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7.5 Measles

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

7.5.3 *Key points*

- The number of measles cases in 2019 was relatively high with 84 reported cases. In the first six months of 2020 only 2 cases were reported, possibly related to the COVID-19 pandemic.
- From June to August 2019 a local outbreak occurred in a low vaccination municipality with 32 reported cases, mainly among unvaccinated children.
- Genotype D8 was the only genotype detected.
- Results from the 2016/2017 PIENTER study indicate high overall seroprevalence of protective antibodies in 97% of the general population.

7.5.4 *Tables and figures*

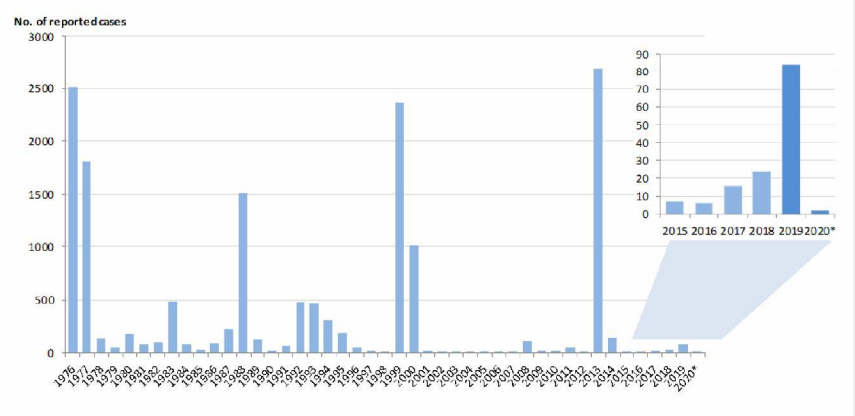
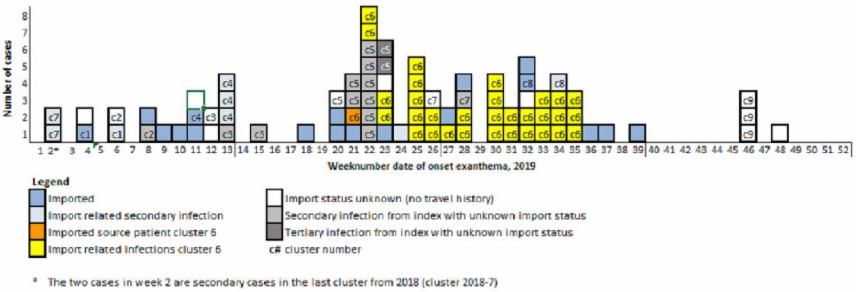


Figure 7.5.1 Annual reported measles cases since the introduction of measles in the Dutch vaccination programme.
* up to July



* The two cases in week 2 are secondary cases in the last cluster from 2018 (cluster 2018-7)

Figure 7.5.2 Epidemic curve of reported measles cases in 2019 by week of onset and import status.

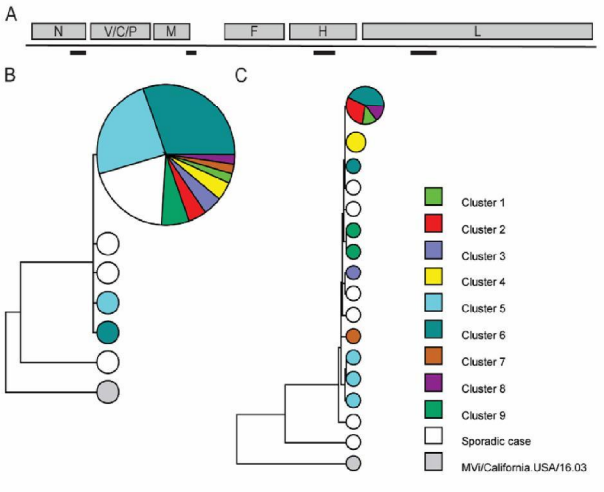


Figure 7.5.3 Analysis of nucleotide sequence data of 23 measles viruses detected in the Netherlands in 2019. A. To increase the molecular resolution, sequence data of multiple parts of the measles virus genome were determined (black bars) in addition to the standard N450 sequence used for genotyping according to the WHO protocol. B, C. Dendograms (prepared with Bionumerics version 7.6.3) provide insights in the nucleotide variation between different viruses based on the N450 sequence data only (B) or all obtained sequence information (C). Viruses with identical nucleotide sequences were grouped together and size of circles displays the number of viruses, while the colour represent the epidemiological cluster or sporadic case.

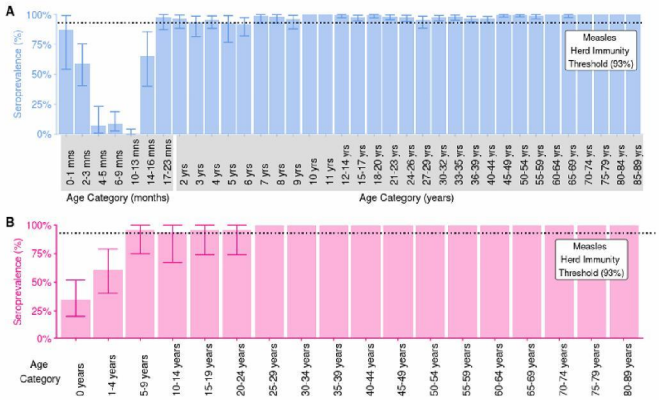


Figure 7.5.4 Seroprevalence of measles IgG antibodies (cut-off is ≥12 IU/ml) by age category in The Netherlands, 2016/17. Panel A: Results for the general Dutch Population (N=5,146); Panel B: Results for the Protestant Orthodox Reformed community (N=1,355).

7.5.5 *Epidemiology*

The number of reported measles cases was 84 in 2019 which was relatively high compared to the previous years and corresponds to an incidence of 0.5 per 100.000 population (Figure 7.5.1). In the first six months of 2020 only two cases were reported, with dates of onset in January and February. The low number of cases in the first half of 2020 could be related to reduced travel and social distancing measures as a result of the COVID-19 pandemic. The mean age of the patients in 2019 was 19 years (range 7 months to 54 years), and 48 (57% were male).

An epidemic curve of the cases in 2019 is shown in Figure 7.5.2. In 2019, 20 cases (24%) were imported with measles acquired in France (n=4), Poland (n=3), Ukraine (n=2), Belgium (n=2) and 9 other countries. Four of these led to onward transmission resulting in 38 import-related infections (45%). For the remaining 26 patients (31%) the import status was unknown as they were infected in the Netherlands from an unknown source or part of a cluster for which the index patient had an unknown source. Overall 69% of the measles cases in 2019 were imported or import related.

In 2019 nine clusters were identified including 61 patients. One cluster in May 2019 occurred in a work setting and included 9 patients born between 1974 and 1980. The largest cluster included 32 patients notified in a municipality with low vaccination coverage between June and August 2019. This number is likely an underestimate of the true number of infections. The cluster consisted mainly of unvaccinated children (91%) and 23 of the 32 patients (72%) were born after 2012 (i.e. just before or after the last epidemic in 2013/2014). The three children who were vaccinated had received MMR0 at the age of 6

months in the previous outbreak, and MMR1 at 14 months of age. The clinical picture in these children was mild.

Of the cases reported in 2019, 52 (68%) were unvaccinated, eight of them were 14 months or younger and therefore too young to be vaccinated. Twenty-five patients (32%) were reportedly vaccinated, although 11 with only one dose. For seven patients the vaccination status was unknown. Fourteen patients were hospitalised, one of them with pneumonia. Five (36%) of the hospitalised patients were vaccinated, three with one dose and two with unknown number of doses.

In the first half of 2020, only two cases were reported, with dates of onset in January and February. The first patient had an unknown vaccination status and got infected with measles virus in Romania. The second patient was an unvaccinated 3 year old who was admitted to the hospital. The source of infection remained unknown for this patient.

7.5.6 *Pathogen*

A genotype was determined of the detected measles virus of 56 (67%) reported cases in 2019 and 2 (100%) reported cases in the first six months of 2020. Measles virus genotype D8 was detected in all cases. Measles virus genotype D8 was in 2019 also the genotype that was most often detected in Europe based on sequence data available in the global Measles Nucleotide Surveillance (MeaNS) database [1, 2].

In 49 out of 56 measles viruses for which a genotype was obtained in 2019, the obtained nucleotide sequence data from measles viruses (450 nucleotides of the nucleoprotein gene) was exactly identical to measles virus D8 named strain MVs/Gir Somnath.IND/42.16 and epidemiological clusters could not be supported with nucleotide sequence data. Therefore, additional sequence information was obtained from a selection of measles viruses. The partial non-coding region between the M and F protein genes, the partial H protein gene and the partial L protein gene (in total 1605 nucleotides) were selected based on relatively high sequence variation between different strains [3]. Use of these data increased the molecular resolution and improved support of epidemiological clustering, although for four epidemiological clusters no sequence variation between detected measles viruses was observed (Figure 7.5.3). To further increase the molecular resolution, analysis of complete measles virus genomes (typically 15894 nucleotides) would be the next step.

7.5.7 *Research*

7.5.7.1 Pienter3

Seroepidemiology is an important tool to monitor the (long term) effects of the national immunization programme. In The Netherlands every ten year a population-based study is performed (1995/1996-2006/2007-2016/2017) to assess the immunity in the Dutch population (0-79/89 years of age) and among orthodox reformed individuals that are socio-geographically clustered and often refuse vaccination. The third study was conducted in 2016-2017 and included over 7000 participants [4]. Serum samples were analysed by a bead-based multiplex immunoassay. For measles, IgG levels of ≥0.12 IU/ml were considered protective.

Preliminary analyses indicate high overall seroprevalence of protective antibodies in the Dutch population of 97% for measles. Antibody concentrations are higher in the naturally infected cohorts compared with vaccinated cohorts. The seroprevalence among the population offered two doses of MMR vaccine, those aged between 10 and 39 years, is high and varies between 96.1% and 100%. Susceptibility was higher among orthodox reformed individuals. Of the orthodox Protestant participants, children born after the last measles epidemic in 2013/2014 often lacked protective antibodies against measles. Age-specific prevalence is presented for both the general population and the orthodox Protestant participants in municipalities with low vaccination coverage in Figure 7.5.4.

7.5.7.2 Immune responses to the MMR vaccination of infants between 6 and 14 months old (EMI study)

Children that were at increased risk for measles during the latest measles epidemic in The Netherlands were offered an early MMR vaccination (<12 months in addition to the routine dose at 14 months) to provide immediate immune protection. However, these children showed a slightly stronger waning of antibody concentrations over time (between 2 and 4 years of age) than children with a first MMR dose at age 14 months [5]. For further long term follow-up the participating children will be asked to collect additional blood sample at age 7.

Also the cellular basis of the acquired measles immunity following early and routine MMR vaccination is currently being investigated in more detail.

7.5.7.3 Humoral and cellular response to natural measles virus infection (Immfact study)

Over the past years longitudinal blood samples were collected for immunological studies from a small cohort of mostly non-related, vaccinated, adult measles cases (n=27) recruited in the 2013-2014 measles outbreak. Studies in unvaccinated children during this outbreak illustrated that full blown measles virus infection induces durable anti-measles immunity but causes immunological 'amnesia' for other pathogens. To investigate this paradox in secondary vaccine failure, serum samples from the Immfact cohort were tested in a multiplex immunoassay (MIA), comparing kinetics of IgG antibodies to measles virus with those to other pathogens. Preliminary results are expected end of 2020. Typing of human leukocyte antigens (HLA) in this cohort of mostly vaccinated adult cases indicated a strongly increased prevalence of an ancestral haplotype. Whether this indicates a role for aberrations in cellular immunity in secondary measles vaccine failure needs to be further explored.

7.5.7.4 Measles among vaccinated people

Several patients in a cluster of measles cases in a work setting in May 2019 were vaccinated. To investigate the cluster in more detail additional serological analysis were performed on samples from the employees with complaints, and a questionnaire was sent to all employees in the company. In total 11 employees with complaints were included in the study. Based on the serological analysis and vaccination history 4 unvaccinated employees were classified as having a naïve infection, 1 once vaccinated person had primary vaccine failure, 4 had a breakthrough infection after vaccination (1 was vaccinated with one dose and 3 with two doses), and 1 had no evidence of being exposed to measles virus. The four patients that were hospitalized had a naïve infection (n=3) or primary vaccine failure (n=1). The patients with breakthrough infection had less severe clinical signs than the other cases. Of employees born in or after 1975, 94% was vaccinated. The

small size of this outbreak was most likely due to the high vaccination coverage among employees. A paper about the cluster investigation is in preparation.

7.5.8 *International developments*

Several reviews on the effect of the age at measles vaccination have been published [6-9]. Two reviews by Nic Lochlainn et al focus at children who receive the first dose of measles containing vaccine (MCV1) below 9 months of age. They report that seroconversion after MCV1 increases with age, and that seropositivity after a second dose is high and did not depend on age of MCV1. However, some evidence suggested that MCV1 below 9 months of age resulted in lower antibody titres after one or two subsequent doses of MCV than when measles vaccination is started at age 9 months or older. Epidemiological data reviewed by Carazo et al comparing one-dose vaccine effectiveness for children vaccinated from 6 to ≥15 months indicated older age improved measles. The review by Hughes et al looked at whether measles vaccine effectiveness (VE) waned over time, and if so, whether this differed between measles-eliminated and measles-endemic settings. In measles-endemic settings, one-dose VE increased by 1.5% for every month increase in age at MCV1, and no evidence of waning VE was found. Only three papers from elimination settings were included. These studies indicated two-dose VE estimates increased with increasing age at MCV1 and decreased as time since MCV increased.

A study from France analysed the relation between disease severity and vaccination status in over 10,000 measles cases reported between 2006 and 2019 and born since 1980. Compared to unvaccinated patients, the risk of severe measles was 71% to 83% lower in people vaccinated with two doses depending on the time since the last dose [10].

In Italy, the appropriate immunization strategy for internationally adopted children (IAC) is under debate and different approaches have been suggested. Boccalini et al. developed a decision analysis model to compare three strategies: presumptive immunization, pre-vaccination serotesting and vaccination based on documentation of previous immunization [11]. The strategy currently recommended in Italy (immunize based on documentation) is less expensive. From a cost-effectiveness point of view, vaccination based on serotesting results is the most advantageous strategy. Therefore, the serotesting strategy appears to be the preferred option in IAC.

Also in Italy, the cost-effectiveness of workplace vaccination against measles was assessed. In 2017, 22.3% of measles infections happened in hospital settings and 6.6% of cases occurred in healthcare workers (HCW)s. The immunization strategy with pre-vaccination screening was cost-saving compared to the vaccination without screening [12].

In a vaccination game, individuals respond to an epidemic by engaging in preventive behaviors that, in turn, influence the course of the epidemic. According to Flaig et al. such feedback loops need to be considered in the cost effectiveness evaluations of public health policies [13]. The example of mandatory measles vaccination and the role of its anticipation was elaborated using a SIR compartmental model with fully

rational forward looking participants who can therefore anticipate on the effects of the mandatory vaccination policy. Parents, eager and reluctant towards vaccination were included. The authors stated that individual anticipatory behavior may lead to a transient increase in measles prevalence before steady state eradication. This would cause non negligible welfare transfers between generations. Ironically, reluctant parents benefit the most from mandatory vaccination.

7.5.9 *Literature*

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*RIVM publication.

7.6 Meningococcal disease

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

7.6.3 *Key points*

- In 2019, the overall incidence of meningococcal disease decreased after an increase from 2015 to 2018.
- In April to June 2020, the number of cases was 80% lower than in the same period in the last five years, which may be (partly) related to the COVID-19 measures that were in place during these months, including social distancing and school closures,.
- The number of cases with meningococcal serogroup C disease is still very low, with six cases reported in 2019.
- The vaccination uptake of the MenACWY vaccination campaign in 2018/2019 among 14-18 year olds was 84% and an additional 2% of the eligible population got vaccinated prior to the campaign. A lower uptake was observed when parents were born abroad, especially for parents born in Morocco or Turkey.
- In 2019, the incidence of meningococcal serogroup W (MenW) disease decreased to 0.39 per 100,000 (n=62), after an increase in the number of cases from 2015 to 2018. In the first six months of 2020, only eight cases have been reported with no cases reported in April to June.
- The decrease of MenW in 2019 and the first months of 2020 was observed in vaccinated as well as unvaccinated age groups.
- Among children eligible for MenACWY vaccination at 14 months, there has been one vaccinated and one unvaccinated MenW case. Among adolescents eligible for MenACWY vaccination, there have been no MenW cases.
- The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties and has stabilised at an incidence of 0.5 per 100,000 since 2011.
- In 2019, 72 cases and five deaths of MenB disease were reported, which was similar to 2018 (74 cases and five deaths). The incidence of MenB disease was highest in children aged under 5 years, with 22 cases in 2018 (2.5 per 100,000).
- The number of cases of meningococcal disease caused by serogroup Y or other serogroups is low and stable.

7.6.4 *Figures*

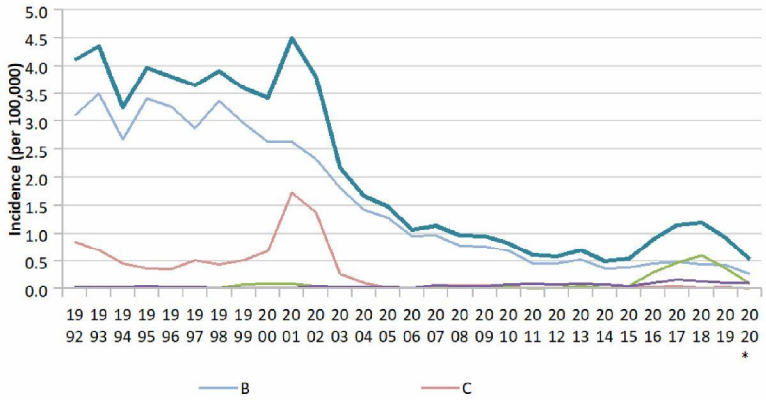

Figure 7.6.1 Incidence of meningococcal disease by serogroup, 1992-2020 (*up to June)*

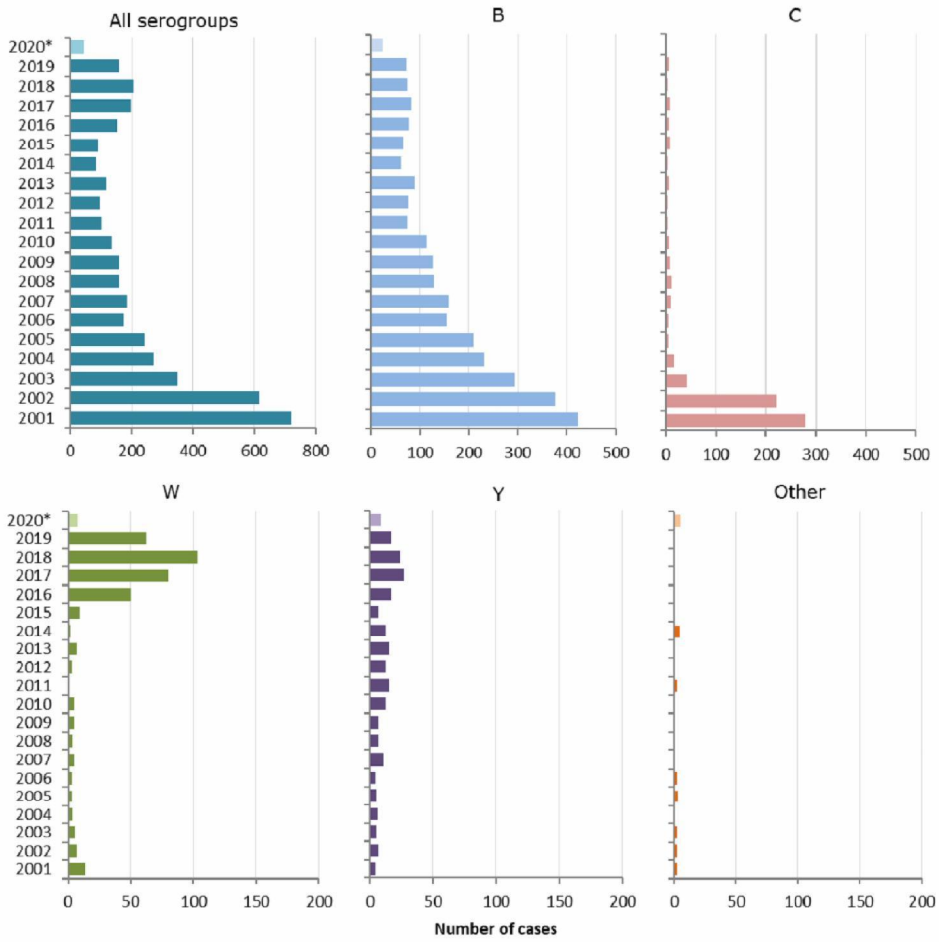

Figure 7.6.2 Number of cases of meningococcal disease by serogroup, 2002-2020 (*up to June)*
Note the different scale in the graphs

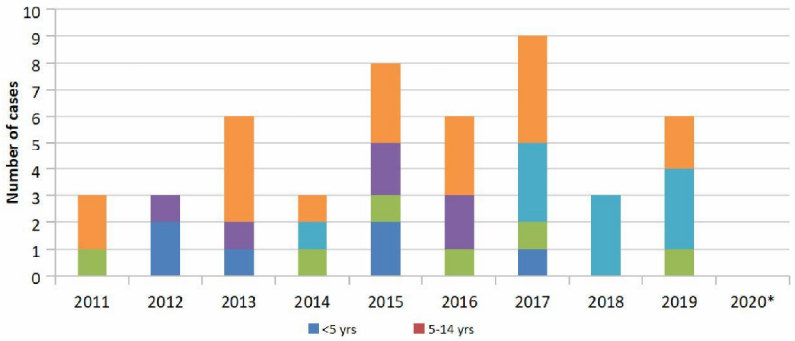

Figure 7.6.3 Number of cases of meningococcal serogroup C disease by age group, 2011-2020 (*up to June)*

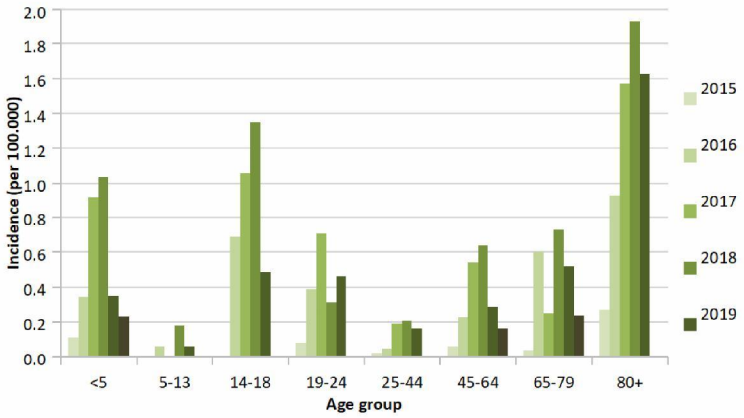

Figure 7.6.4 Age-specific incidence of meningococcal serogroup W disease by year, 2015-2020 (*up to June)*

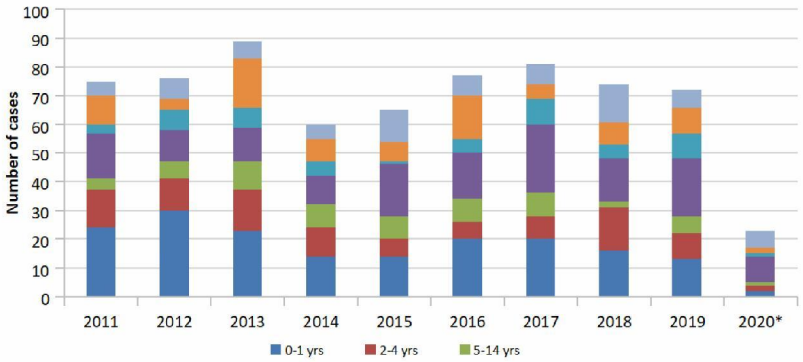

Figure 7.6.5 Number of cases of meningococcal serogroup B disease by age group, 2011-2020 (*up to June)*

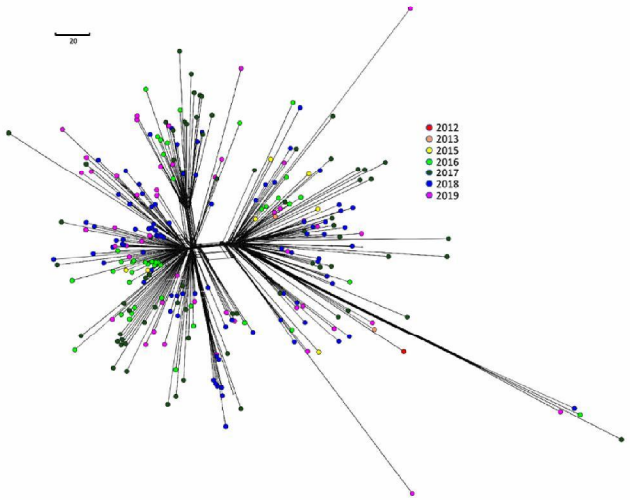

Figure 7.6.6 Neighbour-net phylogenetic network analysis of all available genomes of serogroup W clonal complex 11 isolates from the Netherlands, 2012–2019 (n =266)

Colours represent the years when the isolates were obtained. Genomes were compared using the PubMLST genome comparator tool using core genome multilocus sequence typing (cgMLST v1.0) (1). The resulting distance matrices were visualised with SplitsTree4 version 4.13.1 (2).

7.6.5 *Epidemiology*

7.6.5.1 Meningococcal disease

The incidence of meningococcal disease declined from 4.5 per 100,000 in 2001 to 0.49 per 100,000 in 2014 (Figure 7.6.1). From 2015 it increased to 1.2 per 100,000 in 2018 and in 2019 the incidence decreased to 0.92 per 100,000; these changes were mainly due to changes in serogroup W disease (see section 7.6.3.3). In the first six months of 2020 only 45 cases have been reported, which was much lower than in the same period in previous years (n=98 in 2019). Especially in April to June 2020 the number of reported cases was very low (80% lower than in the previous five years), which may be related to the COVID-19 measures that were in place during these months, including social distancing and school closures.

7.6.5.2 Meningococcal serogroup C

Since the introduction of the conjugated MenC vaccine in 2002 at 14 months of age with a catch-up for 1 to 18-year-olds, the number of cases of meningococcal serogroup C (MenC) disease has decreased enormously, from 277 in 2001 to an average of 6 cases per year since 2005 (Figure 7.6.2). The incidence decreased in all age groups due to herd protection, and has remained lower than 0.1 per 100,000 since 2005 (Figure 7.6.1).
In 2019, six cases of MenC were reported, which is 4% of all meningococcal cases. One patient was between 15 and 24 years of age and was not vaccinated against MenC. The other cases were all 45 years or older (Figure 7.6.3). Up to June 2020, no MenC cases were reported.
Since the introduction of the conjugated MenC vaccine in 2002, there have been 16 MenC cases that were eligible for vaccination according to their date of birth (either for the 14-month program or the catch up campaign in 2002). Seven of these cases were unvaccinated, five were vaccinated and in four cases the vaccination status was unknown. The five vaccinated cases were between 16 and 26 years when diagnosed. Two of the patients had an underlying immune deficiency.
None of the MenC cases in 2019 died. Since 2015, one MenC case has died resulting in a case fatality rate of 3% (1/31).

7.6.5.3 Meningococcal serogroup W

Since May 2018, MenACWY vaccination at 14 months of age is part of the national immunisation programme. Between October 2018 and June 2019, all children born between January 1st 2001 and December 31st 2005 (14-18 year olds) were offered MenACWY vaccination. Vaccination uptake during the vaccination campaign was 84% and an additional 2% of the population got vaccinated prior to the campaign (3). From 2020 onwards, MenACWY vaccination is offered to children in the year they turn 14 as part of the national immunisation programme.
The incidence of MenW disease increased between 2015 and 2018, with a peak incidence of 0.60 per 100,000 in 2018 (n=103) (Figures 7.6.1 and 7.6.2). In 2019, the incidence decreased to 0.39 per 100,000 (n=62); 39% of all meningococcal cases were caused by serogroup W. In the first six months of 2020, only eight cases have been reported with no cases reported in April to June.
The increase in MenW disease between 2015 and 2018 was observed in all age groups, with the highest incidence in <2-year-olds, 14- to 18-year-olds, and >80-year-olds (Figure 7.6.4). In 2019, the incidence

decreased in vaccinated as well as unvaccinated age groups. The eight cases in the first three months of 2020 included one case under one year of age who was too young to be eligible for vaccination and seven cases of 45 years or older.
Among children eligible for MenACWY vaccination at 14 months, there have been two MenW cases (both were two years old), of which one was vaccinated and one was unvaccinated. Among adolescents who were eligible for MenACWY vaccination in 2018-2020, there have been no MenW cases. These data suggest good effectiveness of MenACWY vaccination in the vaccinated age groups. Whether the decrease in incidence in other age groups is due to implementation of MenACWY vaccination is uncertain as the decrease was already seen at the beginning of 2019 when the vaccination campaign was still ongoing.
Since 2015, 49 out of 305 (16%) MenW cases have died, with nine deaths reported in 2019. Deaths occurred in nearly all age groups, with the highest case fatality rate in 14- to 24-year-olds (16/61=26%). None of the eight MenW cases that were reported in the first six months of 2020 died.

7.6.5.4 Meningococcal serogroup B

The incidence of meningococcal serogroup B (MenB) disease has been declining steadily since the late nineties and has stabilised at 0.5 per 100,000 since 2011 (Figure 7.6.1). In 2019, 45% of all meningococcal cases were serogroup B. In total, 72 cases of MenB disease were reported (Figure 7.6.2). Up to June 2020, 23 MenB cases were reported, which was much lower than in the same period in 2019 (n=41). Especially the number of reported cases in April to June was lower than in the previous years, which may be related to the COVID-19 measures.
In 2019, the incidence of MenB disease was highest in children aged under five (2.5 per 100,000, n=22), followed by 15- to 24-year-olds with an incidence of 0.9 per 100,000 (n=20) (Figure 7.6.5). In the first six months of 2020, especially the number of cases in children aged under five was very low with only four cases compared with on average 16 cases in the same period in the last five years.
Since 2015, 18 out of the 364 (5%) MenB cases have died. There were five deaths among MenB cases in 2019 (7%). Case fatality rates are comparable between age groups. In the last five years, 1-3 children under five years of age died of MenB disease each year.

7.6.5.5 Meningococcal serogroup Y

The incidence of meningococcal serogroup Y (MenY) disease has increased slightly over the last 3-4 years with an incidence of 0.10 per 100,000 in 2019 (n=17) (Figure 7.6.1 and 7.6.2). In 2019, 11% of all meningococcal cases were serogroup Y. In the first six months of 2020, nine MenY cases have been reported, which was rather similar to the number of cases in the same period in previous years. Most cases were adults aged 45 years or older (13/17 in 2019 and 7/9 in 2020). There have been no MenY cases in the children or adolescents who were eligible for MenACWY vaccination. Since 2015, 7 out of 87 (9%) MenY cases have died.

7.6.5.6 Other meningococcal serogroups

In 2019, one case of meningococcal disease due to a non-groupable meningococcus was reported (Figure 7.6.2). In the first six months of

2020, there were two cases of meningococcal disease due to serogroup X, one case due to serogroup E and two cases due to a non-groupable meningococcus. Meningococcal disease due to serogroups X and E is rare in the Netherlands with six and eight reported cases, respectively, between 2001 and 2019. These serogroups are also rare in other European countries. Also meningococcal disease due to a non-groupable meningococcus is rare with eight reported cases between 2001 and 2019 and occurs mainly in individuals with immune disorders, which was also true for one of the two cases in 2020.

7.6.6 *Pathogen*

Almost all serogroup W strains from 2015 to 2019 had the same finetype P1.5,2:F1–1 (263/292; 90%) and belonged to clonal complex 11 (cc11; 262/276; 95%). Figure 7.6.6 shows a cluster analysis of all available genome sequences of serogroup W cc11 meningococci isolated in 2012-2019 from Dutch patients. In 2016 and 2017, isolates from the same year seemed to cluster, but for isolates from 2018 and 2019 there was no clear clustering anymore.

Since 2016, an increase was observed in the number of MenB cases with finetype P1.22,14:F5-1, which caused three MenB cases in 2016, twelve in 2017, seven in 2018, 11 in 2019; up to June 2020 no MenB cases with this finetype were reported. Before 2016, this finetype was only detected in one MenB case in 2009 and two cases in 2014. Whole genome sequencing showed that almost all of the B:P1.22,14:F5-1 from 2016-2018 belonged to cc32 (20/22; 91%). In 2019, 6 of 9 isolates (67%) belonged to cc32. Of 33 B:P1.22,14:F5-1 cases since 2016, 12 lived in GGD region Rotterdam Rijnmond and an additional eight cases lived in other GGD regions in the south-west of the Netherlands. Most cases (17/33; 52%) were 10-19 years of age and two cases died (7%). All B:P1.22,14:cc32 isolates were potentially covered by the 4CMenB vaccine (Bexsero) because of an exact match with one of the antigens in the vaccine. Overall coverage of MenB isolates from June 2017 to June 2019 was 73%.

From 2017 to 2019, 469 received meningococcal isolates were assessed by whole genome sequencing. As described above, the vast majority of serogroup W isolates belonged to cc11 (96%). Among serogroup Y, cc23 was the dominant clonal complex (75%). Serogroup B isolates consisted of 12 different clonal complexes, with 85% of assigned isolates belonging to cc32 (36%), cc41/44 (22%), cc269 (13%), or cc213 (14%). Among 15 serogroup C isolates, most belonged to cc11 (67%).

7.6.7 *Current/ongoing research at RIVM*

Conjugated polysaccharide vaccines protect against meningococcal disease but also reduce carriage of vaccine-type *Neisseria meningitidis* strains. In the fall of 2018, Miellet et al. investigated meningococcal carriage in young adults at the time of MenACWY vaccine introduction in The Netherlands and explored the feasibility of testing saliva. Paired saliva and oropharyngeal swabs were collected from 299 college students and tested for meningococci using conventional culture and molecular method of qPCR. Altogether 84 (28.1% of 299) students were identified as carriers of meningococcus by any method used. Carriage of serogroups B, Y, W, C, and A was 8.7%, 6.7%, 1.3%, 0.7%, and 0%,

respectively. All serogroup W strains (n=4) belonged to the hyperinvasive cc11 clone and distribution of other clonal complexes resembled the distribution seen in the Netherlands for invasive meningococcal disease. Detection of meningococcus by qPCR showed that a similar number of students was identified as carrier with oropharyngeal swabs and saliva. Saliva can, therefore, be considered in the surveillance of meningococcal carriage.

The uptake of the MenACWY vaccination campaign of 2018 and 2019 among adolescents born between 2001 and 2005 was 84% as calculated from the national vaccination register (4). Before the start of the campaign, already 1.9% of the eligible adolescents was vaccinated, which was estimated from the number of vaccines administered by Municipal Health Services and dispensed by public pharmacies. Possible determinants of vaccination uptake after the first invitation and recall were investigated among the first group invited for vaccination (born in May-December 2004) using random forest classification analysis. The most important predictor of vaccination after the first invitation was parents' country of birth (lower uptake when parents were born abroad, range: 52%-Morocco to 88%-Netherlands). The most important predictors after the recall were, respectively, distance to vaccination location (lower uptake with larger distance, range: 4-6%), percentage of votes for the conservative Christian (reformed) party in the municipality (lower uptake with higher percentage, range: 4-5%) and parents' country of birth (higher uptake when parents were born abroad, range: 4%-Netherlands to 11%-Syria). The recall strategy enhanced the uptake and was valuable to diminish immunization disparities. Future vaccination campaigns should put more effort into reaching adolescents with immigrant parents.

