder, cancer with current or no treatment, lung disease or asthma, hepatic disease, neurological disease, renal disease, organ or bone-marrow transplant.

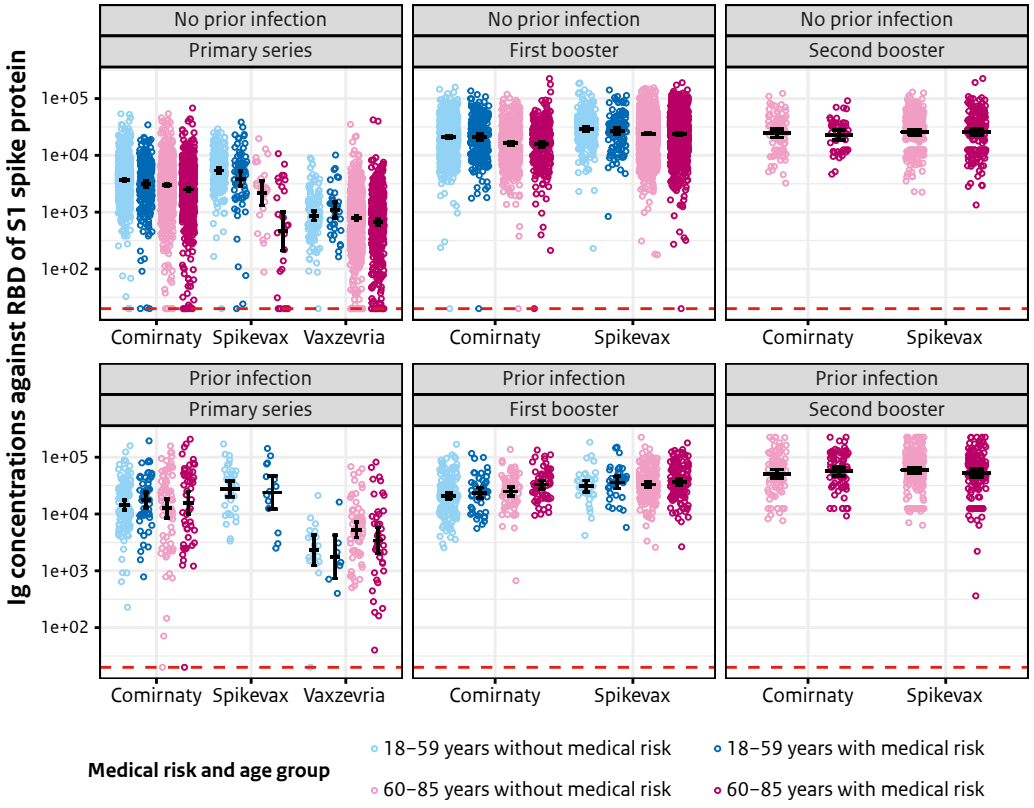
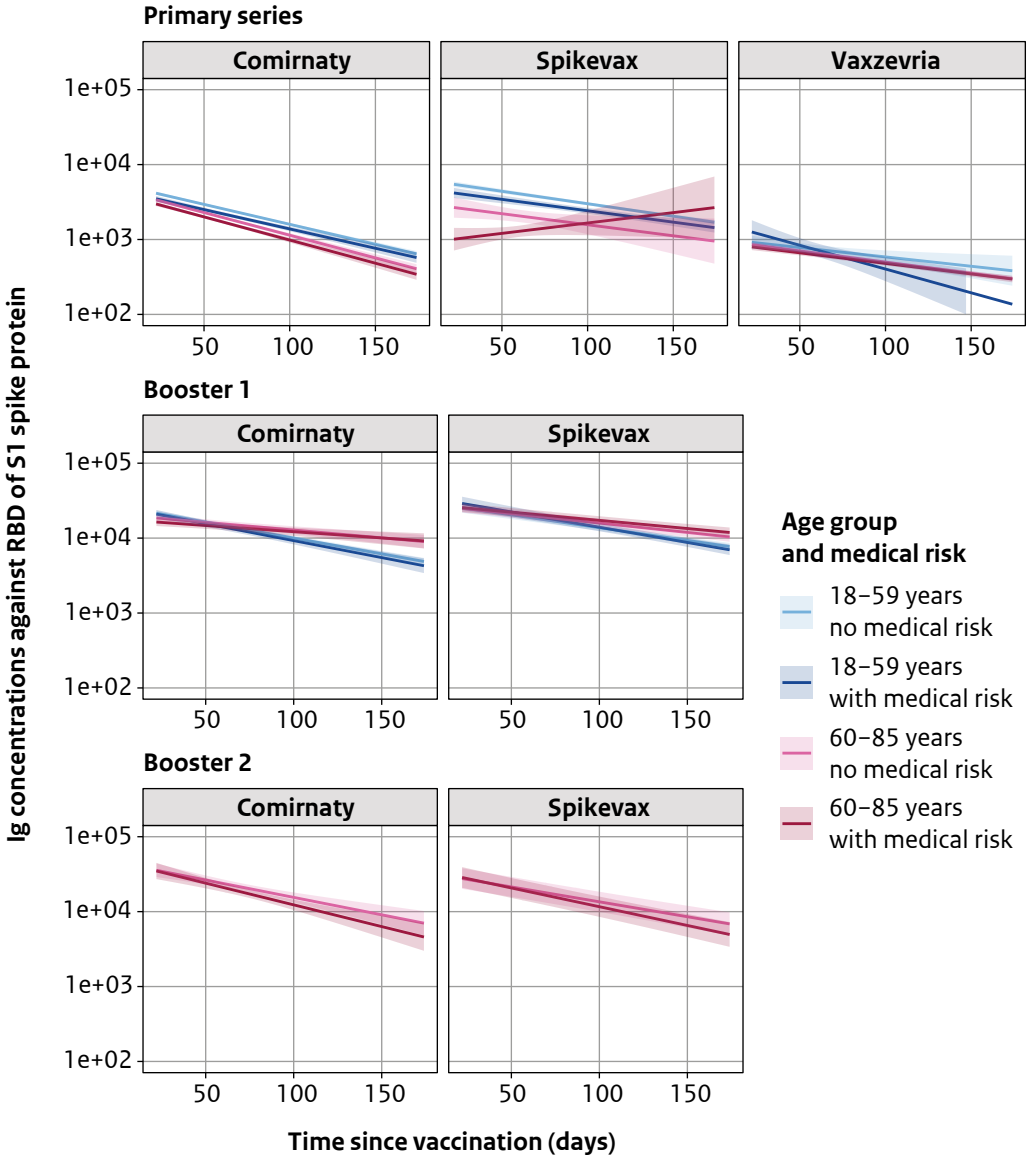


Figure 9.5.6 Estimated effect of age and medical risk group indication on waning Ig antibody concentration against the receptor binding domain (RBD) in the Vaccine Study Corona (VASCO) for female participants in the age groups 18-59 and 60-85, with and without medical risk group indication. Waning is presented by vaccine product and dose. Coloured lines represent estimated mean Ig with 95% confidence intervals. The model for the second booster was only based on data from participants over 60 years of age.



9.5.3 PIENTER Corona (PICO): a nationwide prospective population-based seroepidemiological study of SARS-CoV-2 in the Netherlands

The PIENTER Corona (PICO) study is a nationwide, prospective, population-based study on immunity against SARS-CoV-2. Its primary aim is to assess levels of antibodies to SARS-CoV-2 in consecutive blood samples from a large cohort, representative for the Dutch population. These data have been used widely during the course of the pandemic, for instance to estimate the proportion of the population that was infected and/or vaccinated, as input for modelling purposes, to assess the severity of the disease, to determine risk factors for infection and trends over time, to study the duration of immunity after infection as well as vaccination (stratified by several groups and types of vaccines), and to investigate the role of mucosal antibodies (in the nose) in protection against infection.

In the early stages of the COVID-19 pandemic in the Netherlands, participants from the PIENTER-3 study (conducted in 2016/2017 [1]) who had consented to be approached for follow-ups were contacted for participation in PICO. The first sampling round was carried out in April 2020, and over 3,200 persons participated. Subsequently, additional sampling took place to increase power and enhance geographical spread. We randomly selected 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]. Several sampling rounds followed: the second in June 2020, the third in September 2020, the fourth in February 2021 (i.e. at the start of the Alpha Variant of Concern (VOC)), and the fifth in June 2021 (i.e. at the end of the Alpha VOC). For the sixth study round in November 2021 (i.e. amidst the Delta VOC dominance), additional random sampling from the Dutch population registry was repeated similarly to previous sampling. This resulted in over 8,500 participants who were distributed across the Netherlands in proportion to population density (see Figure 9.5.1). Three subsequent study rounds followed in 2022: the seventh in March 2022 (i.e., at the end of Omicron BA.1), the eighth in June 2022 (i.e., at the end of Omicron BA.2), and the ninth in November 2022 (i.e., at the end of Omicron BA.2 and the start of Omicron BQ.1 dominance). The number of participants ranged between 5,600 and 6,900 persons. A tenth study round was carried out in spring 2023 (from which the data has yet to be analysed), and the study will proceed in the coming period, first with a eleventh round in autumn 2023.

During each study round, data on potential risk factors for SARS-CoV-2 infection (over time) and COVID-19 vaccination data is retrieved via self-completed (online) questionnaires. This documented data from the questionnaires is linked to laboratory measurements assessing humoral immunity obtained from self-sampled fingerstick blood, and measured by a validated bead-based multiplex immunoassay (MIA) developed at RIVM [4]. Antibody concentrations against Spike S1 (anti-S1), induced by infection and vaccination, and Nucleocapsid (anti-N), an antigen that is absent in vaccination and thus solely induced by infection, were analysed and calibrated against the World Health Organization (WHO) standard (NIBSC, 20/136 (where seropositivity for anti-S1 was considered at 10 binding antibody units (BAU)/mL, and for anti-N at 14.3 BAU/mL, as derived from mixture modelling and receiver operator characteristics (ROC) analyses). Serological information from each study round was combined with self-reported vaccination and SARS-CoV-2 testing data to dissect infection-induced (at least once) and

total (i.e., infection- and vaccination-induced following S1-seropositivity) seroprevalence. Seroprevalence estimates were calculated, taking into account the survey design, weighted to represent the Dutch population, and infection estimates were corrected for laboratory test specifics.

9.5.3.1 Epidemiological characteristics

The proportions of participants by sociodemographic groups were very similar across the study rounds in 2022. The participants' age ranged from 1 to 92 years (for instance, in the seventh round, the median age was 54 years (interquartile range (IQR) 33-70)), and slightly more women participated than men (57% vs. 43%). The majority consisted of native Dutch (89%) participants and differences in educational level (low/middle vs. high) were nearly equally divided. In March 2022 (round 7), 95% of adults (weighted) had completed the primary vaccination series, 78% received a booster dose, and 6% already had a fourth dose. The latter increased further to 18% by June 2022 (round 8) and 43% in November 2022 (round 9), while 17% of adults had received (at least) a fifth dose.

9.5.3.1.1 Seroprevalence induced by infection and/or vaccination over time, overall and by age

The weighted overall infection seroprevalence was 4.5% (95% CI 3.8–5.2) after the first wave of infections in June 2020 (round 2) and 12.2% (95% CI 11.1–13.4) after the second wave in February 2021 (round 4). At that time, the total seroprevalence was 14.3% (95% CI 13.1–15.5), with the highest rates in the oldest age groups (>80%), consistent with the start of the nationwide vaccination campaign initiated in the beginning of 2021 and following an age, comorbidity and healthcare worker prioritisation (Figure 9.5.2A). In June 2021 (round 5), after domination of the Alpha VOC, infection seroprevalence increased to 19.8% (95% CI 18.1–21.6), displaying a sustained age pattern since the beginning of the pandemic with the highest rates in young adults (30%), followed by middle-aged adults and the lowest rates in the elderly (15%). Total seroprevalence rose steeply to 64.5% (95% CI 62.7–66.3), reflecting the quick roll-out of vaccines among adults in the first half of the year, with levels above 80% in those of 50 years and over. In the autumn of 2021 (November, round 6), amidst the Delta VOC wave, infection seroprevalence increased to 26.0% (95% CI 24.1–27.9). A relative steep increase was observed in younger age groups between 5-24 years, peaking above 40% in young adults, while levels up to 30% were seen in middle-aged adults and the elderly remained among the lowest infected groups (20%). Meanwhile, overall total seroprevalence rose further to 86.5% (95% CI 85.4–87.7), with levels above 90% in those from adolescent age up to the very oldest, congruent with the availability of the primary series vaccination for everyone from 12 years of age (as well as booster doses among prioritised groups).

In March 2022, after the Omicron BA.1 wave, overall infection seroprevalence rose sharply to 62.4% (95% CI 59.3–65.4). Up till then, the lowest rates of infections were consistently seen among vaccinated individuals. However, with the emergence of Omicron, proportions of breakthrough infections among those vaccinated rose sharply (e.g., >40% after Omicron BA.2). Particularly rapid increases in infections were observed in the population <60 years, with estimates up to 50% in the very youngest age group (<5 years) and 90% in adolescents, from where it decreased linearly with age, reaching 30% in 80-year-olds (Figure 9.5.2B). Overall

total seroprevalence reached 96% and remained high throughout the rest of the year. Most restrictions were lifted in the Netherlands after the first Omicron wave. In June 2022, overall infection seroprevalence rose further to 73.5% (95% CI 70.3–76.8) after the Omicron BA.2 wave, with steepest increases observed in persons over 40 years of age, reaching, for instance, 80% in those aged 50 years and 45% in 80-year-olds. Near the end of the year (November 2022), following the Omicron BA.5 wave, infection seroprevalence had increased further to 86.3% (95% CI 82.9–89.7). Rather similar increases (on average 15% percentage points) were observed among all adults age groups, with 50-year-olds reaching 90% and approximately two out of three 80-year-olds. Hence, despite some lack of infection-induced immunity in the oldest age groups, these data show that the majority of the population had acquired (hybrid) immunity at this point.

9.5.3.1.2 Seroprevalence by sociodemographics

Until the middle of the Delta VOC wave in November 2021, relatively most infections were observed in the South-Eastern region of the Netherlands (31%) and fewest infections were seen in the northern region (20%). Following the emergence of Omicron in 2022, differences between regions diminished, particularly after the Omicron BA.2 wave, although the highest infection seroprevalence was still observed in the South-Eastern region by the end of 2022 (89%). Infection seroprevalence estimates from the low vaccination coverage (LVC) region were persistently higher than in the general Dutch population during the first two years of the pandemic (e.g., fourth round: 20%; fifth round: 29%; sixth round: 38%), and remained higher after the emergence of Omicron, reaching 85% in June 2022 (round 8) and 91% at the end of 2022. Contrarily, the total seroprevalence was consistently lower in the LVC since the Alpha wave (fourth round: 22%; and next, fifth round: 63%; and sixth round: 82%), resulting from lower vaccination uptake, but has started to approximate the general Dutch population since the first Omicron wave in March 2022 (e.g., 93% vs 96%, respectively).

Throughout the pandemic, overall infection seroprevalence did not differ significantly between sexes, although some differences within age groups were observed (e.g., twice as high rates in men vs women among those of 75 years and over across 2021 and until Omicron BA.1 (39% vs. 24%, $p<0.001$)). Moreover, rates among non-Western participants increased particularly sharp during Alpha when compared to native Dutch and Western participants (1.5 times), which was especially noticeable in the age groups below 40 years. These higher infection rates in non-Western participants persisted thereafter (up to 92% overall in November 2022), while the total seroprevalence was consistently lowest among this ethnic group. Low/middle-educated persons had a significantly higher overall infection seroprevalence across all waves up till the end of 2021 as compared to those higher educated (e.g., during Delta 22% vs 25%, $p=0.024$), and this held true for all age groups. Following the emergence of Omicron in 2022, infection rates became more comparable between most groups. Furthermore, rates of infections had been low among those with underlying comorbidities who were targeted for early vaccination, especially up until the end of 2021, congruent with a total seroprevalence of >95% as early as June 2021. Their infection seroprevalence was below the overall estimates in the general population throughout the study period but started to increase with a similar rate following the second Omicron wave (which ended in June 2022), reaching 73% in November 2022.

9.5.3.2 Mucosal immunity

Antibodies at the mucosa of the respiratory tract are likely to contribute directly to protection against a SARS-CoV-2 infection. Therefore, mucosal antibodies were investigated in a random subset of participants (age-stratified) in the eighth round of the PICO cohort (June 2022). The majority (92.9%) of participants (n=778) were positive for mucosal anti-S1 IgG (Figure 9.5.3A), whereas 24.4% participants were positive for mucosal anti-S1 IgA (Figure 9.5.3B). Children below the age of 5 years had the lowest prevalence of both mucosal IgG and IgA out of all age groups (20% and 4%, respectively), followed by children aged 5-11 years (57.8% and 4.4%, respectively). For participants aged 12 years and over, the prevalence of mucosal antibodies was 97.7% for S1-specific IgG and 26.4% for S1-specific IgA. People with a known history of infection had a significantly higher prevalence of mucosal S1-specific IgA (32.5%) compared to those without knowledge of an earlier infection (6.9%, $p<0.0001$), and this was valid across all age groups (Figure 9.5.3B). Mucosal antibody levels were higher in those with a history of infection and increased with age, reaching a plateau around the age of 25-30 years (Figure 9.5.3C for IgG, and Figure 9.5.3D for IgA).

A potential role for mucosal antibodies and other variables in protection was investigated by studying infection data from the subsequent round (PICO9). Random forest analysis was used to assess which parameters predict protection against future infection in the six months following the mucosal sample collection. The variables that turned out to be of the highest importance were: the concentration of anti-N IgG in serum, time since the most recent infection, concentration of mucosal anti-S1 IgA, concentration of serum anti-S1 IgA and IgG, and age (Figure 9.5.4A). The concentration of mucosal anti-S1 IgG, vaccination-related predictors and sex had low importance in the prediction. The probability of infection decreased as mucosal anti-S1 IgG increased (Figure 9.5.4B, Spearman's rho = -0.47), and this correlation was even stronger with respect to the levels of IgA (Figure 9.5.4C, Spearman's rho = -0.62).

In conclusion, the majority of this age-stratified study population, derived from the general population, developed mucosal antibodies involved in protection against future SARS-CoV-2 infection. Particularly the level of mucosal anti-S1 IgA, predominantly induced by previous infections was associated with reduced future infection rate for up to six months. On the basis of these observations, it could be suggested that development of hybrid immunity in a vaccinated population results in development of mucosal immunity in the population. Investigations into the longevity and boosting of mucosal antibody levels by subsequent encounters with SARS-CoV-2 are needed to confirm the protective role of mucosal immunity against COVID-19 in the future.

9.5.4 Vaccine Study Corona (VASCO): a nationwide prospective population-based cohort study on vaccine effectiveness in the Netherlands

The Vaccine Study Corona (VASCO) is a prospective population-based cohort study, primarily aimed at assessing the long-term effectiveness of COVID-19 vaccines among ~45,000 community-dwelling persons aged 18-85 years, and with particular focus on medical risk groups (see chapter 9.4 for a further description of the study and vaccine effectiveness results). Participants in VASCO are asked to provide fingerstick blood samples at baseline,

and six-monthly after entering the study. An additional sample is requested one month after completing the primary vaccination series. Samples are analysed for Ig antibodies against the receptor binding domain (RBD) of the Spike protein (anti-S1), and against the Nucleocapsid (anti-N).

Here, we report on serological results for 43,515 samples collected between May 2021 and December 2022. Nearly all participants without prior infection were seropositive for anti-S1 between 14 to 42 days following their primary series vaccination (ranging from 98.0% for Vaxzevria to 99.4% for Comirnaty). Following the first booster doses, everyone, except five, were seropositive and following the second booster, all participants were seropositive. Participants with a prior infection were nearly always (99.2%-100.0%) seropositive following the primary series, and all were seropositive following the first and second booster.

Geometric mean concentrations (GMC) of the early response after vaccination (2-6 weeks following vaccination) are presented in Figure 9.5.5 and stratified by vaccine, dose, age group, medical risk group (including people with common comorbidities, such as diabetes, cardiovascular disease, cancer), and prior infection status. The early response following the primary series and first booster varied significantly between vaccine products ($p<0.001$), with Spikevax generally showing the highest concentration. Following the second booster, no difference in response was seen between vaccines. Early response was higher for those with an infection prior to vaccination. Some statistically significant differences in early vaccine response were seen within vaccine products. Among those without a prior infection, anti-S1 GMC was lower in the age group of 60-85 years and the medical risk group for those receiving Spikevax or Comirnaty as a primary vaccination. Anti-S1 GMC was also lower in the age group of 60-85 years following the first booster (both for Comirnaty and Spikevax). No differences were seen between those with or without medical risk conditions following the first and second booster. Among those with a prior infection, anti-S1 GMC following primary vaccination was higher among those aged 60-85 years in the Vaxzevria group, but lower in the Spikevax group. Following the first booster, anti-S1 GMC was only higher among those aged 60-85 years with medical risk conditions if they received Comirnaty. No differences between groups were observed following the second booster.

A representation of waning of anti-S1 by vaccine, dose and medical risk group in those without prior infection (and corrected for sex) is shown in Figure 9.5.6. Waning following a primary series with Vaxzevria was significantly faster in the medical risk group (0.767, 95% CI 0.590–0.996). Waning in the age group of 60-85 years was slightly faster following a primary series with Comirnaty (0.951, 95% CI 0.913–0.991), but slower following a primary series with Spikevax (1.524, 95% CI 1.191–1.950). Waning was significantly slower in the 60-85 year age group following the first booster (Comirnaty 1.161, 95% CI 1.101–1.225; Spikevax 1.064, 95% CI 1.019–1.111). Waning was not effected by medical risk following the first or second booster.

9.5.5 Literature

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* *RIVM publication.*

9.6 Immunogenicity of COVID-19 vaccines

A. Buisman, J. Brummelman, M.K. Verheul, A.J. Wijmenga-Monsuur, J. van Beek, J. de Wit, F.R.M. van der Klis, R.S. van Binnendijk, M.C. Boer, N.Y. Rots

9.6.1 Key points

- Data from the RIVM corona vaccination trials (CVTs) in community dwelling individuals show that most of the infection-naïve older adults show a SARS-CoV-2 specific IgG antibody response after primary series vaccinations, which is however lower than in younger adult age groups. Also T cell responses are lower and show more variability in older adults compared to other adult age groups.
- Older adults and specific groups of immune compromised patients require a booster dose to reach antibody levels similar to levels in younger adults.
- Booster doses induce an increase in antibody levels followed by a decline in infected and uninfected persons. Waning of antibody levels is slower when a person had been infected before vaccination.
- In nursing home residents, solid antibody responses were seen following booster vaccinations, although they were slightly lower than in community dwelling older adults.
- Following vaccination with bivalent COVID-19 vaccine, Omicron Spike antibodies increase in all adults and children (5-17 years of age). Antibody levels are slightly higher in individuals with hybrid immunity induced by a combination of infection and vaccination.
- The bivalent vaccine induces T cells that are highly cross-reactive against Spike of the Omicron BA.1 and Omicron BA.4/5 variants.

9.6.2 Tables and figures

Figure 9.6.1 Kinetics of Spike S1-specific antibody concentrations (IgG) following COVID-19 vaccination at the start of vaccination of infection-naïve individuals by age. General population (n=1230) VIDO (>50 years) and IIVAC studies (<60 years) (n~1250) nursing home residents (n=52) VIDO (~100 nursing home participants). Arrows depict (booster) vaccination timepoints. Primary series (Dose 1 and Dose 2) with Comirnaty (Pfizer/BioNTech), booster vaccination (Dose 3) and repeat jab (Dose 4) with an mRNA vaccine (Comirnaty or Moderna). The VIDO study is a sub-study of the Doetinchem Cohort Study, specifically focusing on the humoral response to COVID-19 vaccination. Participants >50 years of age were included irrespective of their health status and are thus representative for the general population. T0; pre vaccination, T1; pre 2nd dose, T2, 28 days post 2nd dose, T3; 3 months post 2nd dose, T4; 6 months post 2nd dose, T5; pre booster dose, B1; 28 days post booster dose (Dose 3), D1; 28 days post repeat jab (Dose 4).

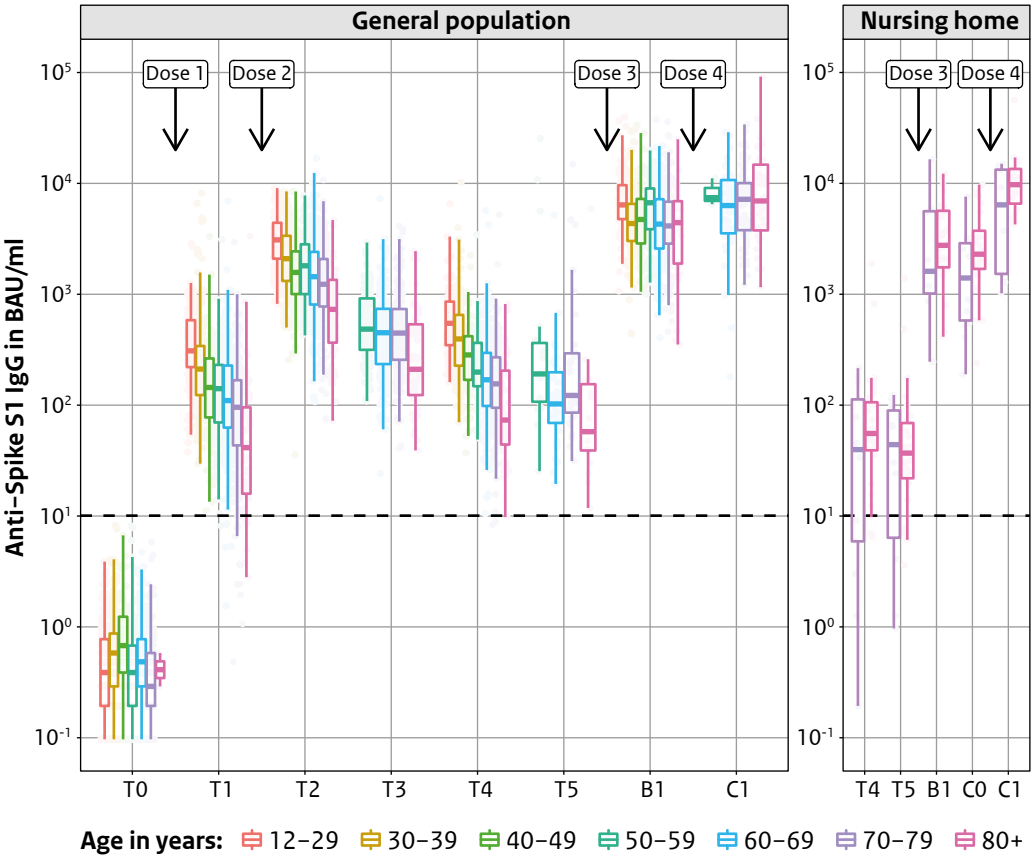


Figure 9.6.2 Kinetics of SARS-Cov-2 Wuhan Spike S1-specific antibodies (IgG) following COVID-19 vaccination. On the left: community dwelling older adults aged 60-86 years and on the right: nursing home residents aged 52-100 years. For the first booster (3rd dose) and the second booster (4th dose), monovalent mRNA vaccines (Comirnaty (Pfizer) have been used, for the 2022 booster vaccination autumn round (5th dose) a bivalent Wuhan-Omicron BA.1 vaccine has been used. Data from participants of the VIDO study, a sub-study of the Doetinchem Cohort Study, that have been included irrespective of their health status and are thus representative for the general population. Incapacitated individuals were excluded from the studies. Grey dots represent post-primary series follow-up timepoints; red dots are data from 1 month post first booster; dark red 1 month post 4th, and blue 1 month post 5th vaccination.

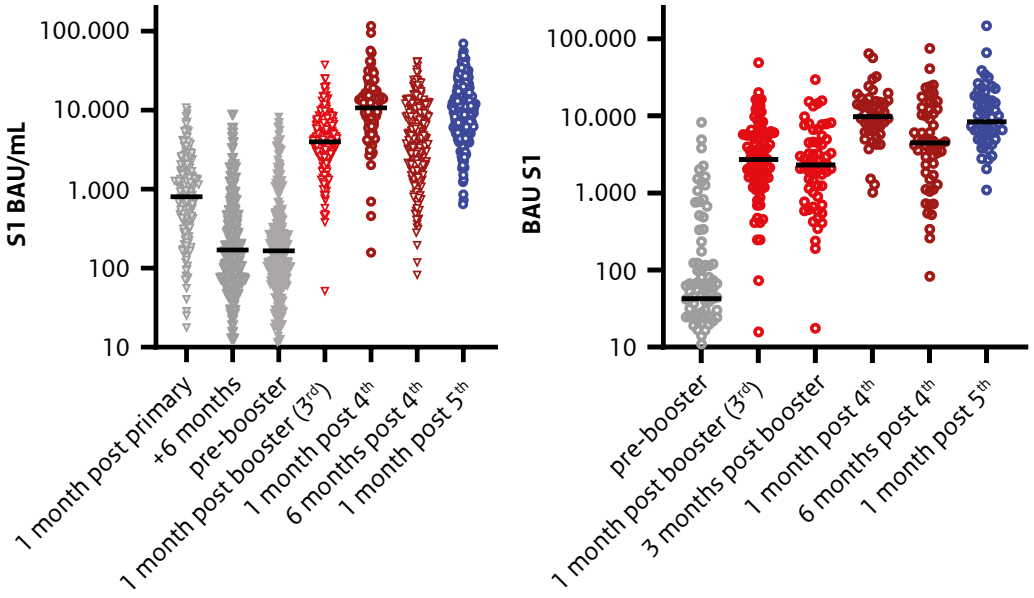


Figure 9.6.3 Kinetics of SARS-CoV-2 Wuhan Spike S1-specific antibodies (IgG) following COVID-19 booster vaccinations with and without infection, by age group. General population VIDO (> 60 years of age; n~900) and Vital studies (<60 years of age; n~130). For first (3rd dose) and second (4th dose) booster vaccinations, a monovalent mRNA vaccine (Comirnaty or Moderna) was used. For the 2022 autumn booster (5th dose), a bivalent Wuhan/Omicron BA.1 mRNA vaccine (Comirnaty or Moderna) was used. Pre 3: before 3rd dose (first booster); Post 3: 1 month post 3rd dose; Post 4: 1 month post 4th dose (2nd booster); Pre 5: pre 5th dose (6-9 months post previous vaccination); Post 5: 1 month post autumn 2022 booster (5th dose).