Persistence of vaccine-induced serological protection is necessary to protect individuals against invasive meningococcal disease, especially in epidemics like the recent Dutch MenW epidemic. However, meningococcal serogroup ACWY polysaccharide-specific antibodies wane after a single MenACWY-TT conjugate vaccination. Blood samples were collected before, 1 month, 1 year and 5 years after a single MenACWY vaccination from 50 healthy adolescents aged 15-20 who were once primed with a MenC conjugate vaccine at young age, and 130 adults (aged 55-70) who were naïve to meningococcal vaccination. Functional antibodies were measured 5 years after a single MenACWY vaccination in both cohorts to predict long-term persistence of serological protection. Protective rSBA titers (≥8) against MenC, MenW or MenY were present in 94-96% of the adolescents 5 years after vaccination. However, adults only showed protective rSBA titers in 32%, 65% and 71% against MenC, MenW and MenY, respectively. Only 25/130 (19%) adults were still protected after 5 years against all three serogroups tested. Functional meningococcal antibodies seem to decline quicker in adults than in adolescents, especially the functional antibodies for MenC. Protection at adolescent age after a MenACWY-TT vaccination when primed with MenC at young age was estimated to be long-lasting using a bi-exponential decay modelling. In contrast, when a meningococcal vaccination is administered to middle-aged adults, a single MenACWY-TT vaccination might not be sufficient for long-term persistence of seroprotection.

MenB vaccination is not included in the Dutch National Immunization Program but is indicated for special groups such as immunocompromised patients. 4CMenB is a multicomponent, protein-based vaccine against MenB consisting of factor H-binding protein, Neisserial heparin binding protein, Neisserial adhesion A and outer membrane vesicles containing Porin A. The RIVM has developed tools and reagents to test vaccine immunogenicity and vaccine-mediated humoral protection to *N. meningitidis* serogroup B. We could show that in children with various complement deficiencies 4CMenB vaccination elevated MenB specific antibodies, which could only kill bacteria through classical serum bactericidal activity with autologous complement if the complement defect was in the alternative pathway but not in the late terminal pathway (5). Irrespective of the complement defect, however, post-vaccination antibodies were shown to be effective by opsonophagocytosis, supporting the recommendation to vaccinate children with a complement deficiency against MenB.

7.6.8 *(Inter)national developments*

7.6.8.1 Carriage

Watle et al. studied meningococcal carriage and its risk factors among Norwegian adolescents and young adults in 2018-2019 (6). Among 2296 12–24-year-olds (majority 13–19-year-olds) meningococcal carriage was identified in 167 (7.3%) individuals. The highest carriage rate was found among 18-year-olds (16.4%). Among carriage isolates, 33.5% was genogroup Y, 9.0% genogroup B, 2.4% genogroup X, 1.8% genogroup C and 1.8% genogroup W. Clonal complexes cc23 (35.9%) and cc198 (32.3%) dominated and 38.9% of carriage strains were similar to invasive strains currently causing IMD in Norway. Use of Swedish snus (smokeless tobacco) (OR 1.56, 95% CI 1.07–2.27), kissing >two persons/month (OR 2.76, 95% CI 1.49–5.10) and partying >10 times/3months (OR 3.50, 95% CI 1.45–8.48) were associated with carriage, while age, cigarette smoking, sharing of drinking bottles and meningococcal vaccination were not.

7.6.8.2 Meningococcal disease

Campbell et al. assessed the relationship between meningococcal capsular group, age, clinical presentation, diagnosis and outcome among invasive meningococcal disease (IMD) cases diagnosed in England during 2014 (7). In 2014, there were 340 laboratory-confirmed IMD cases caused by MenB (n=179), MenW (n=95) and MenY (n=66). Clinical presentation with meningitis alone was more prevalent among MenB cases (28%) and among 15-24 year-olds (20%), whilst bacteraemic pneumonia was most prevalent among MenY cases (26%) and among ≥65 year-olds (24%). Gastrointestinal symptoms were recorded preceding or during presentation in 15% (40/269) of the cases with available information, including 5% (7/140) MenB, 17% (8/47) MenY and 30% (25/82) MenW cases. Upper respiratory tract symptoms were reported in 16% (22/141) MenB, 23% (11/47) MenY and 31% (26/84) MenW cases. Increasing age was also independently associated with bacteraemic meningococcal pneumonia, with no cases among 5-14 year-olds compared to 24% in ≥65 year-olds. Case fatality rates increased with age but no significant associations between serogroup and death were identified.

7.6.8.3 MenB disease

In September 2015, the UK introduced the 4CMenB vaccine into its national immunization program for infants with two primary doses at two and four months and a booster dose at 12 months. Ladhani et al. evaluated the effect of vaccination on the incidence of meningococcal group B disease during the first 3 years of the program (8). From September 2015 through August 2018, the incidence of meningococcal group B disease in England was significantly lower in vaccine-eligible cohorts than the expected incidence (63 observed cases as compared with 253 expected cases) with a 75% reduction in age groups that were fully eligible for vaccination (incidence rate ratio: 0.25; 95% CI: 0.19-0.36). The adjusted vaccine effectiveness against meningococcal group B disease (estimated with the screening method) was 52.7% (95% CI: −33.5 to 83.2) after two primary doses and 59.1% (95% CI: −31.1 to 87.2) after two primary doses and a booster dose. Over the 3-year period, there were 169 cases of meningococcal group B disease in the vaccine-eligible cohorts, and an estimated 277 cases (95% CI, 236 to 323) were prevented.

Marshall et al. performed a cluster randomized trial to assess the effect of the 4CMenB vaccine on meningococcal carriage in 15-18 year olds in Australia (9). Among 237 participating schools, 24,269 students were enrolled in the study during April through June 2017. One year after vaccination, there was no difference in the prevalence of carriage of disease-causing *N. meningitidis* between the vaccination group (2.55%; 326 of 12,746) and the control group (2.52%; 291 of 11,523) (adjusted odds ratio: 1.02; 95% CI: 0.80-1.31). Among carriers, also the carriage density did not differ between vaccinated and unvaccinated students (mean difference: 0.04; 95% CI: -0.19 to 0.27) (10). This study showed no effect of 4CMenB vaccination on carriage and carriage density, and therefore this vaccine is not expected to prevent transmission or provide herd protection.

7.6.8.4 MenW disease

Barret et al. describe a cluster of three MenW cases, including two deaths, at a university campus in 2016 in France (11). The three cases occurred within a 2-month period among students in different academic courses. All three isolates were identical and belonged to the "UK-2013 strain" phylogenetic branch. The attack rate was 10.8/100,000 students. A vaccination campaign was organized 15 days after the third case occurred. In total, 13,198 persons (41% of students and 35% of staff) were vaccinated. No further cases occurred at the campus in the year following the vaccination campaign.

Villena et al. describe the MenW incidence in Chile from 2009-2016 and assess the impact of a MenACWY vaccination campaign implemented in 2012 targeting children of nine months to four years (12). The MenW incidence rose from 0.01/100,000 inhabitants in 2009 to a maximum of 0.6/100,000 in 2014. Infants and adults 80 years of age and older were mostly affected. In the group of children from 1 to 4 years of age MenW incidence declined from 1.3/100,000 in 2012 to 0.1/100,000 in 2016, a 92.3% reduction after vaccination implementation. In the same period and age cohort, the case fatality rate decreased from 23% to 0%. No indirect effects of vaccination were observed.

7.6.8.5 Cost-effectiveness

Serogroup B meningococci are the largest cause of invasive meningococcal disease in Canada. Breton et al. assessed the cost-effectiveness of three adolescent MenB-FHbp immunization strategies (13). These strategies included routine vaccination with MenB-FHbp at: (1) 14 years, along with existing school-based programs, with 75% uptake; (2) 17 years with 75% uptake, assuming school vaccination; and (3) 17 years with 30% uptake, assuming vaccination outside of school. With no vaccination, an estimated 3974 MenB cases would be expected over 30 years. Vaccination with strategies 1–3 were estimated to avert 688, 1033, and 575 cases, respectively. These outcomes were associated with incremental costs per quality-adjusted life-year of $976,000, $685,000, and $490,000 respectively. Therefore, MenB vaccination is unlikely to meet widely accepted cost-effectiveness thresholds.

In Australia, MenACWY vaccination is included in the NIP and is indicated for infants aged 12 months. Si et al. assessed the cost-effectiveness of a broader MenACWY vaccination program for Australians aged 15 to 19 years (14). The total cost for MenACWY vaccination was AU$56 per dose. Costs and health outcomes were discounted by 5% per annum in the base-case analysis. Compared to no vaccination, a MenACWY vaccination program targeted at Australians aged 15–19 years was expected to prevent 1664 invasive meningococcal disease cases in the Australian population aged 0–84 years. The program would lead to 2058 quality adjusted life years (QALYs) gained at a total cost of AU$115 million. This equated to an incremental cost-effectiveness ratio of AU$55,857 per QALY gained. Therefore, the MenACWY immunisation program targeted to Australians aged 15 to 19 years is likely to be cost-effective.

7.6.9 *Literature*

7.6.9.1 References

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*RIVM publication

7.6.9.2 Other RIVM publications

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7.7 Mumps

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7.7.3 *Key points*

- The incidence of mumps in 2019 was low (0.8 per 100,000), but double that of the previous year.
- From January to March 2020, mumps notifications were double that of 2019 for the same period, however, a sharp decrease was seen from 1 April 2020 which coincided with control measures that were put in place in response to the COVID-19 pandemic.
- Most of the mumps cases in the Netherlands were caused by mumps virus genotype G.

7.7.4 *Tables and figures*

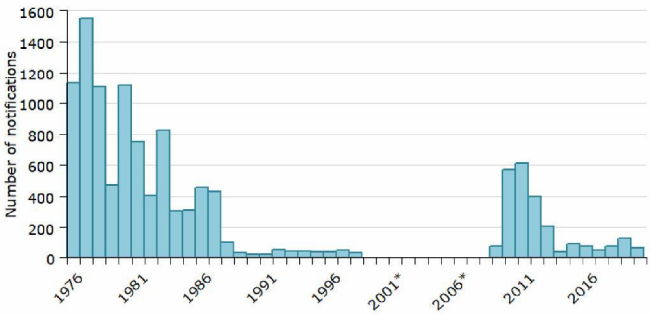

Figure 7.7.1 Number of notified mumps cases in the period 1976-2020
* In the period 1999-2008 mumps was not notifiable
Year 2020: up to 1 May
Source: Osiris

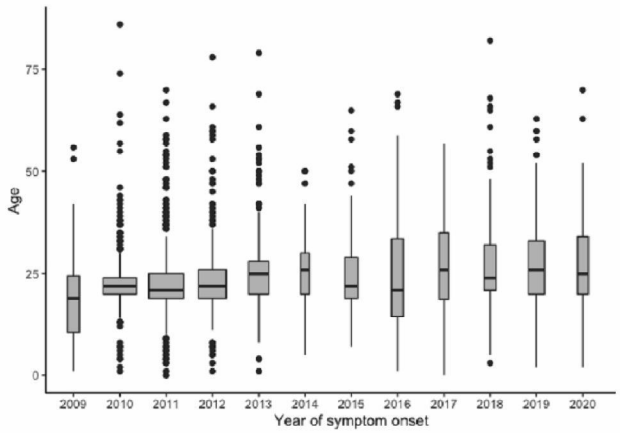

Figure 7.7.2 Age distribution of mumps cases by year in the period 2009-2020.
Year 2020: up to 1 May
The horizontal line which divides the box into two parts indicates the median age, the middle box includes 50% of the values, and the vertical line outside of the box shows the lowest and highest age. Age values which fall outside of the box and vertical line are outliers and are represented by dots.
Source: Osiris

7.7.5 *Epidemiology*

Following the introduction of mumps vaccination in the NIP in 1987, there was a large decline in the incidence of mumps in the Netherlands. From late 2009 until 2012, a countrywide epidemic with over 1500 reported cases occurred that especially affected (vaccinated) student populations (Figure 7.7.1) [1]. Since 2012, the number of reported mumps cases among students has declined in the Netherlands. In the epidemic period (2010-2012), the mean age of reported mumps cases was 23.1 which increased to 26.7 in the years (2013-May 2020) ($p<0.001$) (Figure 7.7.2).

In 2019, 131 cases of mumps were reported (Figure 7.7.1). Among them, males (n=85) were almost double compared to females (n=46) with a mean age of 27 years (range 2-63). Forty-four students were reported with mumps. Ninety-seven cases (79%) were vaccinated; 19 (20%) with one dose, 68 (70%) with two doses, 5 (5%) with three or more doses of vaccine, and 5 (5%) were vaccinated with an unknown number of doses. The vaccination status was not known for the eight remaining cases. On average, the 26 unvaccinated cases were 36 years old (range 4-60). Six patients were hospitalised aged between 19 and 34 years; two of these reported orchitis and one pancreatitis. In addition, nine adults reported complications; eight reported orchitis and one reported orchitis or encephalitis. Among men, orchitis was less prevalent in vaccinated men (5%) compared to unvaccinated men (38%) ($P<0.001$).

Seventeen percent of the cases (n=22) acquired the infection abroad and country of infection is unknown for four persons. Twelve clusters including 50 patients in total were identified in 2019. The largest cluster occurred among attendees of a party and/or secondary school where 12 persons aged between 22 and 46 years were reported with mumps. The second largest cluster involved nine persons who were students or had contact with students and were aged between 20 and 26 years. The remaining 10 clusters consisted of between two and four persons occurring in close-contact settings between either friends, partners, family, or work colleagues.

In 2020, until 1 May, 61 mumps cases have been reported which is higher than for the same period in 2019 (42 cases). In early March 2020, control measures were put in place nationwide in response to the COVID-19 pandemic and from 1 April 2020, a decrease in the number of mumps notifications was seen. As the average incubation period for mumps is between 16 and 18 days, this shows that the decrease coincided with control measures that were put in place. There were more male (57%) patients than female and the mean age was 27 years (range 2-70). Seventeen students were reported and six acquired the infection abroad. In addition, nine persons acquired the infection abroad and country of infection is unknown for four persons. Most cases (n=38, 62%) did not have an epidemiological link, except for eight clusters identified in 2020. All eight clusters included between two to four persons. Three of the eight clusters, included one or more persons who travelled abroad and are most likely imported cases.

7.7.6 *Pathogen*

In the past decade, most mumps cases in the Netherlands were caused by infection with genotype G mumps viruses. In 2019 and the first five months of 2020, a genotype was obtained from mumps viruses detected in 117 cases. The majority of these cases (94%) was genotype G. In addition, 3 other genotypes were detected in a small amount of cases: genotype K (2 cases), H (2 cases) and C (3 cases). Three of the cases with non-G genotypes were imported cases from non-European countries.

7.7.7 *Research*

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

7.7.7.1 Molecular surveillance

In addition to sequencing of the SH protein gene and adjacent non-coding regions (SH; 316 nucleotides) to determine the mumps virus genotype, genome information can be used to analyse the molecular epidemiology. Additional genome information can be obtained to study the increase the molecular resolution. Currently published protocols focus on sequencing of three non-coding regions (NCRs), or the HN and F protein genes or the complete genome [2-5]. Analysis of sequence data from the SH and NCRs of mumps genotype G viruses detected in the Netherlands between 2017 and 2019 revealed that two major genetic lineages were present in these years. Results were confirmed by

analysis of 8 complete genomes from recent mumps genotype G viruses detected in the Netherlands. This indicates that mumps genotype G viruses continued to circulate in the Netherlands and surrounding countries in these years. Furthermore, comparison of molecular resolution obtained with SH and NCRs with complete genomes obtained with next-generation sequencing clearly indicated that additional molecular resolution can be obtained by analysing complete genomes [6]. This can be helpful to support epidemiological data or show transmission links that can not be identified by epidemiological data. From 1 October 2019 to 31 March 2020, 14 epidemiological clusters (including 46 cases) were identified where two or more cases met the mumps notification criteria and had an epidemiological link to a confirmed case with a date of symptom onset between this period. Eleven of the 14 clusters (including 24 cases) were confirmed as clusters using molecular sequencing as the mumps viruses were detected with identical SH+NCRs sequences (manuscript currently in preparation).

7.7.7.2 Humoral and Cellular immunity

The re-emergence of mumps among vaccinated young adults has become a global issue. Mumps-specific antibody titers are the current standard to assess immunity against the mumps virus. Globally waning of the vaccine-induced antibody titers is observed. In addition, suboptimal induction of T-cell responses may also reduce protection. To investigate the mechanisms involved, over the past years longitudinal blood samples from a small cohort of clinically symptomatic mumps cases (n=27) were collected for immunological interrogation in the Immfact natural infection study. To evaluate waning of mumps-specific IgG antibodies longitudinal serum samples were tested in a multiplex immunoassay (MIA). Preliminary results are expected end of 2020. In 2018, we observed a dominant polyfunctional CD8+ T-cell response after natural mumps virus infection that was not present after vaccination [7]. Now, we have identified the first 41 naturally processed CD8+ T-cell epitopes of mumps virus that are conserved amongst various mumps virus strains [8]. HLA-A0201+ restricted CD8+ T-cell responses to 6 epitopes were confirmed in blood samples of mumps cases. The identification of CD8+ T-cell epitopes of mumps virus makes it possible to monitor the CD8+ T cell response after mumps infection and vaccination. This may lead towards a better understanding of mumps vaccine failure, and it could provide clues for interventions to prevent this, such as an extra MMR vaccination [9-12].

7.7.7.3 Clinical MMR-3 study

In 2019, we reported that MMR-3 vaccination is expected to be an effective and safe intervention for controlling a mumps outbreak among young adults based on an immunogenicity and safety study that we performed [9]. In May 2020, collection of extra follow-up samples for this study were completed to be able to determine mumps-specific antibody levels up to 3 years post-MMR-3 vaccination.

7.7.8 *International developments*

In Europe, other countries have reported an increase in the number of mumps cases in 2019 compared to previous years. In England, the number of laboratory confirmed mumps cases in 2019 was the highest number of cases reported since 2009 [13]. This large increase has been

driven by outbreaks in universities and colleges. Ireland also reported a notable increase in mumps cases in 2019 compared to previous years with the highest number of notifications observed in the age group 15-24 years [14]. In both England and Ireland, it was noted that many of the mumps cases in 2019 were from the same birth cohort most affected by low MMR1 vaccination uptakes in the late 1990s and early 2000s [13, 14].

In the United States, research has been carried out to assess waning immunity as a key contributing factor to mumps resurgence. Among participants, it was found that the frequency of circulating mumps specific memory B cells was 5 to 10 times lower than measles and rubella, and 10% of the participants had no detectable memory B cells to mumps. Additional strategies are needed to improve the quality and durability of vaccine-induced immunity [15].

7.7.9 *Literature*

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* RIVM publication

7.8 Pertussis

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7.8.3 *Key points*

- In 2019, the overall incidence rate (IR) of pertussis notifications was 36.8 per 100,000 compared with 28.4 per 100,000 in 2018.
- In 2020 up to April 1st, the IR was 16.6 per 100,000; this IR was probably affected by the control measures in view of the covid-19 pandemic.
- In April and May 2020, vaccination coverage of the maternal pertussis vaccination was estimated to be about 70%.
- In 2019, estimates for the effectiveness of the maternal pertussis vaccination in preventing pertussis in 0-3-month-olds was 73%-90%s , assuming a 20%-40% vaccination coverage. For 2020, the VE amounted to 93%-97%, taking into account 50%-70% coverage.
- The prevalence of prn-deficient strains in the Netherlands sharply increased in 2018-2020.

7.8.4 *Tables and figures*

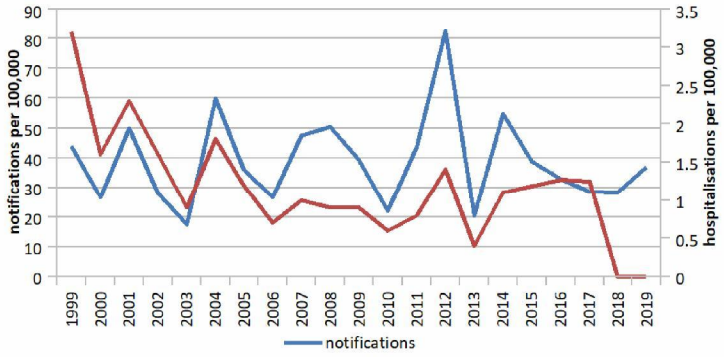

Figure 7.8.1 Pertussis notifications (left Y-axis) and hospitalizations (right Y-axis) per 100,000 for 1999-2019 Source: OSIRIS, Statistics Netherlands
No hospitalization data from 2018 onwards is available yet.

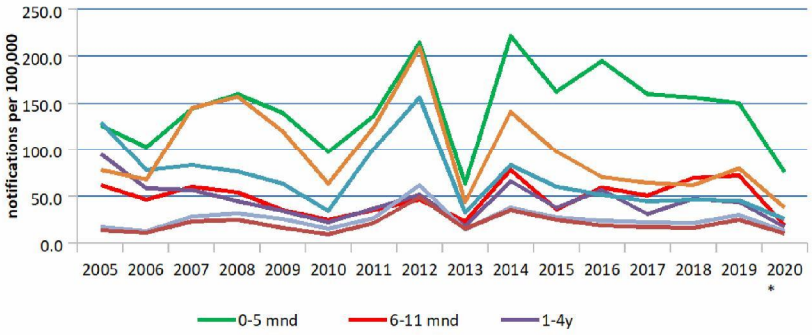

*Figure 7.8.2 Pertussis notification per 100,000 per age category for 2005-2020**
Source: OSIRIS
*reports up to April 1st 2020 are included

Figure 7.8.3 Estimated vaccine coverage of the maternal pertussis vaccine, from 2018 - 2020, July 1st. Up to April 2019, all coverage estimates are the same. From April to November 2019, coverage1 represents the coverage without data from the Municipal Health Services (MHS). Likewise, coverage2 represents the coverage with a fixed number of vaccinations (n=1000), administered via MHS and coverage3 reflects the coverage in which the number of MHS-vaccinations is 0.37 of the number of SFK vaccinations.
Source: Statistics Netherlands, SFK data, municipal health services, Praeventis.

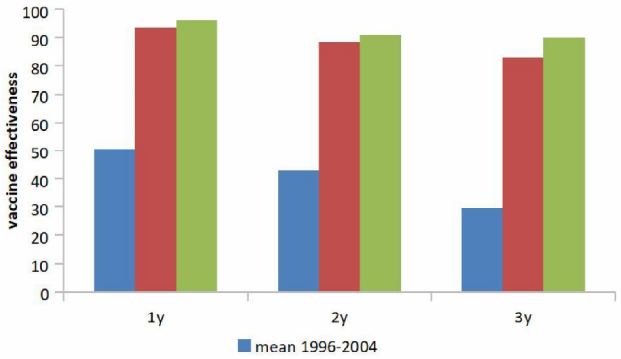

Figure 7.8.4 Vaccine effectiveness of the primary pertussis vaccination, calculated with the screening method, estimated for 1,2, and 3-year-olds during the use of whole-cell pertussis vaccination (mean 1996-2004 and during the use of the acellular pertussis vaccination (mean 2005-2018, and 2019 separate) Source: OSIRIS, National vaccination coverage report*

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

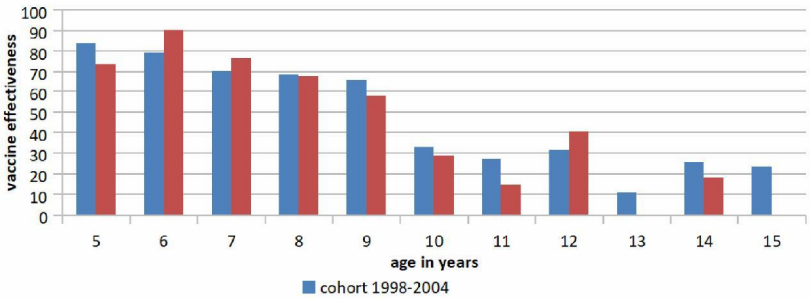

Figure 7.8.5 Mean vaccine effectiveness of the pre-school booster, calculated with the screening method, estimated for 5 to 15-year-olds for the whole cell pertussis priming cohorts (1998-2004) and the acellular pertussis priming cohorts (2005 and younger). Not all cohorts of 2005 and younger have yet reached the age of 10-15 years. Source: OSIRIS , National vaccination coverage report*

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

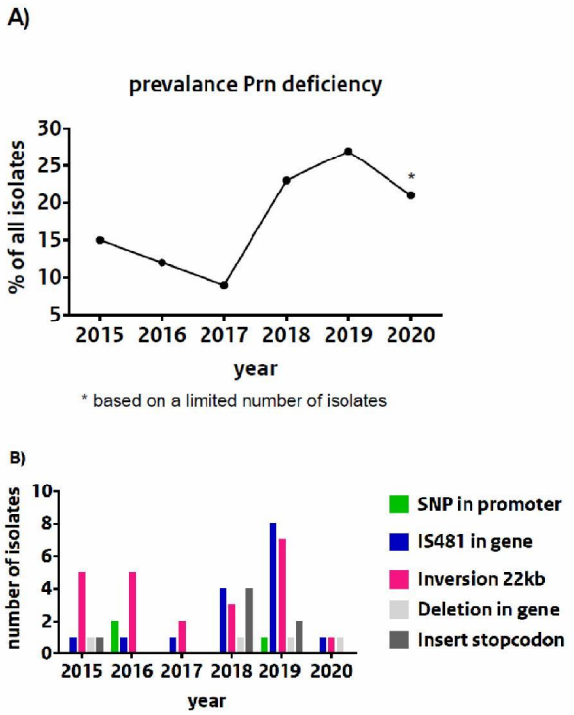

Figure 7.8.6 Prevalence (A) and molecular mechanism (B) of loss of pertactin (Prn) production in clinical isolates collected between 2015 and 2020.*
*: isolates till May 1, 2020 are included

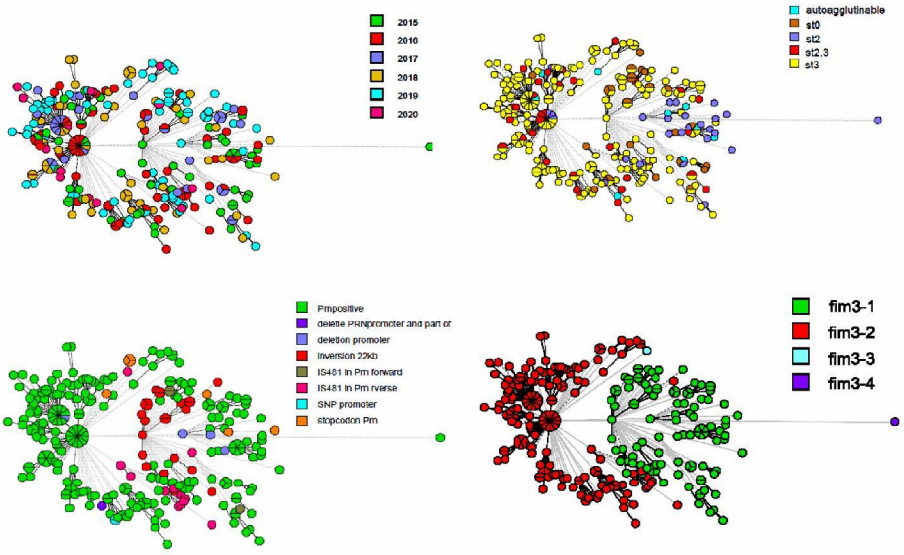

Figure 1.8.7 Genetic relationship between 271 clinical isolates based on wgMLST, with clustering based on year (A) and serotype (B), the genetic relationships between Prn-strains by molecular mechanism (C) and Fim3 subtype (D)

7.8.5 *Epidemiology*

7.8.5.1 Disease

In 2019, the overall incidence rate (IR) of pertussis notifications was higher than in 2018 (36.8 per 100,000 vs 28.4 per 100,000). In 2020 up to April 1st, the IR was considerably lower, i.e. 16.6; maybe the IR was affected by the measures to prepare and control the outbreak of coronavirus. (Figure 7.8.1) The last epidemic peak in pertussis notifications was seen in 2014/2015, so the epidemiological rise in pertussis notifications in 2019 is conform expectations, with a peak pattern of 3-5 years in countries with a high vaccination coverage. Hospitalization data of 2018-2019 are not yet available.
The increase of IRs of notifications in 2019 is mainly due to rises in IRs in adolescents, adults and elderly. (Figure 7.8.2) IRs in the younger age groups remained stable. Looking at the first trimester of 2020 (January 1 – April 1), we see an decreased IR for all age categories. (Figure 7.8.2) For 0-5-month-olds, the decrease can also be due to the implementation of a maternal pertussis vaccination programme from December 16, 2019 onwards.
Five pertussis related deaths were notified in 2019. It concerned three elderly (70, 86 and 89 years old), of whom two had underlying cardio-respiratory conditions. Furthermore two 0-year-olds died. One was too young to be vaccinated and one received the first vaccination 2 weeks before the estimated disease onset. Statistics Netherlands reported 2 pertussis related deaths.

7.8.5.2 Maternal pertussis vaccination coverage

Since 2016, pregnant women were able to get a maternal pertussis vaccination at own cost. A maternal pertussis vaccination was introduced in the NIP from 16 December 2019 onwards. From that moment onwards, all pregnant women with a gestational age of 22+0w and can be vaccinated through the youth health care.
In 2016 and 2017, vaccination coverage of the maternal pertussis vaccination was <2% [1]. In 2018, vaccination coverage slowly increased to 20% (Figure 7.8.3). In 2019, it ranged between 19%-31%. In this estimate the maternal pertussis vaccinations, administered through the Municipal Health Services were not taken into account because they were not available. After correction for this bias, coverage increased to 40%.
During the first months of 2020, sort of catch up campaign occurred, during which pregnant women that were eligible for a maternal pertussis vaccination already before introduction in the NIP could be vaccinated. They might have postponed the vaccination because within the NIP de vaccination is free of charge. In April and May 2020 the catch up effect was not present anymore and the vaccination coverage was 63% and 59%, respectively.
For 2018-2020, the monthly number of pregnant women in 2018, retrieved from Perined, was used as numerator for all estimates; no more recent estimate was available.
For a description of the methodology, see appendix 1.

7.8.5.3 Vaccine effectiveness (VE)

In 2019, the estimate of effectiveness for the maternal dTap vaccination in preventing pertussis in 0-3-month-olds was 73% when assuming a 20% vaccination coverage. With 30% and 40% coverage, VE estimates increased to 84% and 90%, respectively. In 2020, VE estimate was 93%, taken into account 50% vaccination coverage. At 60% and 70% coverage, this VE increased to 95% and 97%, respectively. These estimates are in line with estimates from other countries [2].
Figure 1.8.3 shows the VE estimates of the infant series. Since the switch from whole-cell pertussis vaccine to an infant combination vaccine with an acellular pertussis component in 2005, the VE estimate has been continuously high up to the booster vaccination given at 4 years old.
However, after the booster dose at 4 years of age the VE estimate shows a decrease after ~5 years, i.e. when children reach the age of 10 years (figure 7.8.4). This is in agreement with the notification rates of these age-groups, as the 10-19-year-olds have a higher IR compared to the 1-9-year-olds.
The VE's estimates described above, are calculated with the 'screening method'. The presented VE should not be interpreted as the 'true' absolute estimate of the effectiveness. It is merely a way to study the trend in VE estimations. See appendix 1 on surveillance methodology for details of the methodology to calculate VE.

7.8.6 *Pathogen*

To study the possible adaptions of the bacteria, Dutch medical microbiology laboratories are requested to submit their *B. pertussis* suspected samples to the RIVM. The strain surveillance focuses on the

changes in the genotype and phenotype of the *B. pertussis* family in the Netherlands. Confirmed *B. pertussis* strains are being whole genome sequenced (WGS) and an antigen expression validation assay is performed for the pertussis antigens; pertussis toxin (Ptx), pertactin (Prn), and filamentous hemagglutinin (FHA).
Although *B.pertussis* was confirmed by molecular diagnostics methods in almost all submitted samples, a single *Bordetella* colony cannot always be obtained due to lack of viability or polymicrobial overgrowth. In 2019, a Bordetella species could be culture-confirmed from 65 out of 313 (21%) submitted samples, of which 63 were *B. pertussis*. Other species identified were *B. holmesii* (n=1) and *B. parapertussis* (n=1). Compared to 2017, RIVM largely extended its network of participating laboratories resulting in an increase of received samples. In 2019, Bordetella suspected specimens were obtained from 17 different medical microbiology laboratories, however ~50% of all isolates were derived from only four sites. The aim is to increase the number of contributing laboratories further, for a complete geographical coverage of The Netherlands. After week 16 of 2020, COVID-19 related restrictions in society resulted in a sudden and dramatic drop of pertussis notifications reported after diagnostic confirmation. Therefore, we also received only a minor fraction of the expected *B.pertussis* isolates in our surveillance program. We are committed to increase the number of isolates in the 2nd half of 2020, to have a clear picture of the current circulating strains in the Netherlands.
In The Netherlands, the national immunization program uses an acellular pertussis vaccine consisting of three pertussis antigens namely Ptx, FHA and Prn. The reemergence of pertussis has been attributed to several factors including bacterial strain adaptation due to vaccine pressure [3]. Therefore, carefully monitoring of the expression of vaccine targets, in particular Prn, by the bacteria is essential. A high frequency of Prn or FHA deficient *B. pertussis* isolates could be prognostic for vaccine evasion, leading to more pertussis cases.
Between 2010-2015, an emergence of *B. pertussis* isolates was seen that are deficient in the vaccine component Prn, with a prevalence of 10-15% in 2015 to 2017. However, in 2018 a sharp increase was seen, with Prn deficiency in 24% (11/46) of the clinical isolates. This alarming rise continued in 2019, with Prn deficiency in 27% of all isolates (19/71). In 2020 up to May 1st,, 21% (3/14) of the collected were found Prn-deficient (Figure 7.8.6A). Sequence analysis showed that an inversion of ~22 Kb in the promotor region was the most frequently found (n = 23) cause of prn-deficiency followed by an insertion of the IS481 element in the *prn*-gene (n = 17), and insertion of a stop-codon (n=6) as shown in figure 7.8.6B.
In 2018, one clinical strain was isolated that lacks the production of the acellular vaccine immunogen FHA. Results for FHA production for the strains collected in 2019 and 2020 are expected at the end of this year.

A core-genome whole genome multi locus sequence typing (cgMLST), using an in-house scheme consisting of 3,180 genes based on *B. pertussis* isolate B1917, was used to infer genetic relationships between the isolates. Figure 1.8.7 shows the genetic relationship between all 271 *B. pertussis* strains isolated between 2015 and 2018. No clustering of isolates based on year (Fig 7.8.7A) or serotype (Fig 7.8.7B) was observed, but distinct Fim3 subtype clusters could be identified (Fig

7.8.7D). This is of interest in view of an observed shift from Fim3-1 to Fim3-2 strains, which comprised 65% of all *B. pertussis* strains in 2016 and 2017, and 76% of all isolates in 2018.

7.8.7 *Research*

7.8.7.1 Cost effectiveness

In the United States, persons ≥11 years are recommended to receive one dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine, followed by decennial tetanus- and diphtheria-toxoid (Td) boosters. Many providers use Tdap instead of Td. Havers et al. evaluated epidemiologic and economic impacts of replacing Td boosters with Tdap [4]. At lowest incidence estimates, administering Tdap resulted in high costs per QALY saved ($8,972,848). As incidence increased, cost per QALY saved decreased rapidly. With incidence estimates of 250 cases/100,000 person-years and 500 cases/100,000, cost per QALY saved were $81,678 and $35,474 respectively. The authors conclude that replacing Td with Tdap for the decennial booster would not be cost-effective based on reported cases. If pertussis incidence, which is incompletely measured, is assumed to be higher than reported through national surveillance, substituting Tdap for Td may lead to moderate decreases in pertussis cases and cost per QALY.
In another American study, the cost-effectiveness of Tdap vaccination for Tdap-eligible adults aged 19 through 85 in the United States was evaluated [5]. The incremental cost-effectiveness ratios (ICERs) for vaccinating US adults aged 19 to 85 with Tdap ranged from $248,000/QALY to $900,000/QALY. Sensitivity analysis showed the most dramatic changes in ICER occurred when changing the underreporting factor, vaccine effectiveness and vaccination costs. Further investigation of the true burden of pertussis disease among adults and the effectiveness of Tdap vaccination in this population is needed to better estimate the impact of Tdap vaccination.
In Canada, pertussis immunization is administrated at 2, 4, 6, and 18 months, followed by a childhood dose at 4 to 6 years. Immunization of pregnant women between 27 and 32 weeks of gestation is recommended, with the goal of protecting infants. Additionally, in Ontario, pertussis immunization of adolescents at 14 years of age was introduced in 2003. Aniywe et al. assessed the cost-effectiveness of adolescent pertussis immunization strategies in Canada [6].
Three Tdap vaccination strategies were evaluated (1) immunization of 10 year olds, (2) removal of adolescent vaccination, and (3) immunization of 14 year olds (that is the status quo). The findings suggest that alternate adolescent Tdap vaccine strategies – either immunization of 10 year olds, or removal of the adolescent vaccine – are more cost-effective than the current practice of immunizing 14 year olds.
Sandmann et al. evaluated the cost-effectiveness of the maternal pertussis vaccination program in England, implemented in 2012 [7] Following the program, pertussis-related infant hospitalizations and deaths in 2012–2017 were assessed and compared with non-vaccination scenarios. Overall, the incremental costs per QALY gained from the program versus the non-vaccination scenarios ranged between £11 000–£28 200/QALY. Despite considerable uncertainties, findings support the cost-effectiveness of the program.

7.8.7.2 Immunology

7.8.7.1.1 Maternal pertussis vaccination

In the MIKI study, a group of pregnant women received dTap at 30-32w GA and was compared with a control group of unvaccinated pregnant women [8]. Memory B and T-cell responses have been determined pre and post booster vaccination at 11 months of age. Numbers of antigen - specific B-cell and T-cells were detectable one month post booster and were not affected by the maternal vaccination (Barug et al., manuscript in preparation).

7.8.7.1.2 Humoral immunity

In the cross-sectional, nationwide serosurveillance study more than 7000 serum samples have been collected during 2016 -2017. The specific IgG antibody levels against 3 vaccine antigens (PT, FHA and Prn) have been determined with the MIA and the analyses are ongoing at the moment. Preliminary data reveal that the proportion of recently infected individuals aged 10 years and above remained at the same level or a bit higher as in the serosurveillance study from ten years earlier (2006-2007). This implicates that the overall circulation of B. pertussis is on the same level. The vaccination coverage and thus participation to the NIP seems to increase in the orthodox reformed groups within the low vaccinations communities. In the natural infection Immfact study between 2015 and 2020 serum and saliva samples were collected longitudinally up to 3 years after symptomatic pertussis from 105 cases and at one time point from 156 age-matched healthy controls. IgG and IgA antibody levels against 9 antigens from *B. pertussis* were determined with an experimentally extended MIA. The first set of data indicating the pace of natural waning immunity and diversity of the antibody responses is expected end of 2020.

7.8.7.1.3 Innate and Cellular immunity to *B. pertussis*

Despite vaccination, pertussis remains capable of circulating and infecting individuals of all ages. This is due to a combination of waning or suboptimal immunity and emergence of *B. pertussis* strains that can escape or modulate pre-existing immunity. Evidence is accumulating that the initial priming of the specific cellular immunity to *B. pertussis*, steered by innate cells, determines the duration of the acquired protective immunity. The underlying mechanisms why natural infection or the previous whole cell pertussis vaccine induce a far more effective and durable immune response than the current acellular vaccine are being studied in detail in a PhD project. Priming of IFNγ and IL-17-type cellular immunity and avoidance of IL-4/IL-13 type cellular immunity seems to be crucial in durable protection to pertussis, and therefore an important hallmark for future improved pertussis vaccines, as recently reviewed [9]. Insight was gained in how *B. pertussis* can interact with local innate immune cells and epithelium cells to modulate subsequent cellular immunity [10]. In order to provide further understanding on the host defense mechanism against *B. pertussis,* the activation of macrophages and the cross-talk with other innate cells were investigated [11]. Together these findings highlight the importance of studying emerging *B. pertussis* strains and their modulatory effect on the immune response.

7.8.8 *International developments*

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria and tetanus in the age groups 40-60 years has been conducted by the RIVM and funded by ECDC [12]. 18 Countries have participated and collected the requested sera (around 500). Measurement of the antibody levels against pertussis toxin (PT), diphtheria toxoid (DT) and tetanus toxin (TT) with the MIA has been completed resulting in a final database of around 30,000 values. The percentages of sera per country with a level for IgG-PT ≥100 IU/mL, indicative for a recent pertussis infection, varied between 1.8% (Finland)
and 9.4% (Norway) with 13/18 countries showing a level between 4.0% and 6.4 %. In the samples of the Netherlands, based on the Pienter3 serosurvey, 5.4% had IgG-PT ≥100 IU/ml. In addition, the GMC's of IgG-PT antibodies in all countries varied between 7-15 IU/mL, suggesting that the epidemiological situation for pertussis across EU/EEA is broadly similar. This cross-sectional retrospective seroprevalence study among middle-aged adults in 18 European countries showed that the circulation of B. pertussis is widespread despite highly implemented childhood vaccination programs (manuscript submitted).

The Periscope consortium, consisting of pertussis experts from 2 vaccine companies, 4 national institutes including the RIVM, and 16 European universities, are working on an extensive IMI-2 project. The main objective of this project is to unravel the difference in protective properties between the acellular pertussis vaccines, the whole cell pertussis vaccines and natural infection, and to characterize new biomarkers for protective immunity to *B. pertussis*. The role of the RIVM is to develop and apply immunological assays for the measurement of antibodies, T-cells and B-cells, and to conduct natural infection and clinical vaccine studies. An assay for the measurement of specific memory and plasma B cells was standardized and applied to show that colonization is an immunizing event in a novel human experimental infection model based on the well characterized RIVM-originating *B. pertussis* isolate BP1917 [13]. Also a highly standardized platform technique was developed within the consortium suitable to monitor CD4 T-cell dynamics in whole blood after vaccination or infections [14].
The multi-center BERT study, involving a booster vaccination in four different age groups, has started in October 2017, and has been completed including the longitudinal samples of 1 year after the booster by January 2020 in the Netherlands, the UK and Finland. Vaccine antigen-specific IgG and IgA antibody levels in the BERT samples before, 28 days after and 1 year after vaccination have been measured by the RIVM. Next to this, B-cell responses have been determined by measuring numbers of circulating antigen-specific plasma cells producing IgG and IgA around day 7 post booster. In addition antigen specific memory B-cell responses were determined pre-booster and at 28 days and 1 year post booster vaccination. Furthermore, novel *B. pertussis* specific T-cell tests are being developed, and a whole blood assay is being evaluated in the BERT study, as recently published [15].

7.8.9 *Literature*

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*RIVM publication.

7.9 Pneumococcal disease

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7.9.3 *Key points*

- In April and May 2020, the number of IPD dropped by 80% compared with the 5-year average, most likely related to COVID-19 measures. This influenced the overall and age-specific incidence and time trends of IPD in 2019/2020.
- In epidemiological year 2019/2020 (June to May), 43 children <5 years of age with IPD were reported, of which only one case was caused by a serotype included in the 10-valent PCV.
- In children <5 years of age, introduction of pneumococcal conjugate vaccination (PCV) in 2006 led to a large reduction of IPD. Since 2013/2014, however, the IPD incidence in children <5 years of age has been increasing slightly due to a slow increase of IPD caused by serotypes not covered by the 10-valent PCV.
- In other age groups, similar trends were observed with very low incidence of IPD caused by vaccine serotypes and increasing incidence of IPD due to non-vaccine serotypes, compromising the overall impact of PCV implementation.
- Vaccine effectiveness (VE) of at least two doses of PCV10 was 89% (95%CI 72-96%) against vaccine type IPD.
- In 2020, PPV23 vaccination was to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups, meaning that in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination.

7.9.4 *Tables and figures*

Figure 7.9.1 Number of cases of invasive pneumococcal disease (IPD) from June 2019 to May 2020 reported by nine sentinel labs (covering ~25% of the Dutch population) by month compared with the 5-year moving average

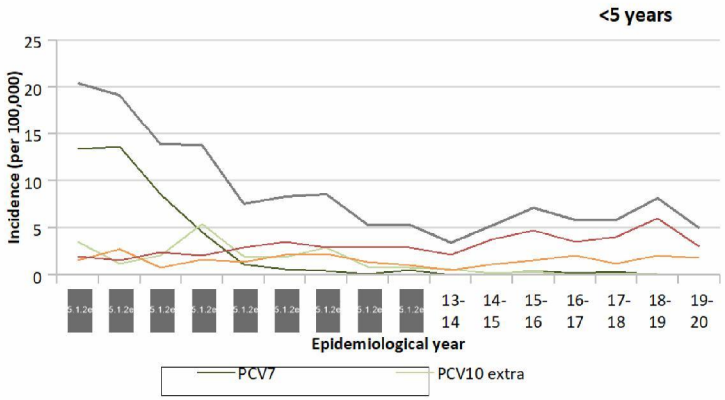

Figure 7.9.2 Incidence of invasive pneumococcal disease (IPD) in children <5 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

PCV7 was introduced in June 2006 and PCV10 in May 2011. From 2004-2005 to 2007-2008, sentinel surveillance data have been used and extrapolated to the Dutch population. From 2008-2009 to 2019-2020, data of national surveillance have been used.

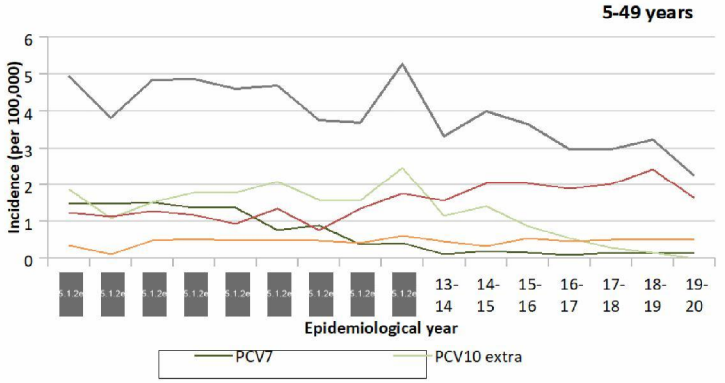

Figure 7.9.3 Incidence of invasive pneumococcal disease (IPD) in persons 5-49 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)

PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.

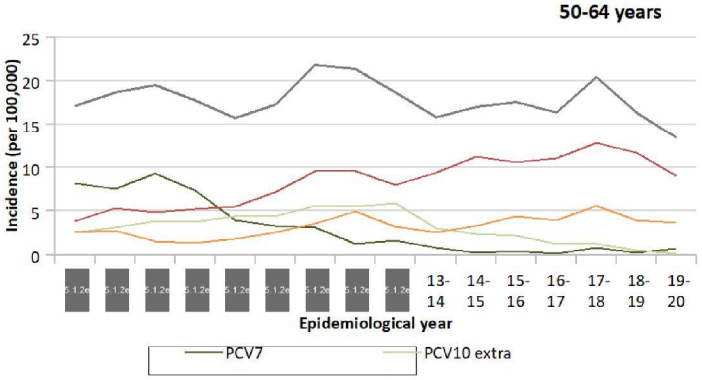

Figure 7.9.4 Incidence of invasive pneumococcal disease (IPD) in persons 50-64 years of age by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)
PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.

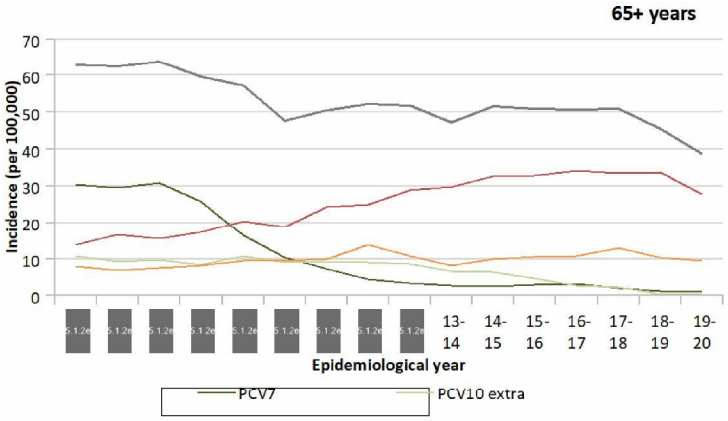

Figure 7.9.5 Incidence of invasive pneumococcal disease (IPD) in persons aged 65 years or more by serotype (PCV7 serotypes, additional PCV10 serotypes, additional PCV13 serotypes, non-PCV13 serotypes and all serotypes), presented by epidemiological year (e.g. 04/05 = June 2004-May 2005)
PCV7 was introduced in June 2006 and PCV10 in May 2011. Sentinel surveillance data have been used and extrapolated to the Dutch population.

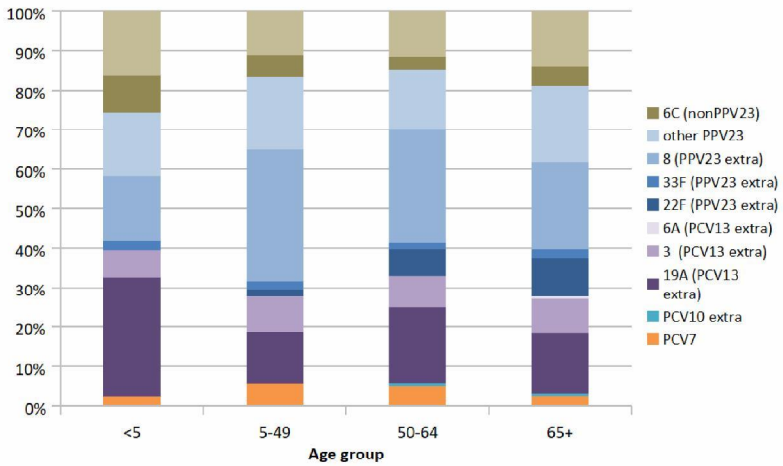

Figure 7.9.6 Distribution of serotypes causing invasive pneumococcal disease (IPD) in epidemiological year 2019/2020
For children <5 years, data of the national surveillance system have been used. For other age groups, sentinel surveillance data have been used.

Table 7.9.1 Serotypes included in the different pneumococcal vaccines

Serotype	Vaccine			
	PCV7	PCV10	PCV13	PPV23
4	X	X	X	X
6B	X	X	X	X
9V	X	X	X	X
14	X	X	X	X
18C	X	X	X	X
19F	X	X	X	X
23F	X	X	X	X
1		X	X	X
5		X	X	X
7F		X	X	X
3			X	X
6A			X	
19A			X	X
2				X
8				X
9N				X
10A				X
11A				X
12F				X
15B				X
17F				X
20				X
22F				X
33F				X

Table 7.9.2 Children eligible for vaccination (born since June 2006) with vaccine-type invasive pneumococcal disease (IPD) who received at least two vaccinations (with at least two weeks between the second dose and diagnosis) based on nationwide surveillance data using data up to May 2018

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

7.9.5 *Epidemiology*

7.9.5.1 Overall

While the overall IPD incidence has been quite stable over time since 2004/2005 with an average incidence of 15.2 per 100,000 per year (range: 13.4 to 16.7 per 100,000 per year), the incidence in epidemiological year 2019/2020 (June to May) decreased to 11.9 per 100,000 per year. The number of cases suddenly dropped by 80% in April and May 2020 compared with the 5-year moving average (Figure 7.9.1). This is most likely related to the COVID-19 measures (e.g. social distancing and school closures) that were issued mid-March, most probably causing less transmission of pneumococci and influencing health care seeking behaviour. This drop in cases was seen in all age groups and affects the age-specific time trends described below.

7.9.5.2 Children <5 years of age (Figure 7.9.2)

In the epidemiological year 2019/2020, 43 IPD cases were reported in children <5 years of age, resulting in an incidence of 5.0 per 100,000 per year. The incidence decreased substantially after the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2006, up to 80% in 2013/2014. However, after 2013/2014 the incidence started rising slightly again. In 2019/2020, the incidence decreased and was significantly lower than in 2018/2019 (39% reduction), which is probably (partly) caused by the COVID-19 measures (see section 7.9.3.1). The incidence in 2019/2020 was 75% lower than before the introduction of PCV7 and 41% lower than before PCV10 introduction.

In 2019/2020, there was only one IPD case caused by a serotype included in PCV10. The IPD incidence caused by serotypes not included in PCV10 has been increasing slowly since PCV7 introduction, which explains the increase in overall IPD in the last years, although in 2019/2020 the non-PCV10 incidence decreased, again presumably partly caused by the COVID-19 measures. In 2019/2020, there were 16 IPD cases (37%; 1.8 per 100,000 per year) caused by the three additional serotypes included in PCV13 (serotype 3, 6A and 19A, see Table 7.9.1). This incidence has been stable in the last four years. In 2019/2020, the most common serotypes were 19A (13 cases), 8 (7 cases) and 6C (4 cases) causing 56% of all cases in this age group (Figure 7.9.6).

7.9.5.3 Persons aged 5-49 years (Figure 7.9.3)

In the epidemiological year 2019/2020, 54 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 5-49 years, resulting in an incidence of 2.3 per 100,000 per year. The incidence in this age group has decreased slightly over time since the introduction of PCV7. In 2019/2020, the incidence decreased significantly compared with 2018/2019 (30% reduction), presumably partly caused by the COVID-19 measures (see section 7.9.3.1).
IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV in 2006, dropping from 3.0 to 0.1 per 100,000 per year in 2019/2020. However, a significant increase has been observed in IPD incidence caused by serotypes not included in PCV10, rising from 1.5 to 2.1 per 100,000 per year in 2019/2020. In 2019/2020, the most common serotypes were 8 (18 cases) and 19A (7 cases) causing 46% of all cases in this age group (Figure 7.9.6).

7.9.5.4 Persons aged 50-64 years (Figure 7.9.4)

In the epidemiological year 2019/2020, 121 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 50-64 years, resulting in an incidence of 13.4 per 100,000 per year. The incidence in this age group has been quite stable over time, fluctuating around ~18 per 100,000 per year. Although in 2019/2020, a decrease was seen, presumably caused by the COVID-19 measures (see section 7.9.3.1).
IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV in 2006, from 10.7 to less than 1.0 per 100,000 per year in 2019/2020. However, a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10, from 7.2 to 12.6 per 100,000 per year in 2019/2020. In 2019/2020, the most common serotypes were 8 (35 cases), 19A (23 cases), and 3 (10 cases) causing 56% of all cases in this age group (Figure 7.9.6).

7.9.5.5 Persons aged 65 years or more (Figure 7.9.5)

In the epidemiological year 2019/2020, 320 IPD cases were reported by the nine sentinel laboratories (covering 25% of the Dutch population) in persons aged 65 years or more, resulting in an incidence of 38.6 per 100,000 per year. The incidence in this age group decreased in the first years after PCV7 introduction and has remained stable over the past 10 years. However, a significant decrease of 15% was observed in

2019/2020 compared with the year before, presumably partly caused by the COVID-19 measures (see section 7.9.3.1).
IPD incidence due to serotypes included in PCV10 has decreased substantially compared to the incidence before introduction of PCV in 2006, from 40.2 to less than 1.5 per 100,000 per year in 2019/2020 (97% reduction). However, a significant increase has been seen in IPD incidence caused by serotypes not included in PCV10, from 22.5 to 37.4 per 100,000 per year in 2019/2020. IPD incidence due to serotypes included in PCV13 but not PCV10 has increased by 30% compared to the incidence before introduction of PCV in 2006. IPD due to serotypes not included in PCV13 has increased by 83%. In 2019/2020, 171 (53%) of the IPD cases among >65-year-olds were caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPV23) but not in PCV13 (PPV23-PCV13). The incidence of PPV23-PCV13 type IPD in >65-year-olds has risen steadily from 10.6 in 2004/2005 to 20.6 per 100,000 per year in 2019/2020. In 2019/2020, the most common serotypes were 8 (70 cases), 19A (49 cases), and 22F (31 cases) causing 47% of all cases in this age group (Figure 7.9.6).
In 2020, PPV23 vaccination was planned to be offered to all 60-, 65-, 70- and 75-year-olds in the Netherlands. However, due to the COVID-19 pandemic, priority has been given to the oldest age groups. Therefore, in Autumn 2020 all 73-79 year olds will be offered PPV23 vaccination. It has not yet been decided which age groups will be targeted in 2021.

7.9.5.6 Vaccine failure

Since the introduction of PCV7, 44 cases of vaccine-type IPD have been reported among vaccine-eligible children (born after 1 April 2006 and aged 2 months and over) in the nationwide surveillance. Of these, 21 children (48%) were vaccinated with at least two doses (with the second dose given at least two weeks before diagnosis), and therefore were considered vaccine failures (Table 7.9.2). Serotype 19F was the most common serotype among vaccine failure cases (n=7, 33%). There was one vaccine failure case in 2019, vaccinated with PCV10.

7.9.5.7 Vaccine effectiveness (VE) against IPD

VE of PCV10 was calculated using the indirect cohort (or Broome) method, in which the odds of vaccination in vaccine type cases is compared with the odds of vaccination in non-vaccine type cases. The population included all reported IPD cases up to December 2018 that were eligible for PCV10 vaccination and aged 2 months over, and with known serotype and vaccination status.
Nine of the 19 (47%) vaccine type IPD cases were vaccinated with at least two doses, as were 254 of the 284 (89%) non-vaccine type IPD cases. This resulted in a VE of 89% (95%CI 72-96%) for at least two doses of PCV10 compared with zero doses. The VE against serotype 19A (not covered by PCV10) was 48% (95%CI -20 to 78%). From these results, cross-protection of PCV10 against vaccine-related IPD including serotype 19A cannot be confirmed.

7.9.5.8 IPD mortality among children <5 years

From 2014 to May 2020, 347 IPD cases among children aged under five were reported nationally. For 235 cases (68%), the mortality status was known. Seventeen of the 235 cases (7%) died. These 17 cases all had non-vaccine type IPD (serotypes 8 (n=4), 3 (n=2), 12F (n=2), 6C

(n=2), 22F, 10A, 15C, 19A, 23A, 24F, 31). Fifteen cases were <2 years of age and four had known comorbidity.

7.9.6 *Pathogen*

In the period 2004-2016, capsular switches occured within the Dutch invasive pneumococcal population based on MLVA and cgMLST. However, the number and proportion of capsular switches remains very low and increased only slightly over time.

7.9.7 *Current/ongoing research at RIVM*

In older adults, pneumococcal disease is strongly associated with respiratory viral infections, but the impact of viruses on *Streptococcus pneumoniae* carriage prevalence and load remains poorly understood. Miellet et al. investigated the effects of influenza-like illness (ILI) on pneumococcal carriage in community-dwelling older adults by quantifying pneumococcal DNA with quantitative-PCRs in saliva samples, collected in the 2014/2015 influenza season from 232 individuals with ILI and 194 asymptomatic controls (Preprint on BioRivx:xxxxx). The prevalence of pneumococcus-positive samples was highest at onset of ILI (18%; 42/232) and lowest among controls (11%; 22/194), though these differences were not significant. Pneumococcal carriage was associated with exposure to young children and rhinovirus infection. When compared with carriers among controls, pneumococcal abundances were significantly higher at onset of ILI, and remained elevated beyond recovery from ILI. Finally, predicted pneumococcal abundances were highest in carriage events newly-detected after ILI compared with pre-existing carriage. Taken together, this study shows that ILI enhances pneumococcal colonization of the airways in older adults, and this effect persists beyond recovery from ILI.

7.9.8 *(Inter)national developments*

7.9.8.1 Carriage

Wouters et al assessed pneumococcal carriage in Belgium in children during/after the switch from PCV13 to PCV10 in 2015/2016 [1]. A total of 2,615 nasopharyngeal swabs from children (6–30 months old) attending day care were collected in three periods over 2016–2018. The overall pneumococcal carriage prevalence remained stable over the study period (76-80%). The proportion of non-PCV13 vaccine serotypes among carriers decreased over the study period from 95% in 2016 to 90% in 2017–2018. The proportion of PCV13-non-PCV10 vaccine serotypes increased from 1% in 2016 to 8% in 2017–2018. This increase was mainly due to an increase in serotype 19A carriage.

7.9.8.2 PCV10

Rinta-Kokko et al estimated the VE of PCV10 in children in Finland using three different study designs, namely a cohort study, nested case-control study and the indirect cohort design [2]. VE against PCV10 serotype IPD was 93% (87-97%), 98% (90-100%) and 100% (98-100%) for the three designs, respectively. The VE against PCV10-related serotypes ranged between 46 and 78% for the different study designs, and was not significant in any of the designs. VE against all IPD was estimated at 54% (24-71%) in the cohort study and at 61% (26-79%) in the case-control study.

Karppinen et al estimated the VE of PCV10 against respiratory tract infections in 424 children in a follow up study of the Finnish Invasive Pneumococcal disease vaccine trial, a cluster-randomised double-blind trial [3]. The children vaccinated with PCV10 had lower mean annual rates of respiratory tract infections than control children in the first two years of life. The VE was 12% (2-22%) against all respiratory tract infections, 23% (0-40%) against respiratory tract infections with acute otitis media and 10% (0-19%) against respiratory tract infections without acute otitis media.

7.9.8.3 PCV13

Yildirim et al assessed predictors of PCV13 vaccine failure, where vaccine failure was defined as diagnosis of IPD due to a vaccine serotype in a child who received age recommended doses [4]. During seven years, 37 (34%) vaccine failure cases were identified among a total of 296 IPD cases. Older age (>5 years), presenting with pneumonia and underlying comorbidity were predictors of vaccine failure.

Amin-Chowdhurry et al assessed clinical characteristics of patients with IPD caused by the emerging serotypes 8, 12F and 9N in England from 2014-2018 [5]. These three emerging serotypes are responsible for 38% of the IPD cases in England. Serotypes 8 and 12F were more likely to cause IPD in younger, healthier individuals and less likely to be fatal, while serotype 9N affected older adults with comorbidities and had higher cases fatality.

7.9.8.4 Pneumococcal pneumonia

Cassir et al reported an outbreak of pneumococcal pneumonia among shipyard workers in Marseille, France, from January to February 2020 [6]. A total of 37 cases were identified of which 18 were hospitalized including five in an intensive care unit. The cases presented several risk factors for pneumococcal disease including exposure to respiratory irritants (dust, solvent, metal fumes), smoking and viral coinfections. In addition, the workers lived and worked in crowded environments. Following the outbreak, a mass vaccination campaign with PPV23 was implemented for 4300 workers and crew members, of which 1460 were vaccinated. Pneumococcal outbreaks on shipyards have been described before in Singapore, Norway and Finland. Some European countries have recommendations for PPV23 vaccination for specific occupations like welders.

7.9.8.5 Schedule

Adebanjo et al showed that vaccine failure rates of PCV13 were higher in children <1 year receiving a 2+0 versus a 3+0 schedule (incidence rate ratio: 12.9; 4.1-40.4) [7]. Results for PCV7 were similar. There were no differences between schedules in children >= 1 year of age.

Cost-effectiveness

7.9.8.6 Children

Pugh et al. estimated the clinical and economic benefit of replacing PCV10 with PCV13 in three countries: Colombia, Finland, and The Netherlands [8]. Over a 5-year time period, a switch to a PCV13 program was estimated to reduce overall IPD among 0–2 year olds by

37.6% in Colombia, 32.9% in Finland, and 26% in The Netherlands. In adults > 65 years, decrease in overall IPD were estimated in Colombia (32.2%), Finland (15%), and The Netherlands (3.7%). For Colombia and Finland, the implementation of PCV13 would be cost saving. For the Netherlands the incremental costs per quality adjusted life-year (QALY) gained would be €28,260. Ansaldi et al. found similar results for Italy [9]; in this country PCV13 is already included in the National Immunization Program. The economic impact of changing the vaccination program from PCV13 to PCV10 in Italy were assessed. The incremental cost-effectiveness ratio (ICER) for PCV13 compared to PCV10 was €28,963 per QALY gained. Switching from PCV13 to PCV10 would increase the incidence of pneumococcal disease primarily linked to re-emergence of serotypes 3 and 19A. Both studies were performed by Pfizer Inc.

7.9.8.7 Adults

In 2018, the Dutch Health Council advised on elderly pneumococcal vaccination favouring the polysaccharide vaccine over the conjugated vaccine. This advice was based on a cost-effectiveness analysis showing favourable outcomes for the polysaccharide but not for the conjugated vaccine. Zeevat et al recalculated the cost-effectiveness using a longer time horizon and lower vaccine prices [10]. In this recalculation, also the conjugated vaccine becomes cost-effective; i.e. well below the threshold of €20,000 per QALY gained. This study received an unrestricted grant from Pfizer Inc.

Continued indirect effects provided by the childhood PCV13 program in the United States have decreased disease in the adult population, reducing the potential direct effects of vaccinating older adults. Stoecker et al evaluated the incremental cost-effectiveness of continuing to recommend PCV13 in series with PPV23 at age 65 compared to a strategy that only included a recommendation for PPV23 at this age [11]. In the base case scenario, continuing to recommend PCV13 at age 65 costs $561,682 per QALY gained. The costs per QALY have increased nearly 10-fold since the last analysis in 2014, when this recommendation was made by the ACIP. Therefore, according to the authors, routine PCV13 use among immunocompetent adults 65 years or older is to be discussed in a setting of fully realized PCV13 indirect effects.
Wateska et al. have published five economic evaluations of pneumococcal vaccination programs in US adults. In line with Stoecker et al she found that the current pneumococcal vaccination recommendations for US older people are economically unfavourable compared to an alternative strategy omitting PCV13 in the immunocompetent [12, 13]. In another study vaccinating high-risk individuals with PPV23/PCV13 proved to be the most favourable strategy, with $57,786/QALY gained [14]. In a fourth study the cost-effectiveness of a vaccine uptake improvement program among the US black and general population cohorts aged 50 years with high-risk conditions was assessed [15]. In both black and general population cohorts, an uptake improvement program for current vaccination recommendations was favoured, costing $48,621 per QALY gained in black populations ($54,929/QALY in the general population) compared to current recommendations without a program. A fifth study focused on

underserved minority populations [16]. Prior analyses suggest routine pneumococcal vaccination at age 50 could be considered, which could disproportionately benefit underserved populations. However, the current CDC recommendations (both vaccines for the immunocompromised, polysaccharide vaccine for other high-risk conditions) were economically favourable as vaccinating all 50-year-olds would not be cost-effective at >$250,000 per QALY gained.

7.9.8.8 Pneumococcal vaccines in development

Pfizer is developing a 20-valent pneumococcal conjugate vaccine (20vPnC) that is being investigated for the prevention of invasive disease and pneumonia caused by Streptococcus pneumoniae serotypes covered in the vaccine in adults aged 18 years and older. 20vPnC includes the 13 serotypes contained in PCV13 (see Table 7.9.1) plus 7 additional serotypes (8, 10A, 11A, 12F, 15BC, 22F and 33F). These 20 serotypes are currently responsible for the majority of pneumococcal disease in adults and the seven additional serotypes are global causes of IPD, and are associated with high case-fatality rates, antibiotic resistance, and/or meningitis.
Three phase III trials have been completed. One of the studies (NCT03760146) evaluated the safety and immunogenicity of 20vPnC compared with PCV13 and PPV23 in 3880 adults aged 18 years or older who were not previously vaccinated against pneumococcal disease [17]. This study showed non-inferiority at one month after vaccination for all serotypes in common with PCV13 and for six of the seven additional serotypes when compared to the PPV23 in adults of 60 years and older; one of the new seven serotypes missed non-inferiority criteria by a small margin. Antibody levels in adults 18-59 years old were non-inferior compared to those in 60-64 years old for all 20 serotypes. The safety and tolerability of 20vPnC was comparable to licensed pneumococcal vaccines. Clinical development for use in paediatric populations is in progress. The adult indication of 20vPnC will be submitted to the FDA by the end 2020.

MSD is developing a 15-valent pneumococcal conjugate vaccine (V114) including serotypes 22F and 23F in addition to the serotypes included in PCV13. A phase II trial compared V114 with PCV13 in 1,050 healthy infants who were vaccinated at two, four, six and 12-15 months of age [18]. The study showed that the percentage of subjects who achieved the WHO-accepted threshold of protection (IgG≥0.35 mcg/mL) with V114 was non-inferior to the percentage seen with PCV13 for the 13 serotypes shared between the two vaccines. For serotype 3, the percentage of subjects who achieved this threshold was higher for V114 (96.0% for lot 1; 94.1% for lot 2) compared with PCV13 (71.8%). For the two serotypes not included in PCV13, the percentage of subjects who achieved the threshold was above 98% for serotype 22F and above 87% for serotype 33F. Results were consistent between the two lots of V114 studied. The adverse event profile for V114 was found to be comparable to PCV13. The most commonly reported adverse events were injection site reactions, the majority of which were mild to moderate in severity and of short duration. The vaccine is currently being tested in 11 Phase 3 clinical trials including adults and infants and immunocompromised persons and those at increased risk for IPD.

Both vaccines have received a Breakthrough Therapy Designation from the FDA. This designation is designed to expedite the development and review of drugs and vaccines that are intended to treat or prevent serious conditions and for which preliminary clinical evidence indicates that the drug or vaccine may demonstrate substantial improvement over available therapy on a clinically significant endpoint.

In addition to PCVs, several other vaccine concepts are currently being tested in clinical development programs including a new generation (killed) whole cell pneumococcal vaccine based on an unencapsulated serotype that allows the expression of many bacterial antigens. These vaccines are currently being tested in phase I/II trials. Another concept is pneumococcal protein (PnPs) vaccines with proteins that are universally expressed among serotypes; these are also being tested in phase I/II trials. Both vaccine types may induce broader protection while they are easier to manufacture and less expensive than PCVs.

7.9.9 *Literature*

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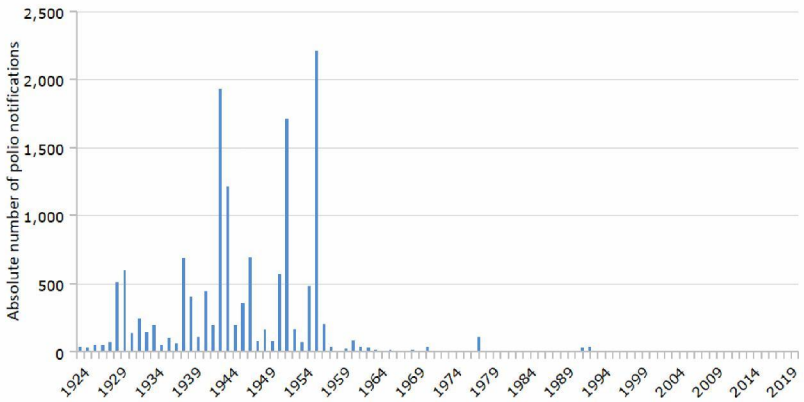
7.10 **Poliomyelitis**

N.A.T. van der Maas, E. Duizer, K. Benschop, W. Luytjes, H.E. de Melker

7.10.3 *Key points*

- In 2019 and 2020 up to July 1st, no cases of poliomyelitis were reported in the Netherlands, including the Caribbean Netherlands.
- In an historic announcement on World Polio Day (24 October 2019), an independent commission of experts concluded that wild poliovirus type 3 (WPV3) has been eradicated worldwide. Two of three wildtype polioviruses (i.e. WPV2 and WPV3) have been declared eradicated.
- In 2019-2020, poliovirus remained endemic in three countries; Nigeria, Afghanistan and Pakistan.
- On 21 Augustus 2019 Nigeria, and thus the Afro region, was free of wildtype poliovirus for 3 consecutive years. The certification process to declare the 5th of 6 WHO regions wildtype polio free is in progress and will likely be finalized in 2020.
- Worldwide, the number of circulating vaccine derived poliovirus (cVDPV) was higher in 2019 (368) than in 2018 (105).
- To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) has released a Polio Endgame Strategy 2019-2023 in 2019.