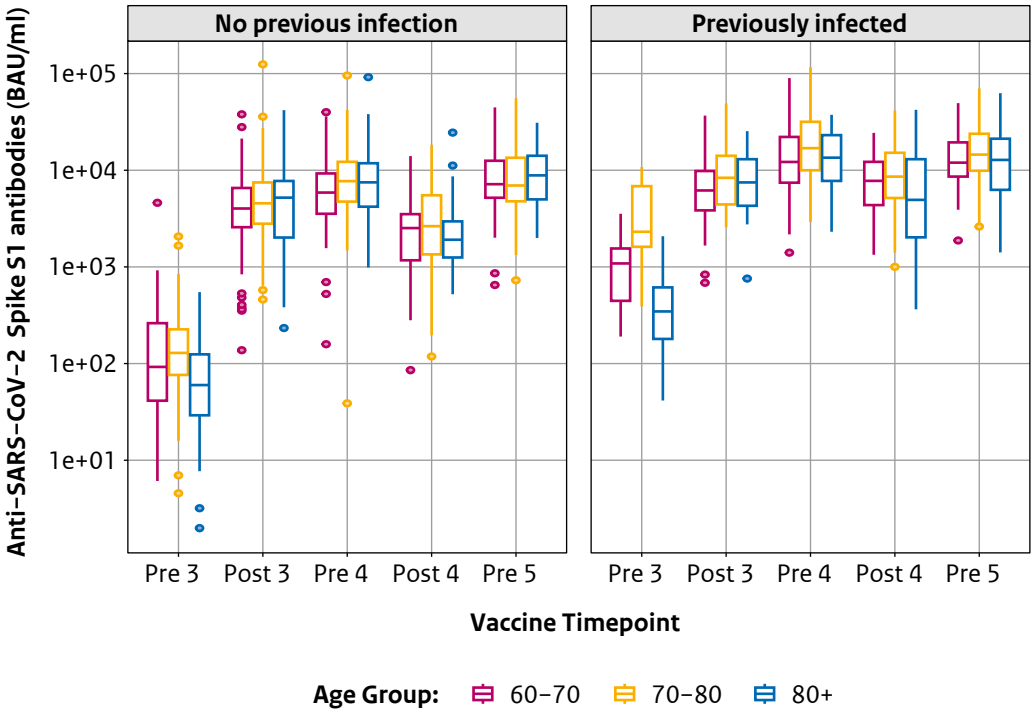


Figure 9.6.4 A) A comparison of Spike S1 antibody levels between participants 5-17 years of age after a first or second SARS-CoV-2 vaccine dose. Participants who experienced a SARS-CoV-2 infection before the start of vaccination are shown separately from those who did not experience an infection. B) Antibody levels were compared between participants 5-11 years of age and participants 12-17 years of age in previously infected participants after their first vaccination.

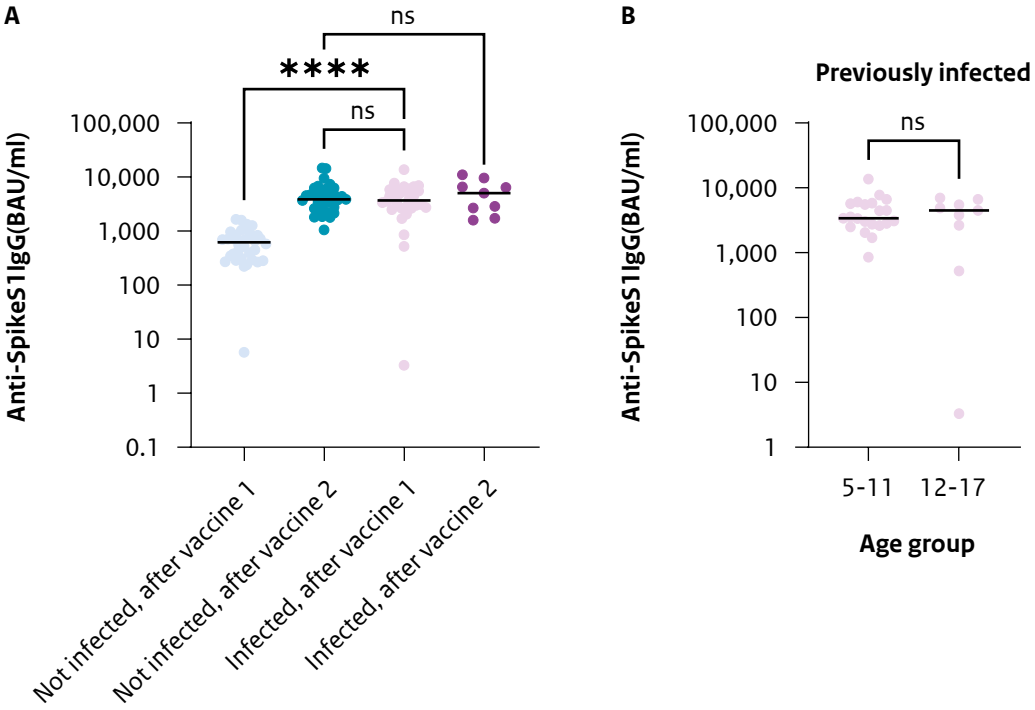


Figure 9.6.5 SARS-CoV-2 Omicron BA.1 Spike S1-specific antibodies (IgG in arbitrary units (AU)/mL), before and following the fall booster dose (5th dose) with a Wuhan/Omicron BA.1 bivalent mRNA vaccine, with and without infection history by age group in individuals of 60 years and older from the general population participating in the VIDO and Vital studies.

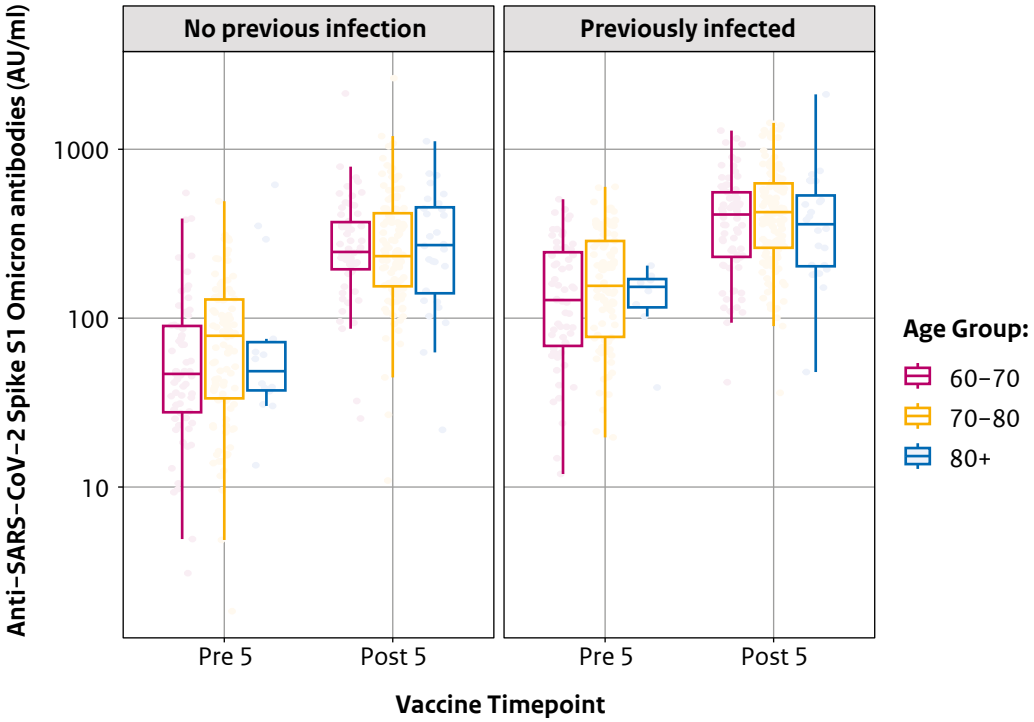


Figure 9.6.6 (A) Memory B cell response to the primary series SARS-COV-2 vaccinations. The SARS-CoV-2 Spike S1 memory B cell response 28 days after completion of the primary immunisation series for 20-50 years of age and 50 years and older age groups. Samples within the grey area are considered low-responders. The lower and upper hinges of the boxplot indicate the 25th and 75th percentile, with the horizontal line indicating the median. (B) Booster vaccination with SARS-CoV-2 mRNA vaccine increases the memory B cell response. SARS-CoV-2 Spike S1-specific memory B cell responses are shown at 28 days post primary series vaccinations (P28; n=87) and before (B0; n=44) and after (B28; n=59) the first booster dose with mRNA vaccine.

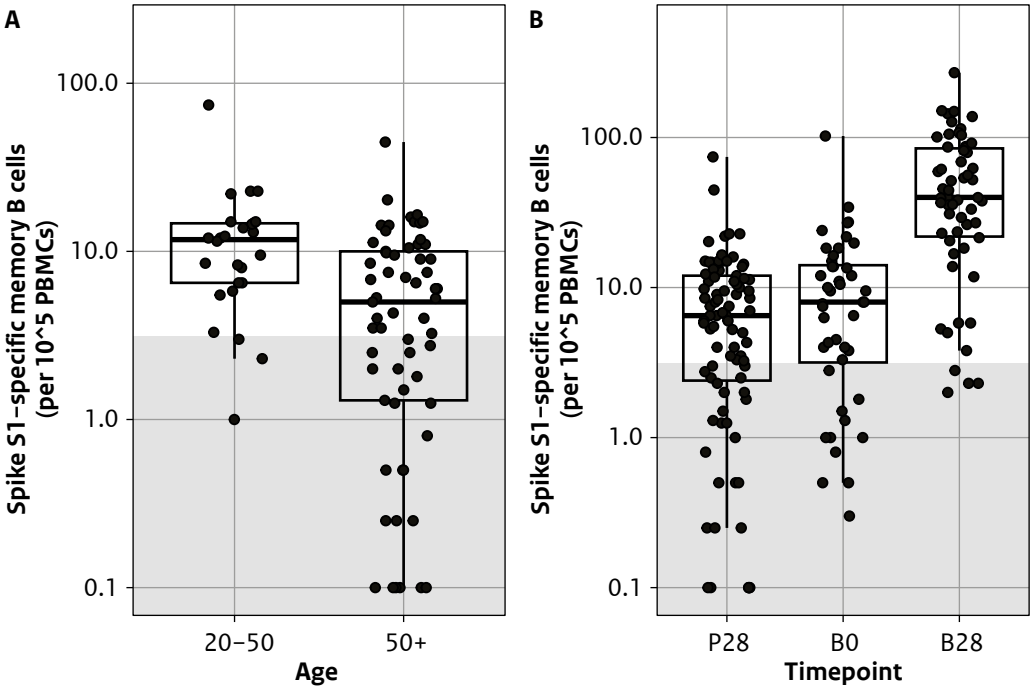


Figure 9.6.7 Anti-Spike T-cell response to primary series vaccinations for all COVID-19 vaccines by age. Spike-specific T cell response Po (pre) and P28; 1 month post-primary series vaccinations with BNT162b2 (Comirnaty, Pfizer/BioNTech), mRNA-1273 (Spikevax, Moderna), ChAdOx1 nCoV-19 (AstraZeneca), or Ad26.COV2.S (Janssen) vaccines. **p<0.01,****p<0.0001 P28 versus Po; Kruskal-Wallis tests and Dunn's test with Benjamini-Hochberg adapted to multiple comparisons. T cell frequencies are presented in IFNγ-Spot Forming Units (SFU) per 1x10^6 PBMCs, individual data is depicted as individual dots. The horizontal line in boxplots represents the median.

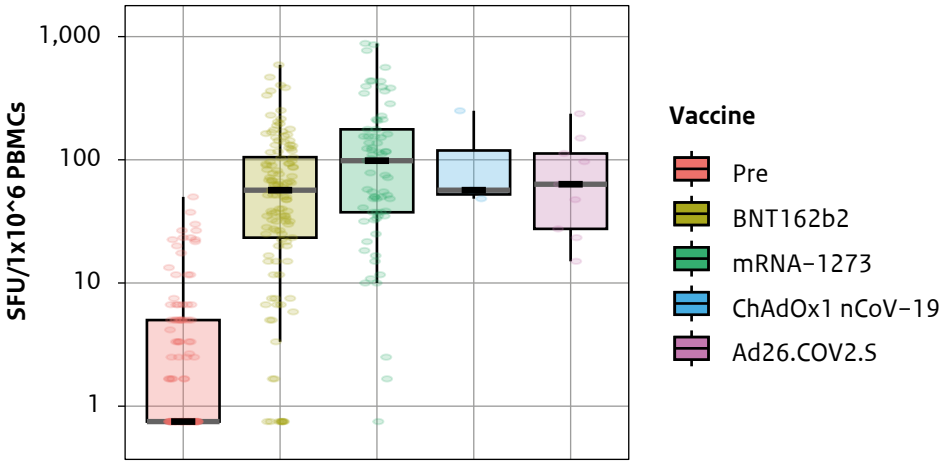


Figure 9.6.8 Spike-specific T cell frequencies following primary series and booster vaccinations. T cell responses were measured using an IFNγ T cell ELISpot upon stimulation with an overlapping peptide pool of the Wuhan vaccine strain Spike. Spike-specific T cell responses to primary and booster vaccination stratified by age group, as indicated. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001; ^^^^p<0.0001 of 70+ versus same timepoint of 18-59 age group. #p<0.05, ##p<0.01 of 70+ versus same timepoint of 60-69 age group; Kruskal-Wallis test and Dunn's test with Benjamini-Hochberg adjustment for multiple comparisons. T cell frequencies are given in IFNγ-Spot Forming Units (SFU) per 1x10^6 PBMCs and individual data is presented as dots. In the boxplots, median and IQR are provided. P0, pre-vaccination; P28, 1 month post-primary vaccination series; B0, pre-booster vaccination; B28, 1 month post-booster vaccination.

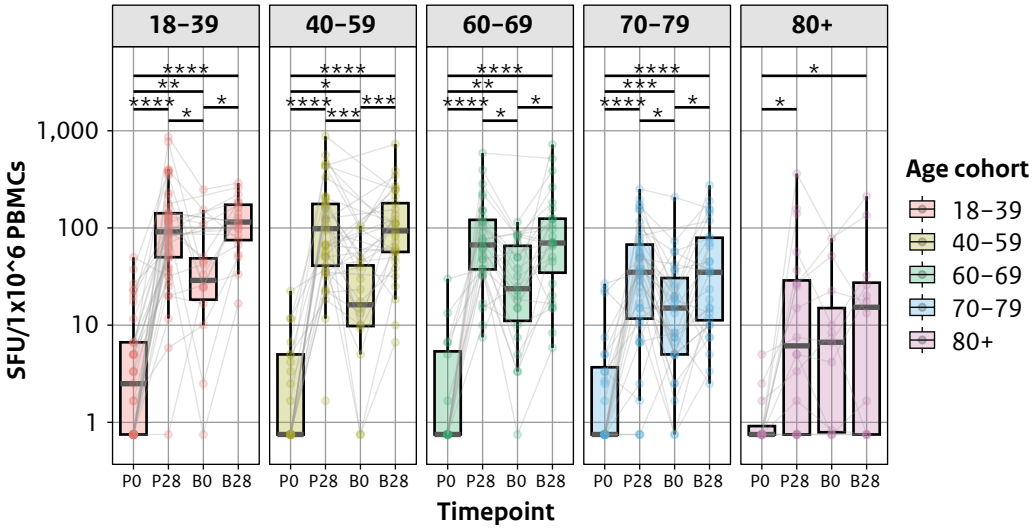


Figure 9.6.9A Cross-reactivity of primary and booster vaccination-induced anti-spike T cell responses with Spikes of different VOC.
The frequencies of T cells (in SFU/1x106 PBMCs) specific for the Spike protein of the different VOCs were measured at P28 (primary) and B28 (booster) using distinct VOC overlapping peptide pools as stimulation in an IFNγ T cell ELISpot. Comparison of the VOC Spike-specific T cell levels across the whole cohort at P28 and B28, as indicated.

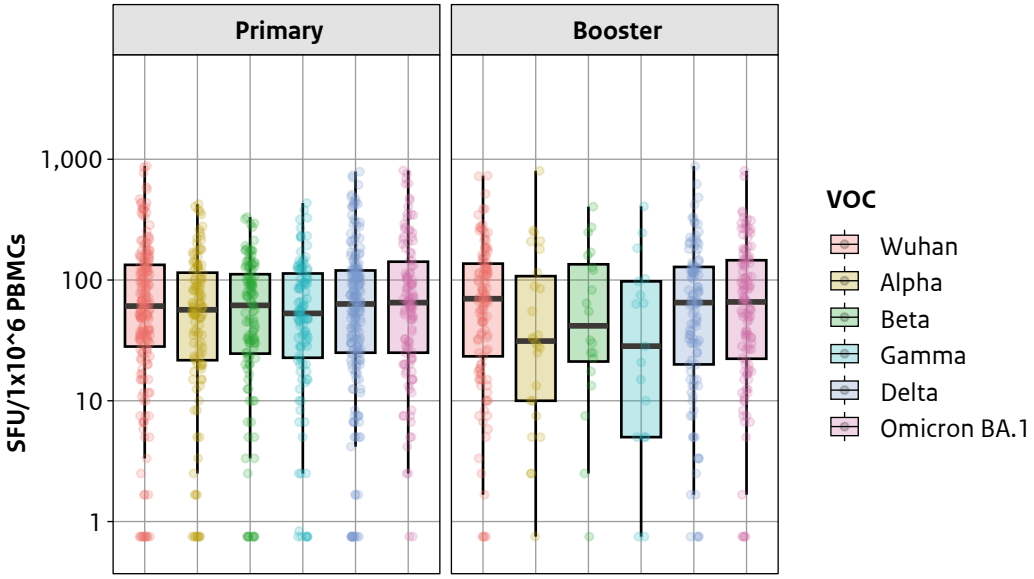
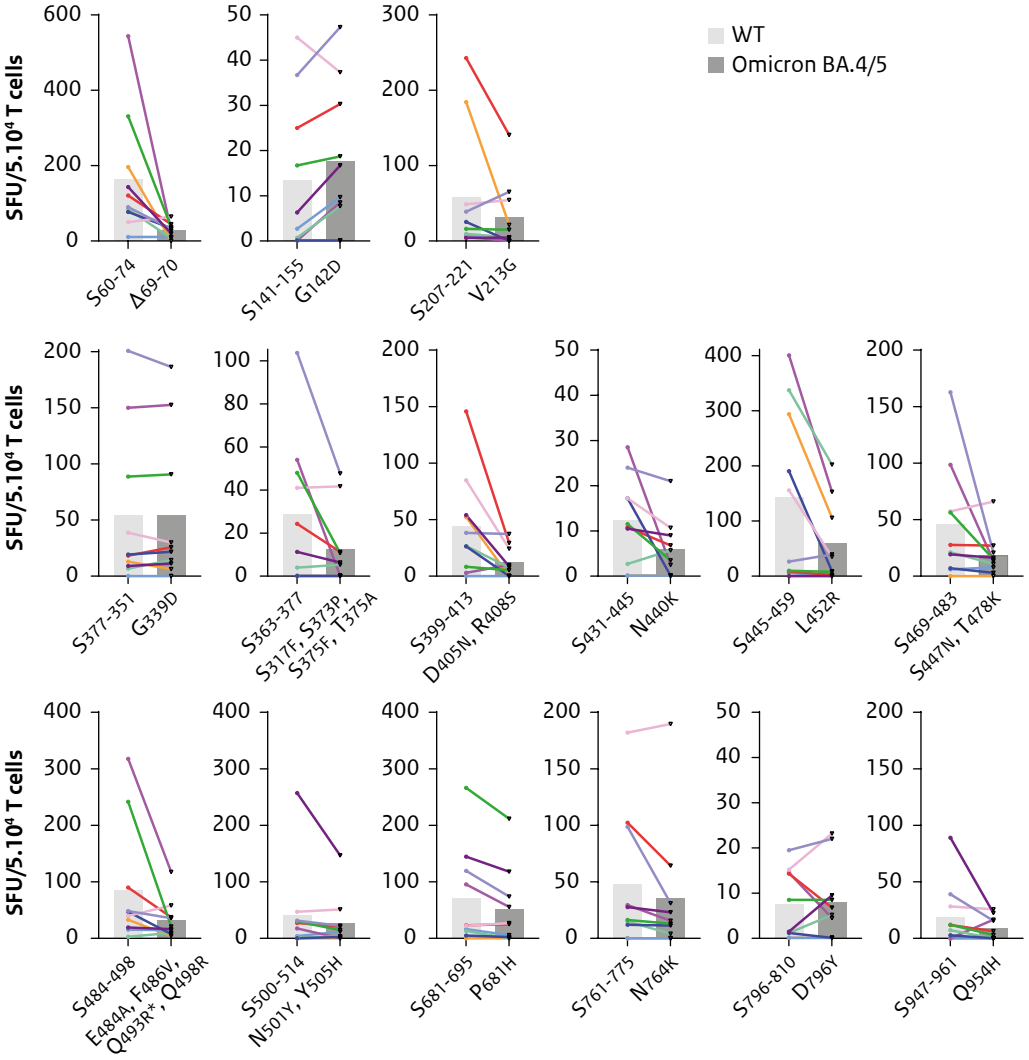


Figure 9.6.9B Cross-reactivity of primary and booster vaccination-induced anti-spike T cell responses with Spikes of different VOC.
T cells that specifically recognise spike regions containing mutations in the Omicron variant often fail to recognise the Omicron variant. T cells often respond well to the original Wuhan wildtype (WT) spike epitopes (light grey bars) but show a diminished IFNγ response to the corresponding spike sequences of the Omicron BA.4/BA.5 variants (dark grey bars), as measured in an IFNγ T cell ELISpot. Each colour represents an individual sample from a recently vaccinated person who received two doses of the mRNA vaccine (BNT162b2).



9.6.3 Antibody responses

The Corona Vaccination Studies (CVTs: IIVAC, VITAL-corona, VIDO and VOCAAL) are longitudinal observational vaccine response studies, performed in the general healthy population of the Netherlands. The VIDO study includes a group of participants who live in a nursing home. The aim of the studies is to monitor and evaluate immune responses induced by primary and booster vaccinations that are given as part of the national COVID-19 vaccination programme. This includes all age groups starting at 5 years and over and for all different vaccines that have been used within the programme. Amplitude and kinetics of humoral, cellular (B- and T cells), and innate immune responses induced by (booster) vaccinations are evaluated to support further evidence-based vaccination strategies aimed at maintaining optimal immunity against COVID-19 across the population. Moreover, vaccine response data of these generally healthy study participants will be used as control groups for vaccine responses in groups with high risk for severe COVID-19 that are being assessed in other studies (overview in Dutch on the ZonMw website). Across the RIVM studies, 3356 participants aged 5-101 years have been included. For the primary vaccination series, the mRNA vaccines Comirnaty® (Pfizer/BioNTech) and Spikevax® (Moderna) and the viral vector vaccines Vaxzevria® (AstraZeneca) and JCOVDEN® (Janssen) have been used. For booster vaccinations, Comirnaty and Spikevax have been used almost exclusively. Spikevax was only used for individuals aged 45 years and over.

9.6.3.1 Longitudinal antibody analyses in serum across ages

SARS-CoV-2 Spike S1-specific antibody (IgG) concentrations in serum were determined using the bead-based multiplex immunoassay (MIA). Specific IgG antibody concentrations are expressed as international BAU/ml serum and measured before vaccination, at one month after the first vaccination, one month after completion of (the second) primary-series vaccinations, and subsequently the pre- and post-booster vaccination(s). Also, waning of antibody concentrations over time is currently being assessed in these studies, at six months after vaccination, and will also be determined at twelve months post vaccination if no additional vaccine dose is given.

9.6.3.2 Immune response to COVID-19 booster vaccinations in all age groups

Most of the infection-naïve older adults show an adequate SARS-CoV-2-specific IgG antibody response, above the threshold of 300 BAU/mL, following primary series vaccinations. An even larger increase following the first booster (third dose) compared to younger age groups has been shown [1]. Following a COVID-19 vaccine booster, the more vulnerable older adults also had high antibody concentrations that were similar to the concentrations measured in the younger age groups (Figure 9.6.1), although the variability in responses is larger in the older age groups. The increase in antibody concentrations following each subsequent booster dose is smaller compared to the increase following the primary series and first booster vaccinations, but the antibody concentrations reached are similar following each booster (third, fourth and fifth) dose (Figures 9.6.1 and 9.6.2, dose 4 and 5). For all age groups, antibody waning is slower following booster vaccinations compared to waning following the primary series. Overall, antibody kinetics following booster vaccinations are similar for all older age groups and are not influenced by infection history before vaccination (Figure 9.6.3).

Six months after the fourth vaccination, just before the fifth dose, around 20% of the infection-naïve older adults had a relatively low antibody concentration that could potentially result in less protection. Older adults with an infection history (54% of the older adult participants) have slightly higher antibody titers, but they also show a less strong increase following the 2022 booster vaccination autumn round (fifth dose) (Figure 9.6.3).

9.6.3.3 Antibody responses to booster vaccinations in nursing home residents compared to community dwelling older adults

A group of 110 nursing home residents has been followed to evaluate Spike S1-specific IgG concentrations from 6 months post primary vaccination series onwards. Antibody kinetics following booster vaccinations (third, fourth and fifth dose) with Comirnaty® were similar for nursing home residents compared to age-matched community dwelling older adults (Figures 9.6.1 and 9.6.2). Both groups showed a large increase in Spike-specific antibody concentrations following the first booster (third dose) followed by a much smaller increase following the fourth and fifth vaccine doses. However, absolute antibody concentrations were lower in nursing home residents.

9.6.3.4 S-protein-specific antibodies in 5-11-year-old children following vaccination with bivalent COVID-19 vaccine

All children show a SARS-CoV-2 S-protein-specific IgG response to primary series vaccinations. Almost 80% of this age group already had a SARS-CoV-2 infection prior to vaccination. They received only one vaccine dose instead of the regular two-dose primary vaccination series. This one dose boosts infection-induced antibody concentrations to levels similar to those following two doses in infection-naïve children (Figure 9.6.4). Vaccine response in previously infected 5-11-year-old children is comparable to the response in 12-17-year-old adolescents.

9.6.3.5 Omicron BA.1 Spike protein-specific antibodies in all older adults following vaccination with bivalent COVID-19 vaccine

For all vaccination rounds, monovalent vaccine based on the S-protein of the original Wuhan strain has been used except for the 2022 booster autumn campaign, for which a bivalent Wuhan-Omicron BA.1 vaccine has been used.
In all age groups, vaccination with the bivalent vaccine resulted in an increase in S1-protein-specific IgG antibodies against both vaccine strains, original Wuhan and Omicron BA.1 strain (Figure 9.6.5). Titers are slightly higher in the group with a previous infection compared to the group with only vaccination-induced immunity.

9.6.4 Memory B cells

Part of the older adults require a booster dose for SARS-CoV-2-specific memory B cell response. Upon re-exposure to SARS-CoV-2 or to a vaccine based on this virus-specific memory, B-cells rapidly produce large amounts of specific antibodies.
Following the primary immunisation series, memory B cells specific for Spike S1 were detected in the majority of participants. All individuals under the age of 60 years showed a good B cell response, whereas the 65+ age group showed more variation in response, including a proportion of mostly older adults with low frequencies of SARS-CoV-2-specific memory B cells

(Figure 9.6.6A). Booster vaccination, however, resulted in a large increase in frequencies of S1- and RBD-specific memory B cells, also for those in whom low or no memory B cell frequencies were detected following the primary series (Figure 9.6.6B). Following the first booster vaccination, no differences in B cell frequencies were seen between age groups.
B cell populations specific for the receptor-binding-domain (RBD) of Wuhan as well as Omicron BA.5 S-protein could be identified following a booster with a monovalent (Wuhan) or a bivalent (Wuhan-Omicron BA.5) vaccine in persons with vaccine-induced or hybrid immunity (data not shown).

9.6.5 Memory T cell immunity

In addition to antibodies, virus-specific memory T cells are an important line of acquired defence that is activated once human cells have been infected with SARS-CoV-2 and fragments of the S-protein of the virus have been presented on the surface of the infected cell. SARS-CoV-2-specific T cells recognise these viral fragments on the infected cells and subsequently kill these cells, thus preventing further production of the virus and confining the infection.
In addition to killing virus infected cells, T cells are also involved in other defence mechanisms, including cytokine production and release, as well as in helping B cells to produce large amounts of (functional) antibodies. Thus, in addition to antibody responses, COVID-19 vaccination also elicits T cell responses against SARS-CoV-2. There responses are associated with limiting the severity of COVID-19 and reduction of transmission of the virus, and they are thought to be less susceptible to VOC escape mutants [7, 8]. T cell responses have been determined by IFNγ T cell ELISpot assay following stimulation with overlapping Spike peptide pools of the Wuhan original virus strain.
Results of the RIVM COVID-19 vaccination studies show a solid SARS-CoV-2 S-protein-specific T cell response to primary series and booster vaccinations in all adult age groups that are vaccine-type independent (Figure 9.6.7). Spike-specific T cell frequencies increase following vaccination, subsequently decline and increase again following a booster vaccination 4-9 months later to levels similar to those following the primary series (Figure 9.6.8). In the oldest age groups (70 years and over), the overall T cell responses were lower and more variable compared to those in the younger age groups. Some older adults (80+ age group) have very low or even undetectable S-specific T cell numbers following primary vaccination.

The primary series and booster vaccinations, involving a vaccine based on the original (Wuhan) S-protein, induced anti-Spike memory T cells that cross-reacted with the Spike protein of the Omicron BA.1 variant in all adult age groups (Figure 9.6.9). However, the primary series response to Omicron BA.1 is slightly lower compared to the response to the original SARS-CoV-2 Wuhan virus strain. More in-depth analysis reveals that T cells that specifically recognise spike regions containing mutations in the Omicron BA.1 or BA.4/BA.5 variant often fail to recognise the Omicron variants (Figure 9.6.9B). Apparently, these mutations lead to impaired recognition by memory T cells that were induced by previous vaccination or infection with the original Wuhan strain [2,3]. This may explain the slightly lower T cell responses to the Omicron variants found following the primary series vaccinations.

Preliminary data from the longitudinal vaccination studies in participants aged 18-50 years and 60 years and over show stable Wuhan S-specific T cell frequencies over time with very little decline following the booster dose and an increase following the 2022 autumn booster dose with the bivalent vaccine.
The T cells induced by primary vaccination cross-reacted with the Spike proteins of different variants of the virus. Only for the Alpha, Delta and Omicron BA.1 variants, T cell frequencies were lower compared to the original Wuhan strain S-protein (Figure 9.6.9). This was not observed following booster vaccination. The bivalent vaccine induces T cells that are highly cross-reactive against Spikes of the Omicron BA.1 and Omicron BA4/5 variants.

9.6.6 Comparison of vaccine responses in immunocompromised people

In addition to the RIVM studies investigating the quantity and the quality of the COVID-19 vaccine-induced immune response in the general Dutch population, ZonMw-funded trials are being conducted in (academic) hospitals to investigate the response in various groups with a high risk for severe COVID-19. These include patients who are immunocompromised due to disease, use of specific immunosuppressive medication, or an inherited immune deficiency, as well as people with Down Syndrome. RIVM (IIV department) coordinated harmonisation of the study design of these studies, as well as the assays used for analyses of humoral and cellular immune responses, allowing comparisons between different vulnerable groups (cancer patients, haematology patients and people with Down Syndrome) and with healthy controls. Together with ZonMw, RIVM is working on an infrastructure for data sharing and cross-project data analyses for all COVID-19 vaccine response studies.