7.10.4 *Tables and figures*



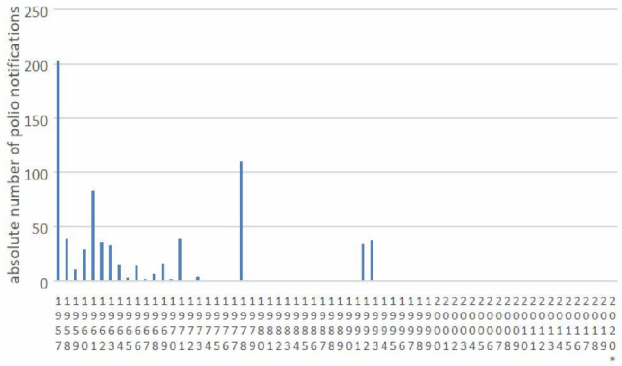


Figure 7.10.1 Notifications of poliomyelitis in the Netherlands from 1924-2020 and zoomed in on 1957-2020* (lower part)*
*for 2020, reports up to July 1st were included

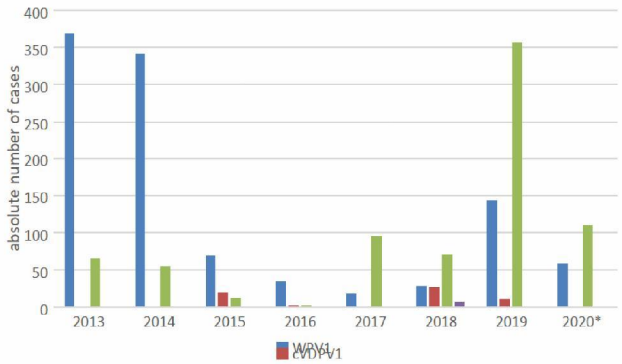


Figure 7.10.2 Total number of global polio cases 2013-2020 as reported to WHO HQ. For 2020, data up to May 20 were included.*

7.10.5 *Epidemiology & pathogen*

In 2019 and 2020 up to July 1st, no cases of poliomyelitis were reported in the Netherlands (Figure 7.10.1). Since the accidental cVDPV2 spillage in 2017, no poliovirus has been detected in the Netherlands.

7.10.6 *Research*

The National Polio Laboratory (NPL) at the RIVM participates in several projects of 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.
Additionally, the NPL had piloted an Environmental Surveillance Quality Assurance program to support the GPLN and the Environmental Surveillance expansion plan. In 2019-2020, 30 laboratories have participated in ESQA pilot 3 and the ESQA is awaiting full implementation in the GPLN QA program. In cooperation with the immune-surveillance department at the RIVM, the NPL is developing new serological assays that can be used outside of GAPIII containment Additionally, the NPL RIVM participates in the validation of new poliovirus strains (S19 strains), including type 2, that can be used outside of GAPIII containment for use in the poliovirus neutralization assay.

7.10.7 *International developments*

In 2019-2020, WHO classified three countries – Nigeria, Afghanistan and Pakistan as polio-endemic countries. Importation of polio into non-endemic countries was not observed. From 2016 onwards, no WPV cases were notified in Nigeria. As a result, Nigeria, and thus the Afro region, was free of wildtype poliovirus for 3 consecutive years. The certification process to declare the 5th of 6 WHO regions wildtype polio free is in progress and will likely be finalized in 2020.
In Afghanistan and Pakistan, a combined total of 176 WPV1 cases were notified in 2019, and 59 WPV1 cases in 2020 up to May 20 [1]. In 2019, 3 WPV1 were detected in Iran's environmental surveillance. Fortunately, this did not result in ongoing transmission and up to July 1, 2020 no cases were reported in Iran.
The number of circulating vaccine derived poliovirus (cVDPV) was higher in 2019 (368) compared to 2018 (105) and mainly concerned cVDPV2. (Figure 7.10.2). Therefore there has been a higher demand of mOPV2, a WHO-prequalified vaccine with the same operational characteristics as bivalent oral polio vaccine (bOPV). This high demand has even threatened the stock of this vaccine. The WHO advised that all countries should destroy the materials containing poliovirus type 2, and provide at least one inactivated polio vaccine (IPV) in their routine vaccination schedule. In May 2019 WHO announced that all countries worldwide had introduced at least 1 IPV dose [2]. Polio eradication progress is hampered by the Covid19 pandemic.
The current approach to fight cVDPV2 outbreaks is by using mOPV2, i.e. fighting fire with fire. The newly developed newOPV2 (nOPV2) strain is in an Emergency Use Listing procedure (EUL) that would allow use of this (presumably) safer vaccine in regions where cVDPV2 outbreaks are occurring. The NPL RIVM participates in the development of detection methods for this specific strain in environmental surveillance.
To sustain a world free of all polioviruses, the Global Polio Eradication Initiative (GPEI) has released a Polio Endgame Strategy 2019-2023 in 2019 [3]. This so-called roadmap builds on the proven lessons and tools of the strategic plan 2013-2018, and focuses on eradication, integration, containment and certification [4].

7.10.8 *Literature*

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7.11 Rubella

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

7.11.3 *Key points*

- In 2019 and the first six months of 2020, no rubella cases were reported in The Netherlands.
- Results from the 2016/2017 PIENTER study indicate high overall seroprevalence of protective antibodies in 95% of the general population.
- In the PIENTER study the highest susceptibility was seen among children within the orthodox Protestant community, born after the last rubella epidemic in 2005, indicating an outbreak can be expected after introduction of rubella virus in this community.
- Across Europe, the number of rubella cases continued to decline in 2019.

7.11.4 *Tables and figures*

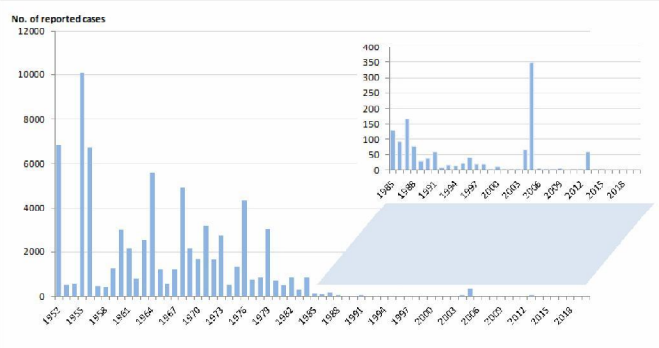

Figure 7.11.1 Total annual reported rubella cases in The Netherlands, from 1952 – 2018

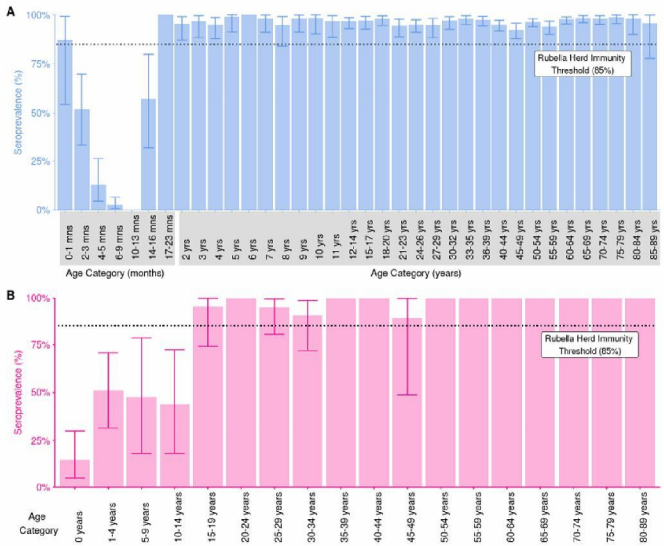

Figure 7.11.2 Seroprevalence of rubella IgG antibodies (cut-off is ≥10 IU/ml) by age category in The Netherlands, 2016/17. Panel A: Results for the general Dutch Population (N=5,146); Panel B: Results for the Protestant Orthodox Reformed community (N=1,355).

7.11.5 *Epidemiology*

Throughout 2019 and during the first six months of 2020, no new rubella cases were reported in The Netherlands. The last case of rubella was reported in 2015 (Figure 7.11.1).

7.11.6 *Research*

Seroepidemiology is an important tool to monitor the (long-term) effects of the national immunization programme (NIP) on population level immunity. In The Netherlands a population-based study is performed every ten years (1995/1996-2006/2007-2016/2017) to assess immunity within the Dutch population (0-79/89 years of age), and among the socio-geographically clustered Protestant orthodox reformed community, who often refuse vaccination. The third PIENTER study (PIENTER 3) was conducted during 2016 and 2017, and included over 7000 participants. Serum samples were analysed by a bead-based multiplex immunoassay.

Immunity against rubella was assessed and protective immunity defined as a concentration of rubella IgG ≥10 IU/ml [1]. Preliminary analyses indicate that the Dutch population is well protected against rubella, with a high overall seroprevalence of protective antibodies of 94.8% (95% CI 94.0-95.5%). Highest susceptibility was seen in children under 14 months of age, prior to the administration of the 1st dose of a rubella containing vaccine (Figure 7.11.2A.)

Analyses indicated that susceptibility was higher among orthodox reformed individuals than in the general Dutch population, with an overall seroprevalence of rubella protective antibodies of 86.6% (95% CI 80.7-91.2%). The highest susceptibility was seen among children under 12 years of age within the orthodox Protestant community, born after the last rubella epidemic in 2005 (Figure 7.11.2B). This situation requires ongoing sensitive surveillance monitoring, as with low rubella incidence within The Netherlands a considerable pool of rubella susceptible individuals will accumulate. ~~*This group could be at risk of a new outbreak due to imported cases of rubella, as internationally levels of rubella vaccination coverage and incidence vary. This is particularly concerning for women and girls of child bearing age within this community, due to the risk of Congenital Rubella Syndrome (CRS), of which there was a high burden as a result of the last large epidemic.*~~

7.11.7 *International developments*

In Europe, reported rubella cases declined from 1326 in 2016, to 579 in 2018. In 2019, the same tendency was observed with 389 rubella cases reported by 9 EU/EEA Member States. Nineteen countries reported no cases. The highest numbers of cases were reported by Poland (292), Germany (57) and Italy (22) [2, 3]. The data from Poland should be interpreted with caution as rubella is reported based on clinical symptoms and only 4 of 292 cases (1%) was laboratory confirmed [3].

Further afield, rubella-containing vaccine has been introduced nationwide in 173 of 194 WHO Member States as of the start of 2020, and global coverage is estimated to be 71% [4]

A meta-analysis of 42 studies found no evidence that rubella-containing vaccines caused congenital rubella syndrome (CRS) in infants born to mothers inadvertently vaccinated against rubella during early pregnancy. The authors found that CRS was effectively prevented by vaccination, and thus support continued rubella vaccination efforts. The data confirmed previous recommendations that inadvertent vaccination during pregnancy is not an indication for termination [5].

A study in Japan found evidence for decreased fertility following a large outbreak of Rubella from 2012-2014. Fertility rates were found to decline after each geographical epidemic peak, and were also strongly associated with the frequency of online google searches for "rubella" during the epidemic. As the overall number of cases in Japan was relatively small and online search activity considerably elevated, the authors proposed that reduced fertility was associated not with stillbirths or miscarriages, but due to perceived increased risk of CRS during the outbreak and subsequent voluntary pregnancy delays [6].

7.11.8 *Literature*

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*RIVM publication.

7.12 Tetanus

N.A.T. van der Maas, D.W. Notermans

7.12.3 Key points

- In 2019, no cases of tetanus were notified.
- In 2020, up to June 1st, two cases were reported, one elderly women who was not eligible for routine vaccination and one unvaccinated 12-year-old.
- In a European seroprevalence study among 40-59-year-olds, seroprotection levels for tetanus were sufficient with only very few sera lacking basic immunity. In the Dutch serum samples, based on Pienter3 participants, only 0.3% and 5.2% had anti-tetanus antibody levels <0.01 IU/ml and <0.1 IU/ml, respectively.

7.12.4 Tables and figures

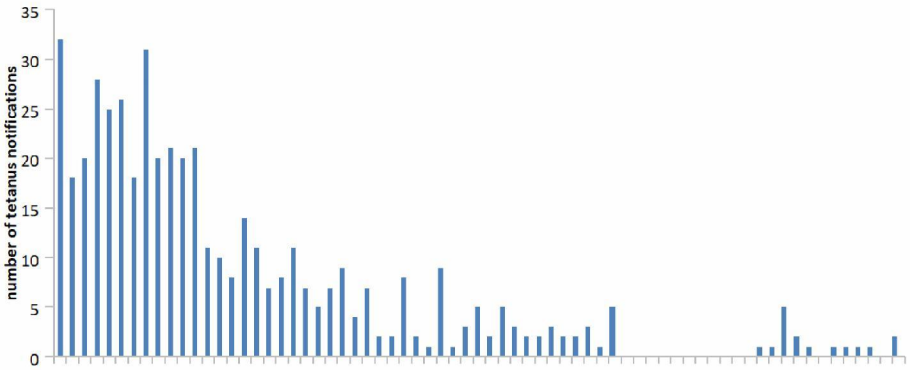

*Figure 7.12.1. Reported cases of tetanus in the Netherlands by year, 1952-2020^*
*Between 1999 and 2009 tetanus was not notifiable.
^ For 2020, notification up to June 1st were counted.

7.12.5 Epidemiology

In 2019, no cases of tetanus were reported. Up to June 2020, two cases were reported. One case concerned a woman, born in 1943 and therefore not eligible for the NIP. She contracted a wound after falling off her bike. For post exposure prophylaxis, she received tetanus toxoid but no tetanus immunoglobulins although the latter is recommended. She was hospitalized with clinical signs of tetanus. No *Clostridium tetani* was cultured from the wound.
The second case concerned an unvaccinated 12 year old boy, who contracted a headwound due to a slap with a branch. Within several days he developed clear signs of tetanus: neck stiffness, cramps of the facial muscles including a lockjaw, and of the chest musculature. He was hospitalized and due to difficulties with breathing he was transferred to the intensive care unit. After several weeks of severe illness he recovered. *Clostridium tetani* was cultured from the wound, although no tetanus toxin was found.

7.1.6 *International developments*

Within the framework of the EUPertstrain group, a collaboration between European experts on whooping cough, a seroprevalence study in European countries for pertussis, diphtheria and tetanus antibody levels in the 40-60 years age groups has been conducted by the RIVM and funded by ECDC [1]. 18 European countries have participated and collected the requested sera (around 500). Measurement of the antibody levels against pertussis toxin, diphtheria toxoid and tetanus toxin with the MIA has been completed last year establishing a final database of around 30,000 results. The seroprotection levels for tetanus were sufficient with only very few sera lacking basic immunity. The proportion of sera with levels below 0.01 IU/mL ranged from 0-1.2%, apart from Greece (2.8%). For the total cohort, seven countries were considered as fully protected. The protective level of 0.1 IU/mL was reached in more than 90% of the sera in all countries, apart from Greece (79%) and Ireland (83%). In the other 16 countries the proportion of sera with unprotected levels (<0.1 IU/mL) ranged from 0.4% to 8.2%. In the Dutch serum sample, based on Pienter 3 participants, 0.3% and 5.2% had anti-tetanus antibody levels <0.01 IU/ml and <0.1 IU/ml, respectively.

7.1.7 *Literature*

1. *G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

8. Immunisation programme in the Dutch overseas territories, including Dutch Caribbean islands

5.1.2e 5.1.2e *'t Klooster, E.A. van Lier, E. Vos, H. Pasmans, K. Hulshof, J. van Slobbe, F. Rooyer*

8.1 Key points

- In general, vaccination coverage in the Dutch overseas territories, including Caribbean Netherlands (i.e., Bonaire, St. Eustatius and Saba) is high.
- In 2019, no vaccine preventable diseases were reported on Bonaire and Saba.
- Findings from the Health Study Caribbean Netherlands indicate that HPV seroprevalence was high among individuals aged ≥15 years (34%), with over half of them being seropositive for ≥2 high-risk HPV types. Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program in Caribbean Netherlands.

8.2 Tables and figures

Table 8.1 Vaccination coverage[a,b] in Caribbean Netherlands

	Aruba	Bonaire	Curaçao	Saba	St, Eustatius	St. Maarten
Newborns (2 years)						
Number in cohort 2017	*	*218*	*	*25*	*32*	*
Number DTaP-IPV-Hib-HBV	*	199	*	25	26	*
% DTaP-IPV-Hib-HBV	*	91,3%	*	100%	81,3%	*
Number HBV	*	n.a.	n.a.	n.a.	n.a.	*
% HBV	*	n.a.	n.a.	n.a.	n.a.	*
Number Polio	n.a.	n.a.	*	n.a.	n.a.	n.a.
% Polio	n.a.	n.a.	*	n.a.	n.a.	n.a.
Number Pneu	*	199	*	25	26	*
% Pneu	*	91,3%	*	100%	81,3%	*
Number MMR1	*	207	*	25	23	*
% MMR1	*	95,0%	*	100%	71,9%	*
Number MMR2	n.a.	n.a.	*	n.a.	n.a.	n.a.
% MMR2	n.a.	n.a.	*	n.a.	n.a.	n.a.
Number Men C	n.a.	204	n.a.	24	23	n.a.
% Men C	n.a.	93,6%	n.a.	96,0%	71,9%	n.a.
Toddlers (5 years)						
Number in cohort 2014	*	*	*	*22*	*37*	*
Number DTaP-IPV	*	*	*	22	30	*
% DTaP-IPV	*	*	*	100%	81,1%	*
Aantal MMR2	*	n.a.	n.a.	22	30	*
% MMR2	*	n.a.	n.a.	100%	81,1%	*

Schoolchildren (10 years)						
Number in cohort 2009	*	*	*	*15*	*48*	*
Number DTP	*	*	*	11	42	*
% DTP	*	*	*	[c] 73,3%	87,5%	*
Number MMR2	*	*	n.a.	13	n.a.	*
% MMR2	*	*	n.a.	[c] 86,7%	n.a.	*
Adolescent girls (10 years)						
Number in cohort 2009	*	*	*	*<10*	*27*	*
Number HPV	*	*	*	<10	21	*
% HPV	*	*	*	[c] 50,0%	77,8%	*

*Unknown because of research technical issues or not available yet due to special circumstances concerning the corona crisis.

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

[b] Vaccination status at two years of age: DTaP-IPV/MMR = basic immunity, Hib/HBV/PCV/MenC = completely closed; at age five: DT(aP)-IPV = re-vaccinated; at the age of ten: DTaP/MMR/HPV = full participation.

[c] Interim vaccination coverage: the vaccination is linked to school year and not to birth year; for a part of these children vaccination will be offered in 2020.

Table 8.2 Number of reports of NIP-diseases in Caribbean Netherlands, 2017-2019

	Aruba	Bonaire	Curaçao	Saba	St. Eustatius	St. Maarten
Diphtheria						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
***Haemophilus influenzae* type b**						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Measles						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Meningococcal disease						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Mumps						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Pertussis						
Number of reports in 2017	*	2	*	0	*	*
Number of reports in 2018	*	1	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Pneumococcal disease						
Number of reports in 2017	*	0	*	0	*	*

Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Poliomyelitis						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Rubella						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*
Tetanus						
Number of reports in 2017	*	0	*	0	*	*
Number of reports in 2018	*	0	*	0	*	*
Number of reports in 2019	*	0	*	0	*	*

*Not available yet due to special circumstances concerning the corona crisis.

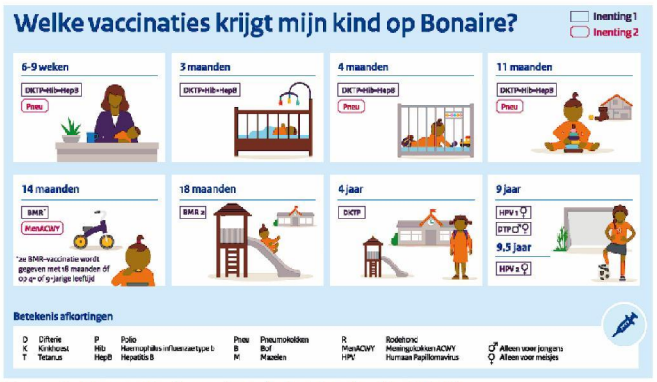

Figure 8.1 Immunisation schedule for Bonaire (in Dutch)

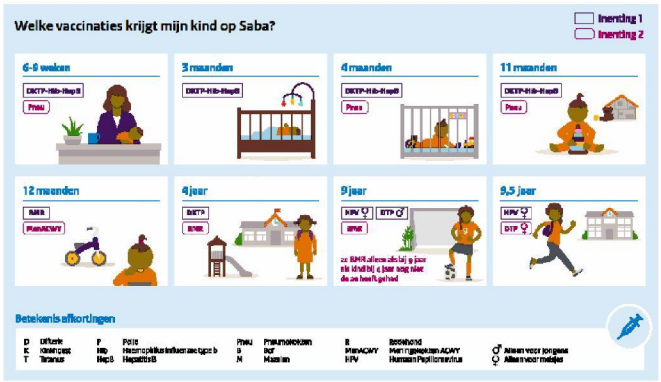

Figure 8.2 Immunisation schedule for Saba (in Dutch)

Vaccinatieschema			
Leeftijden	Vaccinatie 1	Vaccinatie 2	Vaccinatie 3
2 maanden (= 7 - 9 weken)	DKT 1 + HepB 1+ Hib 1	Polio 1 (IPV)	
3 ½ maanden	DKT 2 + HepB 2+ Hib 2	Polio 2 (bOPV)	Pneu 1 (10 valent)
5 maanden	DKT 3 + HepB 3+ Hib 3	Polio 3 (bOPV)	Pneu 2 (10 valent)
vanaf 12 maanden	BMR 1		Pneu 3 (10 valent)
15 maanden	DKT 4 + Hib 4 + HepB 4	Polio 4 (bOPV)	BMR 2
4 jaar	DT 1 (pediatric)	Polio 5 (bOPV)	
10 jaar	dT 2 (adult)		

Betekenis afkortingen

DKT	Difterie-Kinkhoest-Tetanus
DT	Difterie-Tetanus
dT	difterie-Tetanus (adult concentration)
HepB	Hepatitis B
Hib	Haemophilus influenzae type b
IPV	Inactivated Polio Vaccin
bOPV	bivalent Oral Polio Vaccin
BMR	Bof Mazelen Rubella
Pneu	Pneumokokken vaccin (PCV 10 valent)

Figure 8.3 Immunisation schedule for Curaçao

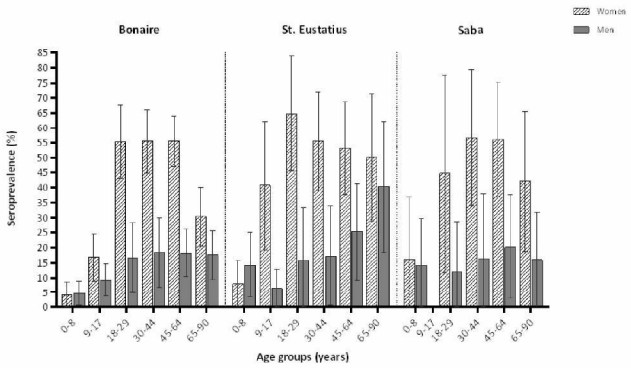

Figure 8.4 Age-specific seroprevalence (%) (with 95% confidence intervals) of any high-risk type human papillomavirus (HPV) IgG-antibodies in the general population of Bonaire, St. Eustatius and Saba, 2017, by sex

8.3 Immunisation schedules

Immunisation schedules in Caribbean Netherlands were presented in Figures 8.1-8.3.

8.4 Vaccination coverage

Table 8.1 presents the vaccination coverage in the Caribbean part of the Netherlands. Due to the special circumstances concerning the corona crisis, for the islands of Curaçao, Aruba and Sint Maarten it was not possible to provide timely data on the vaccination coverage. For research-technical reasons, not all data on vaccination coverage for Bonaire could be included in this report this year. However, there are no indications that there are any major changes in vaccination coverage compared to last year.

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

8.5 Epidemiology of diseases included in the NIP

Table 8.2 shows the number of reports of NIP-diseases in Caribbean Netherlands in 2017 to 2019.

8.5.3 *Epidemiology in Bonaire*

There have been a few cases of pertussis reported in 2017 and 2018 in Bonaire. In 2019 no cases of pertussis were reported.

8.5.4 *Epidemiology in Saba*

In the winter of 2019-2020, more people than usual were ill with flu-like symptoms, several dozen contacted the GPs for this. Diagnosis was conducted in a few people, in which Influenza A H1N1 was found.

8.6 Research

8.6.3 *Health Study Caribbean Netherlands: HPV seroprevalence and risk factors in Caribbean Netherlands*

Incidence and mortality of human papillomavirus (HPV)-related cancers differs geographically, with high rates in Caribbean countries. Seroepidemiological data provide information on lifetime cumulative HPV exposure and contributing risk factors, but this has not been available yet for Caribbean Netherlands. By means of the Health Study Caribbean Netherlands, a cross-sectional population-based serosurveillance study conducted in 2017, we aimed to estimate the seroprevalence in this (recently girls-only HPV-vaccinated) population (n=1,823, 0-90 years), and to identify risk factors for seropositivity among persons unvaccinated aged ≥15 years who ever had sex (n = 1,080). Blood samples were tested for seven high-risk HPV-type-specific IgG-antibodies (HPV16, 18, 31, 33, 45, 52, 58) using a viral-like particles-based multiplex-immunoassay.

Our findings indicate that seropositivity was high among individuals aged ≥15 years (34% (95% confidence interval 30.8-37.3)), with over half of them being seropositive for ≥2 high-risk HPV types, and HPV16 and 52 being most prevalent (13%). Seroprevalence was substantial higher in women (51%) than men (18%), predominantly peaking in women aged 20-59 years, and was highest on St. Eustatius (38%) (Figure 8.4). In addition to age group 25-34 years and female sex, sexual risk factors were associated with HPV-seropositivity, such as a higher number of lifetime partners and a history of sexual transmitted infection(s). Taken together, in accordance with the Caribbean region, seroprevalence of multiple hr-HPV types was high in Caribbean Netherlands. These data corroborate the decision regarding introduction of a sex-neutral HPV-vaccination program and the relevance for considering a population-based cervical cancer screening program.

8.7 Literature

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9. Future NIP candidates

9.1 Hepatitis A

I.H.M. Friesema, A.W.M. Suijkerbuijk, W. Luytjes, H. Vennema

9.1.3 *Key points*

- In 2019, the number of reported hepatitis A cases (n=164) slightly decreased compared to 2018 (n=188). Two new strains caused outbreaks among men who have sex with men (MSM).
- The number of cases in 2019 remains higher compared to 2011-2016 (80-125 cases).
- About two-third of the cases is 20 years or older.
- Forty-one per cent of the Dutch cases were reported to be travel-related, with Morocco reported for almost half of these cases.

9.1.4 *Tables and figures*

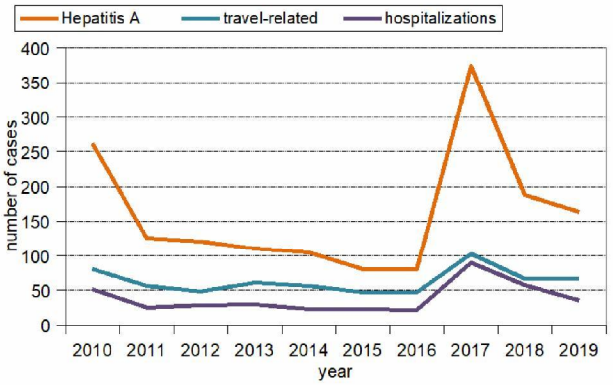

Figure 9.1.1 Number of reported, hospitalised and travel-related cases of hepatitis A, 2010-2019
Source: Osiris

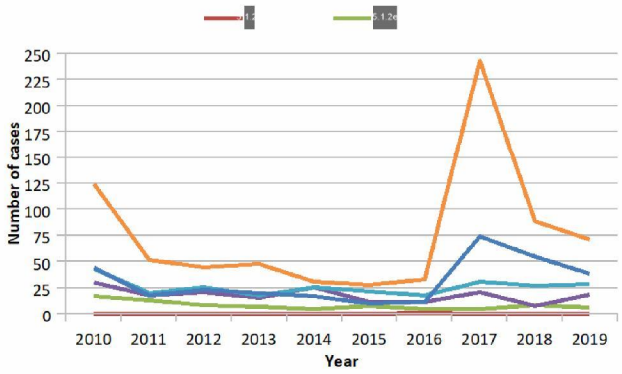

Figure 9.1.2 Age distribution of hepatitis A-cases, 2010-2019
Source: Osiris

9.1.5 *Epidemiology*

A large, international, hepatitis A outbreak occurred in 2017 with in the Netherlands 243 outbreak-related cases. Two-third of these cases were men who have sex with men (MSM) [1]. The outbreak lagged in 2018, both national as international [2]. In 2019, two new strains caused again outbreaks among mainly MSM with seven (five MSM) and 41 cases (22 MSM), respectively.
In 2019, 164 cases of hepatitis A were reported in the Netherlands, corresponding to 0.9 cases per 100,000 population. This is a small decline compared to 2018 (n-188), but it is still higher than in the years 2011-2016 where 80-125 cases were reported (Figure 9.1.1 / Appendix 2). No mortality due to hepatitis A was reported in 2019. The age distribution over the years 2009-2018 is given in Figure 9.1.2. Infections are mainly seen in the 20 to 49 years old. Adults (> 19 years) account for 67% of the cases. In total 35 patients were hospitalised (21%), which is on the low end of percentages hospitalizations seen in the previous years (2010-2018: 20-30%; mean: 24%).

The percentage of travel-related cases was between 28% (2017) and 59% (2015) in previous years (2010-2018; mean: 39%). In 2019, the proportion of travel-related cases was in between with 41% (Figure 9.1.1). Among travel-related cases Morocco (30/67; 45%) was reported most frequently; other countries were reported four times or less. Based on the notifications, 21 epidemiologically linked clusters could be deduced of which 14 clusters at least partly travel related (Morocco: 10 clusters). Ten of these epidemiologically linked clusters were molecularly confirmed. In the other clusters, for none or only one of the cases within the particular cluster a strain was available.

9.1.6 *Pathogen*

Hepatitis A virus (HAV) specific IgM-positive samples can be sent to IDS of the RIVM for typing as part of the molecular surveillance of this virus. In 2019, of 136 of 164 reported cases (83%) samples were submitted

for virus typing. 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.

Of the samples of cases 131 (96%) were positive by PCR and available for sequence analysis. A total of 294 serum and faecal samples of 274 unique persons were tested. HAV RNA was detected in 148 samples (50%) and 129, of reported cases, could be typed which resulted in 58 unique sequences; a total of 90 cases could be assigned to clusters of two or more cases. These concerned 20 molecular clusters varying between two and 41 cases. In 2019, there were no major foodborne hepatitis A clusters in the Netherlands. A single case probably belonged to a cluster in Germany, for which the vehicle was probably strawberries.
The three different strains that circulated in the MSM-outbreak in 2017, were not present in 2019. However, two new strains caused outbreaks among MSM. Early in the year, a IB strain, closely related to strains circulating in the US, caused 7 cases of which 5 among MSM. From the end of March to the end of July, a IA strain caused a total of 41 cases of which 23 were MSM. This strain was also reported in Ireland and Denmark and twice in England.
All clusters were contained by contact tracing and vaccination. At the end of the year a cluster was detected with three cases in 2019, which continued in 2020 with another 14 cases. Transmission occurred within households and a school.
Progress has been made towards whole genome sequence analysis for HAV. The biggest advantage is the increased resolution which makes it possible to examine transmission chains in outbreaks and which also reveals small differences between old and recent strains from the same origin.

9.1.7 *Research*

The international outbreak of hepatitis A in 2016-2018 and the smaller outbreaks in 2019 in the Netherlands show susceptibility to the virus in adults, and especially in MSM. An analysis is ongoing to determine whether vaccination of MSM could be cost-effective.

9.1.8 *International developments*

Bravo et al [3] reviewed the safety and immunogenicity of the Avaxim 80U Pediatric Hepatitis A vaccin. They included nine Sanofi Pasteur sponsored studies. Pooled analyses of these studies showed a consistent >95% of participants with concentrations ≥20 mIU/ml after the first dose and near 100% after the second dose (two cases of vaccin failure have been reported). The geometric mean concentrations (GMCs) after the second dose were around 30% lower among 12-15 year-olds compared to the 12-23 month-olds and 2-11 year-olds. Also three independent studies (included age group(s) within 12 months to 15 years) are described, in which 100% seroprotection was reported after the second dose. Anti-HAV antibody GMCs appear to increase quicker after the first dose when using Avaxim 80U Pediatric compared to other childhood HAV vaccines, which may be relevant when rapid immunization is required.

In Mendoza, Argentina, data of ten years of follow-up (2008-2018) after vaccination with Avaxim 80U Pediatric are completed [4]. Two groups are followed: 436 children with routine HAV vaccination with 1 dose and 108 children with 2 doses. Ten children (group 1: n=9; group 2: n=1) received a booster after having titres below the seroprotective treshold in the first seven years (none happening between seven and ten years of follow-up), and were excluded from analyses. At ten years of follow-up, 190 (group 1) and 51 (group 2) participants remained for analyses. Seroprotection (≥3 mIU/ml by electrochemiluminescence immunoassay (ECLIA)) was 100% in both groups at year 10. GMCs were 78 [95% CI: 69.8-87.6] mIU/ml in group 1 and 352 [271-456] mIU/ml in group 2. Modelling of the available data demonstrated seroprotection of 89% (1 dose) or 85% (2 doses) after 30 years with higher predicted GMCs after 2 doses (37 [13-97] mIU/ml) compared to 1 dose (19 [11-34] mIU/ml).

In South Korea, children aged 12 to 18 months received two doses of Avaxim (n=37), Epaxal (n=34) or Havrix (n=37) [5]. At four to six weeks after the second dose, seropositivity (≥20 mIU/ml) was 100% in all three groups. GMCs increased to 5836.9 [95% CI: 4188.0-8022.8], 1957.3 [1159.0-2908.2], and 2221.3 [1404.8-3410.7] mIU/ml, respectively. The differences in GMCs between Avaxim and the other two vaccines were significant.

Data of 11 years of post-immunization with the inactivated vaccines Healive and Havrix are reported by Wang et al. [6]. Three hunderd Chinese children were assigned to the Healive vaccine and 100 children to the Havrix group (control group), all aged between 1 and 8 years. Both vaccines were given twice, with six months between vaccinations. At the 11-year follow-up visit, 217 and 92 persons were present, respectively. The GMCs were significantly higher in the Healive group compared to the Havrix group at each time point from 1 to 138 months (n=10). At 138 months, the GMCs were 166.2 (Healive) and 117.1 (Havrix) mIU/ml and seroprotection rate was 100% in both groups. Modelling of the available data indicates that Healive will be efficacious for at least 30 years.