The generated data has been used to develop vaccination strategies for specific risk group, or subsets within risk groups. Most of the participants of evaluated immunocompromised groups were able to mount an adequate immune response that was comparable to healthy controls. The subsets that showed a low or no response were offered an additional third primary series vaccination. The subset included, but was not limited to, organ, bone marrow and stem cell transplant patients, patients with solid tumors within three months after chemo and/or immune therapy with checkpoint inhibitors, and patients treated with specific immunosuppressive agents.
A significant part of the participants who received a third primary series vaccine dose showed an increase in SARS-CoV-2-specific antibody concentrations, but some patients – including part of lung (transplant) patients and patients with a haematological malignancy – required additional vaccine doses to develop a response [4, 5, 6]. For the majority of the patients of the latter group, a fourth vaccination improved S1 IgG concentrations. Whereas primary series vaccination during B cell depletion followed by two additional vaccinations during the recovery phase resulted in a similar antibody response to that in patients with normal B cell numbers who had two doses, the neutralising capacity of the generated antibodies was significantly better [7].

9.6.7 Literature

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9.7 Adverse events after COVID-19 vaccination

C. van Roekel, C.E. Hoeve, B. de Gier

9.8.1 Key points

- National and international health authorities continuously monitor adverse events following immunisation (AEFI) in people who have received a vaccine, including COVID-19 vaccines.

9.7.2 Tables and figures

Table 9.7.1 Number of reports to Lareb associated with COVID-19 vaccination up to 28 May 2023*.

Vaccine	Number of reports
Pfizer/BioNTech	125,627
Pfizer/BioNTech bivalent vaccine	2,212
Moderna vaccine	49,822
Moderna bivalent vaccine	3,563
AstraZeneca	38,012
Janssen vaccine	15,087
Novavax	58
Vaccine unknown	577

**For the most recent information, see the Lareb page on side effects after corona vaccination.*

Table 9.7.2 Most frequently local reactions and systemic events reported to Lareb up to 28 May 2023*.

Adverse event	Number of reports	Adverse event	Number of reports
Fatigue	110,378	Pain at injection site	71,986
Headache	109,775	Fever	59,050
Malaise	109,208	Nausea	57,749
Myalgia	101,422	Joint pain	57,430
Chills	82,408	Swelling at injection site	30,332

**For the most recent information, see the Lareb page on side effects after corona vaccination.*

Table 9.7.3 Frequency of selected serious adverse events reported by the VASCO study population between 10 May 2021 and 20 February 2023.

Adverse event	MedDRA* preferred terms	Frequency	Proportion of all questionnaires
Anaphylactic reaction	Anaphylactic reaction	1	0.0%
Bell's palsy	Bell's palsy, Facial paralysis	1	0.0%
Guillain-Barré syndrome	Guillain-Barré syndrome	0	0.0%
Menstruation disorder	Absence of menstruation, Disorder menstrual, Heavy menstrual bleeding, Irregular menstrual cycle, Late period, Menstrual cramps, Menstrual cycle shortened, Menstrual discomfort, Menstrual disorder, Pain menstrual (all PTs identified searching for *menstr* and *period*)	36	0.1%**
Myocarditis	Myocarditis	0	0.0%
Thrombosis	Thrombosis, Thrombosis leg, Thrombophlebitis (all PTs identified searching for *thrombo*)	7	0.0%

** Medical Dictionary for Regulatory Activities*
*** Proportion based on questionnaires from female participants only*

Figure 9.7.1 Reported local reactions in the VASCO study population. A) The percentage of participants who reported local reactions following each dose. B) The duration of reported local reactions in days following each dose. C) The severity of the reported local reactions following each dose on a scale of 1 (extremely mild) to 10 (extremely severe).

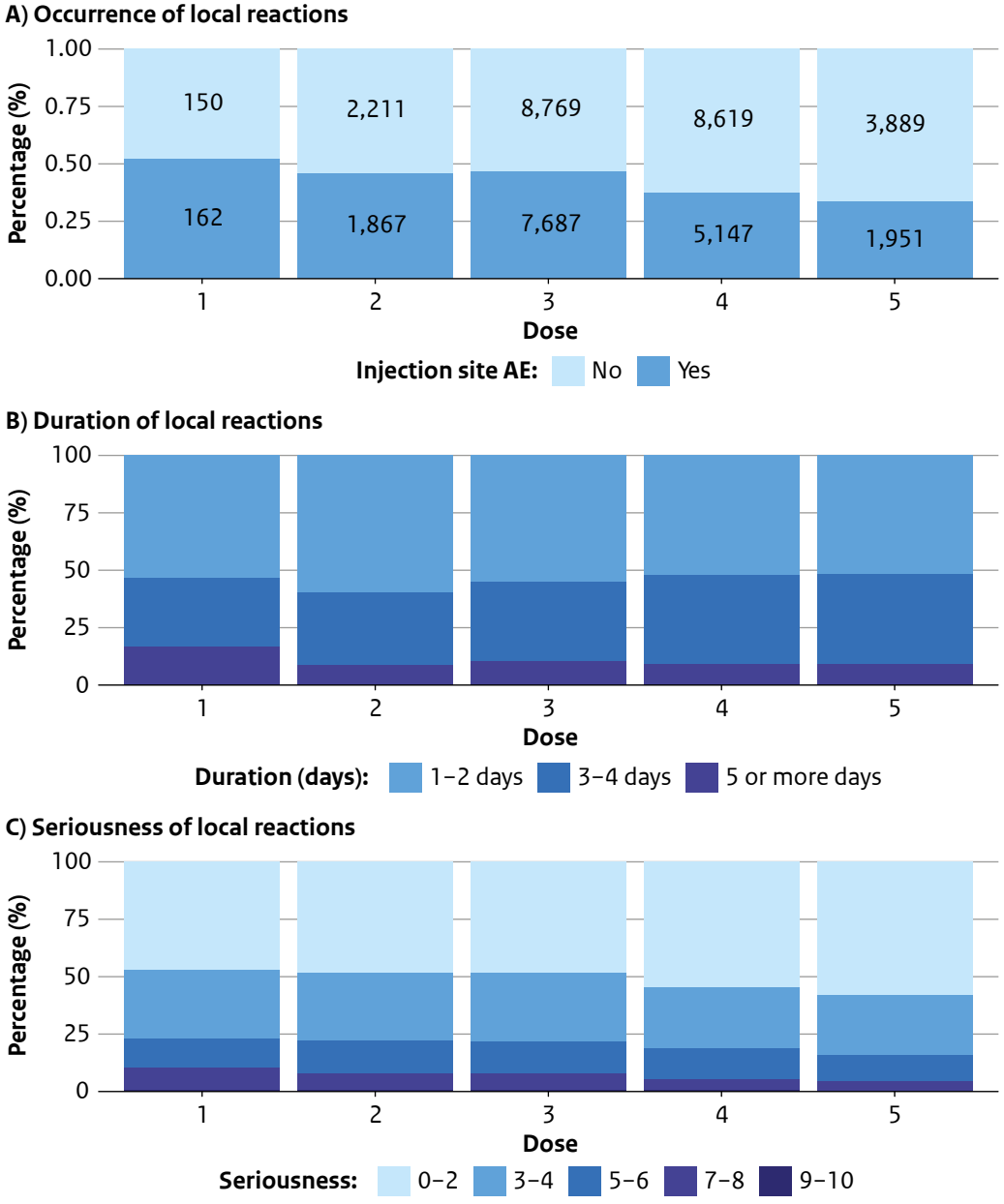


Figure 9.7.2 Reported systemic reactions in the VASCO study population. A) The percentage of participants who reported systemic reactions following each dose. B) The duration of reported systemic reactions in days following each dose. C) The severity of the reported systemic reactions following each dose on a scale of 1 (extremely mild) to 10 (extremely severe).

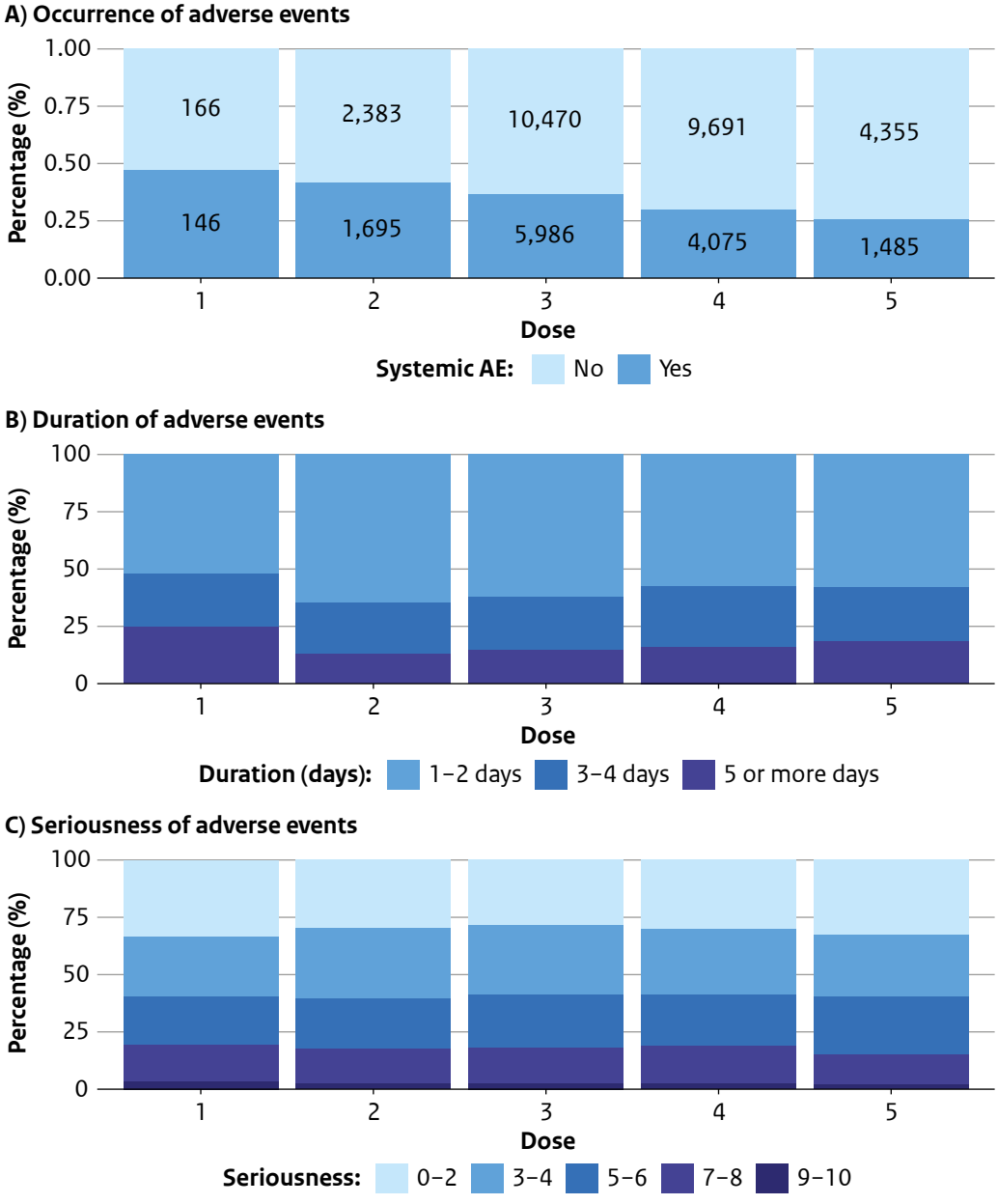
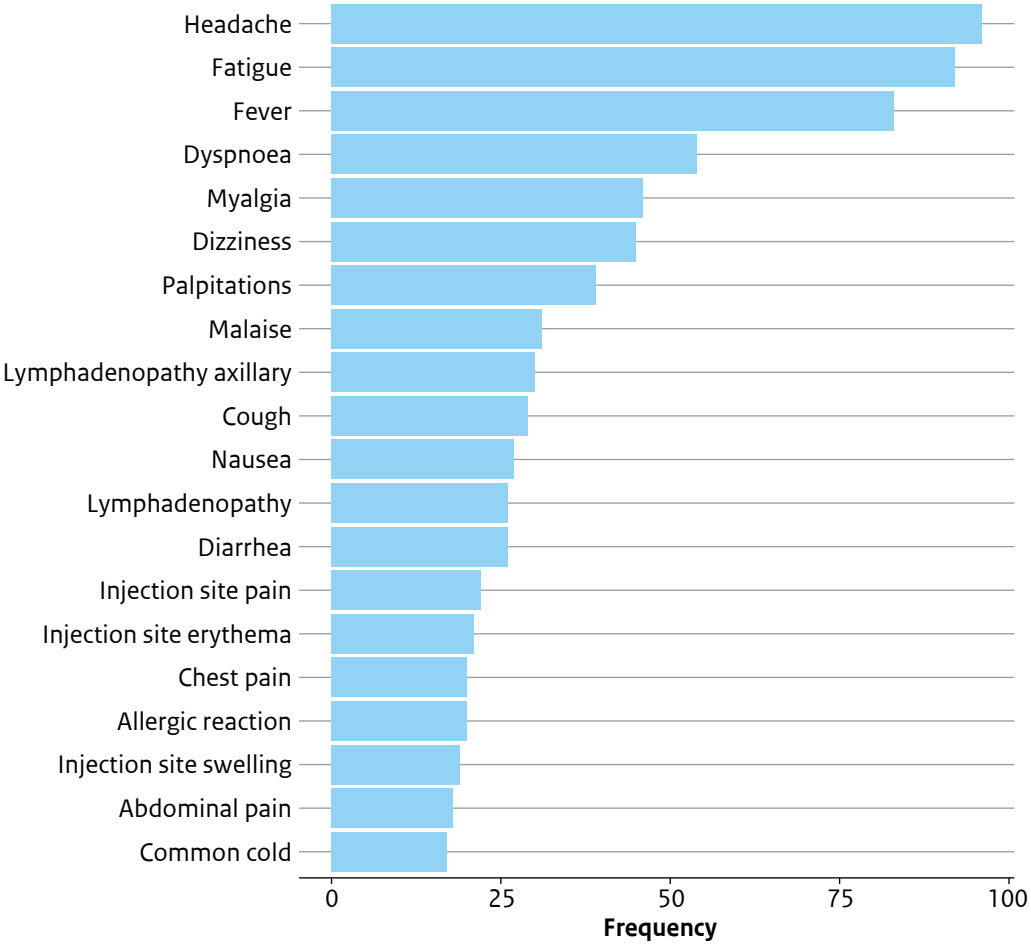


Figure 9.7.3 Top 20 of reported adverse events in the VASCO study for which contact was sought with the GP following any dose.



9.7.3 Adverse events in the Netherlands

9.7.3.1 Lareb

The spontaneous reporting system managed by the National Centre for Pharmacovigilance Lareb receives adverse events following immunisation (AEFI) reports for all COVID-19 vaccines. Up to 28 May 2023, Lareb received 234,958 reports (see Table 9.7.1). The most frequently reported adverse events are listed in Table 9.7.2. Causality cannot be established, since the reports are based on observational data.

Lareb studied the observed over expected (O:E) ratio (based on the background incidence in the Netherlands in 2017-2019) for Guillain-Barré syndrome (GBS) and Bell's palsy.

9.7.3.1.1 Guillain-Barré syndrome

Until 22 October 2022, Lareb received 72 reports of GBS following vaccination with BNT162b2 (n=30), mRNA-1273 (n=8), ChAdOx1 (n=18) and Ad26.COV2.S (n=16). The mean age of the patients was 55 years and the majority (58%) was male. One case was fatal. For all ages and for both men and women, O:E ratios were significantly elevated for vector-based vaccines (O:E 12.5 (95%CI 7.5-18.9)) and for the second dose of BNT162b2 (O:E 2.3 (95%CI 1.1-4.2)) for a 14-day risk period [1].

9.7.3.1.2 Bell's palsy

Until 24 March 2022, Lareb received 301 reports of Bell's palsy following vaccination with BNT162b2 (n=191), mRNA-1273 (n=39), ChAdOx1 (n=21) and Ad26.COV2.S (n=21). The mean age of the patients was 52 years and the majority (59%) was female. The O:E ratio was significantly higher than expected for boys aged 5-14 years after receiving the second dose of BNT162b2 (O:E 10.2, 95%CI 1.2-36.9) and for women aged 25-64 years after receiving the first dose of BNT162b2 (OE 1.48, 95%CI 1.01-2.04) [2].

9.7.3.2 Study RIVM and CBS on mortality following COVID-19 vaccination

In our previous report, we described preliminary results from a population-wide linkage study on non-COVID-mortality in the five or eight weeks following a COVID-19 vaccine dose [3]. We updated these analyses with adjustments for medical risk groups. National registries of causes of death, COVID-19 vaccination and long-term care reimbursements were linked by a unique identifier using data from 1 January 2021 to 31 January 2022. We used Cox regression with calendar time as the underlying time scale to estimate risk of non-COVID-19 mortality in the five weeks following a first mRNA vaccine and the eight weeks following a first vector vaccine, second or booster dose, adjusting for birth year, sex, medical risk group and country of origin. The results showed a lower to similar risk, compared to the vaccination status before the respective vaccine dose. This was observed for all ages and included long-term care recipients [4].

A true protective effect of COVID-19 vaccination on non-COVID-19 mortality is biologically implausible. Probably, healthy vaccinee bias has affected the results. For example, fever was a contraindication for vaccination, resulting in a selection of relatively healthy person-time shortly after vaccination. Also, people with a short remaining life expectancy may have opted to forego vaccination. Another possibility is that in deaths that were not attributed to COVID-19,

SARS-CoV-2 infection actually had an unrecognised role in the causal pathway to death.
In conclusion, this study found high effectiveness of COVID-19 vaccination against COVID-19 mortality, and no indication of increased risk of non-COVID mortality after vaccination.

9.7.3.3 VASCO study

9.7.3.3.1 Adverse events reported after vaccination

Participants in VASCO are requested to complete a questionnaire one month after each COVID-19 vaccination. In this questionnaire, questions are asked about potential adverse events following vaccination. A distinction was made between local (injection site) and systemic reactions. Participants were asked how serious the reactions were and how long they lasted. In the period between 10 May 2021 and 20 February 2023, a total of 30,383 participants completed the questionnaire. The questionnaires include the primary series and up to three booster doses. A total of 10,561 participants completed a questionnaire following the first dose, 9,523 following the second dose, 16,482 following the first booster, 13,766 following the second booster, and 5,840 following the third booster.

9.7.3.3.2 Local reactions

In 41% of the questionnaires, participants reported injection-site reactions following COVID-19 vaccination (Figure 9.7.1). Injection-site reactions were most commonly reported following vaccination with Pfizer (43%) and Moderna (41%) vaccines. The frequency of injection-site reactions did not vary for the five doses. Participants under the age of 60 years reported injection-site reactions more frequently (42%-56% per dose) than participants over 60 years (33%-42% per dose). Women reported injection-site reactions more frequently than men (49% vs 28%). To compare, the most commonly reported injection-site reactions following influenza vaccination (varying from 18%-37% in a cohort of intensively followed vaccine recipients) were pain, inflammation, swelling and erythema. These reactions are largely similar to the local reactions following COVID-19 vaccination [5].
For more than half of the participants, injection-site reactions lasted a maximum of two days. Half of the participants rated the events between 1 and 2 in severity (with 1 being extremely mild and 10 extremely severe). Overall, less than 8% of the participants reported a severity of 7 or higher, with the highest rate occurring after the first dose (11%).

9.7.3.3.3 Systemic reactions

A total of 33% of the participants reported systemic reactions (Figure 9.7.2). Systemic reactions were most frequently reported following administration of the Janssen vaccine (44%). Participants under the age of 60 years reported more systemic reactions than participants over 60 years. A trend was observed among participants under the age of 60 years where the proportion of systemic reactions declined with the number of doses (52% after the first dose and 30% after the fifth dose). Among participants over 60 years, the proportion of systemic reactions declined from 35% after the first dose to 25% after the fifth dose. Women reported more adverse events than men (37% vs 25%).
The most frequently reported systemic reactions following influenza vaccination are fatigue, headache and malaise (varying from 5% to 6% in the Lareb intensive monitoring cohort) [5].

This is also highly comparable to the systemic reactions seen after COVID-19 reactions. For more than half of the participants, systemic reactions lasted a maximum of two days following the first dose. For the subsequent doses, the systemic reactions lasted a maximum of two days for approximately two-thirds of the participants. Half of the participants rated the severity of the systemic reactions between 1 and 4 and a quarter rated the severity with at least a 6 (with 1 being extremely mild and 10 extremely severe). Overall, less than 18% of the participants reported a severity of 7 or higher, with the highest rate occurring after the first dose (26%). The differences in the duration or severity of the reported systemic reactions between the different vaccines or age groups were limited.

9.7.3.3.4 General practitioner contact

Of all vaccinated participants reporting a systemic or local reaction, 3% contacted their GP for an adverse event. Among participants under the age of 60 years, the GP was contacted most often after receiving the AstraZeneca vaccine (8% following the first dose, and 6% following the second dose). Among participants over 60 years, the GP was contacted most frequently following vaccination with Moderna (5%) or AstraZeneca (6%). For all vaccines (Pfizer, AstraZeneca, Moderna and Janssen), participants contacted the GP most frequently for headache, fatigue and fever (Figure 9.7.3). An additional search within the reported adverse events was carried out for specific serious adverse events with a suspected or confirmed association with COVID-19 vaccines (anaphylactic reaction, Bell's palsy, GBS, menstruation disorder, myocarditis and thrombosis). For thrombosis, menstruation disorder and Bell's palsy, additional multiple relevant MedDRA preferred terms (PTs) were used (Table 9.7.3). Myocarditis and GBS were never reported. Menstruation disorder was reported 36 times (0.1% of all questionnaires) (Table 9.7.3). Among the cases reporting menstruation disorder PTs, 25% concerned reports of heavy bleeding, which is listed as an adverse event for Spikevax and Comirnaty.

9.7.4 International literature

In December 2022, a Cochrane review on the safety of COVID-19 vaccines by Grana *et al.* was published. On the basis of 41 RCTs, it was estimated that the Moderna, AstraZeneca and Janssen vaccines probably result in little or no difference in the risk of serious adverse events (SAEs) compared to a placebo. However, evidence for SAEs is uncertain for Pfizer/BioNtech compared to a placebo, because the number of SAEs in the RCTs was too low [6]. Moreover, although the sample sizes of the included RCTs were large, their power may be insufficient to investigate rare adverse events. There are many large(r) observational studies as well, indicating increased risks for some adverse events after COVID-19 vaccination. The latest literature on the most severe/notable adverse events is summarised below: myocarditis, Bell's palsy, GBS, vaccine-induced thrombotic thrombocytopenia/thrombosis with thrombocytopenia syndrome (VITT/TTS) and menstrual disorders. Yechezkel *et al.* conducted a prospective and retrospective cohort study on the safety of the fourth Pfizer/BioNtech dose (second booster). Compared with the first booster, the second booster was not associated with any of 25 adverse events investigated, including myocarditis and Bell's palsy [7].

Harris *et al.* compared the risk of adverse events between the Pfizer/BioNtech and Moderna vaccines overall, by frailty level and by prior history of adverse events of interest in almost 6.4 million vaccinated older adults aged ≥66 years. The risk of all adverse events was low, with each occurring in <1% of participants and the vaccines did not differ in risk for most outcomes. However, the Moderna vaccine was associated with a lower risk of pulmonary embolism (risk ratio (RR) 0.96, 95%CI 0.93-1.00) and diagnosed COVID-19 (RR 0.86, 95%CI 0.83-0.87) [8].

9.7.4.1 Myocarditis/pericarditis

Myocarditis is a well-known, rare adverse event that can be caused by mRNA COVID-19 vaccination. Several recent studies confirm that this adverse event is most common in young males following the second dose. Bots *et al.* estimated the association between COVID-19 vaccines and risk of myocarditis/pericarditis in a population-based cohort study using healthcare data from five European databases (the Netherlands, Spain, Italy and the UK). The incidence risk ratios (IRRs) for myocarditis in over 35 million individuals were elevated in people <30 years following the second dose of Pfizer/BioNtech (IRR 7.8, 95%CI 2.6-23.5) and following the second dose of Moderna (IRR 6.1 95%CI 1.1-33.5). There was a non-significant elevation of the IRR after the second dose of AstraZeneca (IRR 2.42, 95%CI 0.96-6.07) [9]. The key study of Patone *et al.* involving almost 43 million vaccinated people found that risk of myocarditis was increased following the first, second and booster doses of Pfizer/BioNtech and following the second and booster doses of Moderna but was generally lower than the risk of myocarditis following SARS-CoV-2 infection. However, in men under the age of 40 years, the risk of myocarditis following the second dose of Moderna vaccination was higher [10]. In adolescents, a shorter interval between the first and second dose was associated with a higher incidence of myocarditis [11]. Husby *et al.* investigated the clinical outcomes of myocarditis associated with mRNA COVID-19 vaccination in four Nordic countries. Within ninety days of hospital admission for myocarditis, COVID-19 vaccination-related myocarditis was associated with much better clinical outcomes than myocarditis associated with COVID-19 disease and myocarditis caused by another pathogen [12]. Tsun Lai *et al.* confirm the much better clinical outcomes of post-vaccination myocarditis compared to viral infection-related myocarditis, with a 92% lower mortality risk [13]. In studies investigating outcomes in adolescents only, clinical function after three to six months was generally good [14, 15, 16].

Several studies investigated the risk of myocarditis following the booster (third or fourth) dose. An analysis, based on the VAERS database, of a period during which over 538 million doses of mRNA vaccines were administered showed that the incidence rate (per million doses) of myocarditis/pericarditis following the booster vaccination (third dose) was 2.84 (95%CI 2.51-3.20), which was significantly lower than the incidence rate following the primary series (IR 3.03 (95%CI 2.81-3.25) after the first dose, IR 9.26 (95%CI 8.84-9.69) after the second dose) [17]. The observation that the booster dose entails a lower risk than the primary series is confirmed in an Israeli study by Mevorach *et al.*, with a significant risk difference (RD) across all age groups of -2.72 (95%CI -3.67 - -1.73), which was highest for males aged 16-19 years (RD -8.45 (95%CI -15.30 - -0.44) [18]. In a cohort of over 3 million vaccinated people, the incidence rate ratio for myocarditis was 0.86 (95%CI 0.31-1.91) for the first dose, 4.22 (2.63-6.53) for the second dose and 2.61 (1.13-5.29) for the third dose [19]. Analysis of the Moderna Global Safety Database, comprising over 252 million vaccinated people, showed that the rate ratio of

myocarditis/pericarditis for men aged 18-24 years was lowest after the third dose: 0.47 after the first dose, 2.21 after the second dose and 0.22 after the third dose [20].
The risk of myocarditis was generally higher following vaccination with Moderna than following vaccination with Pfizer/BioNtech [10, 21, 22].
The literature on myocarditis and pericarditis in the context of the other COVID-19 vaccines is limited. Patone *et al.* found an increased risk of myocarditis following the first dose of AstraZeneca (incidence rate ratio 1.33 (95%CI 1.09-1.62)) [10]. On the contrary, analysis of the WHO VigiBase database showed that the reporting odds ratio (OR) for myocarditis following vaccination with AstraZeneca was 0.57 (95%CI 0.52-0.62), whereas the reporting OR for NovaVax was 14.47 (95%CI 11.2-18.7) [23].

9.7.4.2 Guillain-Barré syndrome
There are several studies describing the risk of GBS following COVID-19 vaccination. All studies are observational and discover only associations, not causality. Two analyses of the VAERS database established that the O:E ratios of GBS following mRNA vaccination were not significantly increased, in contrast to the O:E ratio following vaccination with the Janssen vaccine (O:E 3.1 – 3.8) [24, 25]. In their analysis of the Vaccine Safety Datalink, Hanson *et al.* also found an elevated incidence of GBS following vaccination with the Janssen vaccine [26]. This increased incidence following vaccination with the Janssen vaccine was observed in Mexico as well, together with a slightly elevated risk of GBS following vaccination with Pfizer/BioNtech [27]. Furthermore, the risk of GBS is higher than expected following vaccination with AstraZeneca, with an incidence of 1.85 reports per 100,000 doses [28]. In a prospective surveillance study in South Korea, an elevated incidence rate of GBS was observed following viral vector-based vaccination (IR 4.5 per million doses (95%CI 2.85-6.12). Risk factors for GBS following COVID-19 vaccination were male sex and first vaccination dose [29]. Lehmann *et al.* analysed excess GBS cases following administration of different COVID-19 and influenza vaccines in Germany versus the expected numbers estimated on pre-pandemic background incidence rates. They found that standardised morbidity ratio estimates 3-42 days after vaccination were 3.10 (95%CI 2.44-3.88) for AstraZeneca and 4.16 (95%CI 2.64-6.24) for the Janssen vaccine, while they were not elevated for Pfizer/BioNtech, Moderna or influenza vaccines [30].
The WHO states that there is currently not enough evidence to maintain that GBS can be caused by COVID-19 vaccines, and that the benefits of the COVID-19 Janssen and AstraZeneca vaccines are far greater than the very small risk of developing GBS [31].

9.7.4.3 Bell's palsy
As yet, the literature on the possible association between COVID-19 vaccination and Bell's palsy is inconclusive. A systematic review and meta-analysis of pooled randomised clinical trials by Rafati *et al.* found a significantly higher incidence of Bell's palsy in vaccine recipients than in placebo recipients (OR 3.0 (95%CI 1.1-8.2)). However, this higher incidence was not found in their meta-analysis of observational studies (OR 0.7 (95%CI 0.4-1.2)) [32].
In the nested case-control study and self-controlled case series of Yuk Fai Wan *et al.*in the population of Hong Kong, the incidence of Bell's palsy was 1.58 (95%CI 1.29-2.07) per 100,000 administered doses. The odds ratio for Bell's palsy after the 2nd dose of Pfizer/BioNtech

was 2.44 (95%CI 1.32-4.50) [33]. In the self-controlled case series of Walker *et al.*, there was no evidence of any association with Bell's palsy among British Pfizer/BioNtech vaccinees. However, an increased rate of Bell's palsy was found following a first dose of AstraZeneca (IRR 1.39 (95%CI 1.27-1.53) [34]. Chamboux *et al.* describe 23 cases of Bell's palsy following vaccination with Pfizer/BioNtech (n=22) or AstraZeneca (n=1). Other possible causes of Bell's palsy were ruled out. Most cases occurred after the first dose, with a median time to onset of nine days following vaccination. At four-month follow-up, clinical manifestations had regressed completely or partially in twenty patients [35].

9.7.4.4 Menstrual disorders

There was quite some public concern regarding the possible association between COVID-19 vaccination and menstrual disorders. Wong *et al.* investigated COVID-19 vaccine recipients who reported their health experiences to v-safe, a voluntary active surveillance system. Among almost 63,000 participants, reports concerning cycle length and the intensity of menstrual bleeding were most common (84% and 67%) [36]. In a cross-sectional study of over 14,000 vaccinated women who completed vaccination at least three months before inclusion, 78% of participants experienced menstrual cycle changes. The changes reported most often were heavier menstrual bleeding (43%), more menstrual pain (41%), delayed menstruation (38%), shorter length of menstruation (34.5%) and shorter cycle length (32%). In this study, the duration of the menstrual cycle changes was not reported [37]. In a population-based cohort study of 6196 girls aged 12-15 years in Norway, Caspersen *et al.* investigated menstrual disturbances after one dose of Pfizer/BioNtech. Menstrual cycle changes were a little more common in the first cycle following vaccination (25%, RR 1.6 (95%CI 1.43-1.81) for heavier bleeding) than prior to vaccination (23%) [38]. Ljung *et al.* conducted a nationwide register-based cohort study in Sweden and included almost three million women aged 12-74 years. An association between bleeding after menopause and mRNA COVID-19 vaccination was found, with the highest risk of bleeding following the third dose (HR 1.48 (1.12 to 1.94)) during the 1-7-day risk window. There was no evidence for any association between menstrual cycle disorders and COVID-19 vaccination in premenopausal women. In this study, higher crude HRs were found during the 1-7-day risk window than during the 8-90-day window, indicating that menstrual cycle changes may have been temporary [39]. Indeed, there are several studies that indicate that menstrual disorders are resolved quickly [40, 41, 42]. The WHO also refers to studies that found that there can be small and temporary changes in menstrual cycle length and flow [43].

9.7.4.5 VITT/TTS

TTS is a rare adverse event that has been reported in individuals vaccinated with the Janssen and AstraZeneca COVID-19 vaccines. In patients with platelet activating anti-PF4 antibodies, this has been characterised as VITT. The WHO states that the cumulative incidence of TTS following COVID-19 vaccination ranges from 0.5-6.8 cases per 100,000 vaccinees. However, not all blood clots that occur after vaccination will be due to TTS, as blood clotting problems can be caused by many factors [31]. The WHO provided an update of their guideline on treatment of patients presenting with VITT/TTS [44]. Li *et al.* quantified the comparative risk of VITT/TTS with the use of the AstraZeneca/Janssen vaccines versus mRNA-based vaccines.

In their international network cohort study, AstraZeneca recipients were matched to Pfizer/BioNtech recipients, and Janssen vaccine recipients were matched to Pfizer/BioNtech or Moderna recipients. A 30% increased risk of TTS was seen after the first dose of AstraZeneca compared to the first dose of Pfizer/BioNtech (pooled calibrated incidence rate ratio 1.33 (95%CI 1.18-1.50)). A trend towards an increased risk of TTS was observed after a first vaccine dose of Janssen compared to Pfizer/BioNtech (pooled calibrated incidence rate ratio 2.26 (95%CI 0.93-5.52) [45]. On the basis of an international registry of 133 VITT/TTS cases, it was found that the majority (77%) of cases was female and that women were more severely affected at presentation, although the clinical course did not differ between men and women [46]. Shaw *et al.* re-evaluated risk estimates of VITT/TTS following AstraZeneca vaccination. Using the haematology results of vaccinated and unvaccinated hospital-admitted VITT/TTS patients in the UK, they found that the attributable risk estimates for a cerebral venous sinus thrombosis or other venous thromboembolism with thrombocytopenia following vaccination were 2.82 and 9.62 per million doses, respectively [47]. Struyf *et al.* investigated the occurrence of VITT/TTS following vaccination with the Janssen vaccine. On the basis of the clinical trials database, the incidence was 46 per 100,000 person-years. In the Global Medical Safety Database, 335 reports of VITT/TTS were found, of whom 27 met the highest level of diagnostic certainty. This study confirms that VITT/TTS induced by the Janssen vaccine is very rare [48].

9.7.4.6 Mortality

Xu *et al.* studied non-COVID-19 mortality risk following COVID-19 vaccination. Almost 7 million vaccinated and unvaccinated US inhabitants were included in the study. After adjusting for confounders, the adjusted HRs for mortality were 0.46 (95%CI 0.44-0.49) and 0.48 (95%CI 0.46-0.50) for the first and second doses of Pfizer/BioNtech; 0.41 (95%CI 0.39-0.44) and 0.38 (95%CI 0.37-0.40) for the first and second doses of Moderna and 0.55 (95%CI 0.51-0.59) for the Janssen vaccine. In this study, no increased risk was found for non-COVID-19 mortality following COVID-19 vaccination [49]. Day *et al.* analysed reports of death to VAERS following COVID-19 vaccination. Between December 2020 and November 2021, 9201 death events were reported for COVID-19 vaccine recipients. Reporting rates for death events were lower than the all-cause death rates expected in the general population. Moreover, these findings do not suggest an association between COVID-19 vaccination and overall increased mortality [50].

9.7.5 Literature

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10
Vaccines in development for other potential future NIP target diseases

N.Y. Rots

10.1 Chapter overview

The tables below present an update of information on vaccines in development for infectious diseases that have reached the clinical testing phase and are relevant for the Netherlands. In general, vaccine development takes ten to twenty years, while only a small percentage (6%) of vaccines that have been tested in phase I reach marketing authorisation. On average, clinical development phase I takes one to two years, phase II two to three years, and phase III four to six years. However, with the SARS-CoV-2 vaccines, we have seen that, during a pandemic, it is possible to develop a vaccine, from research to market authorisation, within one year. The mRNA vaccine platform that has been successfully used for the development of SARS-CoV-2 vaccines is also being used for the development of other vaccines, for example for influenza, RSV, CMV and rabies.

In April 2023, the European Medicines Agency (EMA) approved the first vaccine to prevent RSV infections in older adults of 60 years and over, followed by EU market authorisation granted by the European Commission EC on 7 June 2023 (see this press-release). It concerns a recombinant adjuvanted stabilised prefusion F-protein vaccine (Arexvy) developed by GSK [1]. Results of the phase-III study with the vaccine show a vaccine efficacy of 82.6% against RSV-associated lower respiratory track disease (LRTD) and of 94.1% against severe LRTD (see this press-release). Pfizer has developed a similar vaccine that has been approved by the EC in August 2023 for use in older adults and pregnant women to help protect their infants after birth (see this press-release). Phase-III results showed a vaccine efficacy of 57.1% against medically attended RSV-associated lower respiratory tract illness within 90 days after birth [2]. GSK has stopped the phase-III trial for its RSV vaccine in pregnant women after observing an increase in neonatal deaths and preterm births. Moderna has submitted its mRNA vaccine for approval to the EMA in the first half of 2023.

The WHO provides an overview of the SARS-CoV-2 vaccines in development on its website, (see the WHO COVID-19 vaccine landscape), summarised in a separate table in chapter 10.4. The number of SARS-CoV-2 vaccines currently in development has increased to 382, of which 183 have reached the clinical phase (as of 30 March 2023). Most of them are RNA (24%) or protein subunit (32%) vaccines, followed by viral vector (14% replicating and 2% non-replicating), inactivated vaccines (12%), and DNA vaccines (9%). The European Medicines Agency (EMA) has granted (conditional) approval for eight vaccines, which is three more (for Sanofi, Valneva and HIPRA) than last year. Pfizer/BioNTech and Moderna received marketing authorisation for their vaccines that have been adapted to VOCs. Both companies developed bivalent vaccines (Wuhan/Omicron BA.1 and Wuhan/Omicron BA.4/5). Marketing authorisation evaluation has started for the vaccines developed by SK Chemicals GmbH, while the vaccines developed by Sinovac and Russia's Gamaleya National Centre of Epidemiology and Microbiology (Sputnik V) have been under rolling review since 2021.
The European Commission (EC) has purchased agreements for SARS-CoV-2 vaccines from eight manufacturers. Out of these SARS-CoV-2 vaccines, only the vaccines that are relevant for the Netherlands and that are being tested in humans have been included in the overview.

10.2 Bacteria

Vaccine	Status, clinical phase
Chlamydia	
• Adjuvanted chlamydia vaccine CTH522 (SSI/ Imperial College London)	I completed, safe, humoral and cellular immune response
Clostridium difficile	
• Toxoid inactivated (Pfizer, PF-07941314)	III, FDA fast track
• PF-078316941 (Pfizer) novel formulation	I
• Recombinant toxoid VLA84, genetic fusion (Valneva)	II completed III, waiting for partner
• Recombinant protein adjuvant (GSK)	I
Gonorrhoeae	
• Membrane antigen vaccine (GSK)	I, 16 years and over
Helicobacter pylori	
• HP3 (Chiron/Novartis)	I/II completed, limited protective immunity, not pursued
• Oral recombinant vaccine (China)	III, discontinued
Lyme	
• Outer surface protein-based vaccine (GSK)	Licensed but removed from market in 2002 due to poor market performance
• Multivalent (6) outer surface protein A subunit vaccine VLA15, 6 strains (Valneva/ Pfizer)	III, 5-65-year-olds, FDA fast track, EMA submission expected 2025
Meningococcal ABCWY	
• MenABCWY recombinant conjugated (Novartis/GSK)	IIIB, 15-25-year-olds booster dose study
• MenABCWY recombinant conjugated, 2nd generation (GSK)	IIA, adolescents and infants >6 weeks of age
• MenACWY infants (GSK)	III, infants (>6weeks) and adolescents
• MenACWY Menquadfi infants >6wks (Sanofi)	III
• Nimenrix-Trumemba combinations (Pfizer)	III, adolescents, young adults positive results, Submission FDA
• Multicomponent Men B (Sanofi)	II
• Multicomponent Men B Bexero (GSK)	III, infants >2 months of age

Vaccine	Status, clinical phase
Moraxella catarrhalis, non-typeable Haemophilus influenza COPD	
• Recombinant COPD reduction with adjuvant (GSK)	II completed
Shigella	
• Live attenuated oral single-strain (University Maryland US)	II and IIB challenge study terminated due to safety issues
• Monovalent synthetic carbohydrate based conjugate vaccine (University Maryland)	II
• Inactivated oral whole cell (University Maryland)	II terminated
• Single-component O-antigen *S. sonnei* vaccine (Pasteur/GSK)	II completed
• Monovalent O-antigen *S. Flexneri* serotype vaccine (Pasteur)	II results expected 2023
• Recombinant glycoconjugate (biconjugate)	III
• Bioconjugate outer membrane tetravalent (Novartis/GSK)	II
• Generalised Modules for Membrane Antigens (GMMA) vaccine (GSK)	II
Staphylococcus aureus	
• Conjugate (SA4Ag, 4 antigen) (Pfizer)	IIB failed Previous phase I-III with different single antigen vaccine candidates all failed due to safety concerns and low efficacy
• Recombinant Protein bioconjugated adjuvated (GSK)	II
Streptococcus group A	
• N-terminal M protein-based multivalent vaccines (26-valent and 30-valent)	II
• Conserved M protein vaccines (the J8 vaccine and the StreptInCor vaccine)	I completed
• C-terminal M-protein DTconjugate, AlOH adjuvanted	I

Vaccine	Status, clinical phase
Streptococcus group B	
• CPS-protein conjugate (mono and trivalent) (Novartis/GSK)	II, maternal
• 6-valent polysaccharide CRM197 conjugated vaccine (Pfizer)	II, maternal interim results, breakthrough therapy designation
• Recombinant fusion antigen (Minervax, APS, GBS-NN)	I completed
Pneumococcus*	
• (Killed) whole-cell vaccine	II
• PCV15 with Alum adjuvant children (MSD)	EMA registration, Vaxneuvance adults and children > 6 weeks
• PCV21 adults including older adults (MSD)	II completed, breakthrough therapy designation FDA
• PCV20 (Pfizer)	III, infants and children <18yrs, approved adults
• Protein-based? PCV24 vaccine MAPS (Multiple antigen Presenting System (GSK)	II, adults, 6 weeks-17 yrs
• Protein-based conjugate vaccine, next generation (Sanofi)	II
Tuberculosis (all forms, all ages)	
• Live attenuated vaccine BCG	On market but low efficacy
• M72/ASO1 adjuvanted recombinant fusion protein (GSK licensed to Gates, IAVI)	II(B) published VE 54%
• Subunit adjuvanted recombinant fusion protein (H4:IC31®) (Aeras/Sanofi/SSI now IAVI)	II published
• Modified Recombinant BCG	II
• Recombinant Subunit (GSK, Sanofi)	II completed
• Live attenuated (MTBVAC)	III
• Lysate of NTM	III
• Killed whole cell (booster) (Aeras, IAVI)	II
• Viral vector ChAdOx1 85A (Oxford)	I-II

** For conjugate serotype specific vaccines, see section 6.9 on pneumococcal disease.*

10.3 Viruses

Vaccine	Status, clinical phase
Chikungunya	
• Live recombinant measles virus-based, Merck V184 (Merck)	II completed
• Virus-like particle (NIAID)	I/II completed
• Live attenuated (Valneva)	III completed, positive results, FDA fast track, pre-submission FDA Q2 2022, PRIME designation by EMA submission expected H2 2023, adults 18 years and over
Cytomegalo (CMV)	
• Glycoprotein B bivalent	I and III
• Replication defective V160 (MSD)	II completed
• Recombinant, subunit adjuvant (GSK)	I, females age 16-49 years
• RNA vaccine (Moderna)	II
Dengue	
• Live recombinant (tetravalent) (Butantan/ NIAID)	III data
• Live-attenuated (tetravalent) TDV (Takeda)	III, authorised for use EMA, 4 years and over
• Live virus (GSK)	II
• Recombinant Subunit (tetravalent) V181 (GSK/Merck)	II
• Inactivated virus (GSK/Merck)	I
• Live attenuated, Dengavaxia (Sanofi)	Registration approved for 9-45 years of age, for seropositive people only
Ebola	
• rVSVΔG-ZEBOV-GP V920 (Merck/NewLink Genetics)	III, approved for compassionate use
• CAd3-EBOZ (GSK/NIH/NIAID)	III
• Ad26-EBOV and MVA-EBOV (Johnson & Johnson/Janssen vaccines/Bavarian Nordic)	EMA registration
• Recombinant nanoparticle based (Novavax)	III
• Recombinant Viral vector (GSK, 2019 Sabin vaccine institute)	II

Vaccine	Status, clinical phase
• VRC-EBOADC069-0-VP (Okairos/NIAID)	I
• Adjuvanted (Matrix-M) glycoprotein vaccine (Novavax)	I
Epstein–Barr	
• Recombinant gp350, glycoprotein subunit	II
• mRNA (Moderna)	II
• Live attenuated vaccines	On hold
Hepatitis C	
• Recombinant, heterologous viral vector (GSK)	II, not effective in preventing infection
Hepatitis E	
• Recombinant protein (Hecolin®) (Xiamen Innovax Biotech)	IV Approved in China, not registered in EU
Herpes simplex	
• HSV-529 replication defective live attenuated (Sanofi, Immune design)	I results
• Recombinant protein adjuvanted (GSK)	I adults
Herpes zoster (Shingles)	
• Recombinant (Shingrix, GSK)	Approved in US and EU
• Inactivated V212 (Merck)	III on hold
HIV	
• Recombinant protein (GSK)	II
• Viral vector Prime/boost (Sanofi)	II
• Ad26 Mos HIV vaccine (Janssen vaccines)	III
• DNA (GeoVax)	II completed
• mRNA (Moderna)	I
Hookworm	
• iBio	I, not in iBio pipline anymore
Noro	
• Virus-like particles (bi-valent) (Takeda, now Hillvax)	III
• Oral tablet vaccine (Vaxart), bivalent and monovalent (Vaxart)	II results expected mid 2023

Vaccine	Status, clinical phase
Malaria	
• Recombinant protein subunit CSP antigen fusion with hepatitis B protein with adjuvant RTS,S/AS01 (Mosquirix) (GSK/PATH)	EMA registration for use outside EU for children 6 weeks to 17 months of age, prequalified by WHO 2022, VE@30% hospitalisation
• Protein subunit vaccine CSP antigen with matrix M adjuvant, R21/Matrix-M (Jenner institute, Novavax, SII)	I, VE77% symptomatic malaria III, VE 74% severe malaria Registration in Ghana April 2023 VE@80%, FDA fast track III
• Radiation attenuated sporozoities PfSPZ vaccine (Sanaria), requires storage liquid nitrogen	III
MERS-CoV	
• MVA-MERS-S	I, booster dose safe and sign NT response
• DNA (GeneOne Life Science/Inovio)	II started in August 2021
Parainfluenza type I	
• Live attenuated	I-II
Respiratory syncytial (RSV) (17 in clinical development)	
• Live attenuated (Sanofi/NIH)	II, toddlers
• Live attenuated (Intravacc)	I, paediatric
• Inactivated whole-cell	0
• Nanoparticle-based (Novavax)	III, maternal data 2021, FDA fast track, failed
• Recombinant protein (Novavax)	I, 2-6 years
• Recombinant protein nanoparticle with Matrix Adjuvant (Novavax)	I, 60+ years
• Subunit, F-protein with adjuvant (GSK)	Elderly 60+ yrs EMA registration April 2023 III, adults 50-59 yrs III, maternal, stopped due to safety concerns
• Subunit, F-protein (NIH/NIAID/VRC)	I, paediatric
• Subunit, F-protein (Pfizer)	III, maternal III, older adults Both indications accelerated assessment EMA and fast track FDA Combination with influenza I

Vaccine	Status, clinical phase
• Subunit, F-protein (Janssen)	III elderly stopped, combined with vector vaccine
• Subunit, F-protein (Merck)	II, elderly-maternal I, elderly
• Gene-based vector MVA bivalent targeting 5 proteins (Bavarian Nordic)	III, older aduls
• Ad26.RSV.preF with a prefusion F (preF) protein (Janssen)	III, older adults, development stopped after portfolio review. Phase II VE 70-80%, III 27.000 enrolled
• Gene-based vector AV (Vaxart)	I, paediatric
• RNA vaccine (Moderna)	III, older adults II, pediatric
• RNA vaccine (Sanofi)	I, older adults
Typhoid	
• TT-conjugate (Bharat Biotech)	III published
• Conjugate vaccine TCV (GSK)	I
• Typhoid and para-typhoid conjugate vaccine (GSK)	I
West Nile	
• Inactivated (NIAID)	I completed
• Chimeric vaccine; live attenuated recombinant (ChimeriVax) (NIAID/Acambis)	II completed
• Recombinant subunit (NIAID/Hawaii Biotech)	I completed
• DNA (NIAID/NIH)	1 completed
Zika	
• DNA (GeneOne Life Scinence/Inovio/NIAID)	II
• RNA (Moderna)	II
• Live attenuated	II
• Whole virus inactivated (Sanofi, Takeda, NIAID)	II completed (Sanofi did not start phase III limited funding Barda)
• Whole virus inactivated (Valneva)	I completed, on hold priority to vaccines for greater health crisis

Source: WHO and clinicaltrial.gov, websites of pharmaceutical companies.

10.4 SARS-CoV-2

Company	Status
Inactivated whole virus	
• Sinovac (China)	EMA rolling review since May 2021
• Bharat Biotech	III, emergency use listing WHO
• Valneva#	EMA-approved
Live attenuated virus	
• Meissa vaccines	I
• Intranasal vaccine (Conagenix/SII)	III
Non-replicating Viral vector	
• ChAd# (Oxford University/AstraZeneca)	EMA conditional marketing authorisation
• Ad5 (CanSino Beijing Institute Biotech)	Registration in China
• Ad26# (Janssen Pharmaceutical)	EMA standard marketing authorisation
• Ad26, Sputnik V (Gamaleya Res. Ins)	EMA rolling review since March 2021
• ReiThera/Leukocare/Univercells	II/III
• Ad5, adjuvanted, oral vaccine (Vaxart)	II
• hAd5 S + N (immunityBio)	II
• MVA modified vaccinia Ankara + synthetic SARS-CoV-2 (Ludwich Maximilinas University Munich)	I completed
• MVA modified vaccinia Ankara + synthetic SARS-CoV-2 (City of Hope Medical Center California)	II/III
Replicating Viral Vector	
• MVA (MSD/Inst Pasteur/Themis/University of Pittsburg)	I/II, development discontinued
• rVSV (Israel Institute for Biological Research)	II/III
Protein (sub-unit)	
• Matrix M adjuvant# (Novavx)	EMA conditional marketing authorisation
• ASO3 adjuvant# (Sanofi/GSK)	EMA marketing authorisation November 2022
• With adjuvant* (HIPRA)	EMA-approved March 2023

Company	Status
• ASO3 or CPG and aluminium adjuvant (Clover/GSK/Dynavax)	III completed
• MF59 adjuvanted sclamp (University of Queensland, CSL, Sequirus)	II/III, development suspended
• Plant based KBio holdings Ltd. (former Kentucky Bioprocess)	I/II
• Vaxine Meditox, CinnaGen (Advax adj)	III
• Medigen/NIAID, Dynavax (CpG 1018 adj) (Taiwan)	III completed, authorised in Taiwan
• TT-conjugate, AlOH adjuvant (Finlay inst. Cuba)	III, authorised emergency use in Cuba and Iran
• Vaxxinity, multitope peptide base vaccine (former COVAXX)	III
• UMCGroningen Akston	II, booster trial
• OMV-linked HexaPro Spike (Intravacc)	I
RNA	
• LNP encapsulated mRNA#, mRNA-1273 (Moderna)	EEMA marketing authorisation 6 yrs and over and for 6 months-5 yrs and adapted strain bivalent vaccines (Wuhan-Omicron BA.1 and Wuhan-Omicron BA.4/5)
• LNP encapsulated mRNA#, Comirnaty (BioNTech/Pfizer)	EMA marketing authorisation > 6 months and over, monovalent and bivalent adapted strain vaccines Wuhan-Omicron BA.1 and Wuhan-Omicron BA.4/5)
• LNP encapsulated mRNA, Comirnaty combination with influenza vaccine (BioNTech/Pfizer)	I
• Imperial College London (LNP)	I
• Curevac#	IIII, withdrawn from EMA review, VE 49%, failed
• Acturus Duke/NUS	II
• Sanofi Pasteur Translate Bio	II
• GSK, self amplifying RNA, LNP platform	I, 16 years and over

Company	Status
DNA	
• DNA plasmid electroporation (Inovio/IVI)	III
• Zydus Cadila Healthcare Limited	III
• Genexine consortium	II/III
• Adjuvanted (Osaka University/Takara bio)	II/III
VLP	
• Medicago	III
• SII SpyBiotech (HBsAg RBD S)	I/II
• Radboud University (MF59)	III

 # COVID-19 vaccines with EC contract.

10.5 Literature

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11
List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
95%CI	95% confidence interval
95%CrI	95% credibitily interval
AdV	adenovirus
AEFI	adverse event following immunisation
AEs	adverse events
AFP	acute flaccid paralysis
aHR	adjusted hazard ratio
aP	acellular pertussis
ARI	acute respiratory infection
B. parapertussis	*Bordetella parapertussis*
B. pertussis	*Bordetella pertussis*
BAU/mL	binding antibody units per milliliter
BES	Bonaire, St. Eustatius, Saba
bOPV	bivalent oral polio vaccine
BRP	Personal Records Database; Basisregistratie Personen
CAAP	community-acquired alveolar pneumonia
C. belfantii	*Corynebacterium belfantii*
C. diphtheriae	*Corynebacterium diphtheriae*
C. ulcerans	*Corynebacterium ulcerans*
C. tetani	*Clostridium tetani*
CAS	Curacao, Aruba, St. Maarten
CBS	Statistics Netherlands; Centraal Bureau voor de Statistiek
CC	clonal complex
CC	cervical cancer
CD4/8	cluster of differentiation 4/8
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CIb	Centre for Infectious Disease Control Netherlands
CIMS	COVID-vaccination Information Monitoring System
CIN	cervical intraepithelial neoplasia
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRM	cross-reactive material
CRM197	genetically modified CRM of the diphtheria toxin
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
cVDPV1	circulating vaccine derived polio virus type 1
cVDPV2	circulating vaccine derived polio virus type 2
cVDPV3	circulating vaccine derived polio virus type 3

DALY	disability-adjusted life years
DHD	Dutch Hospital Data
DNA	deoxyribonucleic acid
DPR	Dutch Perinatal Registry
DR (of Congo)	Democratic Republic (of Congo)
DTaP	combination of diphtheria, tetanus and acellular pertussis vaccines
DTaP-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines
dT3aP-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines, containing 3 pertussis antigens
dTa5P-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines, containing 5 pertussis antigens
DTPa-IPV/Hib	combination of diphtheria, tetanus, pertussis, inactivated polio and *Haemophilus influenzae* type b vaccines
DTaP-IPV-HBV-Hib	combination of diphtheria, tetanus, pertussis, inactivated polio, hepatitis B virus and *Haemophilus influenzae* type b vaccines
DT-IPV	combination of diphtheria, tetanus and inactivated polio vaccines
DTP3	third dose of a combination of diphtheria, tetanus and pertussis vaccine
ECDC	European Centre for Disease Control and Prevention
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMI	Early measles Immunised children study
EU	European Union
EUL	Emergency Use Listing
EV	enterovirus
FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
FHbp	factor H-binding protein
Fim 2	serotype 2 fimbriae
Fim3	serotype 3 fimbriae
GA	gestational age
GAPIV	Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use
GE	gastroenteritis
GGD	municipal health services; gemeentelijke gezondheidsdiensten
gMATS	Genetic Meningococcal Antigen Typing System
GMC	geometric mean concentrations
GNV	gender neutral vaccination
GP	general practitioner

GPLN	WHO Global Polio Laboratory Network
GSL	Global Specialized Laboratory
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	Health Council
HepB	hepatitis B virus
Hi	*Haemophilus influenzae*
Hia	*Haemophilus influenzae* type a
Hib	*Haemophilus influenzae* type b
Hie	*Haemophilus influenzae* type e
Hif	*Haemophilus influenzae* type f
HIV	human immunodeficiency virus
hMPV	human metapneumovirus
HPV	human papillomavirus
HR	hazard ratio
hrHPV	high-risk human papillomavirus
HSIL+	high-grade squamous intraepithelial lesions or worse
HWS	The Netherlands Ministry of Health, Welfare and Sport
HZ	herpes zoster
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IKNL	Netherlands Comprehensive Cancer Organisation; Integraal Kankercentrum Nederland
ILI	influenza-like illness
IMD	invasive meningococcal disease
IMD-ACWY	invasive meningococcal disease caused by the serogroups A, C, W or Y
IMD-B/C/W/X/Y/Z	invasive meningococcal disease caused by serogroup B/C/W/X/Y/Z
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rate
IRR	incidence rate ratio
IQR	interquartile range
IU	international unit
JCVI	Joint Committee on Vaccination and Immunisation
KNCV	Royal Dutch Chemical Organisation; Koninklijke Nederlandse Chemische Vereniging

LINH	Netherlands Information Network of General Practice; Landelijk informatienetwerk huisartsenzorg
LSIL	low-grade squamous intraepithelial lesions
LTCF	long-term care facility
MCV1	first dose of a measles-containing vaccine
MenACWY	quadrivalent meningococcal conjugate vaccine
MenACWY-CRM	quadrivalent meningococcal vaccine conjugated to mutant diphtheria toxin
MenA/B/C/E/W/Y/Z	Meningococcal serogroup A/B/C/W
MenB-fHbp	Meningococcal B vaccine targeting factor H-binding protein
MLST	multilocus sequence typing
MMR	combination of measles, mumps and rubella vaccines
MMRV	combination of measles, mumps, rubella and Varicella vaccines
mOPV2	monovalent type 2 Oral Polio Vaccine
MPV	maternal pertussis vaccination
MSM	men who have sex with men
MSW	men who have sex with women
NA	not available/applicable
NIBSC	National Institute for Biological Standards and Control
NIC	National Influenza Centre
NICE	Dutch National Intensive Care Evaluation; Nationale Intensive Care Evaluatie
NIP	National Immunisation Programme
Nivel	Netherlands Institute for Health Services Research; Nederlands Instituut Voor onderzoek van de Eerstelijnstgezondheidszorg
NKR	Netherlands Cancer Registry
nonPPV23	pneumococcal serotypes not included in the PPV23 vaccine
nOPV2	novel oral polio vaccine type 2
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NRLBM	Netherlands Reference Laboratory for Bacterial Meningitis
nOPV2	novel type 2 oral polio vaccine
NTHi	nontypeable *Haemophilus influenzae*
NWKV	Dutch Working Group for Clinical Virology; Nederlandse Werkgroep voor Klinische Virologie
NYSDOH	New York State Department of Health
OMT-V	Outbreak Management Team Vaccination
OR	odds ratio
OSIRIS	Dutch information system for infectious disease surveillance; Online systeem voor infectieziekten registratie binnen ISIS

PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV10-extra	serotypes included in PCV10 that are not included in PCV7
PCV13	13-valent pneumococcal conjugate vaccine
PCV15	15-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PCV21	21-valent pneumococcal conjugate vaccine
PHN	postherpetic neuralgia
PIV	parainfluenza viruses
PorA	porin A protein
POTS	postural orthostatic tachycardia
PPV	pneumococcal polysaccharide vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
Prn	pertactin
Ptx	pertussis toxin
PV	poliovirus
QALY	quality-adjusted life year
RBD	receptor binding domain
RCT	randomized controlled trial
RhV	rhinovirus
RIVM	Netherlands National Institute for Public Health and the Environment
RNA	ribonucleic acid
RR	relative risk
RSV	respiratory syncytial virus
RZV	recombinant zoster vaccine (Shingrix®)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIDS	sudden infant death syndrome
SHC	sexual health clinic
SL3	Sabin like type 3
SNP	single nucleotide polymorphisms
SSPE	subacute sclerosing panencephalitis
ST	sequence type
Tdap	tetanus, diphtheria and pertussis vaccine
STP	Sewage Treatment Plant
TIG	tetanus immunoglobulin
T-PEP	tetanus post- exposure prophylaxis
TTS	thrombocytopenia syndrome

UK	United Kingdom
UNICEF	United Nations Children's Fund
US	United States
USPB	Utrecht Science Park Bilthoven
VAERS	Vaccine Adverse Event Reporting System
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VITT	Vaccine Induced Prothrombotic Immune Thrombocytopenia/ Vaccine-Induced Immune Thrombotic Thrombocytopenia
VOC	variant of concern
VR	variable region
VZV	varicella zoster virus
WGS	whole-genome sequencing
WHO	World Health Organisation
WKZ	Wilhelmina Children's Hospital
wP	whole-cell pertussis
WPV	wild poliovirus
WPV1	type 1 wild poliovirus
WPV3	type 3 wild poliovirus
ZVL	zoster vaccine live (Zostavax®)

12
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 an online platform hosted by RIVM. In addition to patient characteristics (e.g. year of birth, sex, postal code), GGD collects epidemiological (e.g. related cases, risk factors) and clinical data (e.g. hospital admission, death, vaccination status).

Table A1.1 Periods and category of statutory notifications for vaccine-preventable diseases (VPDs) included in the current National Immunisation Programme (NIP).

Disease	Category	Periods of notification by legislation
Diphtheria	B1	from 1872 onwards
Pertussis	B2	from 1975 onwards
Tetanus	C	1950–1999, from December 2008 onwards
Poliomyelitis	A	from 1923 onwards
Invasive *Haemophilus influenzae* type b	C	from December 2008 onwards
Hepatitis B disease	B2	from 1950 onwards
Invasive pneumococcal disease	C	from December 2008 onwards (cases born in or after 2006) from April 2021 onwards (cases aged 60+)
Mumps	C	1975–1999, from December 2008 onwards
Measles	B2	1872–1899, from 1975 onwards
Rubella	B2	from 1950 onwards
Invasive meningococcal disease	C	from 1905 onwards

A1.1.1.2 Register-based data

A1.1.1.2.1 Death statistics

Statistics Netherlands (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerns a natural death, a non-natural death, or a stillborn child. In the event of a natural death, the physician is required to report the illness or disease that has led to death (primary cause), any complication directly related to the primary cause that has led to death (secondary cause), as well as additional diseases and specifics present at the moment of death that have contributed to death (secondary causes). 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 implemented an IRIS algorithm? to automatically code the causes of death [3]. One of the advantages of this procedure is that it increases the international comparability of data. The change in coding did however cause considerable (once only) shifts in the statistics.