In November 2012, HAV vaccination was added to the routine vaccinations in Turkey. Within January 2008 and December 2015, a total of 272 children (<18 years) diagnosed with HAV infection at one of five hospitals in Ankara were enrolled [7]. Most children got infected before the start of the routine vaccination, 72 cases (31.7%) got ill after the introduction. Among the cases, only one child was vaccinated (0.4%), for 27 (9.9%) the immune status was unknown, the other 244 children were unvaccinated (89.7%).

Recruits of the army in South Korea receive a single-dose HAV vaccination since 2013 [8]. The effectiveness of this administration schedule was analysed. The total observation period between 1 January 2013 and 31 December 2016 was 603,550 and 1,020,450 person-years for the vaccinated and unvaccinated group, respectively. A total of 24 confirmed cases of hepatitis A occurred, of which three in the vaccinated group. Vaccine effectiveness was estimated to be 75.9% [95% CI: 19.0-92.8].

In a study of 131 HIV-positive, HAV-negative adults, 77 were vaccinated with HAV/HBV co-vaccine Twinrix (when also HBV-negative; 3 doses) and 54 with an HAV mono-vaccine (2 doses) [9]. A total of 81.5% in the mono-vaccine group and 79.2% in the Twinrix group developed anti-HAV antibodies. Vaccine response depended on absolute CD4 cell count and CD4/CD8 ratio in the mono-vaccine group, and only on age and sex in the Twinrix group. Patients whose titers were checked after more than 5 years were less often seropositive (66.6%; 20/30) than those checked within a year of vaccination (88.9%; 40/45). These results suggest a lower response to hepatitis A vaccination and a possible quicker decline in titers than in immune-responsive adults.

During July 1, 2016–February 7, 2020, US' state health departments publicly reported >31,000 outbreak-associated cases, primarily affecting persons who use drugs and persons experiencing homelessness. More than 18,900 (61%) outbreak-associated patients have reportedly been hospitalized in these outbreaks. Hofmeier et al. estimated the average direct medical costs per hepatitis A–related hospitalization, which can be used to guide investment in outbreak prevention efforts [10]. Overall, the average costs per hepatitis A–related hospitalization in the United States in 2017 were $16,232 (95% CI $15,052–$17,411). Despite longstanding vaccination recommendations for adults at increased risk for hepatitis A virus infection or adverse consequences of infection, self-reported adult hepatitis A vaccination coverage with >2 doses was only 10.9% for persons >19 years of age in 2017. These findings underscore the importance of improving hepatitis A vaccination coverage among at-risk adults.

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*RIVM publication.

9.2 Respiratory Syncytial Virus

A.C. Teirlinck, [redacted] 5.1.2e, W. van der Hoek, P.B. van Kasteren, N.A.T. van der Maas

9.2.3 Key points

- A total of 95 RS-viruses (6,4%) were detected in 1493 combined nose swabs and throat swabs of patients with an acute respiratory infection (ARI), collected by sentinel GPs in the 2019/2020 respiratory season, compared with 12% in 2018/2019, 6% in 2017/2018 and 12% in 2016/2017.
- Due to the Covid-19 pandemic, more samples were collected with different age distribution than previous seasons in weeks 10-20, possibly partly explaining the relatively low RSV percentage.

9.2.4 Tables and figures

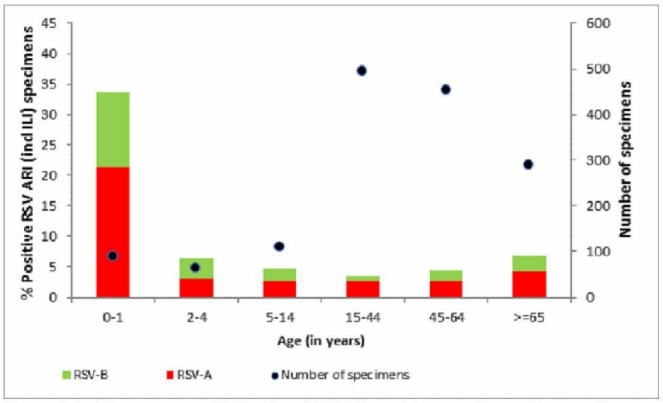

Figure 9.2.1 Percentage of RSV-A and RSV-B positive specimens from patients with acute respiratory infections (ARI), and the number of tested specimens, taken by sentinel general practitioners (GPs) from community patients during the respiratory season of 2019/2020 (week 40 of 2019 - week 20 of 2020), displayed for six age groups. (Source: NIVEL Primary Care Database, RIVM).
Please note that the ARI syndrome also include influenza-like illness (ILI). ILI patients were oversampled because of de setup of the influenza sentinel surveillance.

9.2.5 Epidemiology and pathogen

Studies show that RSV is a common cause for respiratory infections in young children [1] and in the elderly [2, 3] causing outbreaks in elderly care facilities (Meijer, Overduin et al. 2013). RSV is subdivided in RSV-A and RSV-B, mainly based on the variation in the attachment protein, the G-protein.

The current Dutch RSV surveillance is primarily based 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 tested for influenza virus, RSV, rhinovirus and enterovirus.

In the season 2019/2020, 95 RS-viruses were detected in 1493 nose swabs and throat swabs (6.4%) collected from patients with an acute respiratory infection (ARI) by sentinel GPs. The percentage of positive specimens from the GP sentinel surveillance was lower in this season compared to the previous seasons 2018/2019 (12%) and 2016/2017 (12%) and similar to 2017/2018 (6%). This current season, more samples were collected with different age distribution than previous seasons in weeks 10-20, due to the COVID-19 pandemic, possibly partly explaining the relatively low RSV percentage.
Of the 95 specimens (two patients had a double infection with RSV-A and RSV-B), 61 were RSV-A (64%) and 34 were RSV-B (36%).
The percentage of positive samples was highest in the 0-1 year-olds (34%) and lowest in the 15-44 years-olds (3.4%) (Figure 9.2.1).
See for more information on epidemiology in the Netherlands the annual report 'Surveillance of influenza and other respiratory infections in the Netherlands: winter 2019/2020' that is expected in December 2020.

9.2.6 *Research*

European collaboration on surveillance of RSV and better harmonization in both epidemiological and virological aspects of surveillance is important to strengthen surveillance of RSV at national and European level. RIVM plays an important role in European initiatives on RSV surveillance and works closely together with ECDC and other public health institutes, specifically SSI (Denmark). As a result of this European initiative, an online survey was held in August and September 2017 among EU/EEA countries (n=31) [4]. The questionnaire covered questions on epidemiological and laboratory aspects of RSV surveillance. Eighteen countries reported to have a sentinel surveillance system, 26 countries a non-sentinel surveillance system and three countries to have neither. RSV data collection was mostly done within the context of influenza surveillance. A wide range of diagnostic and characterisation assays was used for the detection of RSV. The prevailing integration of RSV surveillance into the existing influenza sentinel surveillance system may lead to under-reporting of RSV. In the light of a future vaccination programme targeting RSV, the surveillance should be strengthened.

Also, RIVM is partner in the RESCEU project ([http://resc-eu.org/], funded by the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement 116019, receiving support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations). This project aims to explore the clinical, economic and social burden from RSV and strengthen European collaboration by the many different disciplines working on RSV. The aim is to create a sound epidemiological and virological baseline, before the introduction of a vaccine, to identify appropriate target groups for vaccination. As part of the RESCEU project, RIVM therefore combines data from several sources, such as hospitals, general practitioners and the national perinatal registry, to get a better insight in the burden of RSV in the Netherlands [5, 6].

Within this project, a high throughput multiplex immunoassay, measuring antibody levels against 4 RSV proteins simultaneously, is

developed [7]. Using this multiplex, the seroprevalence of RSV in a sample of the Dutch population was measured [8]. Results show that maternal IgG concentrations decline up to 10-12 months of age. After the first year of life, approximately 40% of the children lack infection-induced IgA antibodies and may therefore be uninfected. All Dutch children show serological evidence of RSV infection by the age of 3 years. Antibody concentrations reach a plateau by 5-9 years of age that remains constant throughout life. COPD patients have similar levels and avidity of RSV-specific IgG antibodies compared with age-matched healthy controls.

In addition to epidemiological data, a thorough understanding of the immunological mechanisms underlying (protection from) severe RSV disease is essential for advising on the implementation of novel vaccines. We have recently shown that activation of certain immune cells by (maternal) antibodies is decreased in children with severe RSV disease compared to controls [9]. Furthermore, we showed that activation of these cells correlates with the glycosylation status of the RSV-specific antibodies. These findings highlight that the protective efficacy of RSV-specific antibodies may not depend on neutralization alone.

9.2.7 *International developments*

Currently, a phase 2B clinical trial of a subunit RSV vaccine targeting pregnant women is ongoing [10]. The same vaccine will be administered in a phase 3 clinical trial, that will start in the summer of 2020. Several hospitals in the Netherlands will participate in this study. Several other RSV vaccines and monoclonals are in various stages of (clinical) development [https://path.azureedge.net/media/documents/RSV-snapshot-2020_03_26_High_Resolution_PDF.pdf]. Currently, Covid-19 vaccines using several vaccine platforms are developed. The knowhow that is gained through these developments can be used in the development of RSV vaccines.

9.2.8 *Literature*

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*RIVM publication.

9.3 Rotavirus

M. Middeldorp, I.K. Veldhuijzen, H. Vennema, A.W.M. Suijkerbuijk, M. Hooiveld, R. Pijnacker, P. Bruijning-Verhagen, H.E. de Melker.

9.3.3 *Key points*

- The number of rotavirus detections in 2019 was slightly lower than in 2018. In 2020, until May, fewer rotavirus detections have been reported compared to the same period in 2019. A marked reduction in the number of rotavirus detections have been observed per March 2020.
- G9P8 and G3P8 were the most prevalent genotypes in 2019.
- The Ministry of Health, Welfare and Sport has decided to delay the implementation of rotavirus vaccination in the National Immunization Program. In the RIVAR study lower vaccine-effectiveness estimates were unexpectedly found for high risk infants. The Ministry requested a new advice from the Health Council.

9.3.4 *Tables and figures*

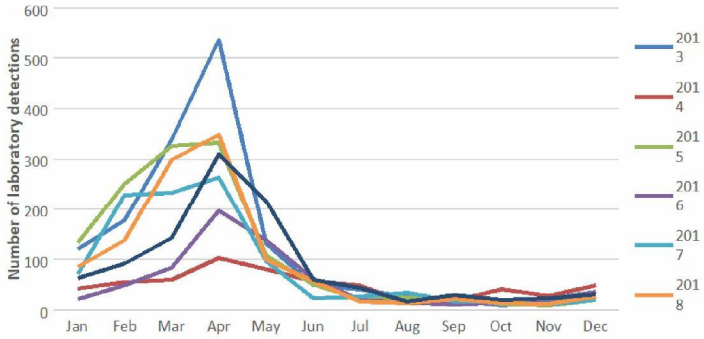

Figure 9.3.1 Number of reported laboratory rotavirus detections per month in the Netherlands, 2013-2019

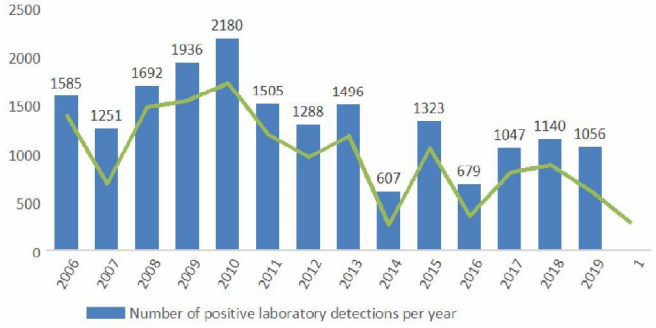

Figure 9.3.2 Number of reported laboratory rotavirus detections per year and between January and May in the Netherlands, 2006-2020

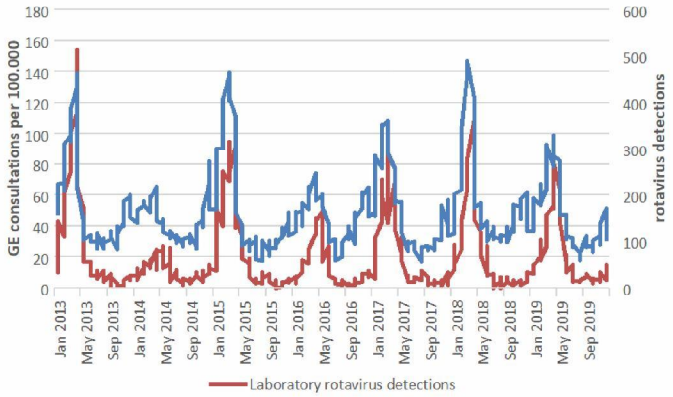

Figure 9.3.3 Overall number of rotavirus laboratory detections and general practice all-cause gastroenteritis consultation in children under 5 years old per week, the Netherlands, 2013-2019

Table 9.3.1 Number of rotavirus samples typed per year and identified genotypes, the Netherlands, 2013-2019

Type	2013	2014	2015	2016	2017	2018	2019	Total
G12P8	1	6	2	0	1	2	1	13
G1P8	**83**	20	25	9	23	7	12	179
G2P4	41	29	34	12	12	6	13	147
G3P8	51	7	14	23	**38**	56	**40**	229
G4P8	35	12	**137**	3	23	3	0	213
G9P8	23	**49**	32	**59**	20	**60**	38	281
G9P4	1	0	1	0	8	29	24	63
Other	52	16	27	12	42	16	17	182
Total	287	139	272	118	167	179	145	1307

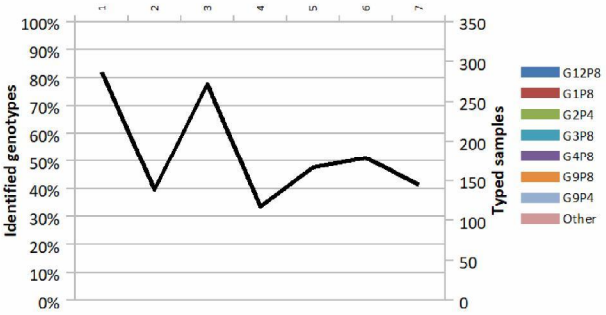

Figure 9.3.4 Absolute number of rotavirus samples genotyped per year and the proportions of identified genotypes, the Netherlands, 2013-2019

9.3.5 *Epidemiology*

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

9.3.5.1 Weekly virology report

In 2019, 1,056 rotavirus cases were notified, slightly less than in 2018 (n=1,140) (Figure 9.3.2). Most rotavirus laboratory detections were reported between February and May (72%), with a peak in the last week of April (81 rotavirus laboratory detections) (Figure 9.3.1). Data from 2020 up to May show almost half of the rotavirus cases compared to the same period in 2019 (2019 n=610; 2020 n=284) (Figure 9.3.2). The difference in number of rotavirus detections is mainly due to a sharp decrease in April 2020 (2020 n=13; 2019 n= 311). This decline in Rotavirus detections is likely mainly due to the preventative measures taking during the COVID-19 pandemic such as the closure of schools and increased hand washing [1].

The remarkably low seasons in 2014 (n=607 detections) and 2016 (n=679 detections) led to the hypothesis of a shift in the rotavirus seasonal pattern to a biennial pattern. However, the rotavirus seasons in 2017, 2018 and 2019 contradict this hypothesis (Figure 9.3.2).

9.3.5.2 Nivel

The Nivel Primary Care Database provided data on all-cause gastroenteritis (GE) in children under the age of 5 years consulting the general practitioner [2].

In 2019, 8,102 all-cause GE consultations were reported per 100,000 children younger than five years of age (on average 164 per 100,000 per week) (Figure 9.3.3). This were less consultations compared to 2018 (n=9,838 per 100,000). Consultations in 2019 were more frequent between January and mid-July with a peak in mid-April (330 per 100,000 children per week). In this period of the year, 5580

consultations per 100,000 children were registered, which is less than the number of consultations registered in the same period in 2018 (n=6,430 per 100,000).

9.3.6 *Pathogen*

The IDS/RIVM receives faecal samples throughout the year from the Working Group Clinical Virology laboratories for rotavirus genotyping. The results are given per calendar year and are shown in Table 9.3.1. and Figure 9.3.4.

In 2019, 145 of 166 the received samples (87%) could be typed (Table 9.3.1). Almost half of the typed samples (62/145) were identified as rotavirus G9, which comprises the genotypes G9P8 and G9P4. The most prevalent genotypes were G9P8 and G3P8, which accounted for, respectively, 26% (38/145) and 28% (40/145) of the typed samples (Figure 9.3.4).

Since the COVID-19 control measures were implemented around mid-March 2020, only 1 sample have been received up to May. From January to mid-March, 36 samples have been received, of which 5 were not typable, and about half of the samples were identified as rotavirus G9.

9.3.7 *Research*

9.3.7.1 RIVAR study

Between May 2016 and November 2017 the RIVAR study (Risk-Group Infant Vaccination Against Rotavirus) offered rotavirus vaccination to high-risk infants (i.e. infants with severe congenital pathology, prematurity and/or low birth weight) born in one of the thirteen participating Dutch hospitals. This project was a pilot study on the feasibility and effectiveness of rotavirus vaccination in high-risk infants. Of the infants eligible for rotavirus vaccination, 49% (726/1482) were vaccinated. Survival probabilities for severe rotavirus AGE for vaccinated and unvaccinated infants between 2 and 18 months of age did not differ between the groups [3]. Vaccine effectiveness for severe rotavirus AGE in the high-risk infants was lower than expected, namely 30% (95% confidence interval, -40%–65%) compared with previously reported 68% to 98% in healthy infants [4]. The RIVAR study showed no reduction in all-cause severe AGE between vaccinated and unvaccinated high-risk infants.

9.3.8 *Cost-effectiveness*

Kotsopoulis et al. assessed the financial consequences of rotavirus vaccination for families, employers and authorities in the Netherlands [5]. A Social Accounting Matrix (SAM) framework has been developed reflecting the distribution of income and spending at equilibrium affected by rotavirus disease among all those concerned for 1 year. The total financial cost difference at equilibrium between presence and absence of rotavirus vaccination was +€26.758 million over one year as a net economic surplus. The payment of vaccination (€19.194 million) by the government was offset by the increase in tax revenue (€14.561 million) and by the lower spending in treatment care (€7.998 million). The manufacturers pay corporate taxes on the profitability of their goods sold. Moreover, vaccination prevents parents being absent from work which is associated with increased productivity, higher wages, more

spending, increased tax revenue, and reduced healthcare costs. This study was funded by GSK.

9.3.9 *(Inter)national developments*

In April 2020, the Ministry of Health, Welfare and Sport decided to delay the implementation of the rotavirus vaccination in the National Immunization Program due the unexpected lower estimates of vaccine-effectiveness found in the RIVAR study for high risk infants [6]. The Ministry will again submit a new request for advice to the Health Council on rotavirus vaccination.

As of April 2020, worldwide, 107 countries have introduced rotavirus vaccination in their national immunisation programmes. In addition, four countries have either phased or sub-national introductions. Of the ten countries with the highest numbers of rotavirus-related deaths, seven countries introduced rotavirus vaccination (Afghanistan, Angola, Ethiopia, India, Kenya, Niger, and Pakistan) [7]. Four World Health Organization (WHO) prequalified rotavirus vaccines are available, namely ROTASILL, ROTAVAC, Rotarix, and RotaTeq [8]. Only Rotarix and RotaTeq are licensed for use in Europe [10].

A systematic literature review on the global impact of rotavirus vaccination on diarrhoea hospitalizations and deaths among children <5 years old analysed published data from 2006-2019 with at least 12 months of data before and after rotavirus vaccine introduction [10]. The review shows a median reduction in rotavirus hospitalizations between 46-74%, AGE hospitalisations between 23-47%, and AGE mortality between 28-46%. The reductions were larger in countries with low child mortality, among younger age groups, and in countries with higher rotavirus vaccination coverage.

9.3.10 *Literature*

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9.4 Varicella zoster virus (VZV) infection

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9.4.3 Key points

- The VZV epidemiology (incidence of GP consultations, hospitalisations and deaths) in the Netherlands has not changed in recent years and is comparable to that in previous years; in 2018 GPs recorded about 45,000 varicella and 93,000 herpes zoster episodes (260 and 540 episodes per 100,000 population respectively).
- In 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella in the NIP in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination against VZV.
- In July 2020, the revised Dutch guideline 'Varicella' has been published. It includes revised opinions on post-exposure prophylaxis (PEP) and a new module on varicella treatment.

9.4.4 Tables and figures

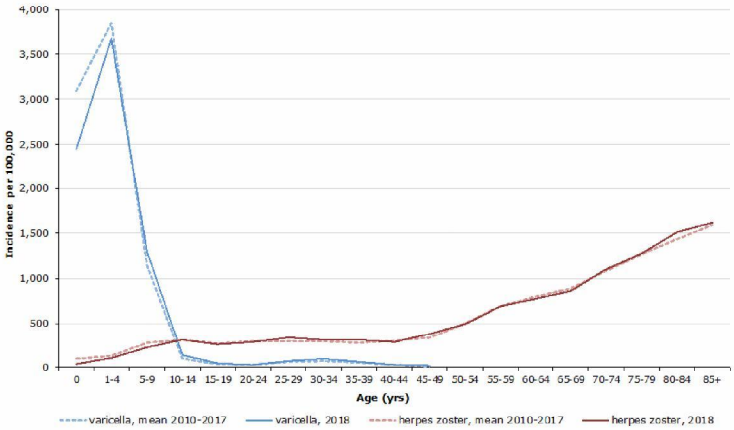

Figure 9.5.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70) in 2018 versus mean 2010–2017 by age group [1]

Note: Varicella cases in people over 49 years of age are only sporadically reported by GPs and therefore not included.

Source: NIVEL

Table 9.5.1 Estimated incidence per 100,000 population of episodes of varicella (ICPC-code A72) and herpes zoster (ICPC-code S70), based on NIVEL-PCD, using the old (2008–2011) and new method (2010–2018) (rounded off to closest ten)

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

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

Table 9.5.2 Incidence per 100,000 population of hospitalisations due to main diagnosis of varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02), 2008–2018 [4]

Syndrome	2008	2009	2010	2011	2012	2013	2014	2015*	2016*	2017*	2018*
Varicella	1.7	1.5	1.9	1.7	1.5	1.7	1.9	1.9	2.1	2.0	1.8
Herpes zoster	2.0	2.4	2.1	2.2	2.1	2.1	2.7	3.0	2.9	2.9	3.2

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

Table 9.5.3 Absolute number of deaths with varicella (ICD-10 code B01) and herpes zoster (ICD-10 code B02) as primary cause of death, 2008–2019 [5]

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

* Preliminary data
Source: CBS

9.4.5 *Epidemiology*

The VZV epidemiology in the Netherlands is comparable to that in previous years (Tables 9.5.1, 9.5.2 and 9.5.3). In 2018, general practitioners (GP) recorded about 45,000 varicella and 93,000 herpes zoster (HZ) episodes (260 and 540 episodes per 100,000 population respectively). The incidence of GP consultations due to varicella episodes per 100,000 population is highest in children aged under five, whereas the incidence of GP consultations due to HZ episodes is highest in those aged over 50 (Figure 9.5.1). According to a new, more precise method for estimating morbidity rates used by NIVEL from 2012 onwards [6],

the incidence of HZ is higher than it was according to the old method (Table 9.5.1). Mahamud et al. found that national death certificate data tend to overestimate the number of deaths in which HZ is the underlying or contributing cause of death [7]. If we apply their rate of deaths for which HZ was validated as the underlying cause of death (0.25 (range 0.10–0.38) per 1 million population) to the Dutch population in 2019, we would expect 4.3 deaths (range 1.7–6.6 instead of the 32 deaths reported preliminary in 2019 (Table 9.5.3).

9.4.6 *Research*

Recently, results of the sero-epidemiological study to obtain insight into VZV susceptibility and its determinants in island populations of the Caribbean Netherlands have been published. Overall VZV seroprevalence in the Caribbean Netherlands was 78%, being lowest on St. Eustatius (73%) and highest on Bonaire and Saba (79%) [8]. This was considerably lower than in the Netherlands (96% based on preliminary results of the Pienter 3 study (2016/2017) and 95% based on the Pienter 2 study (2006/2007) [9]).

Because of the lower VZV seroprevalence in the Caribbean Netherlands, the disease burden of varicella is higher than in the European Netherlands. Therefore, in 2020, the Health Council of the Netherlands issued a positive recommendation to add vaccination against varicella to the NIP (by replacing MMR with MMRV vaccine) in the Caribbean Netherlands and not in the European Netherlands. The council also recommends that residents of these islands who have not yet had an infection be offered a one-off vaccination with a monovalent varicella vaccine. For residents over 50 years old, the council recommends using a herpes zoster vaccine.To support the advice of the council, the RIVM has gathered background information on vaccination against varicella. This overview provides, among other things, information on the number of people in the Netherlands who fall ill each year, the efficacy and safety of vaccines, and the public's opinion on varicella vaccination [10].

In July 2020, the revised Dutch guideline 'Varicella' has been publised (https://richtlijnendatabase.nl/nieuws/richtlijn_varicella_herzien.html). This is a guideline for all professions involved in the care of varicella patients (medical specialists, GPs, nurses, midwives or other health care providers) and patients who are dealing with persons with varicella or who have been exposed to varicella. In particular, the opinions on post-exposure prophylaxis (PEP) have been revised in the guideline, and a new module on varicella treatment has been included [11].

9.4.7 *International developments*

9.4.7.1 Varicella

A study in England, showed an increasing trend over time between 2004 and 2017 in the incidence of varicella hospitalisation and the proportion of admissions with complicated varicella. The reason is unclear but it may be related to improvements in coding over time or a shift in health care utilisation from primary to secondary care [12]. In Germany, where universal varicella vaccination was introduced in 2004, the incidence of varicella-related complications based on hospital data decreased by 77% from 2005 to 2011. The strongest reductions were seen in children <5 years of age (90%) and for varicella-related complications of the

respiratory tract (upper 97%; lower 90%) [13]. In Lu'an, China, with a one-dose voluntary vaccination programme (payment by parents), an increase in reported varicella cases was seen in all age groups including an age shift from 5–9 years to 10–14 years at a moderate overall vaccination coverage of 71.7% (95%CI: 68.5–73.4%) [14]. A population-based study in the United States showed that the HZ incidence rate among children who were vaccinated against varicella (38 per 100,000 person-years) was 78% lower than that among unvaccinated children (170 per 100,000 person-years). Furthermore, the overall incidence of paediatric HZ declined by 72% from 2003 through 2014 [15]. A small study among women of childbearing age showed that natural varicella infection induced higher VZV-specific T cell immune responses than varicella vaccination. Therefore, vaccinated women may be at increased risk of breakthrough varicella but larger studies are needed to confirm this [16].

9.4.7.2 Herpes zoster

A Japanese study using a VZV skin test to measure cell-mediated immunity (CMI) and a serological essay to measure VZV-specific antibodies confirmed that CMI plays an important role in preventing development of HZ, whereas humoral immunity does not [17]. A small study measuring saliva VZV DNA persistence suggested that an initial low VZV CMI response and persistence of VZV DNA in saliva may be associated with the development of postherpetic neuralgia (PHN), even after adjustment for age [18]. Whereas previous studies have varying conclusions on whether HZ is seasonal, results of a large insurance claims database study suggested that the incidence of HZ exhibits an annual trend with a peak in the summer [19]. Forbes et al. conducted a self-controlled case series study using UK electronic healthcare data to explore the exogenous boosting hypothesis. Their study suggested that exogenous boosting provides some protection from the risk of HZ, but not complete immunity. In the two years after household exposure to a child with varicella, adults were 33% less likely to develop HZ compared with baseline time. In the 10–20 years after exposure this was 27% [20]. This may have consequences for cost-effectiveness analyses of childhood varicella vaccination that include effects on the occurrence of HZ.

In Australia, the cumulative uptake in the target population two years after implementation of a national HZ programme with the attenuated zoster vaccine live (ZVL, Zostavax®) for 70–79 years old was estimated at 47% [21]. In the two years since programme launch, HZ antiviral prescription rates decreased in this age group, by an average of 13.6% (95%CI: 1.5–24.2%) per year [22]. Based on data on GP consultations and hospitalisations for HZ and PHN, Andrews et al. showed evidence of sustained population impact of the HZ vaccination programme (with ZVL) 5 years following its implementation in England. Vaccine efficacy was estimated to be approximately 50% to 60% which suggests that the protection from the vaccine does not wane as rapidly in clinical practice compared with the trial settings [23]. The uptake of ZVL in the United States was estimated at 5.7% in adults aged 50–59 years (approved for use but not recommended) and 34.9% in adults aged ≥60 years (recommended in 2006) in 2017 [24]. In a retrospective population-based study conducted with health care registry data from Stockholm

County (Sweden), the overall vaccine effectiveness of ZVL was 34% (hazard ratio (HR) = 0.66; 95%CI: 0.55–0.78) in vaccinated persons. The VE stratified by age was: 50–60 years of age 47% (HR = 0.53; 95%CI: 0.21–1.30), 61–75 years of age 43% (HR = 0.57; 95%CI: 0.44–0.73), and in persons above 75 years 7% (HR = 0.93; 95%CI: 0.68–1.26) [25]. Klein et al. found an overall vaccine effectiveness of ZVL of 64.8% (95%CI: 61.3–68.0%) against PHN. The effectiveness was 82.8% (95%CI: 77.6–86.7%) during the first year after vaccination and waned to 48.7% (95%CI: 30.2–62.3%) during the eighth year after vaccination [26]. Weinberg et al. showed that the lower vaccine immunogenicity of ZVL in older adults is influenced by baseline regulatory T cells (Treg and Tcheck) and VZV-specific T cell immunity. They suggested that immune modulators that block regulatory T cell activity may increase vaccine responses in older adults [27].

Post-hoc analyses of two efficacy studies (ZOE-50 and ZOE-70) of the adjuvanted recombinant zoster vaccine (RZV, Shingrix®) suggested that the number and type of medical conditions at enrollment did not impact the efficacy and safety of RZV [28]. Furthermore, RZV appeared to be effective irrespective of sex, region, or geographic ancestry/ethnicity [29]. Dagnew et al. showed that 2 doses of RZV induced strong humoral and polyfunctional CMI responses in adults ≥65 years, irrespective of previous ZVL vaccination [30]. Hastie et al. showed that immune responses to two initial RZV doses in older adults persisted through 10 years after vaccination and are predicted to persist ≥20 years after vaccination. One additional RZV dose after the initial 2-dose course elicited strong immune responses with no further increase after a second additional dose [31].

A study in the United Kingdom showed that being proactively offered the vaccine by a GP or nurse, perceiving to be at risk of developing HZ and perceived self-efficacy were associated with HZ vaccine uptake [32]. In the United States, where HZ vaccination is recommended since 2008, three surveys among primary care physicians were conducted in 2005, 2008 and 2016. Ten years after licensure of ZVL, physicians were more likely to respond that they perceived HZ as a serious disease and more strongly recommended ZVL. Furthermore, they were less likely to report several major barriers to HZ vaccination [33].

9.4.7.3 Cost-effectiveness

McGirr et al evaluated the cost effectiveness of RZV compared to no vaccination and to ZVL in Canadians aged 60 years and older [34]. Compared with no vaccination the incremental cost-effectiveness ratio (ICER) of RZV was $28,360 (Canadian dollars) per quality-adjusted life-year (QALY) in persons aged ≥60 years, avoiding 554,504 HZ and 166,196 PHN cases. Compared with ZVL, RZV accrued more QALYs through the remaining lifetime and an increase in costs of approximately $50 million resulting in an average ICER of $2396. This analysis suggested that RZV would be cost effective in the Canadian population compared with no vaccination and vaccination with ZVL at a willingness-to-pay threshold of $50,000. This study was funded by GSK. These results are in line with another, unsponsored, study performed in Canada in which the effectiveness and cost-effectiveness of these two vaccines were compared [35]. The number needed to vaccinate (NNV)

was higher for ZVL than for RZV. For example, in persons 65 years old, for HZ, median NNV was 21 (90% uncertainty interval [UI]: 13–31) versus 8 (90%UI: 6–18), and for PHN, NNV was 64 (90%UI: 33–93) versus 31 (90%UI: 23–73). The authors conclude that RZV is likely cost-effective in Canada for adults 60 years or older, and is likely more cost-effective than ZVL.
Carpenter et al. evaluated the cost-effectiveness of these two vaccinations for the United States [36]. For individuals vaccinated at age 50 years, the ICER for ZVL versus no vaccination was $118 535 per QALY at age 60 years, the ICER dropped to $42 712/QALY. The RZV was more expensive but had better ICERs than ZVL. At age 50, the ICER was $91 156/QALY, and it dropped to $19 300/QALY at age 60. Vaccination with RZV was more cost-effective than ZVL in all age groups studied. Following US threshold for cost-effectiveness, vaccination with RZV at age 50 years appears cost-effective.
In a Japanese cost-effectiveness analysis, the RZV proved to be more effective but also more costly [37]. Therefore, the optimal strategy in Japan depends on the willingness-to-pay threshold.

9.4.8 *Literature*

9.4.8.1 References

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(VVL) against herpes zoster and post-herpetic neuralgia among adults aged 65 and over in Japan. Vaccine. 2019;37(27):3588-97.

* RIVM publication

9.1.3.2 Other recent RIVM publications

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10. Vaccines in development for other potential future NIP target diseases

N.Y. Rots

An update of information with regard to vaccines in development, for infectious diseases, that have reached the clinical testing phase and are relevant for the Netherlands is given in the table below. Vaccine development takes 10-20 years, only a small percentage (6%) of vaccines tested in phase I reach marketing authorisation. On average, clinical development phase I takes 1-2 years, phase II 2-3 years, and phase III 4-6 years.
Relevant developments of combination vaccines are described in earlier chapters.
This year the Corona virus SARS-CoV-2 vaccines in development have been added in a separate table. More than 160 vaccines are being developed. Also for these COVID-19 vaccines only the vaccines that are currently (July 2020) being tested in humans have been included in the overview.