A1.1.1.2.2 Hospital admissions

Until 2010, hospital data was managed by the Prismant research institute in the National Medical Register (LMR). After 2011, Dutch Hospital Data (DHD) managed the LMR. Since 2013, the National Register Hospital Care (LBZ) managed by DHD has received the discharge diagnoses of all patients admitted to hospital. Outpatient diagnoses are not registered. Diseases, including all NIP-targeted diseases, are coded as the main or subsidiary diagnosis according to the ICD-10 coding system. Up to 2012, discharge diagnoses were coded according to the ICD-9 coding system, thereafter according to ICD-10. Coverage of this registration system amounted to about 99% until mid-2005. Thereafter, coverage has fluctuated due to changes in funding (Table A1.2). The data presented in this report relate only to clinical admissions and have not been corrected for changes in coverage, causing an underestimation of hospital admissions from 2006 up to 2014. Hospital admission data are also susceptible to under-reporting, as shown by De Greeff *et al.* in a paper on meningococcal disease incidence [4] and by Van der Maas *et al.* for pertussis [5]. Hospitalisation data from 2015 onwards are retrieved from Statistics Netherlands. These data are corrected for non-participating hospitals, which may have resulted in a trend break compared to previous years. Due to privacy regulations, data are also rounded off to the nearest five. With these numbers, one should consider that 0 cases are not always actually 0 but may also mean a few cases. Data for 2021 are not available as yet.

Table A1.2 The completeness of LMR/LBZ data through the years*, by day admissions and clinic admissions.

Year	Day admission		Clinic admission	
	% registered	% generated (=missing)	% registered	% generated (=missing)
2007	87	13	89	11
2008	88	12	88	12
2009	87	13	88	12
2010	86	14	89	11
2011	79	21	85	15
2012	72	28	82	18
2013	74	26	84	16
2014	82	18	99	1

** These numbers are an approximation of the exact percentage.*
Sources: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards.

A1.1.1.2.3 Primary care data

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 (approximately 10%) 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 practices in the Netherlands are generated by extrapolating the reporting rates in these practices to the total number of Dutch residents, by sex, age, and degree of urbanisation, as obtained from Statistics Netherlands (CBS). Incidence rates of a variety of infectious diseases, for example varicella and herpes zoster have been calculated using these data. Note: newborns are not registered at the GP from birth, but from the quarter after first contact with the GP. The number of person-years (denominator) is therefore underestimated in the presented incidences.
The current Dutch RSV surveillance programme is based partly on general practitioner (GP) surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI). Nose and throat swabs are collected from a subset of patients and analysed by National Influenza Centre (NIC) location RIVM for influenza viruses, SARS-CoV-2, RSV, rhinoviruses, enteroviruses, parainfluenza virus types 1-3, human metapneumovirus and human seasonal coronaviruses. For more information, also on other sources for RSV surveillance, 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 diseases under 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 RIVM and the Amsterdam University Medical Center (Amsterdam UMC). On a voluntary basis, microbiological laboratories throughout the Netherlands send isolates from normally sterile sites (e.g., blood and cerebrospinal fluid (CSF)) of patients with invasive meningococcal disease, invasive pneumococcal disease, and invasive *Haemophilus influenzae* disease to the NRLBM for further typing. Furthermore, for invasive meningococcal disease and invasive *H. influenzae* disease, PCR positive samples are sent to the NRLBM for further typing and CSF positive for pneumococci is sent for confirmation. This means that we have nationwide coverage of laboratory surveillance for invasive meningococcal disease and invasive *H. influenzae* disease. For invasive pneumococcal disease, nine sentinel clinical laboratories distributed throughout the country have been sending in all invasive isolates positive for *Streptococcus pneumoniae* since 2004. These nine sentinel laboratories cover approximately 28% of the Dutch population. Since 2008, for children aged under 5, all clinical laboratories send in all invasive isolates positive for *S. pneumoniae*, and since 2017, all medical microbiology laboratories are requested to submit all invasive pneumococcal isolates without restriction to age of the patient.

A1.1.1.3.2 Virological laboratories
Every week, virological laboratories that are members of the Dutch Working Group for Clinical Virology send positive results of virological diagnostics to the RIVM. Approximately 20 laboratories submit information on a regular basis. Aggregated results are shown on the RIVM website. RSV detections in the virological laboratory surveillance mainly represent RSV laboratory analysis from hospitalised paediatric patients who are tested for clinical purposes (4, 5).

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 at the moment these diseases are coded. Notification data in combination with laboratory data from the NRLBM are more reliable for these diseases.
A specific ICD code is available (ICD-9: 008.61, ICD-10: A08.0) for Rotavirus (RV) disease. However, this code is hardly ever used in the Netherlands as more general ICD categories are felt to suffice. Moreover, gastroenteritis hospitalisations are often not tested in general for all causative pathogens, in particular in very young children. For this reason, the number of gastroenteritis hospitalisations attributable to RV is estimated indirectly according to a method proposed by Harris *et al.* [13]. Using this method, the proportion of hospitalisations for gastroenteritis attributable to RV can be estimated by comparing the weekly RV laboratory detections (surveillance virological laboratories) with the number of hospitalisations for specific gastroenteritis ICD codes using linear regression analysis (ICD-9: 86-93, 5589; ICD-10: A0,-A09, K52, K529). This linear regression model estimates a constant representing the background number of events for gastroenteritis other than RV infection, and a constant

scaling factor dependent on the number of RV-positive laboratory detections that varies every week. The number of hospital admissions attributable to RV infection is calculated using the scaling factor times the number of positive laboratory detections per week. For this report, the constant and scaling factor were estimated by imposing the model onto hospitalisation data and weekly laboratory detections (laboratory surveillance) for the five previous years. The scaling factor estimated by this model was used to estimate the RV-attributed hospital admissions for the most recent year by multiplying it with the RV-positive laboratory detections of that year.

In 2012, there was a fourfold increase in the number of general practices participating in Nivel-PCD compared with the previous group of LINH practices, resulting in a representative sample of 386 participating general practices with approximately 1.2 million registered patients (http://www.nivel.nl/NZR/zorgregistraties-eerstelijn). From 2012 onwards, incidence rates from Nivel-PCD have been calculated using an adjusted procedure: changes were made to the definitions of disease episodes and to calculations of incidence, which caused an increased incidence for many diseases. Episode duration is defined as the time between the first and last consultation registered with the same code, plus an additional period in which patients are considered not susceptible (eight weeks for acute morbidities/complaints). Incidence rates are calculated by using a more specific selection of patient years resulting in a more reliable denominator [14, 15]. Because of these changes, we decided to report previously published incidence rates until 2011 based on the old method [16] and incidence rates from 2012 onwards using the new method [17]. Due to the new estimation method, the data for 2012 (based on 219 practices) and onwards are not comparable with the data for previous years.

A1.1.2 Methods for disease surveillance

A1.1.2.1 Burden of disease

The disability-adjusted life year (DALY) is composite health measure that was developed to compare the impact of diseases. The idea behind this approach is that the impact of a particular disease can be divided between the number of years of life lost (i.e. premature mortality) and the number of years lived at less than full health (i.e. morbidity). The result is a single measurement unit that quantifies the years of healthy life lost due to a certain disease or infection. The full methodology used to estimate the disease burden of infectious diseases in the Netherlands expressed in DALYs is described in the State of Infectious Diseases in the Netherlands, 2013 [18, 19].

A1.1.2.2 Impact of implementation of vaccination

The impact of vaccination (programmes) can be estimated by comparing the disease burden after implementation to disease burden before implementation of vaccination. This can be done quite simply by a before/after comparison of incidence. A more complex alternative is by applying time series analysis, in which, for example, time trends before implementation of vaccination, seasonality and vaccination coverage can be taken into account. The vaccination status of individuals is not needed to estimate the impact of a vaccination programme; the vaccination coverage of the population suffices. In addition to effectiveness of the vaccination

itself, the vaccination coverage and the level of herd protection determine the impact of a vaccination programme.

A1.1.2.3 Vaccine effectiveness

To estimate vaccine effectiveness (VE), the vaccination status of at least the cases is necessary. After the implementation of a vaccination in the NIP, VE can be routinely estimated using the 'screening method' [20] with the following equation:
VE (%) = 1- [PCV / (1-PCV) * (1-PPV/PPV)], in which PCV = proportion of cases vaccinated, PPV = proportion of population vaccinated, also called, the vaccine coverage, and VE = vaccine effectiveness.
In addition, several study designs, including case-control and cohort studies, can be used to assess VE after implementation [21]. A specific type of case-control design used to estimate VE is the indirect cohort design or Broome method [22]. This design can be used for a vaccine that protects against specific types of a pathogen, e.g. 10-valent pneumococcal conjugate vaccine, which protects against 10 pneumococcal serotypes. Cases in which the disease is caused by a vaccine type are the 'cases', and cases in which the disease is caused by a type not included in the vaccine serve as 'controls'. Vaccination status is then compared between the 'cases' (vaccine-type cases) and 'controls' (non-vaccine-type cases). The advantage of this design is that it adjusts for ascertainment bias between cases and controls, as both cases and controls are actually ill. An assumption in this design is that vaccinated people are at the same risk of non-vaccine-type infection as unvaccinated people. This means that the VE is underestimated in the case of cross-protection by the vaccine against non-vaccine-type disease. Conversely, if replacement disease occurs only in vaccinated people, the VE is overestimated.
Multiple statistical approaches are available to evaluate the VE against persistent HPV infections through the use of cohort studies. These approaches differ with respect to their underlying assumptions [23]. Based on available literature, absence of violations of the underlying assumptions, and the use of data throughout the follow-up, we suggest the Prentice Williams Peterson Total-Time (PWP-TT) approach as being the most valid method to evaluate vaccine effectiveness against HPV infections in cohort studies conducted among young women. The PWP-TT is a survival analysis method for recurrent events, taking into account the total time at risk. It assumes event-specific hazards, allowing the hazard to be different for each subsequent event [24]. We estimated the VE as one minus the hazard ratio times 100%. If the VE is estimated against a combined endpoint of multiple HPV types, then instead of the total number of infections, being infected with one of these types at that time point is used as outcome.

A1.1.2.4 Pertussis vaccination coverage

In the past a standardised vaccination coverage estimate of 92% was used for the PPV to calculate vaccine effectiveness for the pertussis booster vaccination at the age of 4 years. Nowadays, in response to the changes in vaccination coverage, the vaccination coverage as reported in the national vaccination coverage report is used for each birth cohort. This results in a different PPV for each birth cohort and more accurate VE calculation.

A1.2 Molecular surveillance of the pathogen

Monitoring strain variations due to differences in phenotype and/or genotype is an important part of information gathering on the emergence of (sub)types that may be more virulent or less effectively controlled by vaccination. It is also a useful tool for increasing insights into transmission dynamics.

A1.3 Immunosurveillance

Monitoring the seroprevalence of all NIP-targeted diseases is a way to gather age-specific and sex-specific information on immunity to these diseases, acquired either through infection or vaccination. To achieve this, a random selection of people from the general population of the Netherlands is periodically asked to donate a blood sample and complete a questionnaire (PIENTER survey). This survey was conducted in 1995-1996 (N_{blood}=10,128) [25], 2006–2007 (N_{blood}=7,904) [26], and 2016-2017 (N_{blood}=5,745). People living in regions with low vaccine coverage and non-Western migrants are oversampled in order to gain greater insights into differences in immunity among specific groups.

A1.4 Vaccination coverage

Vaccination coverage data can be used to gain insight into the NIP's effectiveness. Furthermore, this information can help identify groups with low vaccine coverage who are at increased risk of contracting one of the NIP-targeted diseases. In the Netherlands, all vaccinations administered within the framework of the NIP are registered in a central electronic (web-based) database at the individual level (Præventis) [27].

Some of the vaccinations are being anonymised with effect from 1 January 2022. This happens when people do not give permission to share their data with the RIVM. Anonymous vaccinations cannot be counted towards the vaccination coverage (because year of birth, gender, place of residence and the involved dose of the vaccinated person are unknown), Therefore, the coverage is reported to be lower than it actually is.

A1.5 Surveillance of adverse events following vaccination

Passive safety surveillance through an enhanced spontaneous reporting system was used by the RIVM until 2011. An aggregate analysis of all reported adverse events following immunisation (AEFIs) was published annually. The last report, for 2010, also contains a detailed description of the methodology used and a review of trends and important findings over the previous 15 years [28].
On 1 January 2011, this enhanced spontaneous AEFI reporting system was taken over by the Netherlands Pharmacovigilance Centre (Lareb). Detailed information is available at www.lareb.nl. In view of this transition, comparisons between the period before 2011 and the period from 2011 onwards should be made with caution. Furthermore, in 2011, Lareb started a campaign among parents of vaccinated children to promote the reporting of AEFIs. In January 2017, the procedure for registering AEFIs in the Lareb database was changed. Previously, reports

of redness, swelling, pain and warmth at the injection site were recorded as injection-site inflammation. Since January 2017, these local reactions are registered separately. As a result, the number of AEFIs per report is higher.
In addition, the RIVM Centre for Infectious Disease Control (CIb) conducts systematic studies to monitor the safety of the NIP, e.g. questionnaire surveys and linkage studies between different databases.

A1.6 Cost-effectiveness

The decision to include a certain vaccination option in the NIP is based on several factors, including vaccine safety and efficacy, avertable disease burden, acceptability, and cost-effectiveness of vaccination. Cost-effectiveness is defined as the additional cost per additional unit of health benefit produced, compared to an alternative such as the vaccine already in use or no vaccination. In other words, economic evaluation of a vaccination programme provides information on whether the health gain associated with a new vaccine is worth the cost as compared with other options for investing in health improvements or prevention. Most commonly, cost-effectiveness is expressed in cost per quality-adjusted life year (QALY), which is a measure of disease burden comprising both the quality and quantity of life. If provided in a transparent and standardised manner, evidence of cost-effectiveness can contribute to policy recommendations for vaccinations included in the NIP.

A1.7 Literature

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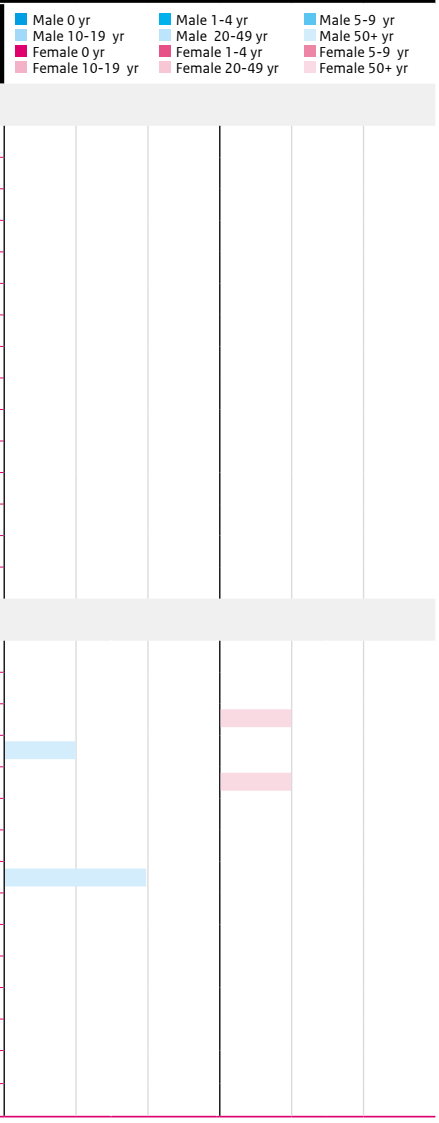
* *RIVM publication.*

Appendix 2 Morbidity and mortality figures

Diseases included in the current NIP

Diphtheria								ICD10: A36
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	0	**0**	
Hospitalisations (source: Prismant/DHD/CBS)**								
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	1	**1**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	2	**2**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	
2018^	0	0	0	0	0	0	**5**	
2019^	0	0	0	0	0	0	**0**	
2020^	0	0	0	0	0	0	**0**	
2021^	0	0	0	0	0	0	**0**	



* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

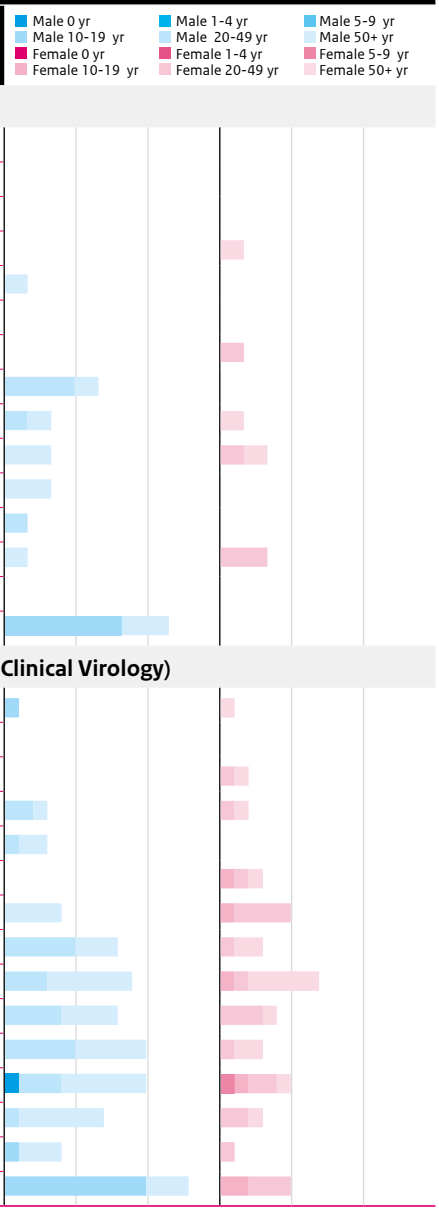
** *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Diphtheria

ICD9: 032
ICD10: A36

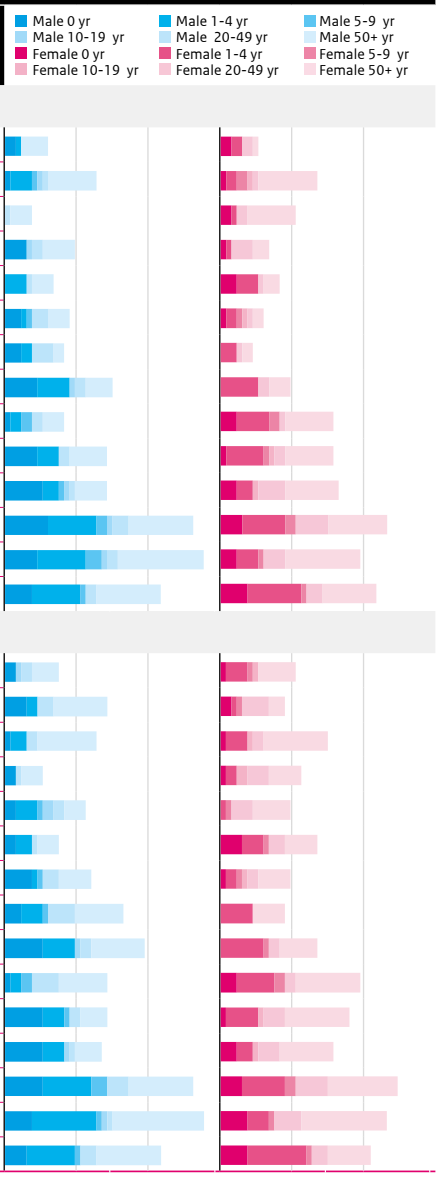
Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
Notifications (source: Osiris)							
2008	0	0	0	0	0	0	**0**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	0	0	**0**
2011	0	0	0	0	0	1	**1**
2012	0	0	0	0	0	1	**1**
2013	0	0	0	0	0	0	**0**
2014	0	0	0	0	1	0	**1**
2015	0	0	0	0	3	1	**4**
2016	0	0	0	0	1	2	**3**
2017	0	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**
2021	0	0	0	0	0	0	**0**
2022	0	0	0	5	0	2	**7**
Laboratory diagnoses* (source: Dutch Working Group for Clinical Virology)							
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**
2021	0	0	0	1	6^	3	**10**
2022	0	0	0	12#	5†	3	**20**



* *Number of diphtheria isolates.*
^ *Two isolates came from the same patient, but were collected at different times and from different sample types.*
# *Twice, two isolates came from the same patient, were collected during the same week, and came from different sample types.*
† *Two isolates came from the same patient (gender unknown),, were collected during the same week, and came from different sample types.*

Haemophilus influenzae

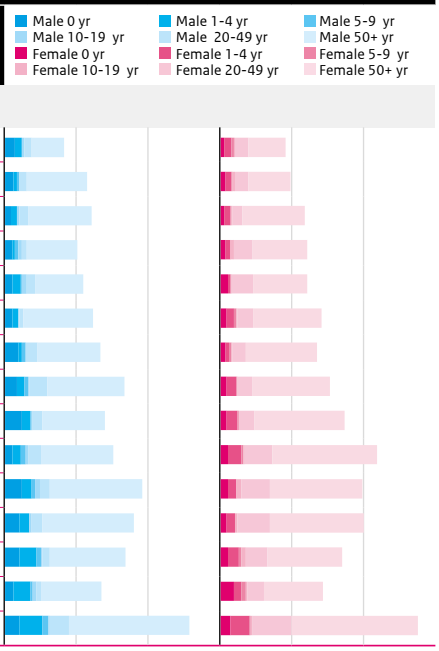
Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Notifications* (serotype b; source: Osiris)							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	20	**35**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	3	8	0	0	2	7	**20**
2014	4	3	2	1	4	6	**20**
2015	3	5	0	0	5	4	**17**
2016	6	13	0	1	4	9	**33**
2017	4	8	4	0	3	13	**32**
2018	7	11	1	1	4	16	**40**
2019	10	6	1	2	6	16	**41**
2020	12	17	4	1	9	23	**66**
2021	11	13	4	1	6	30	**65**
2022	10	19	2	0	5	22	**58**
Laboratory diagnoses (serotype b; source: NRLBM)							
2008	3	5	1	2	2	12	**25**
2009	6	3	1	0	8	14	**32**
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	11	**29**
2014	6	3	2	1	6	12	**30**
2015	3	10	1	0	5	15	**34**
2016	7	14	1	1	4	17	**44**
2017	4	10	4	0	7	21	**46**
2018	8	10	1	1	6	17	**43**
2019	10	7	0	2	5	15	**39**
2020	11	17	5	0	10	25	**68**
2021	10	16	2	1	6	33	**68**
2022	9	20	2	0	6	20	**57**



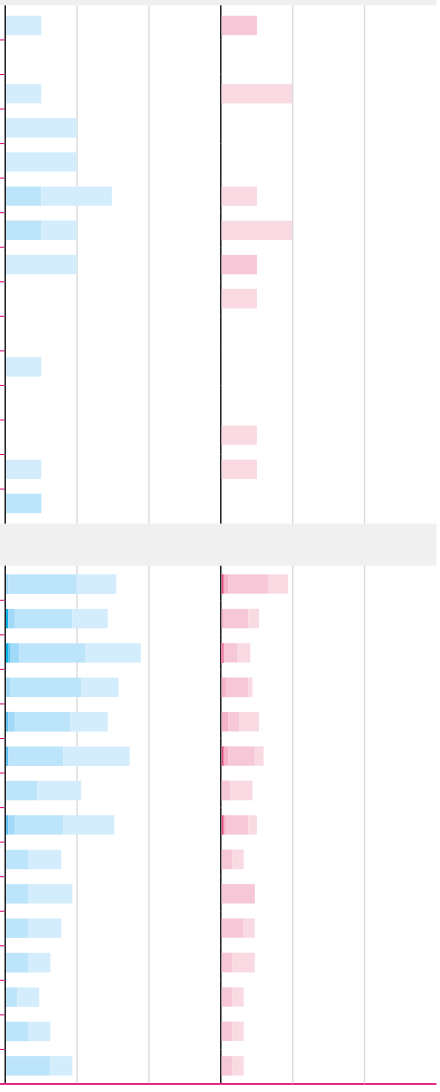
* *Notifiable since 2009.*

Haemophilus influenzae

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Laboratory diagnoses (all serotypes; source: NRLBM)							
2008	11	14	2	3	18	60	**108**
2009	11	8	3	2	18	87	**129**
2010	8	10	1	3	15	106	**143**
2011	11	6	3	6	20	93	**139**
2012	12	11	2	4	26	85	**140**
2013	11	11	2	2	16	117	**159**
2014	16	6	5	1	22	111	**161**
2015	15	14	4	1	27	129	**190**
2016	19	16	2	1	22	130	**190**
2017	12	20	6	3	34	149	**224**
2018	21	15	3	8	32	157	**236**
2019	17	15	0	4	36	155	**227**
2020	18	24	7	5	24	125	**203**
2021	18	20	6	4	18	100	**166**
2022	20	35	6	2	50	207	**320**



Hepatitis B								ICD9: 070.2-3 ICD10: B16, B17.0, B18.0, B18.1
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (B16: Acute; source: CBS)								
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**	
2021	0	0	0	0	0	2	**2**	
2022*	0	0	0	0	1	0	**1**	
Hospitalisations (source: Prismant/DHD/CBS)**								
2007	0	1	0	3	49	27	**81**	
2008	0	1	0	4	37	21	**63**	
2009	0	1	2	4	36	31	**74**	
2010	0	0	0	4	42	19	**66**	
2011	0	0	1	6	30	26	**63**	
2012	0	1	1	2	37	34	**76**	
2013	0	0	0	0	18	30	**48**	
2014	0	1	1	4	32	27	**66**	
2015^	0	0	0	0	20	20	**40**	
2016^	0	0	0	0	25	25	**50**	
2017^	0	0	0	0	20	20	**40**	
2018^	0	0	0	0	15	20	**35**	
2019^	0	0	0	0	10	15	**25**	
2020^	0	0	0	0	20	15	**35**	
2021^	0	0	0	0	25	15	**35**	



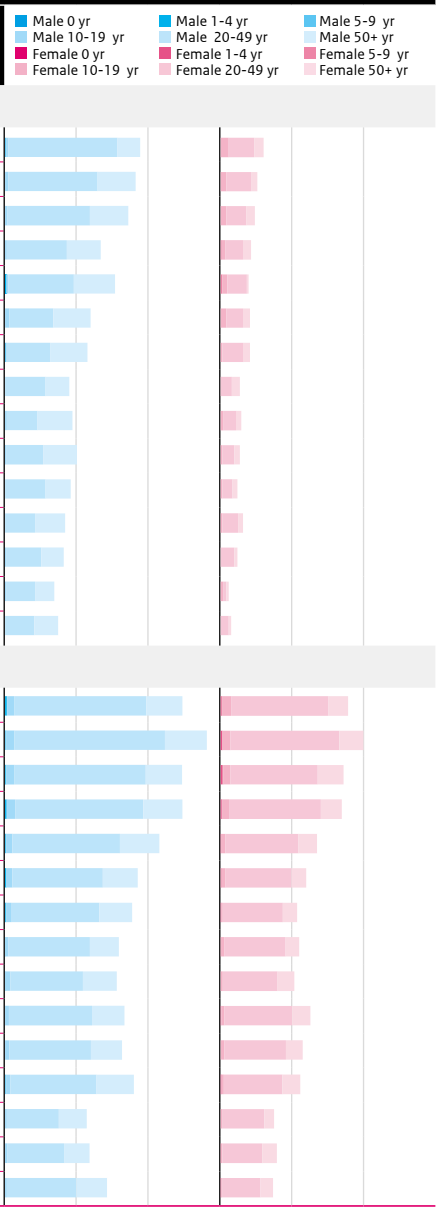
* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Hepatitis B

Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
Notifications (Acute; source: Osiris)							
2008	0	0	1	13	170	41	**225**
2009	0	0	0	11	144	56	**211**
2010	0	0	0	10	129	60	**199**
2011	0	0	1	7	98	53	**159**
2012	0	1	2	9	108	54	**174**
2013	0	0	0	12	77	56	**145**
2014	0	0	1	3	81	56	**141**
2015	0	0	0	1	64	40	**105**
2016	0	0	0	5	55	51	**111**
2017	0	0	0	3	62	50	**115**
2018	0	0	0	2	64	38	**104**
2019	0	0	0	2	58	44	**104**
2020	0	0	0	1	62	32	**95**
2021	0	0	0	4	41	27	**72**
2022	0	0	0	0	47	33	**80**
Notifications (Chronic; source: Osiris)							
2008	0	10	6	87	1,215	295	**1,613**
2009	0	7	7	85	1,373	348	**1,820**
2010	0	9	12	77	1,159	328	**1,585**
2011	0	9	10	77	1,162	319	**1,577**
2012	0	3	3	55	959	307	**1,327**
2013	0	4	5	54	829	261	**1,153**
2014	1	5	3	31	788	247	**1,075**
2015	0	1	1	31	758	226	**1,017**
2016	1	0	0	36	674	269	**980**
2017	0	1	1	37	797	269	**1,105**
2018	0	0	0	40	758	253	**1,051**
2019	0	4	4	33	769	291	**1,101**
2020	0	0	0	15	502^	197	**714**
2021	0	0	2	18	513#	210	**743**
2022	0	1	1	13	570	230	**815**



^ *2 cases without information on gender.*

1 case without information on gender.

Human papillomavirus								ICD10: C53
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (cervical cancer; source: CBS)								
2008	0	0	0	0	51	193	**244**	
2009	0	0	0	0	40	169	**209**	
2010	0	0	0	0	43	162	**205**	
2011	0	0	0	0	46	143	**189**	
2012	0	0	0	0	42	173	**215**	
2013	0	0	0	0	47	176	**223**	
2014	0	0	0	0	50	148	**198**	
2015	0	0	0	0	49	158	**207**	
2016	0	0	0	0	50	179	**229**	
2017	0	0	0	0	44	162	**206**	
2018	0	0	0	0	50	167	**217**	
2019	0	0	0	0	45	171	**216**	
2020	0	0	0	0	52	178	**230**	
2021	0	0	0	0	48	165	**213**	
2022*	0	0	0	0	53	170	**223**	
Registrations (cervical cancer; source: NKR)								
2008	0	0	0	0	376	328	**704**	
2009	0	0	0	0	385	339	**724**	
2010	0	0	0	0	399	332	**731**	
2011	0	0	0	0	381	354	**735**	
2012	0	0	0	1	403	328	**732**	
2013	0	0	0	0	379	281	**660**	
2014	0	0	0	0	418	321	**739**	
2015	0	0	0	0	389	321	**710**	
2016	0	0	0	0	451	356	**807**	
2017	0	0	0	1	433	337	**771**	
2018	0	0	0	0	468	376	**844**	
2019	0	0	1	0	513	396	**910**	
2020	0	0	0	0	452	350	**802**	
2021**	0	0	0	0	558	389	**947**	
2022**	0	0	0	0	531	409	**940**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Preliminary figures.*

Human papillomavirus								ICD10: C51
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (vulva cancer; source: CBS)^								
2008	0	0	0	0	7	92	**99**	
2009	0	0	0	0	3	108	**111**	
2010	0	0	0	0	6	110	**116**	
2011	0	0	0	0	7	134	**141**	
2012	0	0	0	0	1	95	**96**	
2013	0	0	0	0	1	97	**98**	
2014	0	0	0	0	2	115	**117**	
2015	0	0	0	0	8	95	**103**	
2016	0	0	0	0	0	99	**99**	
2017	0	0	0	0	2	112	**114**	
2018	0	0	0	0	4	137	**141**	
2019	0	0	0	0	3	164	**167**	
2020	0	0	0	0	3	147	**150**	
2021	0	0	0	0	4	140	**144**	
2022*	0	0	0	0	5	139	**144**	
Registrations (vulva cancer; source: NKR)^								
2008	0	0	0	0	31	260	**291**	
2009	0	0	0	0	54	298	**352**	
2010	0	0	0	0	41	306	**347**	
2011	0	0	0	1	52	341	**394**	
2012	0	0	0	0	33	317	**350**	
2013	0	0	0	0	38	310	**348**	
2014	0	0	0	0	56	359	**415**	
2015	0	0	0	0	42	335	**377**	
2016	0	0	0	0	37	379	**416**	
2017	0	0	0	0	38	372	**410**	
2018	0	0	0	0	43	384	**427**	
2019	0	0	0	0	51	410	**461**	
2020	0	0	0	0	41	386	**427**	
2021**	0	0	0	1	33	404	**438**	
2022**	0	0	0	0	26	428	**454**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Preliminary figures.*

^ *While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.*

Human papillomavirus								ICD10: C52
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (vagina cancer; source: CBS)^								
2008	0	0	0	0	2	17	**19**	
2009	0	0	0	0	2	15	**17**	
2010	0	0	0	0	1	21	**22**	
2011	0	0	0	0	0	21	**21**	
2012	0	0	0	0	1	26	**27**	
2013	0	0	0	0	0	27	**27**	
2014	0	0	0	0	1	20	**21**	
2015	0	0	0	0	0	21	**21**	
2016	0	0	0	0	1	22	**23**	
2017	0	0	0	0	0	18	**18**	
2018	0	0	0	0	1	24	**25**	
2019	0	0	0	0	2	23	**25**	
2020	0	0	0	0	0	21	**21**	
2021	0	0	0	0	1	26	**27**	
2022*	0	0	0	0	0	15	**15**	
Registrations (vagina cancer; source: NKR)^								
2008	0	0	0	0	4	35	**39**	
2009	0	0	0	0	7	33	**40**	
2010	0	0	0	0	4	45	**49**	
2011	0	0	0	0	4	54	**58**	
2012	0	0	0	0	8	47	**55**	
2013	0	0	0	0	1	37	**38**	
2014	0	0	0	0	8	33	**41**	
2015	0	0	0	0	4	49	**53**	
2016	0	0	0	0	7	33	**40**	
2017	0	0	0	0	4	48	**52**	
2018	0	0	0	0	1	55	**56**	
2019	0	0	0	0	3	39	**42**	
2020	0	0	0	0	3	54	**57**	
2021**	0	0	0	0	8	56	**64**	
2022**	0	0	0	1	4	60	**65**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Preliminary figures.*

^ *While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.*

Human papillomavirus								ICD10: C60
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (penis cancer; source: CBS)^								
2008	0	0	0	0	1	25	**26**	
2009	0	0	0	0	2	22	**24**	
2010	0	0	0	0	1	32	**33**	
2011	0	0	0	0	2	31	**33**	
2012	0	0	0	0	4	34	**38**	
2013	0	0	0	0	2	20	**22**	
2014	0	0	0	0	2	33	**35**	
2015	0	0	0	0	2	33	**35**	
2016	0	0	0	0	1	33	**34**	
2017	0	0	0	0	4	30	**34**	
2018	0	0	0	0	2	32	**34**	
2019	0	0	0	0	1	45	**46**	
2020	0	0	0	0	1	50	**51**	
2021	0	0	0	0	0	37	**37**	
2022*	0	0	0	0	2	36	**38**	
Registrations (penis cancer; source: NKR)^								
2008	0	0	0	0	17	111	**128**	
2009	0	0	0	0	13	127	**140**	
2010	0	0	0	0	19	122	**141**	
2011	0	0	0	0	11	136	**147**	
2012	0	0	0	0	10	128	**138**	
2013	0	0	0	0	11	130	**141**	
2014	0	0	0	0	7	116	**123**	
2015	0	0	0	0	11	142	**153**	
2016	0	0	0	0	9	157	**166**	
2017	0	0	0	0	13	152	**165**	
2018	0	0	0	0	12	175	**187**	
2019	0	0	0	0	11	190	**201**	
2020	0	0	0	0	13	167	**180**	
2021**	0	0	0	0	5	168	**173**	
2022**	0	0	0	0	13	152	**165**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Preliminary figures.*

^ *While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.*

Human papillomavirus								ICD10: C10
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (oropharynx cancer; source: CBS)^								
2008	0	0	0	0	3	63	**66**	
2009	0	0	0	0	3	71	**74**	
2010	0	0	0	0	5	75	**80**	
2011	0	0	0	0	5	89	**94**	
2012	0	0	0	0	2	96	**98**	
2013	0	0	0	0	5	90	**95**	
2014	0	0	0	0	2	95	**97**	
2015	0	0	0	0	2	93	**95**	
2016	0	0	0	0	4	97	**101**	
2017	0	0	0	0	4	96	**100**	
2018	0	0	0	0	2	101	**103**	
2019	0	0	0	0	3	114	**117**	
2020	0	0	0	0	3	114	**117**	
2021	0	0	0	0	1	122	**123**	
2022*	0	0	0	0	4	147	**151**	
Registrations (oropharynx cancer; source: NKR)^								
2008	0	0	0	1	54	499	**554**	
2009	0	0	0	0	52	492	**544**	
2010	0	0	0	0	61	496	**557**	
2011	0	0	0	0	58	561	**619**	
2012	0	0	0	0	44	573	**617**	
2013	0	0	0	0	42	568	**610**	
2014	0	0	0	0	44	591	**635**	
2015	0	0	0	0	40	575	**615**	
2016	0	0	0	0	48	646	**694**	
2017	0	0	0	0	38	629	**667**	
2018	0	0	0	0	35	658	**693**	
2019	0	0	0	1	46	638	**685**	
2020	0	0	0	0	25	665	**690**	
2021**	0	0	0	1	43	609	**653**	
2022**	0	0	0	0	33	656	**689**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Preliminary figures.*

^ *While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.*

Human papillomavirus								ICD10: C21
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (anus cancer; source: CBS)^								
2008	0	0	0	0	3	30	**33**	
2009	0	0	0	0	2	37	**39**	
2010	0	0	0	0	2	39	**41**	
2011	0	0	0	0	1	38	**39**	
2012	0	0	0	0	6	33	**39**	
2013	0	0	0	0	1	35	**36**	
2014	0	0	0	0	2	39	**41**	
2015	0	0	0	0	3	31	**34**	
2016	0	0	0	0	4	49	**53**	
2017	0	0	0	0	2	57	**59**	
2018	0	0	0	0	4	54	**58**	
2019	0	0	0	0	3	61	**64**	
2020	0	0	0	0	3	53	**56**	
2021	0	0	0	0	6	59	**65**	
2022*	0	0	0	0	7	62	**69**	
Registrations (anus cancer; source: NKR)^								
2008	0	0	0	0	29	133	**162**	
2009	0	0	0	0	33	128	**161**	
2010	0	0	0	0	24	152	**176**	
2011	0	0	0	0	28	156	**184**	
2012	0	0	0	0	36	178	**214**	
2013	0	0	0	0	30	187	**217**	
2014	0	0	0	0	30	175	**205**	
2015	0	0	0	0	33	215	**248**	
2016	0	0	0	0	32	225	**257**	
2017	0	0	0	0	25	219	**244**	
2018	0	0	0	0	29	261	**290**	
2019	0	0	0	0	21	234	**255**	
2020	0	0	0	0	25	239	**264**	
2021**	0	0	0	0	32	266	**298**	
2022**	0	0	0	0	27	293	**320**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Preliminary figures.*

^ *While HPV can contribute to the formation of this type of cancer, it is not solely responsible for all registrations or deaths presented here.*

Measles								ICD10: B05
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2008	4	8	38	39	21	0	**110**	
2009	1	2	2	3	7	0	**15**	
2010	1	2	2	1	9	0	**15**	
2011	2	2	7	14	26	0	**51**	
2012	1	2	0	1	6	0	**10**	
2013	53	425	840	1,162	199	9	**2,688**	
2014	18	25	6	17	65	3	**134**	
2015	0	0	0	0	6	1	**7**	
2016	0	0	2	0	4	0	**6**	
2017	0	1	1	3	10	1	**16**	
2018	3	4	0	2	14	1	**24**	
2019	4	15	17	10	37	1	**84**	
2020	0	1	0	0	1	0	**2**	
2021	0	0	0	0	0	0	**0**	
2022	1	1	3	0	1	0	**6**	

** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

Measles								ICD9: 055 ICD10: B05
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations* (source: Prismant/DHD)								
2007	0	0	0	0	2	0	**2**	
2008	0	0	0	0	2	0	**2**	
2009	0	0	0	0	0	0	**0**	
2010	0	1	0	0	3	0	**4**	
2011	1	0	0	1	6	0	**9**	
2012	1	1	0	0	2	0	**4**	
2013	8	34	41	52	23	1	**164**	
2014	6	6	0	4	18	1	**35**	
2015^	0	0	0	0	5	0	**5**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	5	0	**5**	
2018^	0	0	0	0	5	0	**10**	
2019^	0	0	0	0	10	0	**10**	
2020^	0	0	0	0	0	0	**0**	
2021^	0	0	0	0	0	0	**0**	

* *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

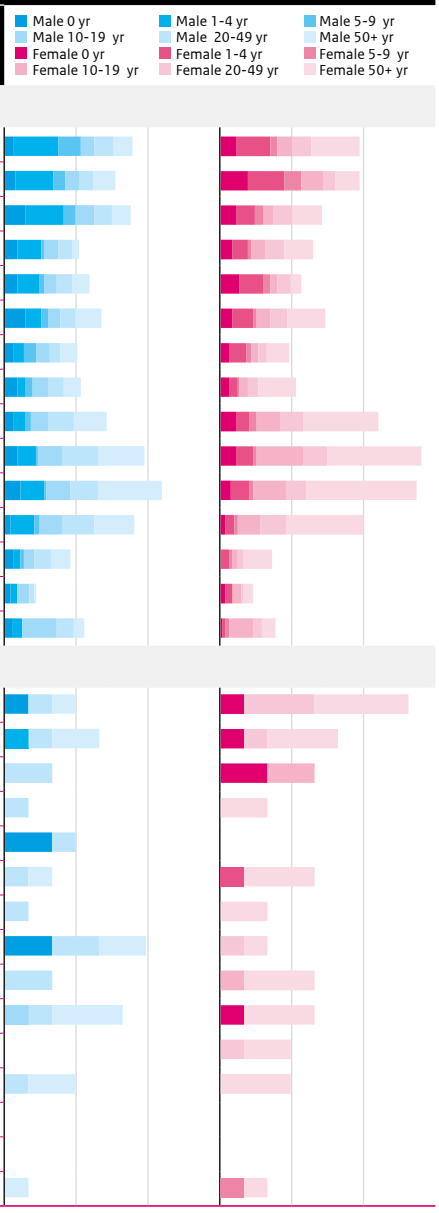
^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Meningococcal disease								ICD10: A39
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	1	1	0	0	2	3	**7**	
2009	1	3	0	0	1	1	**6**	
2010	3	2	0	1	0	2	**8**	
2011	2	0	0	0	1	2	**5**	
2012	0	1	0	0	0	0	**1**	
2013	0	1	0	1	0	1	**3**	
2014	0	1	0	0	0	5	**6**	
2015	0	1	0	0	1	2	**4**	
2016	0	2	0	1	0	3	**6**	
2017	1	2	0	1	2	2	**8**	
2018	0	2	0	4	2	5	**13**	
2019	1	1	0	1	1	4	**8**	
2020	0	0	0	0	0	1	**1**	
2021	0	0	0	0	0	0	**0**	
2022*	0	1	0	0	0	2	**3**	
Notifications (source: Osiris)								
2008	17	47	19	19	17	36	**155**	
2009	24	49	18	25	16	28	**160**	
2010	22	34	14	21	22	28	**141**	
2011	14	24	4	19	20	18	**99**	
2012	18	32	6	15	17	16	**104**	
2013	16	22	6	14	20	32	**110**	
2014	10	17	9	14	10	23	**83**	
2015	13	10	9	13	14	33	**92**	
2016	13	17	8	27	33	58	**156**	
2017	18	22	3	41	34	87	**205**	
2018	16	25	2	37	29	96	**205**	
2019	5	20	5	26	38	67	**161**	
2020	6	9	4	8	13	23	**63**	
2021	6	7	0	9	4	5	**31**	
2022	4	6	3	33	18	11	**75**	

** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

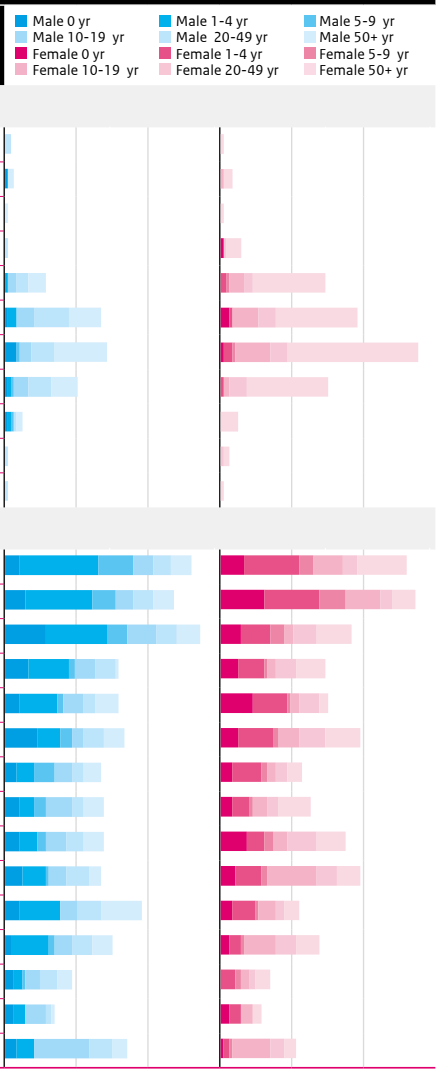
Meningococcal disease

Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses (all serogroups; source: NRLBM)							
2008	15	47	18	18	22	39	**159**
2009	25	47	18	23	16	28	**157**
2010	23	34	13	18	21	28	**137**
2011	15	23	4	18	19	22	**101**
2012	18	28	7	11	17	16	**97**
2013	19	21	6	15	19	37	**117**
2014	10	16	10	12	11	23	**82**
2015	12	10	5	14	15	33	**89**
2016	14	15	7	24	28	63	**151**
2017	16	21	3	41	35	82	**198**
2018	15	25	3	33	28	101	**205**
2019	6	19	5	26	33	68	**157**
2020	5	9	4	9	13	28	**68**
2021	6	8	0	12	4	7	**37**
2022	5	8	2	34	15	14	**78**
Laboratory diagnoses (serogroup C; source: NRLBM)							
2008	2	0	0	0	4	5	**11**
2009	1	1	0	0	2	5	**9**
2010	2	0	0	2	2	0	**6**
2011	0	0	0	0	1	2	**3**
2012	2	0	0	0	1	0	**3**
2013	0	1	0	0	1	4	**6**
2014	0	0	0	0	1	2	**3**
2015	2	0	0	0	3	3	**8**
2016	0	0	0	1	2	3	**6**
2017	1	0	0	1	1	6	**9**
2018	0	0	0	0	1	2	**3**
2019	0	0	0	0	1	5	**6**
2020	0	0	0	0	0	0	**0**
2021	0	0	0	0	0	0	**0**
2022	0	0	1	0	0	2	**3**

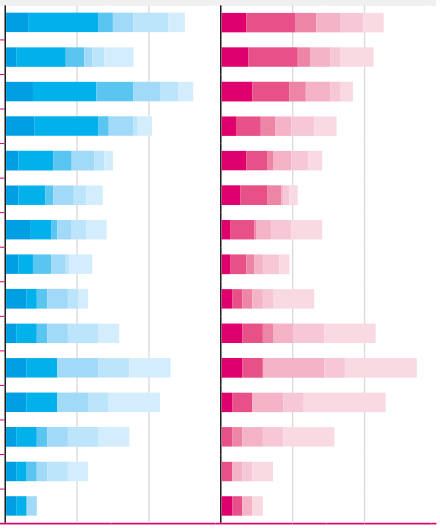


Meningococcal disease

Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses (serogroup W; source: NRLBM)							
2012	0	0	0	0	2	1	**3**
2013	1	0	0	1	0	5	**7**
2014	0	0	0	0	0	2	**2**
2015	1	0	0	0	2	6	**9**
2016	0	3	1	8	7	31	**50**
2017	4	4	0	15	18	39	**80**
2018	5	3	2	16	14	63	**103**
2019	1	2	1	7	14	37	**62**
2020	1	1	1	0	1	8	**12**
2021	0	0	0	0	2	2	**4**
2022	0	0	0	0	1	1	**2**
Laboratory diagnoses (serogroup B; source: NRLBM)							
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	17	14	15	**71**
2020	3	8	3	8	8	10	**40**
2021	6	8	0	11	2	4	**31**
2022	5	8	1	32	13	9	**68**



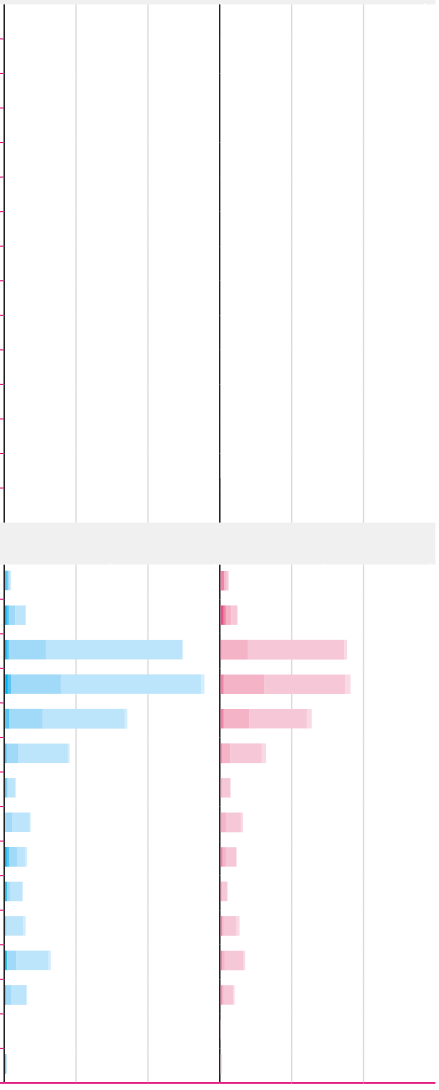
Meningococcal disease								ICD9: 036.0-4, 036.8-9 ICD10: A39
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations* (source: Prismant/DHD/CBS)								
2007	23	58	17	22	28	18	**166**	
2008	18	48	15	14	11	30	**136**	
2009	28	49	26	25	14	13	**156**	
2010	21	37	12	20	13	18	**122**	
2011	18	27	12	20	13	11	**103**	
2012	15	26	11	11	9	12	**84**	
2013	16	22	4	14	17	25	**99**	
2014	10	15	13	11	10	16	**75**	
2015^	15	15	10	15	10	25	**90**	
2016^	15	20	10	20	30	35	**135**	
2017^	15	30	5	50	30	55	**180**	
2018^	15	30	5	30	20	65	**160**	
2019^	5	15	5	20	25	40	**115**	
2020^	5	10	5	5	15	15	**55**	
2021^	5	5	0	10	5	5	**35**	



* *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

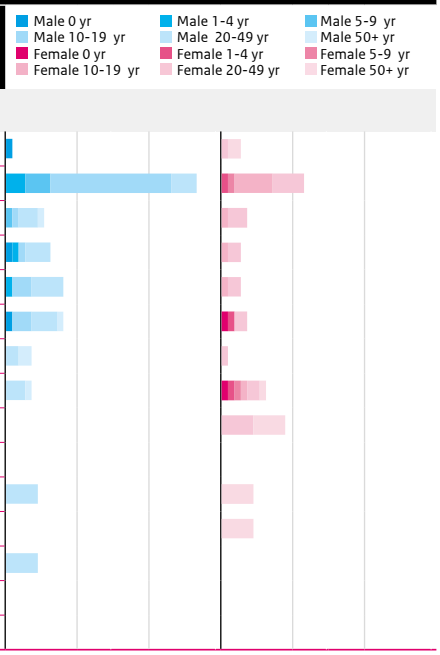
^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Mumps								ICD10: B26
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2008	0	2	10	5	7	1	**25**	
2009	0	9	8	22	30	2	**71**	
2010	0	4	5	119	435	6	**569**	
2011	1	6	10	169	412	15	**613**	
2012	0	2	12	110	260	13	**397**	
2013	0	3	2	37	152	11	**205**	
2014	0	0	4	5	28	2	**39**	
2015	0	0	2	21	61	5	**89**	
2016	0	5	7	20	34	5	**71**	
2017	1	3	0	8	32	2	**46**	
2018	0	1	3	5	54	10	**73**	
2019	0	4	3	22	95	7	**131**	
2020	0	3	0	13	44	4	**64**	
2021	0	0	0	0	0	1	**1**	
2022	0	1	0	0	5	1	**7**	



** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

Mumps								ICD9: 072 ICD10: B26
Year	Age (years)						Total	
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations* (source: Prismant/DHD/CBS)								
2007	1	0	0	0	1	2	**4**	
2008	0	4	5	25	9	0	**43**	
2009	0	0	1	2	6	1	**10**	
2010	1	1	0	2	6	0	**10**	
2011	0	1	0	4	7	0	**12**	
2012	2	1	0	3	6	1	**14**	
2013	0	0	0	0	3	2	**5**	
2014	1	1	1	1	5	2	**11**	
2015^	0	0	0	0	5	5	**15**	
2016^	0	0	0	0	0	5	**5**	
2017^	0	0	0	0	5	5	**10**	
2018^	0	0	0	0	5	5	**10**	
2019^	0	0	0	0	5	0	**10**	
2020^	0	0	0	0	0	0	**5**	
2021^	0	0	0	0	0	0	**0**	



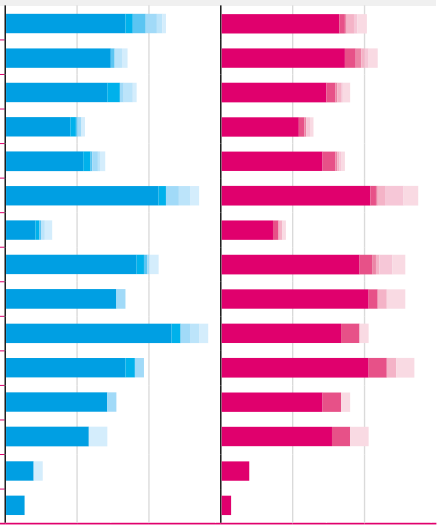
* *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Pertussis								ICD10: A37
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	1	**1**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	1	0	0	0	0	0	**1**	
2012	2	0	0	0	0	0	**2**	
2013	0	0	0	0	0	0	**0**	
2014	1	0	0	0	0	0	**1**	
2015	1	0	0	0	0	0	**1**	
2016	1	0	0	0	0	1	**2**	
2017	1	0	0	0	0	1	**2**	
2018	1	0	0	0	0	0	**1**	
2019	2	0	0	0	0	0	**2**	
2020	1	0	0	0	0	1	**2**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2008	195	346	779	3,154	2,343	1,484	**8,301**	
2009	164	270	658	2,442	1,962	1,064	**6,560**	
2010	115	168	355	1,278	1,212	637	**3,765**	
2011	160	283	1,007	2,531	1,984	1,231	**7,196**	
2012	234	378	1,525	4,192	4,497	3,002	**13,828**	
2013	77	136	315	889	1,054	931	**3,402**	
2014	258	490	788	2,859	2,721	2,138	**9,254**	
2015	174	274	560	1,962	2,053	1,532	**6,555**	
2016	217	402	489	1,426	1,813	1,223	**5,570**	
2017	182	221	416	1,307	1,610	1,146	**4,912**	
2018	193	334	432	1,260	1,534	1,144	**4,897**	
2019	188	311	424	1,608	2,155	1,697	**6,383**	
2020	38	40	77	228	287	271	**941**	
2021	9	7	1	7	23	27	**74**	
2022	18	34	12	14	28	23	**129**	

** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

Pertussis								ICD9: 033 ICD10: A37
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations* (source: Prismant/DHD)								
2007	129	7	8	10	5	7	**166**	
2008	124	6	5	2	6	8	**151**	
2009	112	12	1	4	6	6	**141**	
2010	77	6	2	2	2	4	**93**	
2011	97	11	2	4	2	5	**121**	
2012	164	7	1	11	16	13	**213**	
2013	44	5	1	2	2	6	**60**	
2014	146	11	4	3	7	12	**185**	
2015^	140	10	0	10	5	10	**175**	
2016^	155	15	0	5	5	10	**190**	
2017^	150	10	0	10	0	10	**180**	
2018^	110	10	0	5	0	10	**135**	
2019^	105	10	0	0	5	15	**140**	
2020^	30	5	0	0	0	5	**40**	
2021^	15	0	0	0	0	0	**15**	

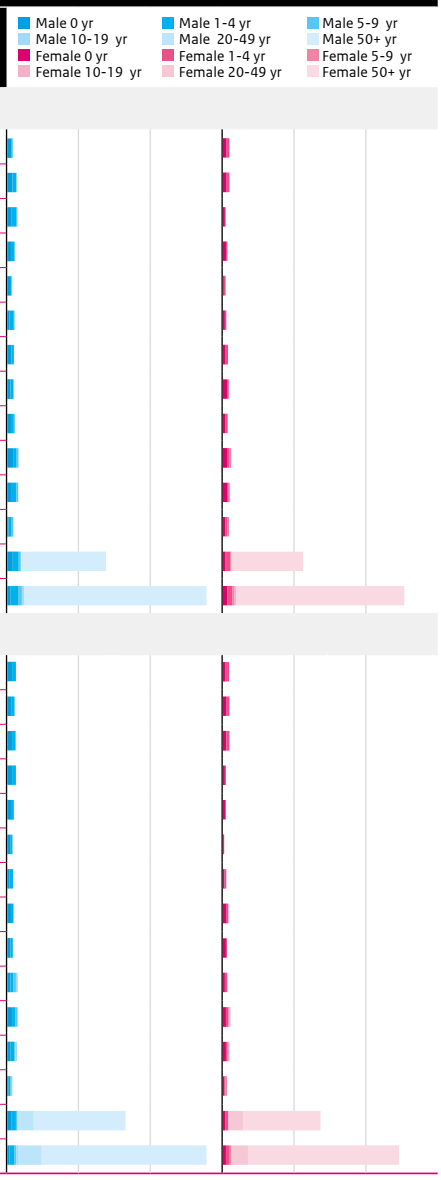


* *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Pneumococcal disease

Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
Notifications IPD* (source: Osiris)							
2009	28	14	1				**43**
2010	31	24	2				**57**
2011	23	21	3				**47**
2012	27	15	2				**44**
2013	13	11	4				**28**
2014	16	20	2				**38**
2015	25	17	0				**42**
2016	25	18	1				**44**
2017	23	17	4	1			**45**
2018	35	21	12	2			**70**
2019	29	24	9	2			**64**
2020	13	16	14	1			**44**
2021	30	37	10	4		555	**636**
2022**	32	47	21	17		1456	**1573**
Laboratory diagnoses IPD (nationwide; source: NRLBM)							
2008	40	40					**80**
2009	45	28					**73**
2010	44	34					**78**
2011	38	26					**64**
2012	33	17					**50**
2013	22	12					**34**
2014	22	25					**47**
2015	38	22					**60**
2016	30	19					**49**
2017	26	24	17	9			**76**
2018	40	28	16	10			**94**
2019	33	28	9	12			**61**
2020	15	17	14	3			**32**
2021	33	36	9	10	147	863	**1098**
2022	28	44	16	20	197	1601	**1906**

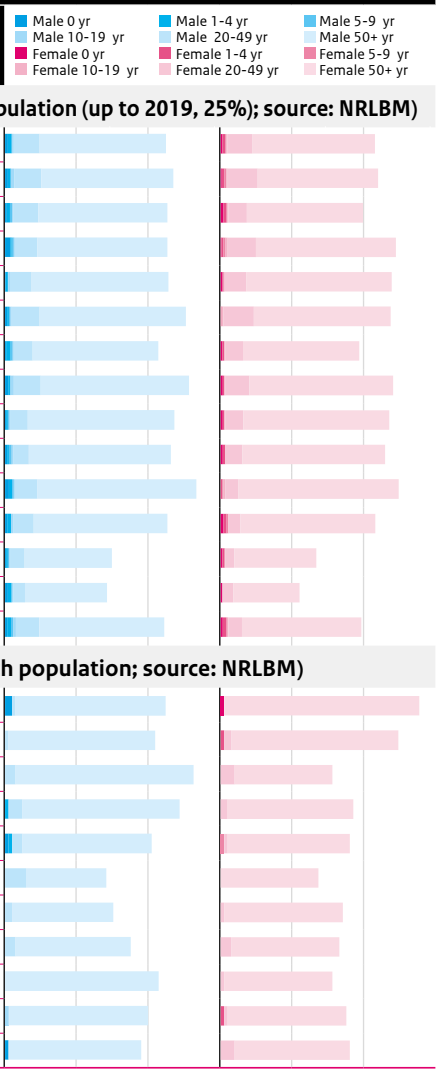


* *Notifiable for children born from 2006 onwards, and from April 2021 also for people aged 60 and over.*

** *Numbers represent all notifications that are approved by the RIVM. Note that, for children, 4 notifications await approval, and for older adults, 70 notifications.*

Pneumococcal disease

Year	Age (years) 0	1-4	5-9	10-19	20-49	50+	Total
Laboratory diagnoses IPD (sentinel labs covering 28% of population (up to 2019, 25%); source: NRLBM)							
2008	10	14	4	5	100	474	**607**
2009	8	10	4	10	110	478	**620**
2010	9	12	6	4	83	459	**573**
2011	11	7	8	7	95	506	**634**
2012	4	7	3	3	81	540	**638**
2013	4	3	4	6	110	525	**652**
2014	5	11	5	5	67	454	**547**
2015	10	5	1	9	95	547	**667**
2016	6	5	3	4	66	547	**631**
2017	8	8	5	4	60	531	**616**
2018	7	9	5	5	67	595	**688**
2019	9	13	3	4	61	503	**593**
2020	5	7	4	2	45	316	**379**
2021	8	7	0	3	42	379	**339**
2022	8	13	7	6	70	456	**560**
Mortality IPD (all ages, sentinel labs covering 25% of Dutch population; source: NRLBM)							
2005	3	0	0	0	1	101	**105**
2006	0	1	0	0	3	91	**95**
2007	0	0	0	0	7	82	**89**
2008	0	1	0	0	7	82	**90**
2009	1	1	1	0	4	75	**82**
2010	0	0	0	0	6	52	**58**
2011	0	0	0	0	3	65	**68**
2012	0	0	0	0	6	68	**74**
2013	0	0	0	0	1	75	**76**
2014	0	1	0	1	1	75	**78**
2015	1	0	0	0	4	72	**77**