10.1 Bacteria

Pathogen	Vaccine	Status, clinical phase
Chlamydia	Adjuvanted chlamydia vaccine CTH522 (SSI/imperial college Londen)	I completed, Safe humoral and cellular immune response
Clostridium difficile	Toxoid inactivated	FDA fast track (Sanofi Pasteur ended its programme, Pfizer Phase III trial ongoing)
	Recombinant toxoid VLA84, genetic fusion (Valneva)	II completed, phase III waiting for partner
	Recombinant protein adjuvant (GSK)	I
Helicobacter pylori	HP3 (Chiron/Novartis)	I/II, completed, limited protective immunity, not pursued
	Oral recombinant vaccine (China)	III, discontinued
Lyme	Outer surface protein based vaccine (GSK)	Licensed but removed from market in 2002 due to poor market performance
	Subunit vaccine VLA15 (Valneva)/**Pfizer** since 2020	II (fast track FDA)
Meningococcal ABCWY	MenABCWY recombinant conjugated Novartis/GSK,	II adolescents booster dose study completed
		I

	Pfizer	
Moraxella catarrhalis, non-typeable Haemophilus influenza COPD	Recombinant COPD reduction with adjuvant (GSK)	II
Shigella	-Live attenuated single-strain, -Inactivated trivalent whole cell,	I completed II
	-Chemical glycoconjugate -Rrecombinant glycoconjugate (biconjugate) - Conjugate outer membrane (Novartis/GSK)	I III II
Staphylococcus aureus	Conjugate (SA4Ag, 4 antigen), fast track FDA (Pfizer) Protein	II Previous phase I-III with different single antigen vaccine candidates all failed, safety concerns and low efficacy I
Streptococcus group A & B	-Group A: N-terminal M protein-based multivalent vaccines (26-valent and 30-valent) Conserved M protein vaccines (the J8 vaccine and the StreptInCor vaccine) C-terminal M-protein DTconjugate, AlOH adj. -Group B: CPS-protein conjugate (mono and trivalent) (GSK) 6-valent polysaccharide CRM197 conjugated vaccine (Pfizer) Recombinant fusion antigen Minervax APS	II I I II maternal II maternal I
Tuberculosis (all forms all ages)	-Live attenuated vaccine BCG -2, 3 or 4 antigen adjuvanted fusion protein (GSK/Areas, Areas)	On market but low efficacy II(b)

	- Subunit adj recombinant fusion protein (Areas/Sanofi/SSI)	II completed
	-Modified recombinant BCG	II
	-Recombinant subunit (GSK, Sanofi)	II
	- Live attenuated (MTBVAC)	IIb start 2018
	- Lysate of NTM	III
	- Killed whole cell (booster) (Areas)	I
	- Viral vector (Oxford)	I

10.2 SARS-CoV-2 vaccines

Vaccine type	Company	Status
Inactivated whole virus	Wuhan Institute/Sinopharma (China) Beijing institute/Sinopharma (China) Sinovac (China) Institute Medical Biology (China)	 II III I/II
Live attenuated virus		Pre-clinical
Non-replicating Viral vector	University Oxford/AstraZeneca CanSino Beijing Institute Biotech Janssen Pharmaceutical	III III, used in military I/II start 22 July 2020
Protein (sub-unit)	Novavax Clover Biopharm (China) University Queensland (Australie)	I/II I/II I/II
RNA	Moderna (LNP encapsulated mRNA) BioNTech/Fosun/Pfizer (LNP mRNA) Imperial College London Curevac (Duitsland)	III start July 2020 I/II, III summer 2020 I/II I/II
DNA	Inovio/IVI (DNA plasmid electroporation) Cadila Healthcare Limited Genexine consortium Osaka University/Takara bio (with adjuvant)	I/II I/II I/II I

10.3 Viruses

Pathogen	Vaccine	status
Chikungunya	Live recombinant Measles Virus based Virus-like particle (NIAID) Live attenuated (Valneva)	II, Immunogenic and safe in adults I FDA fast track
Cytomegalo (CMV)	-Glycoprotein B bivalent -DNA (Astellas/ Vical) -Replication defective V160 (MSD)	I and III III failed CMV+ stem cell transplant patients II

	-Stem cell transplant patients (Merck)	Approved US 2017
Dengue	-Live recombinant (tetravalent) (Butantan/NIAID)	III
	-Live-attenuated (tetravalent) TDV (Takeda)	III
	-Inactivated (tetravalent)V180(Merck)	I
	-Recombinant subunit (tetravalent) (GSK)	I/II
	-Monovalent subunit DNA	Dengvaxia Sanofi registration approved for 9-45 years of age
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 and Bavarian Nordic)	I
	-Recombinant nanoparticle based (Novavax)	III
	-Recombinant viral vector (GSK)	II
	-VRC-EBOADC069-00-VP (Okairos, NIAID)	I
Epstein–Barr	Recombinant gp350 Glycoprotein subunit	II
	Live attenuated vaccines	On hold
Hepatitis C	Recombinant, heterologous viral vector (GSK)	II
Hepatitis E	Recombinant protein	IV, (Hecolin®, Xiamen China Approved in China not registered in EU)
Herpes simplex	-HSV-529 replication defective live attenuated (Sanofi)	I
Herpes zoster (Shingles)	Recombinant (Shingrix, GSK)	Approved US and EU
	Inactivated V212 (Merck)	III, on hold
HIV	Recombinant protein (GSK)	II
	Viral vector Prime/boost (Sanofi)	II
	Ad26 Mos HIV vaccine (Janssen vaccines)	III
	DNA (GeoVax)	II completed
Hookworm	iBio	I
Noro	Virus-like particles (bi-valent) (Takeda)	II
	Oral tablet vaccine (Vaxart)	I

MERS-CoV	MVA-MERS-S DNA (GeneOne Life Scinence/Inovio)	II
Parainfluenza type I	Live attenuated	I-II
Pneumococcocus	(killed) whole cell vaccine Protein-based vaccines (GSK, Sanofi)	II I, II
Respiratory syncytial (RSV) (17 in clinical development)	Live attenuated (Sanofi/NIH) Live attenuated (intravacc) Inactivated whole cell Nanoparticle based (Novavax) Subunit, F-protein (GSK) Subunit, F-protein (NIH/NIAID/VRC) Subunit, F-protein (Pfizer) Subunit, F-protein (Janssen) Subunit, F-protein (Merck) Gene-based vector MVA (Bavarian Nordic Gene-based vector AV (Janssen) Gene-based vector AV (Vaxart) Gene-based vector AV (GSK)	I (paediatric) I (paediatric) 0 III (maternal data 2021) FDA fast track, II (elderly, failed), II maternal stopped I (paediatric) II maternal I (maternal, elderly) II elderly, maternal I (elderly) II II (elderly) II (elderly, paediatric) I (paediatric) II (paediatric) I/II (maternal, elderly)
Typhoid	TT-Conjugate (Bharat Biotech)	III published
West Nile	Inactivated (NIAID) Live attenuated Recombinant subunit (NIAID Hawai Biotech)	I completed I completed
Zika	DNA (GeneOne Life Scinence/Inovio, NIAID) RNA Live attenuated Whole inactivated (Sanofi, Takeda, NIAID)	II II II (Sanofi did not start phase III limited funding Barda)

Source: WHO and clinicaltrial.gov, websites of pharmaceutical companies.

11. List of abbreviations

4CMenB	multicomponent meningococcal B vaccine
2vHPV	bivalent human papillomavirus vaccine
9vHPV	nonavalent HPV-vaccine
AAPC	average annual percentage change
ACIP	Advisory Committee on Immunisation Practices
AE	adverse events
AEFI	adverse events following immunisation
AGE	acute gastroenteritis
AGW	anogenital warts
aP	acellular pertussis
ARI	acute respiratory infections
ASC-US	atypical squamous cells of undetermined significance
BCG	Bacillus Calmette-Guérin
bOPV	bivalent oral polio vaccine
CBS	Statistics Netherlands
Cc	clonal complex
CDC	Centres for Disease Control and Prevention
cgMLST	core genome Multi Locus Sequence Typing
CI	confidence interval
CIb	Centre for Infectious Disease Control
CIN	cervical intraepithelial neoplasia
CMI	cell-mediated immunity
CMV	Cytomegalovirus
CN	Caribbean Netherlands
COPD	chronic obstructive pulmonary disease
CRM	CRM conjugate
CSF	cerebrospinal fluid
DALY	Disability Adjusted Life Years
DHD	Dutch Hospital data
DNA	desoxyribonucleic acid
DTaP	combination of diphtheria, tetanus and acellular pertussis vaccines
DTaP-IPV	combination of diphtheria, tetanus, acellular pertussis and inactivated polio vaccines
DTP	combination of diphtheria, tetanus and pertussis vaccines
DTwP	combination of diphtheria, tetanus and whole-cell pertussis vaccines
ECDC	European Centre for Disease Control and Prevention
EMA	European Medicines Agency
EU/EEA	European Union / European Economic Area
F	fusion
FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
Fim3	serotype 3 fimbriae
FU	Follow-up
GAPIII	the WHO global action plan to minimise poliovirus facility-associated risk
GBD	Global Burden of Disease
GE	gastroenteritis

GMC	geometric mean concentrations
GP	General Practitioner
GPLN	WHO Global Polio Laboratory Network
GSK	Glaxo Smith Kline
GW	genital warts
HAV	hepatitis A virus
HAVANA	Study of HPV prevalence among young girls
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	healthcare professionals
HepB	hepatitis B virus
Hib	*Haemophilus influenzae* type b
Hie	*Haemophilus influenzae* type e
Hif	*Haemophilus influenzae* type f
HIV	human immunodeficiency virus
HN	haemagglutinin-neuraminidase
HPV	human papillomavirus
HPV2D	Study to monitor the immunogenicity of a two-dose schedule of HPV vaccination
hrHPV	high-risk human papillomavirus
(H)SIL	high-grade squamous intraepithelial lesions
HSV	herpes simplex virus
HZ	herpes zoster
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ICPC	International Classification of Primary Care
IDS	Centre for Infectious Disease Research, Diagnostics and Screening
IDU	injecting drug use
IgG	immunoglobulin G
IgM	immunoglobulin M
ILI	influenza-like illness
IMD	invasive meningococcal disease
IPD	invasive pneumococcal disease
IPV	inactivated polio vaccine
IR	incidence rate
IU/ml	international units per millilitre
LBZ	National Register Hospital care
LINH	the Netherlands Information Network of General Practice
LMICs	low-income and lower-middle-income countries
LMR	National Medical Registration
lrHPV	low-risk human papillomavirus
MenACWY-TT	tetravalent meningococcal tetanus toxoid conjugate vaccine
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenW	Meningococcal serogroup W
MenY	Meningococcal serogroup Y
MERS-CoV	Middle East Respiratory Syndrome-coronavirus
MLST	Multilocus sequence typing
MLVA	multiple locus variable number of tandem repeat analysis
MMR	combination of measles, mumps and rubella vaccines

MMRV	combination of measles, mumps, rubella and Varicella vaccines
MSM	men who have sex with men
NIAID	National Institute of Allergy and Infectious Diseases
NIP	national immunisation programme
NIVEL	Netherlands Institute for Health Services Research
NIVEL-PCD	NIVEL Primary Care Database
NKR	the Netherlands Cancer Registry
NPG	National Influenza Prevention Programme
NPL	National Polio Laboratory
NLRBM	Netherlands Reference laboratory for Bacterial Meningitis
NTHi	nontypeable *Haemophilus influenzae*
NTM	neurotrimin
OPV	oral polio vaccine
OR	odds ratio
PASSYON	Papillomavirus Surveillance among STI clinic Youngsters
PCA	principal component analysis
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	heptavalent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PHiD-CV	10-valent pneumococcal nontypeable Haemophilus influenza protein D conjugate vaccine
PHN	postherpetic neuralgia
Pienter	assessing immunisation effect to evaluate the NIP
PPV	pneumococcal polysaccharide vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
PPV23-PCV13	additional types in PCV13 compared to PPV23
Prn	pertactin
PRP	polyribosyl-ribitol-phosphate
Ptx	pertussis toxin
QALY	quality-adjusted life year
qPCR	real-time polymerase chain reaction
rBSA	rabbit Serum Bactericidal Assay
RIVM	National Institute for Public Health and the Environment, the Netherlands
RSV	respiratory syncytial virus
RV	rotavirus
RZV	recombinant zoster vaccine (Shingrix®)
SAGE	strategic advisory group of experts
SHC	sexual health centres
ST	Sequence Type
STI	sexually transmitted infections
Tdap	tetanus, diphtheria and pertussis vaccine
TT	tetanus toxoid
UK	United Kingdom
US	United States
VDPV	vaccine-derived poliovirus
VE	vaccine effectiveness
VLP	virus-like particle
VPD	vaccine-preventable disease

VSCC	vulvar squamous cell carcinoma
VZV	varicella zoster virus
wgMLST	whole-genome multi locus sequence type
WGS	whole genome sequencing
WHO	World Health Organization
wP	whole-cell pertussis
WPV	wild poliovirus
ZVL	zoster vaccine live (Zostavax®)

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

Notifications by law are an important surveillance source for the diseases included in the NIP. The notification of infectious diseases started in the Netherlands in 1865. Since then, several changes in notification procedure have been enforced. Not all diseases targeted by the NIP have been notifiable during the entire period (Table A1.1) [1]. In December 2008, a new law
(Wet Publieke Gezondheid) was passed that required the notification of all NIP-targeted diseases except human papillomavirus (HPV)). There are four categories of notifiable disease. Diseases in category A have to be reported directly by telephone 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 a delay in reporting 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 the spread of the disease.

Physicians and clinical laboratories should notify cases to the Municipal Health Centres (GGDs). The GGD in question reports cases to RIVM through the online OSIRIS platform. In addition to patient characteristics (e.g. year of birth, sex, postal code), epidemiological (e.g. related cases, risk factors) and clinical data (e.g. hospital admission, death, vaccination status) are collected through the notifications.

Table A1.1 Periods and category of statutory notification for vaccine-preventable diseases (VPDs) included in the current National Immunisation Programme (NIP)

Disease	Category	Periods of notification by legislation
Diphtheria	B1	from 1872 onwards
Pertussis	B2	from 1975 onwards
Tetanus	C	1950–1999, from December 2008 onwards
Poliomyelitis	A	from 1923 onwards
Invasive *Haemophilus influenzae* type b	C	from December 2008 onwards
Hepatitis B disease	B2	from 1950 onwards
Invasive pneumococcal disease	C	from December 2008 onwards
Mumps	C	1975–1999, from December 2008 onwards
Measles	B2	1872–1899, from 1975 onwards
Rubella	B2	from 1950 onwards
Invasive meningococcal disease	C	from 1905 onwards

[a]Only for cases born from 2006

A1.1.1.2 Register-based data

A1.1.1.2.1 Death statistics

Statistics Netherlands (CBS) registers mortality data from death certificates on a statutory basis. The registration specifies whether it concerns a natural death, a non-natural death, or a stillborn child. In the event of a natural death, the physician should 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 the death (secondary causes). The CBS codes causes of death according to the International Classification of Diseases (ICD). This classification is adjusted every 10 years or so, which has to be taken into account when identifying mortality trends. Since the statistical year 2013, CBS has used the IRIS programme to automatically code the causes of death [3]. One of the advantages of this procedure is that it increases the international comparability of the figures. The change in coding did however cause (once only) considerable 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. The coverage of this registration 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 were not corrected for changes in coverage, causing an underestimation of hospital admissions from 2006 onwards till 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, this may have resulted in a trend break compared to previous years. Due to privacy, data are also rounded off to closest five. With these numbers one should take into account that 0 cases is not always actually 0, but can also be a few cases. Data for 2018 is not available yet.

Table A1.2 The completeness of LMR/LBZ over the years, by day admissions and clinic admissions*

Year	Day admission		Clinic admission	
	% registered	% generated (=missing)	% registered	% generated (=missing)
2007	87	13	89	11
2008	88	12	88	12
2009	87	13	88	12
2010	86	14	89	11
2011	79	21	85	15
2012	72	28	82	18
2013	74	26	84	16

2014	82	18	99	1

*These numbers are an approximation of the exact percentage
Sources: Statistics Netherlands (CBS) up to 2009 and Dutch Hospital Data (DHD) from 2010 onwards

A1.1.1.2.3 Primary care data
The NIVEL (Netherlands Institute for Health Services Research) Primary Care Database (NIVEL-PCD) includes data from routine electronic medical records of general practitioners (GPs). NIVEL-PCD uses routinely recorded data from health care providers to monitor health and the utilisation of health services in a representative sample of the Dutch population. All symptoms and diagnoses of consulting patients are recorded using the International Classification of Primary Care (ICPC-1). Annual incidence estimates of the total number of new episodes appearing in general practice in the Netherlands are made by extrapolating the reporting rates in these practices to the total number of Dutch residents, as obtained from CBS. For example, incidence rates of varicella and herpes zoster have been calculated using these data.

The current Dutch RSV surveillance programme is based primarily on general practitioner (GP) surveillance of patients with influenza-like illness (ILI) and other acute respiratory infections (ARI). Nose swabs and throat swabs are collected from a subset of patients and tested for influenza virus, RSV, rhinovirus and enterovirus. Furthermore, the weekly reporting of virological laboratory surveillance by 20 virological laboratories yields insights into the number of positive RSV tests, reflecting RSV circulation. These specimens are collected mainly from children [6].

A1.1.1.3 Laboratory data
Laboratory diagnostics are important in monitoring infectious diseases and the effectiveness of vaccination; about 75% of all infectious diseases can only be diagnosed by laboratory tests [7]. However, limited information on patients is registered and, in many cases, laboratory confirmation is not sought for self-limiting vaccine-preventable diseases. Two laboratory surveillance systems used for NIP disease surveillance are the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) and the virological laboratories, which are part of the Dutch Working Group for Clinical Virology.

A1.1.1.3.1 Netherlands Reference Laboratory for Bacterial Meningitis
(NRLBM)The NRLBM is a collaboration between the National Institute for Public Health and the Environment (RIVM) and the Academic Medical Centre of Amsterdam (AMC). On a voluntary basis, microbiological laboratories throughout the Netherlands send isolates from sterile sites (e.g. blood and cerebrospinal fluid (CSF)) of patients with invasive meningococcal disease, invasive pneumococcal disease, and invasive Haemophilus influenzae disease to the NRLBM for further typing. For invasive meningococcal disease and invasive Haemophilus influenzae disease, clinical laboratories in the Netherlands send in all invasive (i.e. from normally sterile sites) isolates.
For invasive pneumococcal disease, all clinical laboratories send in all positive isolates from CSF. Since 2004, nine sentinel clinical laboratories spread across the country send in all invasive isolates positive for

Streptococcus pneumoniae. These nine sentinel laboratories cover approximately 25% of the Dutch population. Since 2008, for children aged under 5, all clinical laboratories send in all invasive isolates positive for Streptococcus pneumoniae. Besides positive isolates, normally sterile PCR positive material (e.g. CSF or blood) can also be sent to the NRLBM for further typing. This means that we have nationwide laboratory surveillance for invasive meningococcal disease and invasive Haemophilus influenzae disease. From 2004 onwards, we have sentinel surveillance for invasive pneumococcal disease covering 25% of the Dutch population for all ages. From 2008 onwards, we have nationwide surveillance for invasive pneumococcal disease for children aged under 5.

A1.1.1.3.2 Virological laboratories
Each week, virological laboratories that are members of the Dutch Working Group for Clinical Virology send positive results of virological diagnostics to the RIVM. Approximately 22 laboratories send information regularly. Aggregated results are shown on the RIVM website.
It is important to bear in mind that the presence of a virus does not automatically imply the presence of disease. Since 1 December 2014, information on the total number of tests done can be reported for each week or each year.

A1.1.1.4 Dedicated studies
In addition to the data sources described above, dedicated disease surveillance studies are performed to collect data on hospitalisation or mortality. For example, every 2-4 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) with 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 Haemophilus influenzae disease, invasive pneumococcal disease, and, to a lesser extent, invasive meningococcal disease, data on mortality and hospital admissions based on registration databases are unreliable. This is because these are syndromic diseases (meningitis, sepsis and pneumonia) and the causative pathogen is not always correctly specified when these diseases are coded. Notification data in combination with laboratory data from the NRLBM are more reliable for these diseases.
For Rotavirus (RV) disease, there is a specific ICD code available (ICD-9: 008.61, ICD-10: A08.0). However, this code is hardly 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 weekly varying number of RV-positive laboratory detections. The number of hospital admissions attributable to RV infection is calculated from the scaling factor times the number of positive laboratory detections per week. For this report, the constant and scaling factor were estimated by fitting the model on 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, 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 that for previous years.

A1.1.2 Methods for disease surveillance

A1.1.2.1 Burden of disease

The composite health measure, the disability-adjusted life year (DALY), has been developed to compare the impact of diseases. The idea behind this approach is that the impact of a particular disease can be divided between the number of years of life lost (i.e. premature mortality) and the number of years lived at less than full health (i.e. morbidity). The result is a single measurement unit that quantifies the years of healthy life lost due to a certain disease or infection. The full methodology used to estimate the disease burden of infectious diseases in the Netherlands expressed in DALYs is described in the State of Infectious Diseases in the Netherlands, 2013 [18, 19].

A1.1.2.2 Impact of implementation of vaccination

The impact of vaccination (programmes) can be estimated by comparing disease burden after implementation to disease burden before implementation of vaccination. This can be done quite simply by a before-after comparison of incidence. A more complex alternative is by applying time series analysis, in which, for example, time trends before implementation of vaccination, seasonality and vaccination coverage can be taken into account. For estimating impact of a vaccination programme, vaccination status of individuals is not needed; the vaccination coverage of the population suffices. In addition to the effectiveness of the vaccination itself, vaccination coverage and the level of herd protection determine the impact of a vaccination programme.

A1.1.2.3 Vaccine effectiveness
To estimate vaccine effectiveness, the vaccination status of at least the cases is necessary.
After the implementation of a vaccination in the NIP, vaccine effectiveness (VE) can be routinely estimated using the 'screening method' with the following equation:

VE (%) = 1- [PCV / (1-PCV) * (1-PPV/PPV], in which PCV = proportion

of cases vaccinated,
PPV = proportion of population vaccinated, and VE = vaccine effectiveness.
In addition, several study designs, including case-control and cohort studies, can be used to assess VE after implementation [20]. A specific type of case-control design used to estimate VE is the indirect cohort design or Broome method [21]. 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 diseased. An assumption for 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 of 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 [22]. Based on available literature, no 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 most valid for the evaluation of the 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 [23]. 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
Previously, to calculate the vaccine effectiveness for the pertussis booster vaccination at 4 years old, a standardised vaccination coverage estimate of 92% was used for the PPV. In response to the recent changes in vaccination coverage, the PPV has been adjusted by birth cohort since last year. For each birth cohort, the vaccination coverage as reported in the national vaccination coverage report was used. This resulted in a different PPV for each birth cohort, and a more accurate VE calculation.

A1.2 Molecular surveillance of the pathogen
The monitoring of strain variations due to differences in phenotype and/or genotype is an important part of information gathering on the emergence of (sub)types that may be more virulent or less effectively controlled by vaccination. It is also a useful tool for increasing insights into transmission dynamics.

A1.3 Immunosurveillance
Monitoring the seroprevalence of all NIP-targeted diseases is a way to gather age-specific and sex-specific information on immunity to these diseases, acquired either through natural infection or vaccination. To achieve this, a random selection of people from the general population of the Netherlands is periodically asked to donate a blood sample and fill in a questionnaire (Pienter survey). This survey was performed in 1995-1996 (N_{blood}=10,128) [24], 2006–2007 (N_{blood}=7,904) [25], 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 insights into the effectiveness of the NIP. Furthermore, this information can 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) [26].

A1.4.1 Maternal pertussis vaccination coverage
The maternal pertussis vaccination is not registered in Præventis, because it has not yet been introduced in the NIP yet. To estimate maternal pertussis vaccination coverage, vaccination data of women in the fertile age group (20-45 years) were collected from the national apothecaries (SFK) and the municipal health services. Data were received from 20 out of the 5 municipal health services. We decided not to correct for the missing municipal health services, as this could easily result in an overestimation of the vaccine coverage.

The number of administered vaccinations of the SFK data and municipal health services that provided monthly data was added together to create the graph with the monthly trend. Due to differences in data registration, some municipal health services were able to provide only numbers per year. These were used to calculate the mean vaccination coverage of each year, but were not used in the figure.
To ensure that we did not overestimate number of administered maternal vaccinations, an approximate baseline number of vaccinations was subtracted from the total number of vaccinations. This baseline consisted of three approximate numbers: 1. the vaccinations given before the maternal vaccination was available, 2. the vaccinations related to travel, and 3. the vaccinations related to healthcare professions.
The first number was obtained by looking at the number of vaccinations administered at the beginning of 2016, as reported in the SFK data. The second number was obtained by counting the travel-related vaccinations as reported by the municipal health services. When a person comes for a travel-related vaccination, the country of destination is reported. Finally, the third number was obtained by looking at the number of pertussis vaccinations administered in 45-to 69-year-olds. These women are less likely to be vaccinated because of a pregnancy, and could be used as a proxy of the healthcare-related vaccinations.
To get an approximation of the number of pregnant women in 2018 and the first three months of 2019, the annual number of pregnant women as reported by Perined in 2017 was used [27]. The number of pregnant women in 2017 was 163,826. For 2019, this number was divided by four, as we only had data up to 1 April for the SFK data, and 1 March for the municipal health services data. To create the graph of the monthly trend, the annual number of pregnant women was divided by 12.

A1.5 Surveillance of adverse events following vaccination
Passive safety surveillance through an enhanced spontaneous reporting system was operated by the RIVM until 2011. An aggregated analysis of all reported adverse events following immunisation (AEFI) 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 reporting system of AEFI 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 Centre for Infectious Disease Control (CIb) of RIVM 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, the avertable disease burden, acceptability, and the 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, an economic evaluation of a vaccination programme provides information on whether the health gain associated with a new vaccine is worth the cost, compared with other options for spending on 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 way, 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
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019*	0	0	0	0	0	0	**0**	
*Hospitalisations** (source: Prismant/DHD/CBS)*								
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	1	0	0	**1**	
2002	0	0	0	0	0	0	**0**	
2003	0	1	0	0	0	1	**2**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	1	**1**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	2	**2**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017^	0	0	0	0	0	0	**0**	

*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

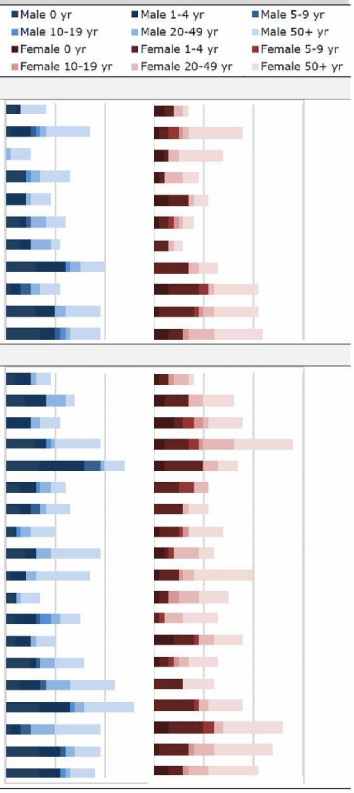
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.
^ Data corrected for non-participating hospitals and rounded off to closest five.

Diphtheria								ICD9: 032 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
Notifications (source: Osiris)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	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**	
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)*								
2000	0	0	0	0	0	1	**1**	
2001	0	0	0	0	0	2	**2**	
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	1	2	**3**	
2008	0	0	0	1	0	1	**2**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	1	1	**2**	
2011	0	0	0	0	3	2	**5**	
2012	0	0	0	0	2	2	**4**	
2013	0	0	0	1	3	1	**5**	
2014	0	0	0	1	4	5	**10**	
2015	0	0	0	0	6	5	**11**	
2016	0	0	0	1	5	10	**16**	
2017	0	0	0	0	7	5	**12**	
2018	0	0	0	0	5	5	**10**	
2019								

*Number of diphtheria isolates.

Haemophilus influenzae

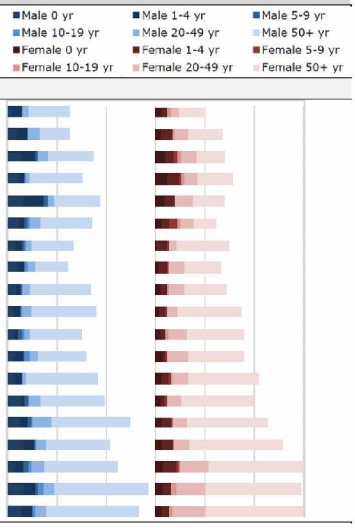
Year	Age (years)						Total
	1	1-4	5-9	10-19	20-49	50+	
Notifications (serotype b; source: Osiris)*							
2009	4	3	0	0	2	6	**15**
2010	2	6	3	2	2	20	**35**
2011	2	1	0	0	3	13	**19**
2012	5	1	0	1	6	9	**22**
2013	3	8	0	0	2	7	**20**
2014	4	3	2	1	4	6	**20**
2015	3	5	0	0	5	4	**17**
2016	6	13	0	1	4	9	**33**
2017	4	8	4	0	3	13	**32**
2018	7	11	1	1	4	16	**40**
2019	10	6	1	2	6	16	**41**
Laboratory diagnoses (serotype b; source: NRLBM)							
2001	3	5	0	1	4	4	**17**
2002	7	9	0	0	7	9	**32**
2003	5	8	2	2	3	11	**31**
2004	8	7	2	2	8	21	**48**
2005	9	17	3	0	4	8	**41**
2006	3	8	3	1	6	3	**24**
2007	3	8	2	0	2	9	**24**
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**



*Notifiable since 2009

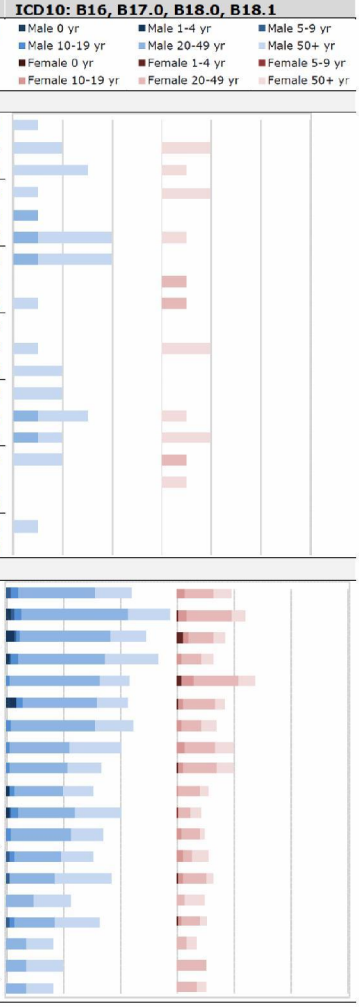
Haemophilus influenzae

Year	Age (years)						Total
	1-2	5.1.2e8	5.1.2e8	5.1.2e8	5.1.2e8	5.1.2e8+	
Laboratory diagnoses (all serotypes; source: NRLBM)							
2001	9	13	2	3	11	55	**93**
2002	13	18	0	2	22	53	**108**
2003	21	19	5	4	20	60	**129**
2004	19	14	2	3	15	72	**125**
2005	21	24	3	1	19	64	**132**
2006	14	12	8	4	21	61	**120**
2007	7	14	5	1	9	79	**115**
2008	11	14	2	3	18	60	**108**
2009	11	8	3	2	18	87	**129**
2010	8	10	1	3	15	106	**143**
2011	11	6	3	6	20	93	**139**
2012	12	11	2	4	26	85	**140**
2013	11	11	2	2	16	117	**159**
2014	16	6	5	1	22	111	**161**
2015	15	14	4	1	27	129	**190**
2016	19	16	2	1	22	130	**190**
2017	12	20	6	3	34	149	**224**
2018	21	15	3	8	32	157	**236**
2019	17	15	0	4	36	155	**227**



Hepatitis B — **ICD9: 070.2-3** — **ICD10: B16, B17.0, B18.0, B18.1**

Year	Age (years)						Total
	1-4	5-9	10-19	20-49	50-69	70+	
Mortality (B16: Acute; source: CBS)							
2000	0	0	0	0	0	1	**1**
2001	0	0	0	0	0	4	**4**
2002	0	0	0	0	0	4	**4**
2003	0	0	0	0	0	3	**3**
2004	0	0	0	0	1	0	**1**
2005	0	0	0	0	1	4	**5**
2006	0	0	0	0	1	3	**4**
2007	0	0	0	0	1	0	**1**
2008	0	0	0	0	1	1	**2**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	0	3	**3**
2011	0	0	0	0	0	2	**2**
2012	0	0	0	0	0	2	**2**
2013	0	0	0	0	1	3	**4**
2014	0	0	0	0	1	3	**4**
2015	0	0	0	0	1	2	**3**
2016	0	0	0	0	0	1	**1**
2017	0	0	0	0	0	0	**0**
2018	0	0	0	0	0	1	**1**
2019*	0	0	0	0	0	0	**0**
*Hospitalisations** (source: Prismant/DHD/CBS)*							
1999	0	0	2	8	56	29	**95**
2000	1	2	2	8	80	32	**127**
2001	0	7	1	5	61	26	**104**
2002	1	0	1	6	57	34	**102**
2003	0	2	0	8	71	25	**106**
2004	2	4	0	6	56	21	**92**
2005	0	0	0	4	56	28	**89**
2006	0	0	0	5	48	38	**92**
2007	0	1	0	3	49	27	**81**
2008	0	1	0	4	37	21	**63**
2009	0	1	2	4	36	31	**74**
2010	0	0	0	4	42	19	**66**
2011	0	0	1	6	30	26	**63**
2012	0	1	1	2	37	34	**76**
2013	0	0	0	0	18	30	**48**
2014	0	1	1	4	32	27	**66**
2015^	0	0	0	0	20	20	**40**
2016^	0	0	0	0	25	25	**50**
2017^	0	0	0	0	20	20	**40**



*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

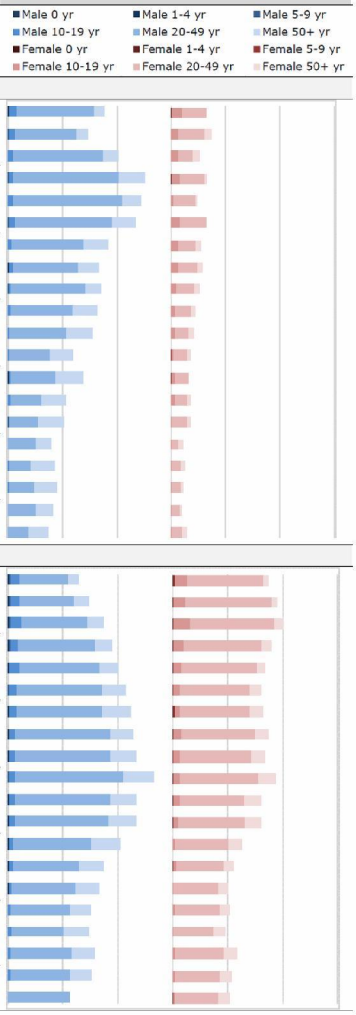
**Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five.