Pneumococcal disease								ICD9: 481 ICD10: J13
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality pneumococcal pneumonia* (source: CBS)								
2008	0	0	0	0	0	47	**47**	
2009	0	0	1	1	2	37	**41**	
2010	0	0	0	0	2	43	**45**	
2011	0	0	0	0	1	26	**27**	
2012	0	0	0	0	2	42	**44**	
2013	0	0	0	0	0	29	**29**	
2014	0	0	0	0	0	28	**28**	
2015	0	0	0	0	1	28	**29**	
2016	0	0	0	0	0	27	**27**	
2017	0	0	0	0	0	15	**15**	
2018	0	0	0	0	1	25	**26**	
2019	0	0	0	0	0	16	**16**	
2020	0	0	0	0	2	21	**23**	
2021	0	0	0	0	1	14	**15**	
2022*	0	0	0	0	0	24	**24**	
Hospitalisations pneumococcal pneumonia (source: Prismant/DHD)**								
2007	10	87	41	33	382	1,502	**2,064**	
2008	8	68	31	21	352	1,452	**1,938**	
2009	28	59	30	36	332	1,465	**1,955**	
2010	23	62	37	35	285	1,560	**2,009**	
2011	17	40	46	38	337	1,631	**2,111**	
2012	4	28	11	20	263	1,506	**1,835**	
2013	0	4	7	17	384	1,606	**2,020**	
2014	3	4	3	19	309	1,754	**2,095**	
2015^	5	10	10	25	305	2,175	**2,525**	
2016^	0	5	5	20	380	2,125	**2,540**	
2017^	5	5	5	15	270	2,180	**2,485**	
2018^	5	10	5	15	290	2,455	**2,785**	
2019^	5	15	5	15	235	2,140	**2,410**	
2020^	5	0	0	5	155	1,230	**1,395**	
2021^	0	10	5	5	165	1,105	**1,285**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Poliomyelitis								ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022	0	0	0	0	1	0	**1**	

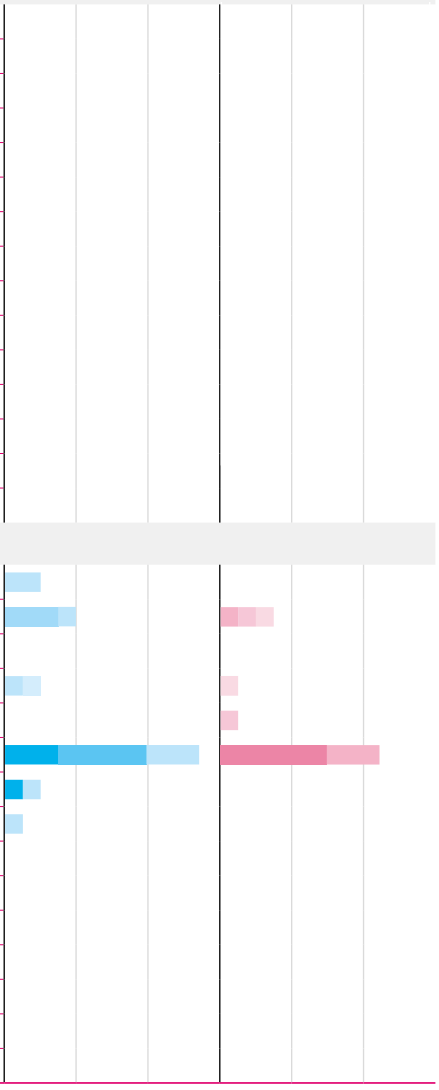
** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

Poliomyelitis								ICD9: 045 ICD10: A80
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations* (source: Prismant/DHD)								
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	
2018^	0	0	0	0	0	0	**0**	
2019^	0	0	0	0	0	0	**0**	
2020^	0	0	0	0	0	0	**0**	
2021^	0	0	0	0	0	0	**0**	

* *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

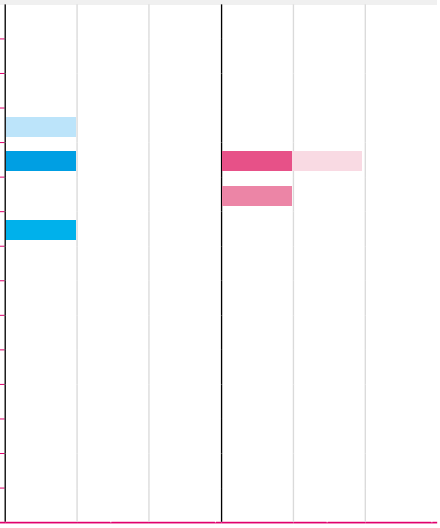
Rubella (acquired)								ICD10: B06
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2008	0	0	0	0	2	0	**2**	
2009	0	0	0	4	2	1	**7**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	1	2	**3**	
2012	0	0	0	0	1	0	**1**	
2013**	0	10	37	7	3	0	**57**	
2014	0	1	0	0	1	0	**2**	
2015	0	0	0	0	1	0	**1**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022	0	0	0	0	0	0	**0**	



* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Gender unknown for 37 cases.*

Rubella (acquired)								ICD9: 056 ICD10: B06
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Hospitalisations* (source: Prisman/DHD)								
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	1	0	**1**	
2011	1	1	0	0	0	1	**3**	
2012	0	0	1	0	0	0	**1**	
2013	0	1	0	0	0	0	**1**	
2014	0	0	0	0	0	0	**0**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	
2018^	0	0	0	0	0	0	**0**	
2019^	0	0	0	0	0	0	**0**	
2020^	0	0	0	0	0	0	**0**	
2021^	0	0	0	0	0	0	**0**	



* *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

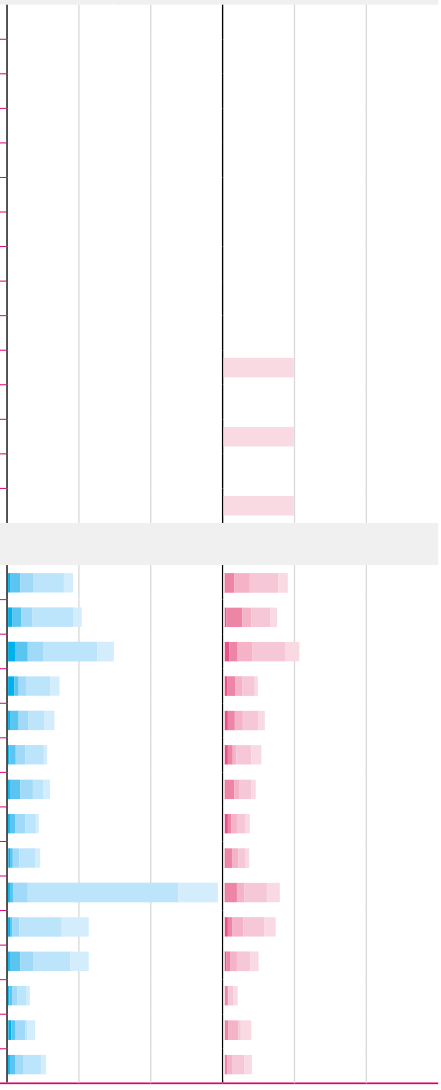
^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Tetanus								ID10: A33-35
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	0	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	1	**1**	
Notifications (source: Osiris)								
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	2	**2**	
2011	0	0	0	0	0	5	**5**	
2012	0	0	0	0	1	1	**2**	
2013	0	0	0	0	1	0	**1**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	1	0	0	**1**	
2016	0	0	0	0	0	1	**1**	
2017	0	0	0	0	0	1	**1**	
2018	0	0	0	0	0	1	**1**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	1	0	1	**2**	
2021	0	0	0	0	0	0	**0**	
2022	0	0	0	0	0	2	**2**	

** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

Potential NIP target diseases

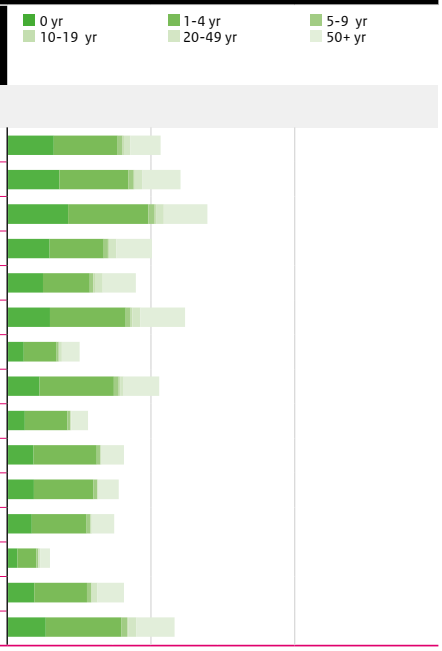
Hepatitis A								ICD10: B15
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (acute; source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	1	**1**	
2019	0	0	0	0	0	0	**0**	
2020	0	0	0	0	0	1	**0**	
2021	0	0	0	0	0	0	**0**	
2022*	0	0	0	0	0	1	**1**	
Notifications (source: Osiris)								
2008	0	6	25	42	85	27	**185**	
2009	0	9	36	28	85	22	**180**	
2010	0	17	30	43	124	44	**258**	
2011	0	13	18	20	52	18	**121**	
2012	0	9	21	26	45	23	**124**	
2013	0	7	16	18	48	20	**109**	
2014	0	5	26	26	31	17	**105**	
2015	0	8	12	22	28	10	**80**	
2016	1	5	12	18	33	12	**81**	
2017	0	5	21	31	243	74	**374**	
2018	0	9	8	27	89	55	**188**	
2019	0	6	19	29	71	38	**163**	
2020	0	2	9	8	20	11	**50**	
2021	1	4	11	28	7	26	**77**	
2022	0	3	11	18	43	18	**93**	



** Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

Rotavirus

Year	Age (years)						Total
	0	1-4	5-9	10-19	20-49	50+	
Hospitalisations* (source: Prismant/DHD)							
2008	1,933	2,702	211	47	274	1,288	**6,455**
2009	2,171	2,924	220	45	301	1,636	**7,297**
2010	2,534	3,398	262	60	329	1,845	**8,428**
2011	1,754	2,294	167	56	305	1,502	**6,078**
2012	1,470	1,985	148	71	329	1,392	**5,395**
2013	1,774	3,195	218	69	331	1,888	**7,477**
2014	669	1,383	83	26	118	753	**3,030**
2015	1,334	3,139	208	52	152	1,509	**6,394**
2016	704	1,812	110	28	18	712	**3,481**
2017	1,075	2,669	155	25	2	980	**4,905**
2018	1,098	2,502	161	31	0	888	**4,681**
2019^	1,009	2,311	163	42	1	955	**4,480**
2020#	399	804	60	12	85	405	**1,766**
2021†	1,109	2,234	167	34	237	1,125	**4,907**
2022†	1,590	3,204	240	49	340	1,614	**7,037**



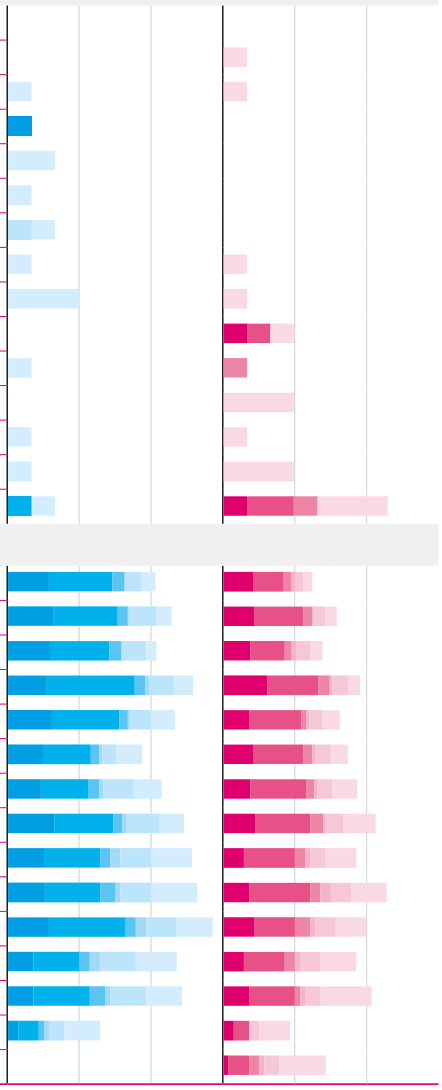
* *Hospitalisations are based on data from 2 years before and 2 years after the concerning year (if available).*

^ *The estimate for 2019 was based on 2017-2019, to exclude the exceptional COVID-19 pandemic years.*

The estimate for 2020 was based on only 2018 and 2019.

† *The estimate for 2021 and 2022 was based on the estimate for 2020.*

Varicella (chickenpox)								ICD9: 052 ICD10: B01
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	2	**2**	
2011	1	0	0	0	0	0	**1**	
2012	0	0	0	0	0	2	**2**	
2013	0	0	0	0	0	1	**1**	
2014	0	0	0	0	1	1	**2**	
2015	0	0	0	0	0	2	**2**	
2016	0	0	0	0	0	4	**4**	
2017	1	1	0	0	0	1	**3**	
2018	0	0	1	0	0	1	**2**	
2019	0	0	0	0	0	3	**3**	
2020	0	0	0	0	0	2	**2**	
2021	0	0	0	0	0	4	**4**	
2022*	1	3	1	0	0	4	**9**	
Hospitalisations (source: Prismant/DHD/CBS)**								
2007	69	92	19	4	24	23	**231**	
2008	74	111	19	3	38	26	**271**	
2009	67	92	18	6	37	22	**242**	
2010	81	136	21	7	39	31	**315**	
2011	67	118	13	5	34	40	**277**	
2012	63	96	17	6	29	42	**253**	
2013	58	102	18	7	45	51	**281**	
2014	76	112	22	6	49	56	**321**	
2015^	55	105	15	10	50	70	**305**	
2016^	55	120	25	15	55	75	**345**	
2017^	70	120	25	10	50	60	**335**	
2018^	45	85	20	15	55	75	**290**	
2019^	55	100	20	10	50	85	**325**	
2020^	15	35	5	5	25	65	**155**	
2021^	10	40	15	5	30	85	**190**	



* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Herpes zoster (shingles)								ICD9: 053 ICD10: B02
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
	0	1-4	5-9	10-19	20-49	50+		
Mortality (source: CBS)								
2008	0	0	0	0	0	14	**14**	
2009	0	0	0	0	0	20	**20**	
2010	0	0	0	0	0	25	**25**	
2011	0	0	0	0	0	20	**20**	
2012	0	0	0	0	0	21	**21**	
2013	0	0	0	0	0	21	**21**	
2014	0	0	0	0	0	26	**26**	
2015	0	0	0	0	0	33	**33**	
2016	0	0	0	0	0	27	**27**	
2017	0	1	0	0	0	32	**33**	
2018	0	0	0	0	0	36	**36**	
2019	0	0	0	0	0	32	**32**	
2020	0	0	0	0	0	43	**43**	
2021	0	0	0	0	0	37	**37**	
2022*	0	0	0	0	0	38	**38**	
Hospitalisations (source: Prismant/DHD/CBS)**								
2007	1	10	7	8	33	267	**326**	
2008	2	8	5	6	43	259	**323**	
2009	0	2	6	7	63	311	**389**	
2010	1	6	6	8	39	292	**352**	
2011	2	9	7	10	44	288	**360**	
2012	1	6	11	8	42	279	**347**	
2013	1	3	6	5	34	302	**351**	
2014	0	9	4	7	58	373	**451**	
2015^	0	10	10	15	60	395	**495**	
2016^	0	10	10	10	45	405	**480**	
2017^	0	15	5	15	45	385	**470**	
2018^	0	10	5	5	70	430	**520**	
2019^	0	5	5	10	60	445	**530**	
2020^	0	5	10	10	60	425	**515**	
2021^	0	0	0	10	55	450	**515**	

* *Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.*

** *Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.*

^ *Data corrected for non-participating hospitals and rounded off to closest five. Therefore, 0 cases can also be a few cases.*

Appendix 3 Overview of vaccine changes in the NIP from 2000

DTaP-IPV-Hib-HBV basic series

	Polio	Diphtheria	Tetanus	Pertussis	*H. influenzae* type B	Hepatitis B
2003, March	**DTwP-IPV and Hib basic series vaccinations merged**					
	← DTwP-IPV vaccine (NVI)				**← Hib vaccine (NVI)**	
	→ DTwP-IPV/Hib vaccine (NVI)					
	🕒 2, 3, 4, and 11 months					
	Children born on or after April 1st, 2002					
2005, January	**Vaccine switch for DTwP-IPV-Hib basic series to DTaP-IPV-Hib**					
	← DTwP-IPV/Hib vaccine (NVI)					
	→ Infanrix IPV+Hib (GSK)					
	🕒 2, 3, 4, and 11 months					
	Children born on or after February 1st, 2004					
2006, January	**Vaccine switch for DTaP-IPV-Hib basic series**					
	← Infanrix IPV+Hib (GSK)					
	→ Pediacel (SP MSD)					
	🕒 2, 3, 4, and 11 months					
	Children born on or after February 1st, 2005					
2008, July-Sept 15th	**Vaccine option added for DTaP-IPV-Hib basic series**					
	Pediacel (SP MSD) **+ Infanrix IPV+Hib (GSK)**					
	🕒 2, 3, 4, and 11 months					
	Children born on or after August 1st, 2007					
2010, January	**Vaccine option removed for DTaP-IPV-Hib basic series**					
	Pediacel (SP MSD) **- Infanrix IPV+Hib (GSK)**					
	🕒 2, 3, 4, and 11 months					
	Children born on or after February 1st, 2009					
2011, October	**HBV vaccination added to the DTaP-IPV-Hib basic series**					
	← Pediacel (SP MSD)					
	→ Infanrix hexa (GSK)					
	🕒 2, 3, 4, and 11 months					
	Children born on or after August 1st, 2011					
2018, December	**Vaccine switch for DTaP-IPV-Hib-HBV basic series**					
	← Infanrix hexa (GSK)					
	→ Vaxelis (MSD)					
	🕒 2, 3, 4, and 11 months					
2019, December	**Maternal Tdap vaccination added**					
		Boostrix (GSK)				
		🕒 Pregnant women after 22 weeks, to protect their baby against pertussis in first few months of life				
2020, January	**DTaP-IPV-HiB-HBV basic series dosing schedule changed**					
	Vaxelis (MSD)					
	← 🕒 2, 3, 4, and 11 months					
	→ 🕒 3, 5, and 11 months					
	Only for children of mothers that received Boostrix after 22 weeks of pregnancy					

Additional DTaP-IPV-Hib-HBV basic vaccination series for risk group children

	DTaP-IPV-Hib	Hepatitis B
2003, March		**HBV vaccination added**
		→ HBVAXPRO (SP MSD)
		🕒 2, 3, 4, and 11 months
		Risk group (1) born on or after January 1st 2003
2006, January		**HBV dose added**
		HBVAXPRO (SP MSD)
		→ 🕒 Birth
		Risk group (2) born on or after January 1st 2006
2006, June	**HBV and DTwP-IPV-Hib vaccination merged + switch from wP to aP**	
	← Pediacel (SP MSD)	**← HBVAXPRO (SP MSD)**
	→ Infanrix hexa (GSK)	
	🕒 2, 3, 4, and 11 months	
	Risk group (1) born on or after April 1st, 2006	
2008, January		**Risk group expanded**
		HBVAXPRO (SP MSD)
		🕒 Birth
		→ Risk group (3) born on or after January 1st 2008
2008, September		**Vaccine switch for HBV vaccination at birth**
		← HBVAXPRO (SP MSD)
		→ Engerix-B junior (GSK)
		🕒 Birth
		Risk group (3) born on or after September 1st 2008

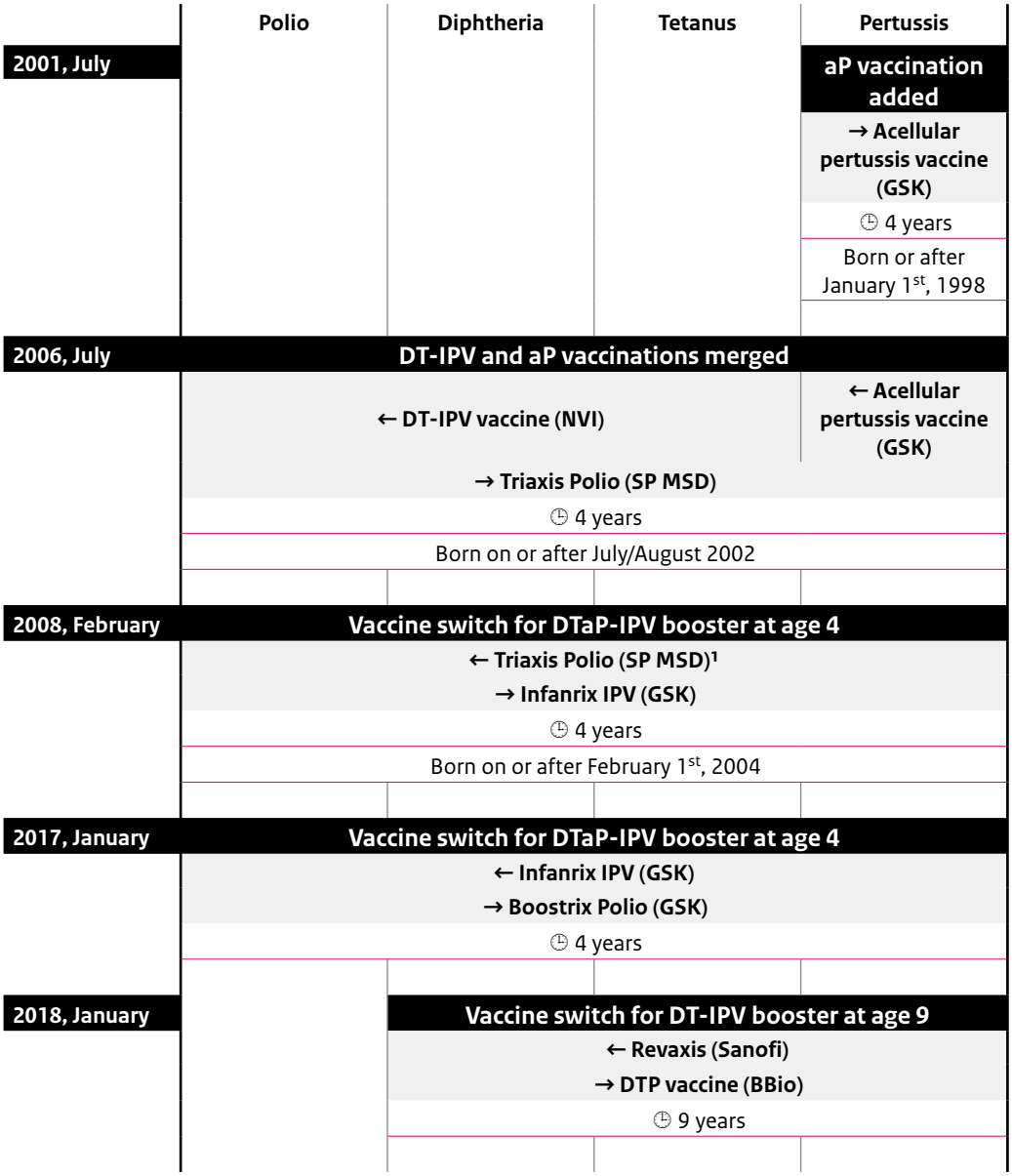
Risk groups:

(1) Only children at least one of whose parents was born in a country where hepatitis B is moderately or highly endemic and children whose mother had tested positive for HBsAg.

(2) Only for children whose mother tested positive for HBsAg.

(3) Only for children whose mother tested positive for HBsAg and children with Down syndrome.

Tdap-IPV booster vaccinations



[1] *Used until March 2008*

Pneumococcal vaccination

2006, June	Pneumococcal vaccination added at 2, 3, 4, and 11 months of age
	→ Prevnar (Wyeth)
	🕒 2, 3, 4, and 11 months
	Children born on or after April 1st, 2006
2011, May	**Vaccine switch**
	← Prevnar (Wyeth)
	→ Synflorix (GSK)
	🕒 2, 3, 4, and 11 months
	Children born on or after March 1st, 2011
2013, December	**Vaccine switch + change in dosing schedule**
	Synflorix (GSK)
	← 🕒 2, 3, 4, 11 months
	→ 🕒 2, 4, 11 months
	Children born on or after October 2013
2020, January	**Change in dosing schedule**
	Synflorix (GSK)
	← 🕒 2, 4, 11 months
	→ 🕒 3, 5, 11 months

MMR vaccination

2006, September	Vaccine switch at age 14 months
	← MMR vaccine (NVI)
	→ MMR-VaxPro (SP MSD) and Priorix (GSK)
	🕒 14 months
	Children born on or after July/August 2005
2008, October	**Vaccine switch at age 9**
	← Priorix (GSK)
	→ MMR-VaxPro (SP MSD)
	🕒 9 years
	Children born on or after September 1st, 1999

HPV vaccination

2010, January	**HPV vaccination added at age 12**
	Cervarix (GSK)
	🕒 12 years, girls only
	Children born on or after January 1st, 1997, 3 doses at 0, 1, and 6 months **Catch-up campaign for children born between January 1st, 1993, to December 31st, 1996**
2014, January	**Change in dosing schedule**
	Cervarix (GSK)
	🕒 12 years, girls only
	← 3 vaccines, intervals of 1 and 5 months **→ 2 vaccines, interval 6 months**
	Children born on or after January 1st, 2001
2022, January	**Boys also offered HPV vaccination + age of vaccination lowered to age 10**
	Cervarix (GSK)
	🕒 Boys *and* girls, at age 10
	Children born on or after January 1st, 2012 Catch-up campaign in 2022 and 2023 for children born between January 1st, 2004, to December 31st, 2011
2022, September	**Change in dosing schedule**
	Cervarix (GSK)
	🕒 Boys *and* girls, aged 15 and over
	← 3 vaccines, intervals of 1 and 5 months **→ 2 vaccines, interval 6 months**

Meningococcal vaccination

2002, September	**Meningococcal type C vaccination added at age 14 months**
	NeisVac-C (Baxter)
	🕒 14 months
	Children born on or after June 1st, 2001 **Catch-up campaign in June 2002 for children born from June 1st, 1983, to May 31st, 2001**
2018, May	**Vaccine types expanded with types A, W, and Y**
	← NeisVac-C (Pfizer)
	→ Nimenrix (Pfizer): expansion from MenC to MenACWY
	🕒 14 months
2018, December	**Catch-up campaign meningococcal types A, C, W, and Y for adolescents**
	Nimenrix (Pfizer)
	Catch-up vaccinations in 2018 and 2019 for children born between 2001 and 2005
2020, January	**Meningococcal type A, C, W, and Y vaccination added at age 14 years**
	Nimenrix (Pfizer)
	🕒 14 years
2022, August	**Vaccine switch at 14 months**
	← Nimenrix (Pfizer)
	→ MenQuadfi (Sanofi)
	🕒 14 months

Appendix 4 Composition of vaccines used in the NIP

Vaccine	Composition
M-M-R VaxPro / MSD	
EU/1/06/337 Mumps, measles and rubella vaccine 0.5 ml	Measles virus[1] (Enders' Edmonston)[3], ≥1000 $TCID_{50}$[4] Mumps virus[1] (Jeryl Lynn, Level B)[3], ≥12,500 $TCID_{50}$[4] Rubella virus[2] (Wistar RA 27/3)[3], ≥1000 $TCID_{50}$[4] [1] produced in chick embryo cells [2] produced in WI-38 human diploïd lung fibroblasts [3] live attenuated [4] 50% tissue culture of infectious doses
Boostrix Polio / GSK	
RVG 35123 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine (adsorbed, reduced antigen) 0.5 ml	Diphtheria toxoid[1], ≥2 IU Tetanus toxoid[1], ≥20 IU *Bordetella pertussis* antigens Pertussis toxoid (PT)[1], 8 µg Filamentous haemagglutinin (FHA)[1], 8 µg Pertactin (PRN)[1], 2.5 µg Inativated poliovirus type 1 poliovirus (Mahoney)[2], 40 DU type 2 poliovirus (MEF-1)[2], 8 DU type 3 poliovirus (Saukett)[2], 32 DU [1] adsorbed to aluminiumhydroxide ($Al(OH)_3$), hydrated, 0.3 mg Al^{3+} and aluminiumphosphate ($AlPO_4$), 0.2 mg Al^{3+} [2] produced in Vero cells
Boostrix / GSK	
RVG 35121 Diphtheria, tetanus and pertussis (acellular component) vaccine (adsorbed, reduced antigen) 0.5 ml	Diphtheria toxoid[1], ≥2 IU Tetanus toxoid[1], ≥20 IU *Bordetella pertussis* antigens Pertussis toxoid (PT)[1], 8 µg Filamentous haemagglutinin (FHA)[1], 8 µg Pertactin (PRN)[1], 2.5 µg [1] adsorbed to aluminiumhydroxide ($Al(OH)_3$), hydrated, 0.3 mg Al^{3+} and aluminiumphosphate ($AlPO_4$), 0.2 mg Al^{3+}

Vaccine	Composition
Vaxelis / MCM Vaccine B.V.	
EU/1/15/1079 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis and *Haemophilus* type b vaccine (adsorbed) 0.5 ml	Diphtheria toxoid[1], ≥20 IU Tetanus toxoid[1], ≥40 IU *Bordetella pertussis* antigens[1]: Pertussis toxoid, 20 µg Filamentous haemagglutinin, 20 µg Fimbriae type 2 and 3, 5 µg Pertactin, 3 µg Hepatitis B surface antigen[2,3] Inactivated poliovirus[4]: Inactivated type 1 poliovirus, 40 DE Inactivated type 2 poliovirus, 8 DE Inactivated type 3 poliovirus, 32 DE Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate), 3 µg Conjugated to meningococcal protein[2], 50 µg [1] adsorbed on aluminiumphosphate, 0.17 mg Al^{3+} [2] adsorbed on amorphous aluminium hydroxyphosphate sulfate, 0.15 mg Al^{3+} [3] produced in yeast (*Saccharomyces cerevisiae*) cells by recombinant DNA technology [4] produced in Vero cells [5] or equivalent antigenic quantity determined by a suitable immunochemical method
REVAXIS / SP	
RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria toxoid[1], ≥2 IU Purified tetanus toxoid[1], ≥20 IU Inactivated poliovirus type 1[2], 29 DU Inactivated poliovirus type 2[2], 7 DU Inactivated poliovirus type 3[2], 26 DU [1]adsorbed to aluminium hydroxide, 0.35 mg (as aluminium) [2]produced in Vero cells
Engerix-B Junior / GSK	
RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen recombinant (S protein)[1,2], 10 µg [1] adsorbed to aluminium hydroxide, hydrated, 0,25 mg Al^{3+} [2] produced on genetically engineered yeast cells (*Saccharomyces cerevisiae*)

Vaccine	Composition
Engerix-B / GSK	
RVG17316 Hepatitis B (rDNA) vaccine (adsorbed) 1 ml	Hepatitis B-virus surface antigen[1,2], 20 µg [1] adsorbed on aluminium hydroxide, hydrated, 0.5 mg Al^{3+} [2] produced on yeast cells (*Saccharomyces cerevisiae*) with recombinant DNA technology
Cervarix / GSK	
EU/1/07/419	Human papillomavirus type 16 L1 protein[1,2,3], 20 µg Human papillomavirus type 18 L1 protein[1,2,3], 20 µg [1] adjuvanted by AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL)[3], 50 µg [2] absorbed on aluminium hydroxide, hydrated ($Al(OH)_3$), 0.5 mg Al^{3+} in total [3] L1 protein in the form of non-infectious virus-like particles (VLPs) produced by recombinant DNA technology using a Baculovirus expression system, which uses Hi-5 Rix4446 cells derived from *Trichoplusia ni*
Nimenrix / Pfizer	
EU/1/12/767 Conjugated meningococcal group A, C, W-135 and Y vaccine 0.5 ml	*Neisseria meningitidis*-group A polysaccharide[1], 5 µg *Neisseria meningitidis*-group C polysaccharide[1], 5 µg *Neisseria meningitidis*-group W-135 polysaccharide[1], 5 µg *Neisseria meningitidis*-group Y polysaccharide[1], 5 µg [1] conjugated to tetanus toxoid carrier protein, 44 µg
MenQuadfi / SP	
EU/1/20/1483 Conjugated meningococcal group A, C, W and Y vaccine 0.5 ml	*Neisseria meningitidis*-group A polysaccharide[1], 10 µg *Neisseria meningitidis*-group C polysaccharide[1], 10 µg *Neisseria meningitidis*-group Y polysaccharide[1], 10 µg *Neisseria meningitidis*-group W polysaccharide[1], 10 µg [1] conjugated to tetanus toxoid carrier protein, 55 µg

Vaccine	Composition
Synflorix / GSK	
EU/1/09/508 Pneumococcal polysaccharide conjugate vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 1[1,2], 1 µg Pneumococcal polysaccharide serotype 4[1,2], 3 µg Pneumococcal polysaccharide serotype 5[1,2], 1 µg Pneumococcal polysaccharide serotype 6B[1,2], 1 µg Pneumococcal polysaccharide serotype 7F[1,2], 1 µg Pneumococcal polysaccharide serotype 9V[1,2], 1 µg Pneumococcal polysaccharide serotype 14[1,2], 1 µg Pneumococcal polysaccharide serotype 18C[1,3], 3 µg Pneumococcal polysaccharide serotype 19F[1,4], 3 µg Pneumococcal polysaccharide serotype 23F[1,2], 1 µg [1] adsorbed on aluminium phosphate, 0.5 mg Al^{3+} in total [2] conjugated to protein D (derived from non-typeable Haemophilus influenzae) carrier protein, 9–16 µg [3] conjugated to tetanus toxoid, 5–10 µg [4] conjugated to diphtheria toxoid, 3–6 µg

More extensive product information can be found at: www.cbg-meb.nl and www.emea.europe.eu.