**Age is unknown for 18 patients.

Hepatitis B

Year	Age (years)						Total
Notifications (Acute; source: Osiris)							
2000	0	3	1	31	186	26	**247**
2001	0	0	2	23	163	33	**221**
2002	0	0	0	22	193	44	**259**
2003	0	1	3	22	240	56	**322**
2004	0	1	0	15	240	40	**296***
2005	0	0	2	26	227	46	**301**
2006	0	0	0	20	166	56	**242**
2007	0	1	1	20	154	50	**226**
2008	0	0	1	13	170	41	**225**
2009	0	0	0	11	144	56	**211**
2010	0	0	0	10	129	60	**199**
2011	0	0	1	7	98	53	**159**
2012	0	1	2	9	108	54	**174**
2013	0	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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**
Notifications (Chronic; source: Osiris)							
2000	2	16	15	149	919	121	**1,222**
2001	2	7	12	158	1,018	159	**1,356**
2002	0	11	15	200	1,099	183	**1,508**
2003	3	7	15	132	1,126	197	**1,480**
2004	2	5	8	128	1,139	208	**1,490**
2005	0	3	9	97	1,134	268	**1,511**
2006	2	18	8	85	1,141	300	**1,554**
2007	0	8	9	95	1,233	265	**1,610**
2008	0	10	6	87	1,215	295	**1,613**
2009	0	7	7	85	1,373	348	**1,820**
2010	0	9	12	77	1,159	328	**1,585**
2011	0	9	10	77	1,162	319	**1,577**
2012	0	3	3	55	959	307	**1,327**
2013	0	4	5	54	829	261	**1,153**
2014	1	5	3	31	788	247	**1,075**
2015	0	1	1	31	758	226	**1,017**
2016	1	0	0	36	674	269	**980**
2017	0	1	1	37	797	269	**1,105**
2018	0	0	0	40	758	253	**1,051**
2019	0	4	4	33	769	291	**1,101**



Hepatitis B

Year	Age (years)	Total	All ages
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)			
2000		**904**	
2001		**827**	
2002		**974**	
2003		**849**	
2004		**932**	
2005		**1,174**	
2006		**1,361**	
2007		**1,588**	
2008		**1,725**	
2009		**1,553**	
2010		**1,403**	
2011		**1,377**	
2012		**1,024**	
2013		**684**	
2014		**722**	
2015		**1,174**	
2016		**754**	
2017		**981**	
2018		**933**	
2019		**763**	

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
Mortality (cervical cancer; source: CBS)								
2000	0	0	0	0	73	185	**258**	
2001	0	0	0	0	66	177	**243**	
2002	0	0	0	0	45	142	**187**	
2003	0	0	0	0	47	167	**214**	
2004	0	0	0	0	49	154	**203**	
2005	0	0	0	0	52	183	**235**	
2006	0	0	0	0	44	170	**214**	
2007	0	0	0	0	57	147	**204**	
2008	0	0	0	0	51	193	**244**	
2009	0	0	0	0	40	169	**209**	
2010	0	0	0	0	43	162	**205**	
2011	0	0	0	0	46	143	**189**	
2012	0	0	0	0	42	173	**215**	
2013	0	0	0	0	47	176	**223**	
2014	0	0	0	0	50	148	**198**	
2015	0	0	0	0	49	158	**207**	
2016	0	0	0	0	50	179	**229**	
2017	0	0	0	0	44	162	**206**	
2018	0	0	0	0	50	167	**217**	
2019*	0	0	0	0	26	171	**216**	
Registrations (cervical cancer; source NKR)								
2000	0	0	0					
2001	0	0	0					
2002	0	0	0					
2003	0	0	0					
2004	0	0	0	1	375	327	**703**	
2005	0	0	0					
2006	0	0	0					
2007	0	0	0					
2008	0	0	0					
2009	0	0	0					
2010	0	0	0					
2011	0	0	0					
2012	0	0	0	1	406	328	**735**	
2013	0	0	0					
2014	0	0	0					
2015	0	0	0					
2016	0	0	0					
2017	0	0	0	1	433	339	**773**	
2018	0	0	0					
2019**	0	0	1					

*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

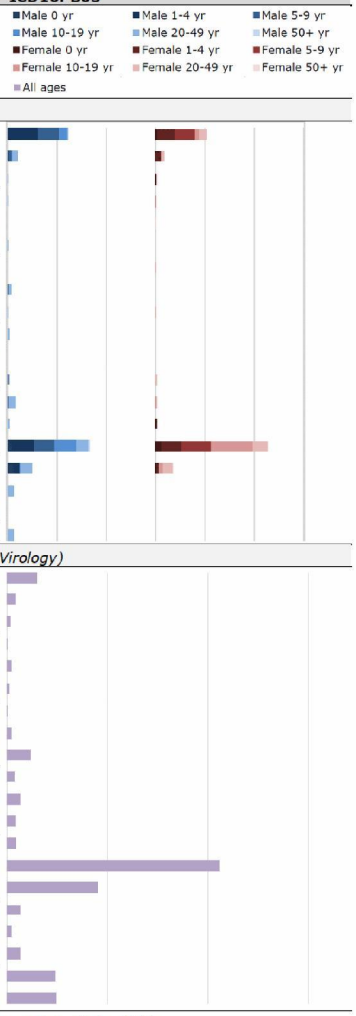
**Preliminary figures

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
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	1	0	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2000	19	225	469	237	64	3	**1,017**	
2001	0	3	4	3	7	0	**17**	
2002	0	2	0	1	0	0	**3**	
2003	0	0	1	2	1	0	**4**	
2004	1	1	0	3	6	0	**11**	
2005	0	0	1	1	1	0	**3**	
2006	0	0	0	0	1	0	**1**	
2007	0	1	0	0	8	0	**9**	
2008	4	8	38	39	21	0	**110**	
2009	1	2	2	3	7	0	**15**	
2010	1	2	2	1	9	0	**15**	
2011	2	2	7	14	26	0	**51**	
2012	1	2	0	1	6	0	**10**	
2013	53	425	840	1,162	199	9	**2,688**	
2014	18	25	6	17	65	1	**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**	

*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
	1.2	5.1.2e	5.1.2e	5.1.2e	5.1.2e	5.1.2e+	
Hospitalisations (source: Prismant/DHD/CBS)*							
1999	2	39	33	9	8	0	**91**
2000	1	4	3	1	6	0	**15**
2001	1	0	0	0	2	0	**3**
2002	0	0	0	1	1	0	**2**
2003	0	0	0	0	0	1	**1**
2004	0	0	0	1	0	0	**1**
2005	0	0	0	0	1	0	**1**
2006	0	1	0	0	2	0	**3**
2007	0	0	0	0	2	0	**2**
2008	0	0	0	0	2	0	**2**
2009	0	0	0	0	0	0	**0**
2010	0	1	0	0	3	0	**4**
2011	1	0	0	1	6	0	**9**
2012	1	1	0	0	2	0	**4**
2013	8	34	41	52	23	1	**164**
2014	6	6	0	4	18	1	**35**
2015^	0	0	0	0	5	0	**5**
2016^	0	0	0	0	0	0	**0**
2017^	0	0	0	0	5	0	**5**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
2000							**30**
2001							**8**
2002							**4**
2003							**1**
2004							**5**
2005							**2**
2006							**1**
2007							**5**
2008							**24**
2009							**7**
2010							**13**
2011							**8**
2012							**9**
2013							**212**
2014							**91**
2015							**13**
2016							**5**
2017							**13**
2018							**48**
2019							**49**



*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.

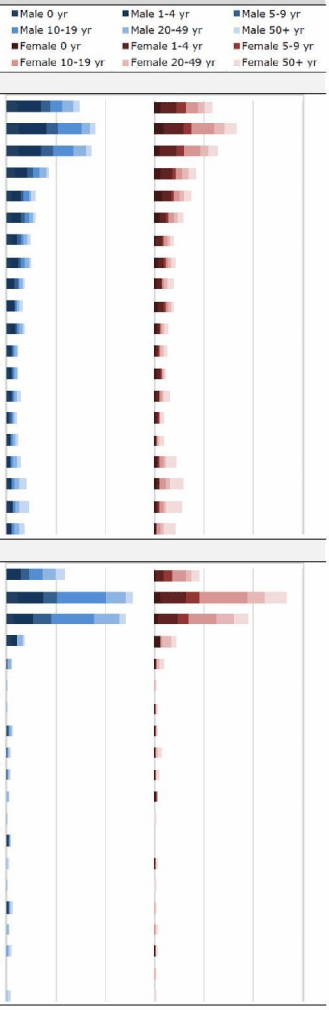
*Age is unknown for six patients.

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
Mortality (source: CBS)								
1997	7	13	6	6	2	7	**41**	
1998	10	19	2	10	2	9	**52**	
1999	9	13	4	7	4	11	**48**	
2000	12	8	1	6	6	9	**42**	
2001	4	16	2	16	10	8	**56**	
2002	4	14	2	8	4	12	**44**	
2003	7	7	0	0	3	3	**20**	
2004	0	5	0	0	2	8	**15**	
2005	3	3	0	3	0	2	**11**	
2006	1	0	1	1	0	1	**4**	
2007	2	3	0	1	0	3	**9**	
2008	1	1	0	0	2	3	**7**	
2009	1	3	0	0	1	1	**6**	
2010	3	2	0	1	0	2	**8**	
2011	2	0	0	0	1	2	**5**	
2012	0	1	0	0	0	0	**1**	
2013	0	1	0	1	0	1	**3**	
2014	0	1	0	0	0	5	**6**	
2015	0	1	0	0	1	2	**4**	
2016	0	2	0	1	0	3	**6**	
2017	1	2	0	1	2	2	**8**	
2018	0	2	0	4	2	5	**13**	
2019*	1	1	0	1	1	4	**8**	
Notifications (source: Osiris)								
2000	79	154	84	104	58	42	**521**	
2001	88	211	93	224	87	63	**766**	
2002	82	173	93	166	91	56	**661**	
2003	62	110	44	64	60	46	**386**	
2004	42	80	25	50	35	34	**266**	
2005	44	71	30	48	30	29	**252**	
2006	25	50	20	34	24	27	**180**	
2007	26	49	24	32	27	23	**181**	
2008	17	47	19	19	17	36	**155**	
2009	23	50	18	25	16	28	**160**	
2010	22	34	14	21	22	28	**141**	
2011	13	25	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	22	**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**	

*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

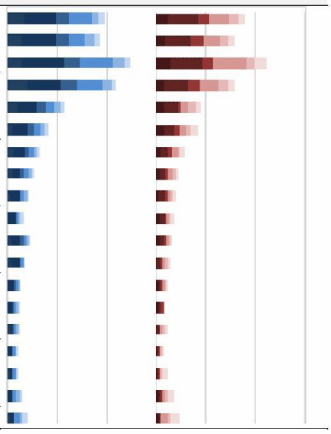
Meningococcal disease

Year	Age (years)						Total
	1	2	3	4	5	6+	
Laboratory diagnoses (all serogroups; source: NRLBM)							
2000	79	161	73	102	67	62	**544**
2001	91	197	82	194	86	69	**719**
2002	79	154	84	148	86	62	**613**
2003	61	98	37	54	56	45	**351**
2004	50	75	27	45	3	3	**5.1.2e**
5.1.2e	41	63	29	45	30	34	**242**
2006	25	49	22	32	23	24	**175**
2007	30	51	20	30	27	28	**186**
2008	15	47	18	18	22	39	**159**
2009	25	47	18	23	16	28	**157**
2010	23	34	13	18	21	28	**137**
2011	15	23	4	18	19	22	**101**
2012	18	28	7	11	17	16	**97**
2013	19	21	6	15	19	37	**117**
2014	10	16	10	12	11	23	**82**
2015	12	10	5	14	15	33	**89**
2016	14	15	7	24	28	63	**151**
2017	16	21	3	41	35	82	**198**
2018	15	25	3	33	28	101	**205**
2019	6	19	5	27	34	68	**159**
Laboratory diagnoses (serogroup C; source: NRLBM)							
2000	2	22	16	29	19	19	**107**
2001	20	53	27	105	43	29	**277**
2002	13	39	30	73	42	25	**222**
2003	11	6	0	1	16	8	**42**
2004	1	1	1	0	7	7	**17**
2005	0	0	0	0	2	2	**4**
2006	0	1	0	0	2	1	**4**
2007	2	0	1	1	4	2	**10**
2008	2	0	0	0	4	5	**11**
2009	1	1	0	0	2	5	**9**
2010	2	0	0	2	2	0	**6**
2011	0	0	0	0	1	2	**3**
2012	2	0	0	0	1	0	**3**
2013	0	1	0	0	1	4	**6**
2014	0	0	0	0	1	2	**3**
2015	2	0	0	0	3	3	**8**
2016	0	0	0	1	2	3	**6**
2017	1	0	0	1	1	6	**9**
2018	0	0	0	0	1	2	**3**
2019	0	0	0	0	1	5	**6**



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
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**	
Laboratory diagnoses (serogroup B; source: NRLBM)								
2000	73	133	55	72	47	38	**418**	
2001	68	142	54	88	37	33	**422**	
2002	65	115	53	72	39	[illegible]	[illegible]	
[illegible]	[illegible]	88	36	49	38	33	**293**	
2004	48	73	22	40	22	27	**232**	
2005	36	60	27	38	22	26	**209**	
2006	25	45	20	28	19	18	**155**	
2007	27	50	18	27	20	17	**159**	
2008	13	46	17	17	11	24	**128**	
2009	23	42	17	18	11	15	**126**	
2010	21	31	12	13	15	20	**112**	
2011	14	23	3	10	14	11	**75**	
2012	16	25	3	10	11	11	**76**	
2013	17	20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
2014	8	16	9	9	8	11	**61**	
2015	9	11	5	14	8	18	**65**	
2016	14	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
2017	11	17	3	23	15	12	**81**	
2018	9	22	1	12	11	19	**74**	
2019	5	17	3	18	14	15	**72**	

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
Hospitalisations (source: Prismant/DHD/CBS)*								
1999	114	251	98	170	66	53	**755**	
2000	98	233	109	132	64	55	**694**	
2001	114	295	113	268	85	66	**949**	
2002	106	238	110	182	72	47	**767**	
2003	72	135	46	64	57	44	**421**	
2004	54	101	46	58	1.2e	1.2e	5.1.2e	
5.1.2e	45	70	36	45	19	27	**244**	
2006	35	50	28	40	20	21	**196**	
2007	23	58	17	22	28	18	**166**	
2008	18	48	15	14	11	30	**136**	
2009	28	49	26	25	14	13	**156**	
2010	21	37	12	20	13	18	**122**	
2011	18	27	12	20	13	11	**103**	
2012	15	26	11	11	9	12	**84**	
2013	16	22	4	14	17	25	**99**	
2014	10	15	13	11	10	16	**75**	
2015^	15	15	10	15	10	25	**90**	
2016^	15	20	10	20	30	35	**135**	
2017^	15	30	5	50	30	55	**180**	

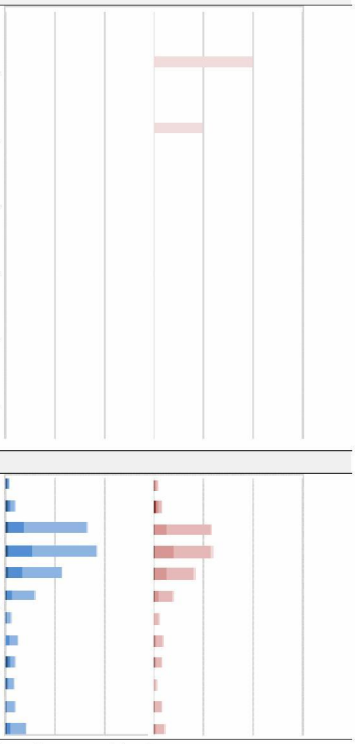


*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five.

*Age is unknown for 12 patients.

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
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	2	**2**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019*	0	0	0	0	0	0	**0**	
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**	

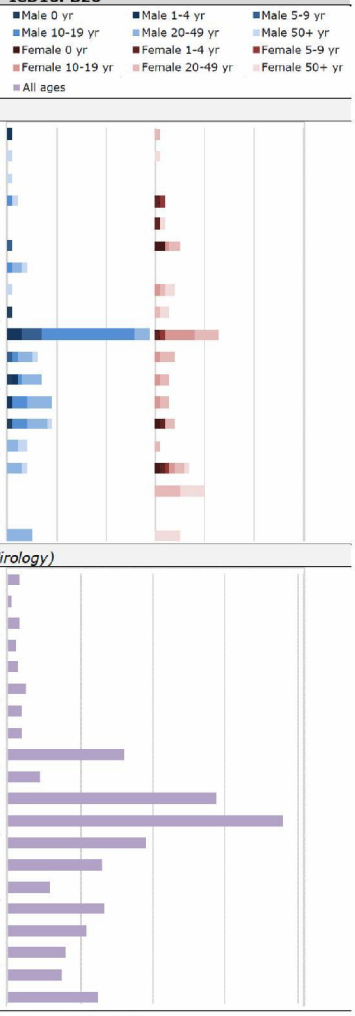


*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

**Notifiable from 1 December 2008 onwards

Mumps — **ICD9: 072** **ICD10: B26**

Year	Age (years)						Total
	1-2	3-5	6-12	13-15	16-17	18+	
Hospitalisations (source: Prisman/DHD/CBS)*							
1999	0	1	0	0	1	0	**2**
2000	0	0	0	0	0	2	**2**
2001	0	0	0	0	0	1	**1**
2002	0	1	1	1	0	1	**4**
2003	0	1	0	0	0	1	**2**
2004	2	0	1	1	2	0	**6**
2005	0	0	0	1	2	1	**4**
2006	0	0	0	1	1	3	**5**
2007	1	0	0	0	1	2	**4**
2008	0	4	5	25	9	0	**43**
2009	0	0	1	2	6	1	**10**
2010	1	1	0	2	6	0	**10**
2011	0	1	0	4	7	0	**12**
2012	2	1	0	3	6	1	**14**
2013	0	0	0	0	3	2	**5**
2014	1	1	1	1	5	2	**11**
2015^	0	0	0	0	5	5	**15**
2016^	0	0	0	0	0	5	**5**
2017^	0	0	0	0	5	5	**10**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
2000							**8**
2001							**2**
2002							**8**
2003							**6**
2004							**7**
2005							**12**
2006							**9**
2007							**9**
2008							**80**
2009							**22**
2010							**144**
2011							**190**
2012							**95**
2013							**65**
2014							**29**
2015							**66**
2016							**54**
2017							**40**
2018							**37**
2019							**62**



*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.

*Age is unknown for one patient.

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
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	1	0	0	0	0	0	**1**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	1	0	0	**1**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	1	**1**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	1	0	0	0	0	0	**1**	
2012	2	0	0	0	0	0	**2**	
2013	0	0	0	0	0	0	**0**	
2014	1	0	0	0	0	0	**1**	
2015	1	0	0	0	0	0	**1**	
2016	1	0	0	0	0	1	**2**	
2017	1	0	0	0	0	1	**2**	
2018	1	0	0	0	0	0	**1**	
2019*	2	0	0	0	0	0	**2**	
Notifications (source: Osiris)								
2000	176	757	1,628	677	651	376	**4,265**	
2001	307	1,164	3,400	1,342	1,212	605	**8,030**	
2002	168	511	1,624	1,004	807	438	**4,552**	
2003	134	367	1,070	582	465	245	**2,863**	
2004	367	1,006	2,750	2,390	2,099	1,139	**9,751**	
2005	190	787	1,292	1,586	1,212	850	**5,917**	
2006	143	471	788	1,353	987	622	**4,364**	
2007	190	450	837	2,888	2,057	1,331	**7,753**	
2008	195	346	779	3,154	2,343	1,484	**8,301**	
2009	164	270	658	2,442	1,962	1,064	**6,560**	
2010	115	168	355	1,278	1,212	637	**3,765**	
2011	160	283	1,007	2,531	1,984	1,231	**7,196**	
2012	234	378	1,525	4,192	4,497	3,002	**13,828**	
2013	77	136	315	889	1,054	931	**3,402**	
2014	258	490	788	2,859	2,721	2,138	**9,254**	
2015	174	274	560	1,962	2,053	1,532	**6,555**	
2016	217	402	489	1,426	1,813	1,223	**5,570**	
2017	182	221	416	1,307	1,610	1,146	**4,912**	
2018	193	334	432	1,260	1,534	1,144	**4,897**	
2019								

*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
Hospitalisations (source: Prismant/DHD/CBS)*								
1999	351	73	24	12	8	4	**472**	
2000	171	37	12	5	0	5	**230**	
2001	301	40	32	1	2	2	**378**	
2002	188	24	23	4	3	3	**245**	
2003	114	14	9	2	0	1	**140**	
2004	221	42	13	10	3	12	**301**	
2005	131	28	11	5	4	6	**185**	
2006	94	7	2	3	1	3	**110**	
2007	129	7	8	10	5	7	**166**	
2008	124	6	5	2	6	8	**151**	
2009	112	12	1	4	6	6	**141**	
2010	77	6	2	2	2	4	**93**	
2011	97	11	2	4	2	5	**121**	
2012	164	7	1	11	16	13	**213**	
2013	44	5	1	2	2	6	**60**	
2014	146	11	4	3	7	12	**185**	
2015^	140	10	0	10	5	10	**175**	
2016^	155	15	0	5	5	10	**190**	
2017^	150	10	0	10	0	10	**180**	

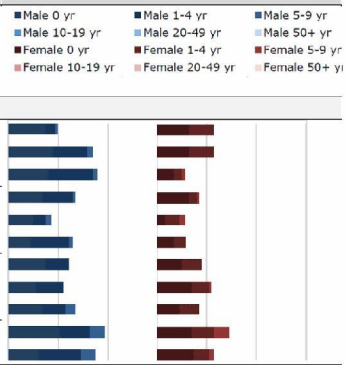
*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ Data corrected for non-participating hospitals and rounded off to closest five.

*Age is unknown for three patients.

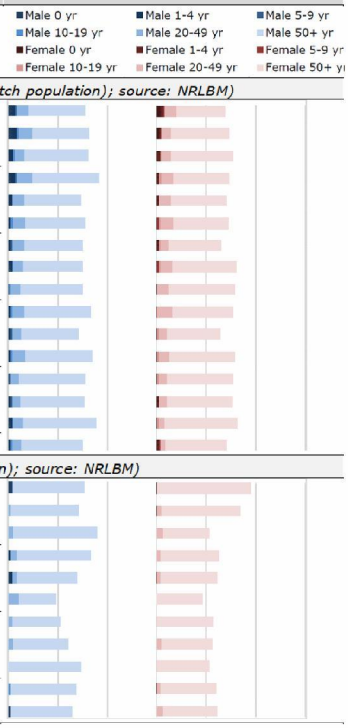
Pneumococcal disease

Year	Age (years)						Total
	1.2	5.1.2e	5.1.2e	5.1.2e	5.1.2e	5.1.2+	
Notifications IPD (source: Osiris)*							
2009	27	15	1	0			**43**
2010	31	24	2	0			**57**
2011	23	20	4	0			**47**
2012	26	16	2	0			**44**
2013	11	13	4	0			**28**
2014	16	20	2	0			**38**
2015	25	17	0	0			**42**
2016	25	18	1	0			**44**
2017	23	17	4	1			**45**
2018	35	21	12	2			**70**
2019	27	23	8	1			**59**
Laboratory diagnoses IPD (<5 years, nationwide; source: NRLBM)							
2008	40	40					**80**
2009	45	28					**73**
2010	44	34					**78**
2011	38	26					**64**
2012	33	17					**50**
2013	22	12					**34**
2014	22	25					**47**
2015	38	22					**60**
2016	30	19					**49**
2017	26	24					**50**
2018	40	28					**68**
2019	33	28					**61**



Pneumococcal disease

Year	Age (years)						Total
	1.2	5.1.2e	5.1.2e	5.1.2e	5.1.2e	5.1.2+	
Laboratory diagnoses IPD (all ages, sentinel labs (covering 25% of Dutch population); source: NRLBM)							
2004	30	20	10	12	88	444	**604**
2005	24	30	3	8	95	480	**640**
2006	11	23	4	4	83	516	**641**
2007	11	24	10	12	110	519	**686**
2008	10	14	4	5	100	474	**607**
2009	8	10	4	10	110	478	**620**
2010	9	12	6	4	83	459	**573**
2011	11	7	8	7	95	506	**634**
2012	4	7	3	3	81	540	**638**
2013	4	3	4	6	110	525	**652**
2014	5	11	5	5	67	454	**547**
2015	10	5	1	9	95	547	**667**
2016	6	5	3	4	66	547	**631**
2017	8	8	5	4	60	531	**616**
2018	7	9	5	5	67	595	**688**
2019	9	13	3	4	61	503	**593**
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**



*Notifiable for 0- to 5-year-old children since 2009.

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
Mortality pneumococcal pneumonia (source: CBS)*								
2000	0	1	0	0	6	51	**58**	
2001	0	0	0	0	6	51	**57**	
2002	0	1	0	0	3	50	**54**	
2003	0	0	0	1	5	46	**52**	
2004	0	0	0	1	6	41	**48**	
2005	0	0	0	0	6	57	**63**	
2006	0	0	0	0	6	50	**56**	
2007	0	0	0	0	8	39	**47**	
2008	0	0	0	0	0	47	**47**	
2009	0	0	1	1	2	37	**41**	
2010	0	0	0	0	2	43	**45**	
2011	0	0	0	0	1	26	**27**	
2012	0	0	0	0	2	42	**44**	
2013	0	0	0	0	0	29	**29**	
2014	0	0	0	0	0	28	**28**	
2015	0	0	0	0	1	28	**29**	
2016	0	0	0	0	0	27	**27**	
2017	0	0	0	0	0	15	**15**	
2018	0	0	0	0	1	25	**26**	
2019*	0	0	0	0	0	16	**16**	
*Hospitalisations pneumococcal pneumonia** (source: Prismant/DHD/CBS)*								
1999	35	74	48	37	394	1,126	**1,719**	
2000	32	75	48	41	360	1,257	**1,817**	
2001	24	102	39	34	421	1,215	**1,839**	
2002	45	123	41	35	414	1,323	**1,987**	
2003	28	115	34	49	454	1,523	**2,215**	
2004	33	103	51	37	409	1,416	**2,051**	
2005	29	95	57	36	461	1,446	**2,130**	
2006	25	72	46	28	333	1,388	**1,893**	
2007	10	87	41	33	382	1,502	**2,064**	
2008	8	68	31	21	352	1,452	**1,938**	
2009	28	59	30	36	332	1,465	**1,955**	
2010	23	62	37	35	285	1,560	**2,009**	
2011	17	40	46	38	337	1,631	**2,111**	
2012	4	28	11	20	263	1,506	**1,835**	
2013	0	4	7	17	384	1,606	**2,020**	
2014	3	4	3	19	309	1,754	**2,095**	
2015^	5	10	10	25	305	2,175	**2,525**	
2016^	0	5	5	20	380	2,125	**2,540**	
2017^	5	5	5	15	270	2,180	**2,485**	

*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.

**Age is unknown for 16 patients.

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
Mortality (acute; source: CBS)								
2000	0	0	0	0	0	2	**2**	
2001	0	0	0	0	1	0	**1**	
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	3	**3**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	

*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Poliomyelitis								ICD9: 045 ICD10: A80
Year	Age (years)						Total	■Male 0 yr ■Male 1-4 yr ■Male 5-9 yr ■Male 10-19 yr ■Male 20-49 yr ■Male 50+ yr ■Female 0 yr ■Female 1-4 yr ■Female 5-9 yr ■Female 10-19 yr ■Female 20-49 yr ■Female 50+ yr
Hospitalisations (source: Prismant/DHD/CBS)*								
1999	0	0	0	0	0	0	**0**	
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015^	0	0	0	0	0	0	**0**	
2016^	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	

*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.

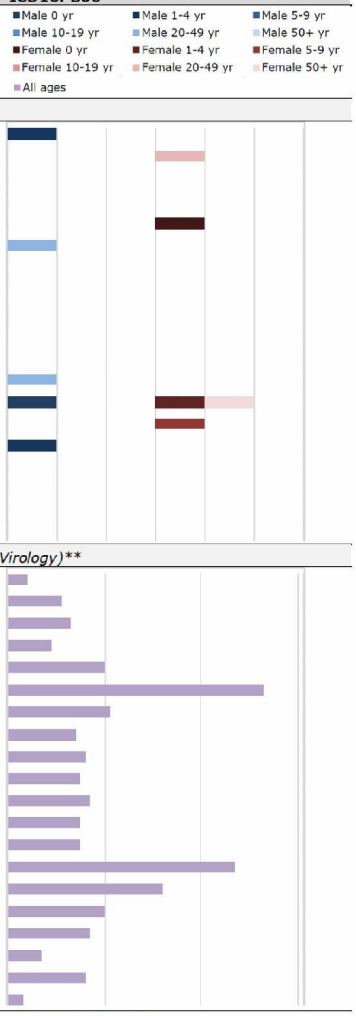
^ Data corrected for non-participating hospitals and rounded off to closest five.

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
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	0	**0**	
2002	0	0	0	0	1	0	**1**	
2003	0	0	0	0	0	0	**0**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	1	0	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019*	0	0	0	0	0	0	**0**	
Notifications (source: Osiris)								
2000	0	1	4	0	7	0	**12**	
2001	0	2	0	0	2	0	**4**	
2002	0	0	0	0	3	0	**3**	
2003	0	0	0	1	0	0	**1**	
2004	2	4	12	33	14	0	**65**	
2005	9	28	66	166	78	2	**349**	
2006	0	0	0	0	4	1	**5**	
2007	0	0	0	0	1	0	**1**	
2008	0	0	0	0	2	0	**2**	
2009	0	0	0	4	2	1	**7**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	1	2	**3**	
2012	0	0	0	0	1	0	**1**	
2013	0	10	37	7	3	0	**57**	
2014	0	1	0	0	1	0	**2**	
2015	0	0	0	0	1	0	**1**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019	0	0	0	0	0	0	**0**	

*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

Rubella (acquired) — **ICD9: 056** **ICD10: B06**

Year	Age (years)						Total
	1-2	5-12	5-12	5-12	5-12	5-12+	
Hospitalisations (source: Prisman/DHD/CBS)*							
1999	0	1	0	0	0	0	**1**
2000	0	0	0	0	1	0	**1**
2001	0	0	0	0	0	0	**0**
2002	0	0	0	0	0	0	**0**
2003	1	0	0	0	0	0	**1**
2004	0	0	0	0	1	0	**1**
2005	0	0	0	0	0	0	**0**
2006	0	0	0	0	0	0	**0**
2007	0	0	0	0	0	0	**0**
2008	0	0	0	0	0	0	**0**
2009	0	0	0	0	0	0	**0**
2010	0	0	0	0	1	0	**1**
2011	1	1	0	0	0	1	**3**
2012	0	0	1	0	0	0	**1**
2013	0	1	0	0	0	0	**1**
2014	0	0	0	0	0	0	**0**
2015^	0	0	0	0	0	0	**0**
2016^	0	0	0	0	0	0	**0**
2017^	0	0	0	0	0	0	**0**
*Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)***							
2000							**4**
2001							**11**
2002							**13**
2003							**9**
2004							**20**
2005							**53**
2006							**21**
2007							**14**
2008							**16**
2009							**15**
2010							**17**
2011							**15**
2012							**15**
2013							**47**
2014							**32**
2015							**20**
2016							**17**
2017							**7**
2018							**16**
2019							**3**



*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.

** The numbers may be higher than the notifications as false-positive results or cases not meeting the notification criteria may be included.

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
Mortality (source: CBS)								
2000	0	0	0	0	0	0	**0**	
2001	0	0	0	0	0	3	**3**	
2002	0	0	0	0	0	0	**0**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	0	**0**	
2005	0	0	0	0	0	0	**0**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	0	**0**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	1	**1**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	0	**0**	
2019*	0	0	0	0	0	0	**0**	
*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**	

*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

**No notifications in 1999–2008

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
Mortality (acute; source: CBS)								
2000	0	0	0	0	0	1	**1**	
2001	0	0	0	0	0	3	**3**	
2002	0	0	0	0	0	1	**1**	
2003	0	0	0	0	0	1	**1**	
2004	0	0	0	0	0	1	**1**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	0	0	0	0	**0**	
2007	0	0	0	0	0	0	**0**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	0	**0**	
2011	0	0	0	0	0	0	**0**	
2012	0	0	0	0	0	0	**0**	
2013	0	0	0	0	0	0	**0**	
2014	0	0	0	0	0	0	**0**	
2015	0	0	0	0	0	0	**0**	
2016	0	0	0	0	0	0	**0**	
2017	0	0	0	0	0	0	**0**	
2018	0	0	0	0	0	1	**1**	
2019*	0	0	0	0	0	0	**0**	

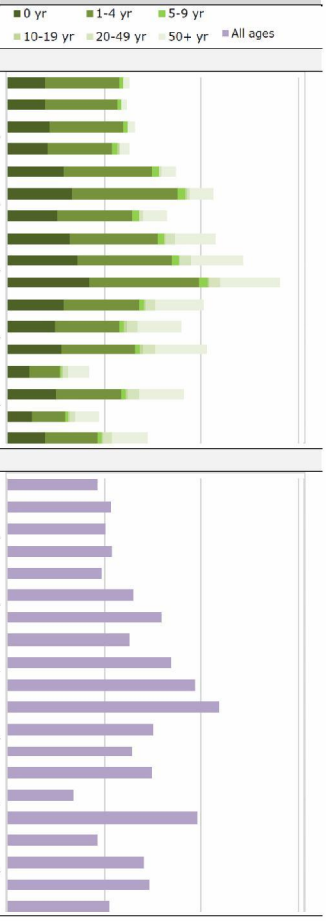
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

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
Notifications (source: Osiris)*								
2000	3	63	174	146	205	54	**647***	
2001	2	43	149	126	318	63	**704***	
2002	0	22	97	119	144	51	**433**	
2003						50	**389**	
2004	1	21	69	76	227	45	**439**	
2005	0	18	28	41	89	36	**212**	
2006	0	17	59	85	78	38	**277**	
2007	0	5	26	42	60	24	**157**	
2008	0						**189**	
2009	0	8	34	28	83	23	**176**	
2010						44	**262**	
2011	0	12	18	22	54	19	**125**	
2012	0	10	21	26	42	22	**121**	
2013	0	7	16	18	49	20	**110**	
2014	0	5	26	27	30	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						**164**	
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)								
2000							**293**	
2001							**284**	
2002							**145**	
2003							**146**	
2004							**153**	
2005							**91**	
2006							**111**	
2007							**72**	
2008							**97**	
2009							**96**	
2010							**107**	
2011							**63**	
2012							**53**	
2013							**38**	
2014							**66**	
2015							**67**	
2016							**66**	
2017							**163**	
2018							**95**	
2019							**90**	

*Age is unknown for 25 patients.

Rotavirus

Year	Age (years)						Total
	1.2	5.1.2e	5.1.2e	5.1.2e	5.1.2e	5.1.2+	
Hospitalisations (estimation; source: Prismant/DHD/CBS)*							
2001	1,154	2,277	147	0	0	184	**3,762**
2002	1,180	2,208	148	0	0	160	**3,696**
2003	1,298	2,287	160	0	0	202	**3,947**
2004	1,240	2,011	160	16	51	298	**3,776**
2005	1,729	2,744	199	19	83	443	**5,217**
2006	1,990	3,254	272	26	109	737	**6,388**
2007	1,532	2,323	189	23	139	722	**4,928**
2008	1,933	2,702	211	47	274	1,288	**6,455**
2009	2,171	2,924	220	45	301	1,636	**7,297**
2010	2,534	3,398	262	60	329	1,845	**8,428**
2011	1,754	2,294	167	56	305	1,502	**6,078**
2012	1,470	1,985	148	71	329	1,392	**5,395**
2013	1,682	2,270	169	81	377	1,592	**6,171**
2014	686	927	69	33	153	650	**2,518**
2015^	1,496	2,020	150	72	335	1,416	**5,490**
2016^	768	1,037	77	37	172	727	**2,818**
2017^	1,184	1,599	119	57	265	1,121	**4,345**
Laboratory diagnoses (source: Dutch Working Group for Clinical Virology)							
2000							**932**
2001							**1,067**
2002							**1,004**
2003							**1,079**
2004							**975**
2005							**1,304**
2006							**1,585**
2007							**1,251**
2008							**1,692**
2009							**1,935**
2010							**2,180**
2011							**1,505**
2012							**1,288**
2013							**1,496**
2014							**681**
2015							**1,957**
2016							**629**
2017							**1,407**
2018							**1,469**
2019							**1,054**



*Up to 2012, diseases were coded according to the ICD-9 coding system. From 2013 onwards, diseases have been coded according to the ICD-10 coding system.

^ The estimates from 2015-2017 are based on the five previous years (2010-2014).

Varicella (chickenpox)								ICD9: 052 ICD10: B01
Year	Age (years)						Total	Male 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
Mortality (source: CBS)								
2000	0	0	0	0	1	0	**1**	
2001	0	1	1	0	1	0	**3**	
2002	2	0	0	0	1	1	**4**	
2003	0	1	0	1	0	4	**6**	
2004	0	1	0	0	0	3	**4**	
2005	0	0	0	0	0	1	**1**	
2006	0	0	1	0	1	1	**3**	
2007	1	1	0	1	1	1	**5**	
2008	0	0	0	0	0	0	**0**	
2009	0	0	0	0	0	1	**1**	
2010	0	0	0	0	0	2	**2**	
2011	1	0	0	0	0	0	**1**	
2012	0	0	0	0	0	2	**2**	
2013	0	0	0	0	0	1	**1**	
2014	0	0	0	0	1	1	**2**	
2015	0	0	0	0	0	2	**2**	
2016	0	0	0	0	0	4	**4**	
2017	1	1	0	0	0	1	**3**	
2018	0	0	1	0	0	1	**2**	
2019*	0	0	0	0	0	3	**3**	
*Hospitalisations** (source: Prismant/DHD/CBS)*								
2000	44	95	14	6	38	14	**211**	
2001	62	104	19	3	36	9	**233**	
2002	47	113	17	4	29	9	**219**	
2003	78	121	10	6	41	17	**273**	
2004	89	115	20	7	26	12	**269**	
2005	64	119	9	1	28	17	**238**	
2006	108	132	17	4	33	19	**313**	
2007	69	92	19	4	24	23	**231**	
2008	74	111	19	3	38	26	**271**	
2009	67	92	18	6	37	22	**242**	
2010	81	136	21	7	39	[illegible]	**[illegible]**	
[illegible]	[illegible]	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**	

*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.