Appendix 5 Overview of recent RIVM publications (01/07/2022 to 31/06/2023)

Vaccination coverage

van Lier EA, Oomen PJ, Giesbers H, Hament JM, van Vliet JA, Drijfhout IH, Hirschberg H, de Melker HE. Vaccination coverage and annual report National Immunisation Programme in the Netherlands 2021 (Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2021). 2022. RIVM report, number 2022-0017.

van Lier EA, Hament JM, Knijff M, Westra M, Ernst A, Giesbers H, Drijfhout IH, Dorn T, van Vliet JA, de Melker HE. Vaccination coverage and annual report National Immunisation Programme in the Netherlands 2022 (Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2022). 2023. RIVM report, number 2023-0031.

Klinkenberg D, van Hoek AJ, Veldhuijzen I, Hahné S, Wallinga J. Social clustering of unvaccinated children in schools in the Netherlands. Epidemiol Infect. 2022;150:e200.

Acceptance of vaccination

Chambon M, Kammeraad WG, van Harreveld F, Dalege J, Elberse JE, van der Maas HLJ. Understanding change in COVID-19 vaccination intention with network analysis of longitudinal data from Dutch adults. npj Vaccines. 2022;7(1):114.

Immink MM, van der Maas NAT, de Melker HE, Ferreira JA, Bekker MN. Socio-psychological determinants of second trimester maternal pertussis vaccination acceptance in the Netherlands. Vaccine. 2023;41(22):3446-3453.

Kemper S, Kupper F, Kengne Kamga, Brabers A, Bongers M, Timen A, *et al.* Public engagement in decision-making regarding the management of the COVID-19 epidemic: Views and expectations of the 'publics'. Health Expect. 2022;25(6):2807-2817.

Maertzdorf KM, Rietman ML, Lambooij MS, Verschuren WMM, Picavet HSJ. Willingness to get vaccinated against influenza, pneumococcal disease, pertussis, and herpes zoster - A pre-COVID-19 exploration among the older adult population. Vaccine. 2023;41(6):1254-1264.

de Vries M, Claassen L, Lambooij MS, Timen A. Did the temporary suspension of Vaxzveria vaccinations influence COVID-19 vaccination intentions, vaccination perceptions and trust in the vaccination campaign? A repeated survey study in the Netherlands. Vaccine. 2023;41(12):1961-1967.

Burden of disease

Charalampous P, Haagsma JA, Jakobsen LS, Gorasso V, MacDonald SA. Burden of infectious disease studies in Europe and the United Kingdom: a review of methodological design choices. Epidemiol Infect. 2023;151:e19.

Current NIP

Diphtheria

Crobach MJI, Hornung BVH, Verduin C, Vos MC, Kuijper EJ, *et al.* Screening for Clostridioides difficile colonization at admission to the hospital: a multi-centre study. Clin Microbiol Infect. 2023;29(7):891-896.

Ducarmon QR, van der Bruggen T, Harmanus C, Sanders IMJG, Daenen LGM, Kuiper EJ, *et al.* Clostridioides difficile infection with isolates of cryptic clade C-II: a genomic analysis of polymerase chain reaction ribotype 151. Clin Microbiol Infect. 2023;29(4):538.e1-538.e6.

Elsinga J, van Meijeren D, Reubsaet F. Surveillance of diphtheria in the Netherlands between 2000-2021: cutaneous diphtheria supersedes the respiratory form. BMC Infect Dis. 2023;23(1):420.

Vandebriel RJ, Stalpers CAL, Vermeulen JP, Remkes M, Schmelter M, *et al.* Development of a cell line-based in vitro assay for assessment of Diphtheria, Tetanus and acellular Pertussis (DTaP)-induced inflammasome activation. Vaccine. 2022;40(38):5601-5607.

Haemophilus influenzae disease

Shaw D, Abad R, Amin-Chowdhury Z, Bautista A, Bennett D, Broughton K, *et al.* Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium. Lancet Digit Health. 2023;5(9):E582-E593.

Hepatitis B

Raven S, Hautvast J, Yiek WK, Veldhuijzen I, van Steenbergen J, van Aar F. Contribution of sexual health services to hepatitis B detection and control (Netherlands, 2008-2016). Sex Transm Infect. 2023;99:373–379.

Sharrock KC, Noori T, Axelsson M, Buti M, van Veldhuijzen I. Monitoring progress towards elimination of hepatitis B and C in the EU/EEA. Plos Glob Public Health. 2022;2(8):e0000841.

Human papillomavirus (HPV) infection

van Eer K, Middeldorp M, Dzebisasjvili T, Lamkaraf N, de Melker HE, King AJ, *et al.* Effects of two and three vaccinations with the bivalent HPV vaccine on the prevalence and load of HPV in clearing and persistent infections in young women. J Infect Dis. 2023;jiad080; online ahead of print.

Hamdiui N, Stein M, van Steenbergen J, Khan A, Cetin MN, Timen A, *et al.* Evaluation of a Web-Based Culturally Sensitive Educational Video to Facilitate Informed Cervical Cancer Screening Decisions Among Turkish- and Moroccan-Dutch Women Aged 30 to 60 Years: Randomized Intervention Study. J Med Internet Res. 2022;24(10):e35962.

Hoes J, King AJ, Berkhof J, de Melker HE. High vaccine effectiveness persists for ten years after HPV16/18 vaccination among young Dutch women. Vaccine. 2023;42(2),285-289.

Kusters JMA, Brouwer JGM, van Benthem BHB, Heijne JCM, Schim van der Loeff MF. Global Type-Specific Genital Human Papillomavirus Prevalence in Men, by Sexual Orientation: a Systematic Review and Meta-Analysis. Euro Surveill. 2023;28(16):pii2200525.

Schurink-van't Klooster TM, Siebers AG, Hoes J, van Kemenade FJ, Berkhof J, Bogaards JA, de Melker HE. Early effect of bivalent human papillomavirus vaccination on cytology outcomes in cervical samples among young women in the Netherlands. Cancer Medicine. 2023;12(10):11786-11794.

Wijstma ES, Jongen VW, Alberts CJ, de Melker HE, Hoes J, *et al.* Approaches to estimating clearance rates for Human Papillomavirus groupings: a systematic review and real data examples. Epidemiology. 2023;34(1):119-130.

Meningococcal disease

Middeldorp M, Steens A, Lagerweij G, van Sorge NM, Freudenburg-de Graaf W, Sanders EAM, de Melker HE, Knol MJ. The burden of invasive meningococcal disease in the Netherlands, 2011-2020. Vaccine. 2023;41(16):2664-70.

Miellet WR, Pluister G, Sikking M, Tappel M, Karczewski J, Visser LJ, *et al.* Surveillance of *Neisseria meningitidis* carriage four years after menACWY vaccine implementation in the Netherlands reveals decline in vaccine-type and rise in genogroup e circulation. Vaccine. 2023.

Ohm M, van Straalen JW, Zijlstra M, de Joode-Smink G, Jasmijn Sellies A, Swart JF, *et al.* Meningococcal ACWY conjugate vaccine immunogenicity and safety in adolescents with juvenile idiopathic arthritis and inflammatory bowel disease: A prospective observational cohort study. Vaccine. 2023;41(25):3782-9

Ohm M, Wolf JJ, van Rooijen D, Visser L, Miellet WR, Mariman R, *et al.* Meningococcal vaccination in adolescents and adults induces bactericidal activity against hyperinvasive complement-resistant meningococcal isolates. MedRxiv (non-peer-reviewed). 2022; online ahead of print.

Oostdijk C, Ferreira JA, Ruijs WLM, Mollema L, Van Zoonen K. Adolescent and parental decision-making for the MenACWY vaccination: influential predictors and parental-adolescent differences among households in the Netherlands. BMC Public Health. 2023;23(1):947.

Shaw D, Abad R, Amin-Chowdhury Z, Bautista A, Bennett D, Broughton K, *et al.* Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium. Lancet Digit Health. 2023;5(9):E582-E593.

Pertussis

Corbière V, Lambert EE, Rodesch M, van Gaans-van den Brink JAM, Misiak A, Simonetti E, van Praet A., *et al.* A semi high-throughput whole blood-based flow cytometry assay to detect and monitor *Bordetella pertussis*-specific Th1, Th2 and Th17 responses. Front Immunol. 2023;14:1101366.

Immink MM, Kemmeren JM, Broeders L, Bekker MN, de Melker HE, Sanders EAM, *et al.* Reactogenicity and safety of second trimester maternal tetanus, diphtheria and acellular pertussis vaccination in the Netherlands. Vaccine. 2023;41(5):1074-80.

Immink MM, van der Maas NAT, de Melker HE, Ferreira JA, Bekker MN. Socio-psychological determinants of second trimester maternal pertussis vaccination acceptance in the Netherlands. Vaccine. 2023;41(22):3446-53.

Immink MM, van Zoonen K, Jager NM, Pluijmaekers AJM, de Melker HE, van der Maas NAT, *et al.* Maternal vaccination against pertussis as part of the national immunization program: a qualitative evaluation among obstetric care providers one year after the implementation in December 2019. BMC Health Serv Res. 2023;23(1):311.
van der Pan K, de Bruin-Versteeg S, Damasceno D, Hernández-Delgado A, van der Sluijs-Gelling AJ, van den Bossche WBL, *et al.* Development of a standardized and validated flow cytometry approach for monitoring of innate myeloid immune cells in human blood. Front Immunol. 2022;13:935879.
van Schuppen E, Froberg J, Versteegen P, van Gageldonk PGM, Berbers GAM, *et al.* Prior exposure to *B. pertussis* shapes the mucosal antibody response to acellular pertussis booster vaccination. Nat Commun. 2022;13(1):7429.
Vandebriel RJ, Stalpers CAL, Vermeulen JP, Remkes M, Schmelter M, *et al.* Development of a cell line-based in vitro assay for assessment of Diphtheria, Tetanus and acellular Pertussis (DTaP)-induced inflammasome activation. Vaccine. 2022;40(38):5601-5607.

Pneumococcal disease

de Boer PT, van Werkhoven CH, van Hoek AJ, Knol M, Sanders EAM, Wallinga J, *et al.* Higher-valency pneumococcal conjugate vaccines in elderly, taking into account indirect protection and serotype replacement from childhood vaccination programs: A cost-effectiveness study. https://rivm.openrepository.com/handle/10029/626769.
Miellet WR, Almeida ST, Trzcinski K, Sa-Leao R. Streptococcus pneumoniae carriage studies in adults: Importance, challenges, and key issues to consider when using quantitative PCR-based approaches. Front Microbiol. 2023;14:1122276.
Miellet WR, van Veldhuizen J, Mariman R, Wijmenga-Monsuur AJ, Bosch T, Rots NY, Sanders EAM, *et al.* A spitting image: molecular diagnostics applied to saliva enhance detection of Streptococcus pneumoniae and pneumococcal serotype carriage. Front Microbiol. 2023;14:1156695.
Shaw D, Abad R, Amin-Chowdhury Z, Bautista A, Bennett D, Broughton K, *et al.* Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium. Lancet Digit Health. 2023;5(9):E582-E593.
Steens A. Pneumococcal vaccination in older adults. Information for the Health Council of the Netherlands. 2022. RIVM-report, number 2022-0047.
Tiley KS, Ratcliffe H, Voysey M, Jefferies K, Tcherniaeva I, Berbers G, *et al.* Nasopharyngeal carriage of pneumococcus in children in England up to ten years after PCV13 introduction: persistence of serotypes 3 and 19A and emergence of 7C. J Infect Dis. 2023;227(5):610-621.

Poliomyelitis

Duizer E, Ruijs W, Hintaran P, Hafkamp M, Veer Mvd, Wierik Mt. Wild poliovirus type 3 (WPV3)-shedding event following detection in environmental surveillance of poliovirus essential facilities, the Netherlands, November 2022 to January 2023. Eurosurveillance. 2023;8(5).

Helfferich J, de Lange MMA, Benschop KSM, Jacobs BC, Van Leer-Buter CC, Meijer A, Bakker DP, de Bie E, Braakman HMH, Brandsma R, Neuteboom RF, Niks EH, Niermeijer J-M, Roelfsema V, Schoenmaker N, Sie LT, Niesters HG, Brouwer OF, te Wierik MJM. Epidemiology of acute flaccid myelitis in children in the Netherlands, 2014 to 2019. Euro Surveill. 2023;27(42):pii=2200157.
van Vliet JHA, Houwaart ES, Rümke HC. Onzekerheden bij invoering nieuwe vaccinaties. Polio- en covid-19-vaccinatie vergeleken. Ned Tijdschr Geneeskde. 2022;166:D6902.

Rubella

de Munter AC, Hautvast JLA, Ruijs WLM, Ruiter RAC, Hulscher MEJL. Considerable doubt about rubella screening and vaccination among unvaccinated orthodox protestant women: a mixed-methods study. BMC Public Health. 2023;23(1):693.

Tetanus

Vandebriel RJ, Stalpers CAL, Vermeulen JP, Remkes M, Schmelter M, *et al.* Development of a cell line-based in vitro assay for assessment of Diphtheria, Tetanus and acellular Pertussis (DTaP)-induced inflammasome activation. Vaccine. 2022;40(38):5601-5607.

Potential NIP target diseases

Hepatitis A

Mac Donald-Ottevanger MS, Prins M, van Dissel J, Rier N, Reimerink J, *et al.* Ethnic differences in hepatitis A and E virus seroprevalence in patients attending the Emergency Department, Paramaribo, Suriname. Trans R Soc Trop Med Hyg. 2023;117(3):197-204.

Respiratory syncytial virus

Besteman SB, Phung E, Raeven HHM, Amatngalim GD, Rumpret M, Crabtree J, *et al.* Recurrent Respiratory Syncytial Virus Infection in a CD14-Deficient Patient. The Journal of infectious diseases. 2022;226(2):258-269.
Billard BM, Wildenbeest J, Bont JL, Nair H, Meijer A, *et al.* Year-to-year variation in attack rates could result in underpowered respiratory syncytial virus vaccine efficacy trials. J Clin Epidemiol. 2022;147:11-20.
Del Riccio M, Spreeuwenberg P, Osei-Yeboah R, Johannesen CK, Vazquez Fernandez L, Teirlinck AC, *et al.* Defining the Burden of Disease of RSV in the European Union: estimates of RSV-associated hospitalisations in children under 5 years of age. A systematic review and modelling study. J Infect Dis. 2023;jiad188.
Deng S, Guo L, Cohen C, Meijer A, Moyes J, Pasittungkul S, *et al.* Impact of subgroup distribution on seasonality of human respiratory syncytial virus: A global systematic analysis. The Journal of infectious diseases. 2023;jiad192.
den Hartog G, van Kasteren PB, Schepp RM, Teirlinck AC, van der Klis FRM, van Binnendijk RS. Decline of RSV-specific antibodies during the COVID-19 pandemic. Lancet Infect Dis. 2023;23(1):23-25.

Heida R, Akkerman R, Jacob Silva PH, Lakerveld AJ, Ortiz D, Bigogno C, *et al.* Development of an inhalable antiviral powder formulation against respiratory syncytial virus. J Control Release. 2023;357:264-73.
Osei-Yeboah R, Spreeuwenberg P, Del Riccio M, Fischer TK, Egeskov-Cavling AM, van Boven M, *et al.* Estimation of the number of RSV-associated hospitalisations in adults in the European Union. J Infect Dis. 2023;:jiad189.
Phijffer E, de Bruin O, Wildenbeest JG, Bont LJ, van der Maas NAT, *et al.* Respiratory syncytial virus vaccination during pregnancy for improving infant outcomes. Cochrane Database Syst Rev. 2022;(10):CD015134.
Reukers DFM, van Asten L, Brandsema PS, Dijkstra F, Hendriksen JMT, Hooiveld M, Jongenotter F, de Lange MMA, Teirlinck AC, Willekens G, Meijer A, van Gageldonk-Lafeber AB. Annual report Surveillance of COVID-19, influenza and other respiratory infections in the Netherlands: winter 2021/2022. 2022. Report number: 2022-0098.
Teirlinck AC, Johannesen CK, Broberg EK, Penttinen P, Campbell H, Nair H, *et al.* New perspectives on respiratory syncytial virus surveillance at the national level: lessons from the COVID-19 pandemic. The European respiratory journal. 2023;61(4).
Zuurbier RP, Bogaert D, de Steenhuijsen Piters WAA, Arp K, Chu MLJN, Sanders EAM, *et al.* Asymptomatic Viral Presence in Early Life Precedes Recurrence of Respiratory Tract Infections. Pediatr Infect Dis J. 2023;42(1):59-65.

COVID-19

Ainslie KEC, Backer JA, de Boer PT, van Hoek AJ, Klinkenberg D, Korthals Altes H, Leung KY, de Melker HE, Miura F, Wallinga J. A scenario modelling analysis to anticipate the impact of COVID-19 vaccination in adolescents and children on disease outcomes in the Netherlands, summer 2021. Euro Surveill. 2022;27(44):pii.2101090.
Andeweg SP, de Gier B, Vennema H, van Walle I, de Melker HE, Hahne SJM, van den Hof S, Eggink D, Knol MJ, *et al.* Higher risk of SARS-CoV-2 Omicron BA.4/5 infection than of BA.2 infection after previous BA.1 infection, the Netherlands, 2 May to 24 July 2022. Euro Surveill. 2023;28(7):pii.22200724.
Andeweg SP, Vennema H, Veldhuijzen I, Smorenburg N, Schmitz D, Zwagemaker F, van Gageldonk-Lafeber AB, Hahné SJM, Reusken C, Knol MJ, Eggink D. Elevated risk of infection with SARS-CoV-2 Beta, Gamma, and Delta variants compared with Alpha variant in vaccinated individuals. Sci Transl Med. 2023;15(684):eabn4338.
Backer JA, Bogaardt L, van Hagen CCE, Vos ERA, Wong D, Wallinga J, *et al.* Dynamics of non-household contacts during the COVID-19 pandemic in 2020 and 2021 in the Netherlands. Sci Rep. 2023;13(1):5166.
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van Dam KPJ, Volkers AG, Wieske L, Stalman EW, de Wit J, van Els CACM, *et al.* Primary SARS-CoV-2 infection in patients with immune-mediated inflammatory diseases: long-term humoral immune responses and effects on disease activity. BMC Infect Dis. 2023;23(1):332.
van Dam KPJ, Wieske L, Stalman EW, van Els CACM, de Wit J, *et al.* Disease activity in patients with immune-mediated inflammatory diseases after SARS-CoV-2 vaccinations. J Autoimmun. 2023;135:102984.
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Emmelot ME, Vos M, Boer MC, Rots NY, van Els CACM, Kaaijk P. SARS-CoV-2 Omicron BA.4/BA.5 Mutations in Spike Leading to T Cell Escape in Recently Vaccinated Individuals. Viruses. 2022;15(1):101.
van Ewijk CE, Hahné SJM, Knol MJ, *et al.* Response to Letter to the Editor: Importance of considering high-risk behaviours in COVID-19 vaccine effectiveness estimates with observational studies. Euro Surveill. 2023;28(4):pii.2300044.
van Ewijk CE, Kooijman MN, Fanoy E, Raven SFH, Middeldorp M, Shah A, de Gier B, de Melker HE, Hahne SJM, Knol MJ. COVID-19 vaccine effectiveness against SARS-CoV-2 infection during the Delta period, a nationwide study adjusting for chance of exposure, the Netherlands, July to December 2021. Euro surveill 2022;27(45):pii.2200217.
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Geers D, Sablerolles RSG, van Baarle D, Kootstra NA, Rietdijk WJR. Ad26.COV2.S priming provided a solid immunological base for mRNA-based COVID-19 booster vaccination. iScience. 2022;26(1):105753.
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de Graaf M, Langeveld J, Post J, Carrizosa C, Franz E, Izquierdo-Lara RW, *et al.* Capturing the SARS-CoV-2 infection pyramid within the municipality of Rotterdam using longitudinal sewage surveillance. Sci Total Environ. 2023;883:163599.
Guo R, Wolff C, Prada JM, Mughini-Gras L. When COVID-19 sits on people's laps: A systematic review of SARS-CoV-2 infection prevalence in household dogs and cats. One Health. 2023;16:100497.
Han AX, Kozanli E, Koopsen J, Vennema H, RIVM COVID-19 molecular epidemiology group, Hajji K, Kroneman A, van Walle I, Klinkenberg D, Wallinga J, Eggink D, Reusken C, *et al.* Regional importation and asymmetric within-country spread of SARS-CoV-2 variants of concern in the Netherlands. Elife. 2022;11:e78770.
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Heijmink L, Tonis J, Gerkema M, Raven S, van den Boogaard J, Hofhuis A, van den Hof S, *et al.* The epidemiological evaluation of mass testing in a small municipality in the Netherlands during the SARS-CoV-2 epidemic. Epidemiol Infect. 2022;150:e193.

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Huiberts AJ, de Gier B, Hoeve CE, de Melker HE, Hahne SJM, den Hartog G, van de Wijgert JHHM, van den Hof S, Knol MJ. Effectiveness of bivalent mRNA booster vaccination against SARS-CoV-2 Omicron infection, the Netherlands, September to December 2022. Euro Surveill. 2023;28(7):pii.2300087.

van Iersel SCJL, Backer JA, van Gaalen RD, Andeweg SP, Wallinga J, van Hoek J, *et al.* Empirical evidence of transmission over a school-household network for SARS-CoV-2; exploration of transmission pairs stratified by primary and secondary school. Epidemics. 2023;43:100675.

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Appendix 6 Overview of relevant websites

General information for NIP professionals

NIP 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

Meldingsplicht infectieziekten
(Mandatory notification of infectious diseases in the Netherlands):
http://www.rivm.nl/Onderwerpen/M/Meldingsplicht_infectieziekten

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker_voor_professionals

Surveillance Atlas of Infectious Diseases:
https://www.ecdc.europa.eu/en/surveillance-atlas-infectious-diseases

General information for the public

RIVM websites for the public:
https://rijksvaccinatieprogramma.nl/

Available vaccines that are not (yet) part of a public vaccination programme:
www.rivm.nl/vaccinaties

Volksgezondheidenzorg.info:
https://www.volksgezondheidenzorg.info/

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker

Vaccines Today:
https://www.vaccinestoday.eu/about-us/who-we-are/

Europees Vaccinatie Informatie Portaal (European Vaccination Information Portal):
https://vaccination-info.eu/nl

Other NIP-related RIVM reports

Vaccination Coverage and Annual Report for the National Immunisation Programme in the Netherlands 2022:
https://www.rivm.nl/publicaties/vaccinatiegraad-en-jaarverslag-rijksvaccinatieprogramma-nederland-2022

Adverse events in the Netherlands Vaccination Programme, reports in 2010 and review 1994–2010:
http://www.rivm.nl/bibliotheek/rapporten/205051004.pdf

Adverse events in the Netherlands Vaccination Programme. Report 2022:
https://www.lareb.nl/media/3j5mhb3q/rvp-jaarrapportage-2022.pdf

Surveillance of acute respiratory infections in the Netherlands: winter 2022/2023. SARS-CoV-2, influenza virus, RSV and other respiratory viruses:
https://www.rivm.nl/publicaties/surveillance-of-acute-respiratory-infections-in-netherlands-winter-2022-2023

Product information

NIP product information and package leaflets:
https://rijksvaccinatieprogramma.nl/professionals/productinformatie-vaccinaties

National organisations

General
Ministry of Health, Welfare and Sport:
http://www.rijksoverheid.nl/onderwerpen/vaccinaties

Gezondheidsraad (Health Council of the Netherlands):
http://www.gezondheidsraad.nl/

GGD GHOR:
http://www.ggdghorkennisnet.nl/

Vaccine safety
Netherlands Pharmacovigilance Centre Lareb:
http://www.lareb.nl/

College ter Beoordeling van Geneesmiddelen (CBG, Netherlands Medicines Evaluation Board):
https://www.cbg-meb.nl/

Data sources
Statistics Netherlands (CBS):
http://www.cbs.nl/

Dutch Hospital Data (DHD):
https://www.dhd.nl/

Nederlands instituut voor onderzoek van de gezondheidszorg
(NIVEL, Netherlands Institute for Health Services Research):
http://www.nivel.nl/

Nederlands Referentielaboratorium voor Bacteriële Meningitis
(NRLBM, Netherlands Reference Laboratory for Bacterial Meningitis):
https://www.amc.nl/web/specialismen/medische-microbiologie/medische-microbiologie/het-nederlands-referentielaboratorium-voor-bacteriele-meningitis.htm

Integrated Primary Care Information (IPCI):
http://www.ipci.nl/

The Netherlands Cancer Registry (NKR):
http://www.cijfersoverkanker.nl/

Nederlandse Werkgroep Klinische Virologie
(NWKV, Netherlands Working Group Clinical Virology):
http://www.nvmm.nl/vereniging/commissies-en-werkgroepen/nederlandse-werkgroep-klinische-virologie/

International organisations

World Health Organization (WHO):
http://www.who.int/en/

World Health Organization (WHO) Europe:
http://www.euro.who.int/en/home

European Centre for Disease Prevention and Control (ECDC):
http://ecdc.europa.eu/en/

Centers for Disease Control and Prevention (CDC):
http://www.cdc.gov/
https://www.cdc.gov/vaccines/growing/

ClinicalTrials.gov:
https://clinicaltrials.gov/

Advisory Committees
Joint Committee on Vaccination and Immunisation (JCVI):
https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation

Advisory Committee on Immunization Practices (ACIP):
http://www.cdc.gov/vaccines/acip/

Standing Committee on Vaccination (STIKO):
http://www.rki.de/EN/Content/infections/Vaccination/Vaccination_node.html

Safety of vaccines
European Medicines Agency (EMA):
http://www.ema.europa.eu/ema/

U.S. Food and Drug Administration (FDA):
http://www.fda.gov/

International vaccine schedules
European Centre for Disease Prevention and Control (ECDC):
http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx

World Health Organization (WHO):
http://apps.who.int/immunization_monitoring/globalsummary

International networks
EUVAC-Net:
http://ecdc.europa.eu/en/healthtopics/vaccine-preventable-diseases/euvac/Pages/index.aspx

HAVNET:
http://www.rivm.nl/en/Topics/H/HAVNET

National Immunization Technical Advisory Groups (NITAGs):
http://www.nitag-resource.org/

National Respiratory and Enteric Virus Surveillance System (NREVSS):
https://www.cdc.gov/surveillance/nrevss/

WHO Global Polio Laboratory Network (GPLN):
https://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/activities/polio-laboratory-network

Respiratory syncytial virus consortium in Europe (RESCEU):
http://resc-eu.org/

Preparing for RSV Immunisation and Surveillance in Europe (PROMISE):
https://imi-promise.eu/

Communication platforms

Epidemic Intelligence Information System (EPIS):
https://ecdc.europa.eu/en/publications-data/epidemic-intelligence-information-system-epis

Vaccination of risk groups

Influenza vaccination
RIVM website on Influenza vaccination:
http://www.rivm.nl/Onderwerpen/G/Griep/Griepprik

Stichting Nationaal Programma Grieppreventie
(SNPG, Foundation for the National Influenza Prevention Programme):
http://www.snpg.nl/

Scientific Institute for Quality of Healthcare:
http://www.iqhealthcare.nl/nl/

Surveillance of acute respiratory infections in the Netherlands: winter 2022/2023.
SARS-CoV-2, influenza virus, RSV and other respiratory viruses:
https://www.rivm.nl/publicaties/surveillance-of-acute-respiratory-infections-in-netherlands-winter-2022-2023

Tuberculosis
KNCV Tuberculosis foundation:
https://www.kncvtbc.org/

Annual Report on Surveillance of Influenza and Other Respiratory Infections in the Netherlands:
https://www.rivm.nl/bibliotheek/rapporten/2019-0079.pdf

National Tuberculosis Control Plan 2016-2020:
http://www.rivm.nl/bibliotheek/rapporten/2016-0028.pdf

Traveller vaccinations
Landelijk Coördinatiecentrum Reizigersadvisering
(National Coordination Centre for Information for Travellers):
https://www.lcr.nl/Index.htm

A.J.M. Pluijmaekers | H.E. de Melker

RIVM report 2023-0330

Published by

National Institute for Public Health and the Environment, RIVM
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

November 2023

Committed to health and sustainability

014868