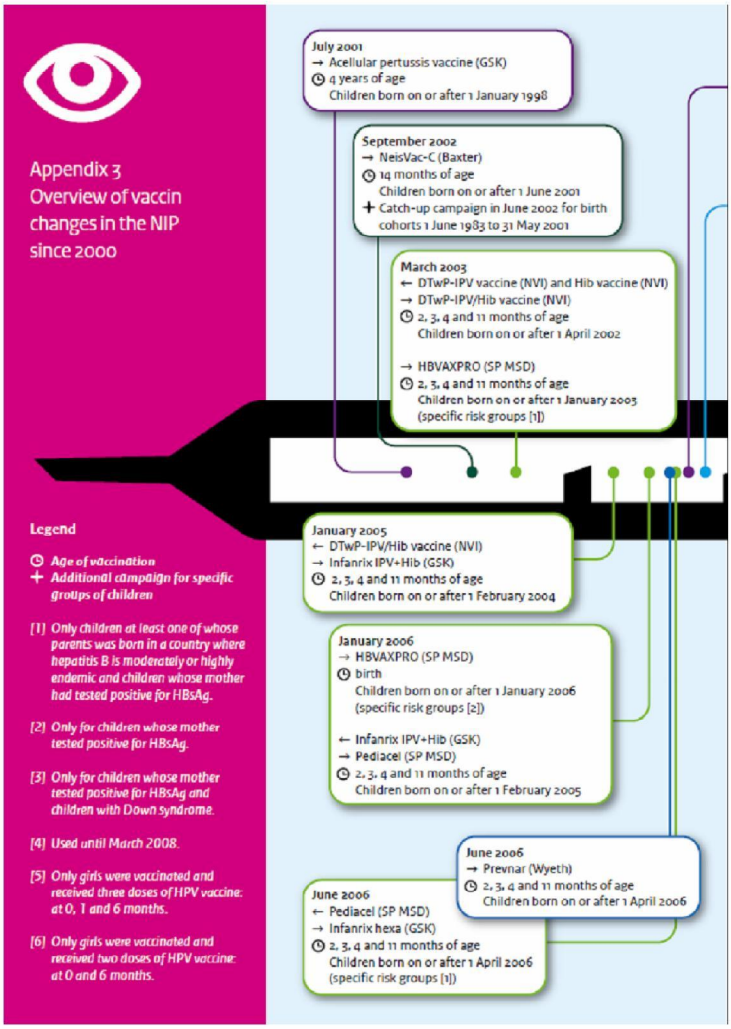
Herpes zoster (shingles)								ICD9: 053 ICD10: B02
Year	Age (years)						Total	Male 0 yr, Male 1-4 yr, Male 5-9 yr, Male 10-19 yr, Male 20-49 yr, Male 50+ yr, Female 0 yr, Female 1-4 yr, Female 5-9 yr, Female 10-19 yr, Female 20-49 yr, Female 50+ yr
Mortality (source: CBS)								
2000	0	0	0	0	0	14	**14**	
2001	0	0	0	0	1	12	**13**	
2002	0	0	0	0	0	26	**26**	
2003	0	0	0	1	0	13	**14**	
2004	0	0	0	0	0	15	**15**	
2005	0	0	0	0	1	14	**15**	
2006	0	0	0	0	0	24	**24**	
2007	0	0	0	0	1	20	**21**	
2008	0	0	0	0	0	14	**14**	
2009	0	0	0	0	0	20	**20**	
2010	0	0	0	0	0	25	**25**	
2011	0	0	0	0	0	20	**20**	
2012	0	0	0	0	0	21	**21**	
2013	0	0	0	0	0	21	**21**	
2014	0	0	0	0	0	26	**26**	
2015	0	0	0	0	0	33	**33**	
2016	0	0	0	0	0	27	**27**	
2017	0	1	0	0	0	32	**33**	
2018	0	0	0	0	0	36	**36**	
2019*	0	0	0	0	0	32	**32**	
*Hospitalisations** (source: Prismant/DHD/CBS)*								
2000	2	6	4	9	68	274	**363**	
2001	1	8	7	9	55	319	**399**	
2002	2	18	7	8	67	340	**442**	
2003	1	9	14	6	51	273	**354**	
2004	4	8	6	7	60	324	**409**	
2005	2	9	5	11	54	278	**359**	
2006	0	11	7	7	43	249	**317**	
2007	1	10	7	8	33	267	**326**	
2008	2	8	5	6	43	259	**323**	
2009	0	2	6	7	63	311	**389**	
2010	1	6	6	8	39	292	**352**	
2011	2	9	7	10	44	288	**360**	
2012	1	6	11	8	42	279	**347**	
2013	1	3	6	5	34	302	**351**	
2014	0	9	4	7	58	373	**451**	
2015^	0	10	10	15	60	395	**495**	
2016^	0	10	10	10	45	405	**480**	
2017^	0	15	5	15	45	385	**470**	

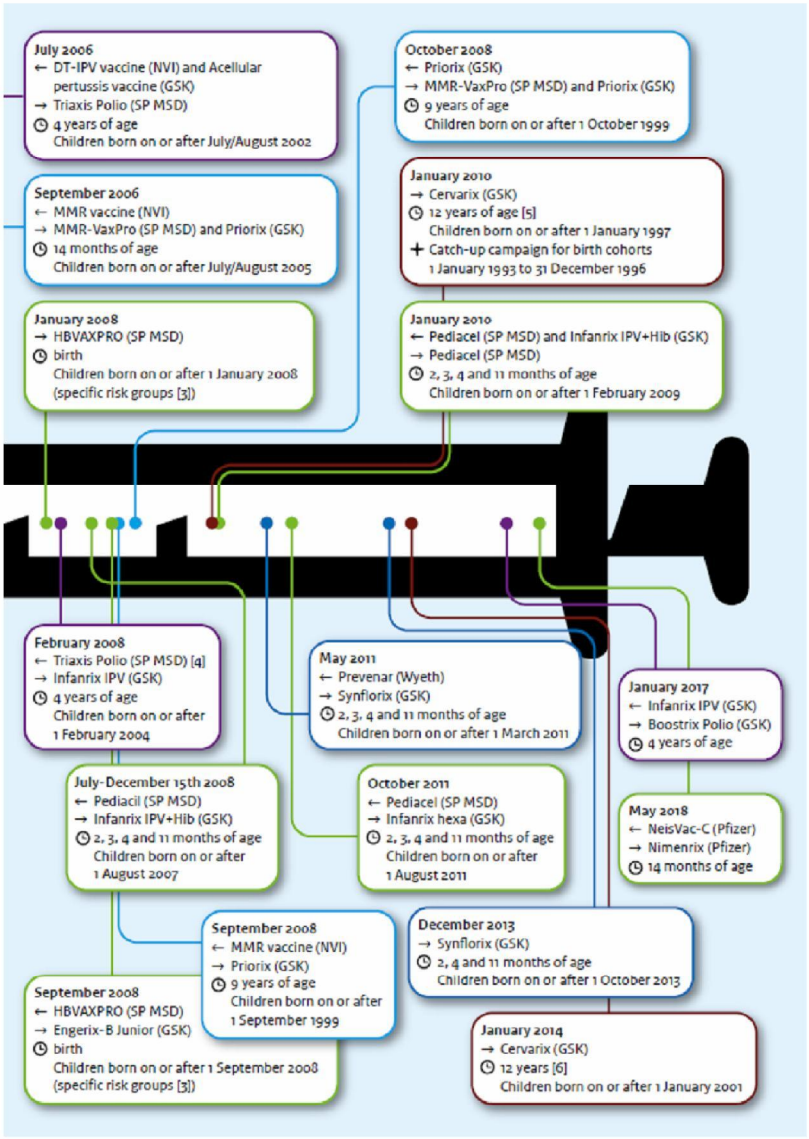
*Preliminary figures. From statistical year 2013 onwards, the coding of causes of death is partly automatic.

**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.

Appendix 3 Overview of vaccine changes in the NIP from 2000




July 2006
← DT-IPV vaccine (NVI) and Acellular pertussis vaccine (GSK)
→ Triaxis Polio (SP MSD)
4 years of age
Children born on or after July/August 2002
September 2006
← MMR vaccine (NVI)
→ MMR-VaxPro (SP MSD) and Priorix (GSK)
14 months of age
Children born on or after July/August 2005
January 2008
→ HBVAXPRO (SP MSD)
birth
Children born on or after 1 January 2008 (specific risk groups [3])
October 2008
← Priorix (GSK)
→ MMR-VaxPro (SP MSD) and Priorix (GSK)
9 years of age
Children born on or after 1 October 1999
January 2010
→ Cervarix (GSK)
12 years of age [5]
Children born on or after 1 January 1997
+ Catch-up campaign for birth cohorts 1 January 1993 to 31 December 1996
January 2010
← Pediacel (SP MSD) and Infanrix IPV+Hib (GSK)
→ Pediacel (SP MSD)
2, 3, 4 and 11 months of age
Children born on or after 1 February 2009
February 2008
← Triaxis Polio (SP MSD) [4]
→ Infanrix IPV (GSK)
4 years of age
Children born on or after 1 February 2004
May 2011
← Prevenar (Wyeth)
→ Synflorix (GSK)
2, 3, 4 and 11 months of age
Children born on or after 1 March 2011
January 2017
← Infanrix IPV (GSK)
→ Boostrix Polio (GSK)
4 years of age
July-December 15th 2008
← Pediacil (SP MSD)
→ Infanrix IPV+Hib (GSK)
2, 3, 4 and 11 months of age
Children born on or after 1 August 2007
October 2011
← Pediacel (SP MSD)
→ Infanrix hexa (GSK)
2, 3, 4 and 11 months of age
Children born on or after 1 August 2011
May 2018
← NeisVac-C (Pfizer)
→ Nimenrix (Pfizer)
14 months of age
September 2008
← MMR vaccine (NVI)
→ Priorix (GSK)
9 years of age
Children born on or after 1 September 1999
December 2013
→ Synflorix (GSK)
2, 4 and 11 months of age
Children born on or after 1 October 2013
September 2008
← HBVAXPRO (SP MSD)
→ Engerix-B Junior (GSK)
birth
Children born on or after 1 September 2008 (specific risk groups [3])
January 2014
→ Cervarix (GSK)
12 years [6]
Children born on or after 1 January 2001

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	Mumps virus (Jeryl Lynn) > 12,500 TCID50 (tissue culture infectious doses) Measles virus (Enders' Edmonston) > 1000 TCID50 Rubella virus (Wistar RA 27/3) > 1000 TCID50
Boostrix Polio / GSK RVG 35124 Diphtheria, tetanus, pertussis (acellular component), inactivated poliomyelitis vaccine (adsorbed, reduced antigen) 0.5 ml	Adsorbed diphtheria toxoid > 2 IU Adsorbed tetanus toxoid > 20 IU Adsorbed pertussis toxoid (PT) 8 µg Adsorbed filamentous haemagglutinin (FHA) 8 µg Absorbed pertactin (PRN) 2.5 µg Inactivated type 1 poliovirus (Mahoney) 40 DU Inactivated type 2 poliovirus (MEF-1) 8 DU Inactivated type 3 poliovirus (Saukett) 32 DU
Boostrix / GSK RVG 35121 Diphtheria, tetanus and pertussis (acellulair component) vaccin (adsorbed, reduced antigen) 0.5 ml	Adsorbed diphtheria toxoid > 2 IU Adsorbed tetanus toxoid > 20 IU Adsorbed pertussis toxoid (PT) 8 µg Adsorbed filamentous haemagglutinin (FHA) 8 µg Absorbed pertactin (PRN) 2.5 µg
Vaxelis / MCM Vaccine B.V. EU/1/15/1079/007 Diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), inactivated poliomyelitis and *Haemophilus* type b vaccine (adsorbed) 0.5 ml	Diphtheria toxoid > 20 IE Tetanus toxoid > 40 IE Pertussis toxoid 20 mcg Filamentous haemagglutinin 20 mcg Fimbriae type 2 and 3 5 mcg Pertactin 3 mcg Inactivated type 1 poliovirus 40 DE Inactivated type 2 poliovirus 8 DE Inactivated type 3 poliovirus 32 DE *Haemophilus influenzae* type b polysaccharide 3 mcg Conjugated to meningococcal protein 50 mcg
REVAXIS / SP RVG24534 Diphtheria, tetanus and inactivated poliomyelitis vaccine (absorbed; limited quantity of antigen(s)) 0.5 ml	Purified diphtheria-toxoid* > 2 IU Purified tetanus toxoid* > 20 IU Inactivated poliovirus type 1** 40 DU Inactivated poliovirus type 2** 8 DU Inactivated poliovirus type 3** 32 DU *adsorbed to aluminiumhydroxide 0.35 mg **produced on Verocells
Engerix-B Junior / GSK RVG24290 Hepatitis B vaccine (recombinant) 0.5 ml	Hepatitis B-virus surface antigen, recombinant* (S protein) absorbed 10 µg *produced on genetically engineered yeast cells (Saccharomyces cerevisiae)
HBVAXPRO / MSD RVG17316 Hepatitis B vaccine (rDNA) 0.5 ml	Hepatitis B virus surface antigen, recombinant (HBsAg)[1,2] 5 µg [1]Adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.25 mg Al+) [2]Produced in Saccharomyces cerevisiae (strain 2150-2-3) yeast by recombinant DNA technology

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
Act-HIB / SP *Haemophilus influenza* type b Conjugate Vaccine (Tetanus Protein - Conjugate) 0.5 ml	Purified polyribose ribitol phosphate capsular polysaccharide (PRP) of *Haemophilus influenzae* type b[1] 10 µg [1]covalently bound to tetanus protein 20 µg
Cervarix / GSK EU/1/07/419	Human papillomavirus type 16 L1 protein[2,3,4] 20 µg Human papillomavirus type 18 L1 protein[2,3,4] 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 Hl-5 Rix4446 cells derived from *Trichoplusia ni.*
Nimenrix / Pfizer EU/1/12/767 Conjugated meningococcal group A, C, W-135 and Y vaccine 0.5 ml	*Neisseria meningitidis*-group A polysaccharide[1] 5 µg *Neisseria meningitidis*-group C polysaccharide[1] 5 µg *Neisseria meningitidis*-group W-135 polysaccharide[1] 5 µg *Neisseria meningitidis*-group Y polysaccharide[1] 5 µg [1]conjugated to tetanus toxoid carrier protein 44 µg
Synflorix / GSK EU/1/09/508 Pneumococcal polysaccharide conjugate vaccine (adsorbed) 0.5 ml	Pneumococcal polysaccharide serotype 1[1,2] 1 µg Pneumococcal polysaccharide serotype 4[1,2] 3 µg Pneumococcal polysaccharide serotype 5[1,2] 1 µg Pneumococcal polysaccharide serotype 6B[1,2] 1 µg Pneumococcal polysaccharide serotype 7F[1,2] 1 µg Pneumococcal polysaccharide serotype 9V[1,2] 1 µg Pneumococcal polysaccharide serotype 14[1,2] 1 µg Pneumococcal polysaccharide serotype 18C[1,3] 3 µg Pneumococcal polysaccharide serotype 19F[1,4] 3 µg Pneumococcal polysaccharide serotype 23F[1,2] 1 µg [1]absorbed to aluminium phosphate 0.5 mg Al3+ [2]conjugated to protein D (obtained from nontypeable *Haemophilus influenzae*) carrier protein 9–16 mg [3]conjugated to tetanus toxoid 5–10 mg [3]conjugated to diphtheria toxoid 3–6 mg

More extensive product information can be found at: www.cbg-meb.nl and www.emea.europe.eu.

Appendix 5 Overview of recent RIVM publications (01/07/2019 to 31/06/2020)

Vaccination coverage

1. van Lier EA, Kamp L, Oomen PJ, Giesbers H, van Vliet JA, Drijfhout IH, et al. Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2019. [Vaccination coverage and annual report National Immunisation Programme Netherlands 2019]. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2020 (RIVM report 2020-0011).
2. de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020;38(34):5516-24.

Acceptance of vaccination

1. Mollema L, Antonise-Kamp L, van Vliet J, de Melker H. Organisatorische en communicatieve interventies die de opkomst voor HPV-vaccinatie kunnen verhogen. JGZ Tijdschrift voor jeugdgezondheidszorg. 2019;51(3-4):101-5.

Burden of disease

1. Lagerweij GR, Schimmer B, Mooij SH, Raven CFH, Schoffelen AF, de Gier B, et al. State of Infectious Diseases in the Netherlands, 2019. Bilthoven: National Institute for Public Health and the Environment (RIVM); 2020. RIVM report 2020-0048.

Adverse events

1. Nic Lochlainn LM, de Gier B, van der Maas N, Strebel PM, Goodman T, van Binnendijk RS, et al. Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis. Lancet Infect Dis. 2019;19(11):1235-45.

NIP-wide research topics

N.A.

Current NIP

Diphtheria

1. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

Haemophilus influenzae disease caused by type b (Hib) and other serotypes

1. Schouls L, Schot C, De Voer RM, Van der Klis F, Knol M, Tcherniaeva I, et al. Lagging Immune Response to Haemophilus influenzae Serotype b (Hib) Conjugate Vaccine after the Primary Vaccination with Hib of Infants in The Netherlands. Vaccines. 2020;8(347).

Hepatitis B

1. Raven SFH, 5.1.2e, Vossen 5.1.2e LG, Hautvast JLA, Roukens AHE, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis. 2020;20(1):92-101.

Human papillomavirus (HPV) infection

1. Woestenberg PJ, van Benthem BH, Bogaards JA, King AJ, van der Klis FR, Pasmans H, et al. HPV infections among young MSM visiting sexual health centers in the Netherlands: Opportunities for targeted HPV vaccination. Vaccine. 2020.
2. Woestenberg PJ, Guevara Morel AE, Bogaards JA, Hooiveld M, van't Klooster TMS, Hoebe CJ, et al. Partial protective effect of bivalent HPV16/18 vaccination against anogenital warts in a large cohort of Dutch primary care patients. Clinical Infectious Diseases. 2020.
3. Vos RA, Pasmans H, Tymchenko L, Janga-Jansen AV, 5.1.2e 1,2, Hulshof K, et al. High seroprevalence of multiple high-risk human papillomavirus types among the general population of Bonaire, St. Eustatius and Saba, Caribbean Netherlands. Vaccine. 2020;38(13):2816-26.
4. Man I, Vänskä S, Lehtinen M, Bogaards JA. Human papillomavirus genotype replacement: still too early to tell? The Journal of infectious diseases. 2020.
5. Pasmans H, Schurink-Van't Klooster TM, Bogaard MJ, van Rooijen DM, de Melker HE, Welters MJ, et al. Long-term HPV-specific immune response after one versus two and three doses of bivalent HPV vaccination in Dutch girls. Vaccine. 2019;37(49):7280-8.
6. Qendri V, Bogaards JA, Berkhof J. Pricing of HPV vaccines in European tender-based settings. The European Journal of Health Economics. 2019;20(2):271-80.
7. Qendri V BJ, Baussano I , Lazzarato F, Vänskä S, Berkhof J. The cost-effectiveness profile of sex-neutral HPV immunization in European tender-based settings. IPVC 2020; (conference abstract); Barcelona2020.
8. Woestenberg, P. J., King, A. J., Van Benthem, B. H., Leussink, S., Van der Sande, M. A., 5.1.2e. J., ... & Medical Microbiological Laboratories and the Public Health Services. (2020). Bivalent vaccine effectiveness against anal human papillomavirus positivity among female sexually transmitted infection clinic visitors in the Netherlands. The Journal of Infectious Diseases, 221(8), 1280-1285.
9. Hoes, J., Pasmans, H., Knol, M. J., Donken, R., van Marm-Wattimena, N., Schepp, R. M., ... & de Melker, H. E. (2020). Persisting Antibody Response Nine Years after Bivalent HPV Vaccination in A Cohort of Dutch Women: Immune Response and the Relation with Genital HPV Infections. The Journal of Infectious Diseases.
10. Donken, R., Hoes, J., Knol, M. J., Ogilvie, G. S., Dobson, S., King, A. J., ... & de Melker, H. E. (2020). Measuring vaccine effectiveness against persistent HPV infections: a comparison of different statistical approaches. BMC Infectious Diseases, 20(1), 1-11.
11. Vos RA, Pasmans H, Tymchenko L, Janga-Jansen AVA, 5.1.2e 5.1.2e 1,2, Hulshof K, de Melker HE, van der Klis FRM. High seroprevalence of multiple high-risk human papillomavirus types

among the general population of Bonaire, St. Eustatius and Saba, Caribbean Netherlands. Vaccine. 2020 Mar 17;38(13):2816-2826. doi: 10.1016/j.vaccine.2020.02.017.

Measles

1. Bodewes R, Reijnen L, Zwagemaker F, Kohl R, Kerkhof J, de Swart R, et al. Verbeteren van moleculaire surveillance van mazelen in Nederland. Analyse. 2020;2:40-3.
2. Verberk JDM, Vos RA, Mollema L, van Vliet J, van Weert JWM, de Melker HE, et al. Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. BMC Infect Dis. 2019;19(1):470.
3. Brinkman ID, de Wit J, Smits GP, Ten Hulscher HI, Jongerius MC, Abreu TC, et al. Early Measles Vaccination During an Outbreak in the Netherlands: Short-Term and Long-Term Decreases in Antibody Responses Among Children Vaccinated Before 12 Months of Age. J Infect Dis. 2019;220(4):594-602.
4. Nic Lochlainn LM, de Gier B, van der Maas N, van Binnendijk R, Strebel PM, Goodman T, et al. Effect of measles vaccination in infants younger than 9 months on the immune response to subsequent measles vaccine doses: a systematic review and meta-analysis. Lancet Infect Dis. 2019.
5. Nic Lochlainn LM, de Gier B, van der Maas N, Strebel PM, Goodman T, van Binnendijk RS, et al. Immunogenicity, effectiveness, and safety of measles vaccination in infants younger than 9 months: a systematic review and meta-analysis. Lancet Infect Dis. 2019.

Meningococcal disease

1. de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020;38(34):5516-24.
2. de Oliveira Bressane Lima P, van Lier A, de Melker H, Ferreira JA, van Vliet H, Knol MJ. MenACWY vaccination campaign for adolescents in the Netherlands: Uptake and its determinants. Vaccine. 2020.
3. van den Broek B, van Els C, Kuipers B, van Aerde K, Henriet SS, de Groot R, et al. Multi-component meningococcal serogroup B (MenB)-4C vaccine induces effective opsonophagocytic killing in children with a complement deficiency. Clin Exp Immunol. 2019;198(3):381-9.
4. Brandwagt DAH, van der Ende A, Ruijs WLM, de Melker HE, Knol MJ. Evaluation of the surveillance system for invasive meningococcal disease (IMD) in the Netherlands, 2004-2016. BMC Infect Dis. 2019 Oct 17;19(1):860.
5. Loenenbach AD, van der Ende A, de Melker HE, Sanders EAM, Knol MJ. The Clinical Picture and Severity of Invasive Meningococcal Disease Serogroup W Compared With Other Serogroups in the Netherlands, 2015-2018. Clin Infect Dis. 2020 May 6;70(10):2036-2044.

Mumps

1. Bodewes, R., et al., Optimizing molecular surveillance of mumps genotype G viruses. Infect Genet Evol, 2019. 69: p. 230-234.

2. Bodewes, R., et al., Molecular epidemiology of mumps viruses detected in the Netherlands, 2017-2019. bioRxiv, 2020.
3. de Wit, J., et al., Identification of Naturally Processed Mumps Virus Epitopes by Mass Spectrometry: Confirmation of Multiple CD8+ T-Cell Responses in Mumps Patients. J Infect Dis, 2020. 221(3): p. 474-482.
4. Kaaijk, P., et al., A Third Dose of Measles-Mumps-Rubella Vaccine to Improve Immunity Against Mumps in Young Adults. J Infect Dis, 2020. 221(6): p. 902-909.

Pertussis

1. Lambert EE, Buisman AM, van Els CACM. Superior B. pertussis specific CD4+ T-cell immunity imprinted by natural infection. Adv Exp Med Biol.2019;1183:81-98. Review.
2. den Hartog G, Schijf MA, Berbers GAM, van der Klis FRM, Buisman AM. Bordetella pertussis induces IFN-γ production by NK cells resulting in chemo-attraction by respiratory epithelial cells. J Infect Dis. 2020 Mar 27:jiaa140.
3. Kroes MM, Mariman R, Hijdra D, Hamstra HJ, van Boxtel KJWM, van Putten JPM, de Wit J, Pinelli E. Activation of Human NK Cells by Bordetella pertussis Requires Inflammasome Activation in Macrophages. Front Immunol. 2019 Aug 27;10:2030.
4. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.
5. Lambert EE, Corbière V, van Gaans-van den Brink JAM, Duijst M, Venkatasubramanian PB, Simonetti E, Huynen M, Diavatopoulos DD, Versteegen P, Berbers GAM, Mascart F, van Els CACM. Uncovering distinct primary vaccination-dependent profiles in human Bordetella pertussis specific CD4+ T-cell responses using a novel whole blood assay. Vaccines. 2020 May 15;8(2):E225.

Pneumococcal disease

1. Van de Garde MDB, Knol MJ, Rots NY, van 5.1.2e , 5.1.2e Els CACM. Vaccines to Protect Older Adults against Pneumococcal Disease. Interdiscip Top Gerontol Geriatr. 2020;43:113-130.

Poliomyelitis

N.A.

Rubella

1. Verberk, J.D.M., et al., Third national biobank for population-based seroprevalence studies in the Netherlands, including the Caribbean Netherlands. BMC Infect Dis, 2019. 19(1): p. 470.

Tetanus

1. G. Berbers, P. van Gageldonk, J. van de Kassteele, U. Wiedermann, I. Desombere et al. Widespread ciriculation of pertussis and poor protection against diphtheria among middle-aged adults in 18 European countries. Nature research 2020, Preprint 2020. DOI 10.21203/rs-35858/v1.

Potential NIP target diseases

Hepatitis A

N.A.

Respiratory syncytial virus

1. Reeves RM, van Wijhe M, Tong S, Lehtonen T, Stona L, Teirlinck AC, et al. Respiratory Syncytial Virus-Associated Hospital Admissions in Children Younger Than 5 Years in 7 European Countries Using Routinely Collected Datasets. J Infect Dis. 2020 Aug 20:jiaa360.
2. van Boven M, Teirlinck AC, 5.1.2e, Hooiveld M, van Dorp CH, Reeves RM, et al. Estimating Transmission Parameters for Respiratory Syncytial Virus and Predicting the Impact of Maternal and Pediatric Vaccination. J Infect Dis. 2020 Aug 21:jiaa424.
3. Schepp, R. M., et al. Development and Standardization of a High-Throughput Multiplex Immunoassay for the Simultaneous Quantification of Specific Antibodies to Five Respiratory Syncytial Virus Proteins. mSphere 2019;4(2).
4. G. Berbers, L. Mollema, F. van der Klis, G. den Hartog, R. Schepp. Antibody responses to Respiratory Syncytial Virus: a cross-sectional serosurveillance study in the Dutch population with emphasis on infants up to 2 years and COPD patients. Accepted.
5. van Erp EA, Lakerveld AJ, de Graaf E, et al. Natural killer cell activation by respiratory syncytial virus-specific antibodies is decreased in infants with severe respiratory infections and correlates with Fc-glycosylation. Clin Transl Immunology. 2020;9(2):e1112. Published 2020 Feb 19.

Rotavirus

N.A.

Varicella zoster virus (VZV) infection

1. van Lier A. Epidemiology of varicella zoster virus in the Netherlands: implications for vaccination strategies [dissertation]; 2019.
2. Vos RA, Mollema L, van Boven M, van Lier A, Smits G, Janga-Jansen AVA, et al. High varicella-zoster virus susceptibility in Caribbean island populations: implications for vaccination. Int J Infect Dis. 2020;94:16-24.
3. van Lier EA, van der Maas NAT, de Melker HE. Varicella in the Netherlands: Background information for the Health Council. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu (RIVM); 2020 (RIVM rapport 2019-0197).
4. van Kampen JJA, Bruns AHW, E. vL, Koelewijn JM, Ruijs WLM, Komen DJC, et al. Herziene multidisciplinaire richtlijn 'Varicella': ruimere indicatie voor postexpositieprofylaxe. Ned Tijdschr Geneeskd. 2020;164:D5380.

Appendix 6 Overview of relevant websites

General information for NIP professionals
RIVM website for professionals:
http://www.rivm.nl/Onderwerpen/R/Rijksvaccinatieprogramma/Professionals

Dienst Vaccinvoorziening en Preventieprogramma's (DVP, Department for Vaccine Supply and Prevention Programmes):
http://www.rivm.nl/RIVM/Organisatie/Centra/Dienst_Vaccinvoorziening_en_Preventieprogramma_s

Meldingsplicht infectieziekten (Duty to notify 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

General information for the public
RIVM websites for the public:
https://rijksvaccinatieprogramma.nl/

Available vaccines that are not (yet) part of a public vaccination programme:
www.rivm.nl/vaccinaties

Volksgezondheidenzorg.info:
https://www.volksgezondheidenzorg.info/

Cervical cancer screening programme:
https://www.rivm.nl/Onderwerpen/B/Bevolkingsonderzoek_baarmoederhalskanker

Vaccines Today:
https://www.vaccinestoday.eu/about-us/who-we-are/

Other NIP-related RIVM reports
Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2019:
https://www.rivm.nl/publicaties/vaccinatiegraad-en-jaarverslag-rijksvaccinatieprogramma-nederland-2019

Adverse events in the Netherlands Vaccination Programme, reports in 2010 and review 1994–2010:
http://www.rivm.nl/bibliotheek/rapporten/205051004.pdf

Product information
Product information and package leaflets NIP:
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

Vaccine European New Integrated Collaboration Effort (VENICE) III project:
http://venice.cineca.org/HAVNET:http://www.rivm.nl/en/Topics/H/HAVNET

National Immunization Technical Advisory Groups (NITAGs):
http://www.nitag-resource.org/

National Respiratory and Enteric Virus Surveillance System (NREVSS):
https://www.cdc.gov/surveillance/nrevss/

The Streptococcus pneumoniae Invasive Disease network (SpIDnet):
http://www.epiconcept.fr/produit/spidnet/

WHO Global Polio Laboratory Network (GPLN):
http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/activities/polio-laboratory-network

Respiratory syncytial virus consortium in Europe (RESCEU):
http://resc-eu.org/

Communication platforms
Epidemic Intelligence Information System (EPIS):
https://ecdc.europa.eu/en/publications-data/epidemic-intelligence-information-system-epis

Vaccination of risk groups
Influenza vaccination
RIVM website on Influenza vaccination:
http://www.rivm.nl/Onderwerpen/G/Griep/Griepprik

Stichting Nationaal Programma Grieppreventie (SNPG, Foundation for the National Influenza Prevention Programme):
http://www.snpg.nl/

Scientific Institute for Quality of Healthcare:
http://www.iqhealthcare.nl/nl/

Annual Report on Surveillance of influenza and other respiratory infections in the Netherlands:
https://www.rivm.nl/bibliotheek/rapporten/2019-0079.pdf

Tuberculosis
KNCV Tuberculosis foundation:
http://www.kncvtbc.nl/

Annual Report on Surveillance of influenza and other respiratory infections in the Netherlands:
https://www.rivm.nl/bibliotheek/rapporten/2019-0079.pdf

National Tuberculosis Control Plan 2016-2020:
http://www.rivm.nl/bibliotheek/rapporten/2016-0028.pdf

Traveller vaccination
Landelijk Coördinatiecentrum Reizigersadvisering (National Coordination Centre for Information for Travellers):
https://www.lcr.nl/Index.htm

Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Epidemiologische situatie COVID-19 in Nederland

Rijksinstituut voor Volksgezondheid en Milieu - RIVM
14 september 2020, 10:00

Samenvatting

Tot en met 14 september 10:00 uur zijn er in Nederland in totaal 83399 COVID-19 patiënten gemeld aan het RIVM. Van alle gemelde patiënten is de helft 49 jaar of ouder. Tot nu toe zijn 12291 van de gemelde patiënten opgenomen in het ziekenhuis en 6256 mensen overleden. De helft van de opgenomen patiënten is 68 jaar of ouder, van de overleden patiënten was de helft 83 jaar of ouder.

Uitleg over surveillance van COVID-19 in Nederland

Door middel van surveillance houdt het RIVM zicht op de verspreiding van COVID-19 in Nederland. Via een samenwerking tussen artsen, laboratoria en de GGD'en wordt informatie verzameld over personen (patiënten) met een positieve SARS-CoV-2 testuitslag. Sinds het begin van de COVID-19 epidemie in Nederland is het testbeleid geleidelijk veranderd. Het huidige testbeleid is hier te vinden. Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijk dat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Aan het RIVM wordt niet gemeld wie hersteld is van COVID-19.

Er worden ook mensen die om andere redenen dan COVID-19 in het ziekenhuis worden opgenomen getest op het nieuwe coronavirus. Dit wordt gedaan om verspreiding van dit virus binnen het ziekenhuis tegen te gaan. Vanaf 1 mei wordt bij melding van een in het ziekenhuis opgenomen positief geteste patient, nagevraagd of de ziekenhuisopname vanwege COVID-19 was. Vanaf 8 mei geven we in de rapportages van de ziekenhuisopnames sinds 1 mei alleen opnames weer waarbij niet is aangegeven dat de opname om een andere reden was. Dit doen we zodat het aantal in het ziekenhuis opgenomen COVID-19 patiënten een zo goed mogelijke indicator blijft van de epidemie. Dit geeft namelijk weer hoeveel mensen ernstig ziek zijn door COVID-19. Patiënten die om een andere reden ziekenhuiszorg nodig hebben en ook COVID-19 blijken te hebben, worden uiteraard wel meegenomen in het totaal aantal meldingen.

Een databestand met de cumulatieve aantallen per gemeente per dag van gemelde COVID-19 patiënten, in het ziekenhuis opgenomen COVID-19 patiënten en overleden COVID-19 patiënten is hier te vinden. Een databestand met karakteristieken van elke positief geteste COVID-19 patiënt in Nederland is hier te vinden.

Weergave van grafieken

In de grafieken wordt in geel weergegeven wat de veranderingen zijn ten opzichte van de voorgaande week in aantallen aan het RIVM gemelde patiënten. Soms worden meldingen van GGD aan RIVM een dag of enkele dagen later gedaan dan de dag dat de patiënt bij de GGD wordt gemeld.

Per 25 augustus worden de COVID-19 meldingen aan de GGD'en in Figuur 1 t/m 5 en 9 t/m 11 weergegeven vanaf 6 juli. De epidemiologische curves met data vanaf 27 februari zijn weergegeven in paragraaf 12.1 (Figuur 25 t/m 31). De kaarten met COVID-19 meldingen vanaf 27 februari per gemeente zijn te vinden in paragraaf 12.2.2 (Figuur 32 t/m 34).

Inhoudsopgave

1 Samenvatting COVID-19 meldingen van de GGD'en vanaf 27 februari 2020

Tabel 1: Aantal door de GGD'en gemelde COVID-19 patiënten, aantal in het ziekenhuis opgenomen COVID-19 patiënten gemeld door GGD'en en aantal overleden COVID-19 patiënten gemeld door GGD'en[1]

Gezondheidsstatus	Totaal	%	Meldingen afgelopen week[2]	Gecorrigeerd[3]	Verschil met vorige week[4]
Totaal gemeld	83399		7858	-43	7815
Ziekenhuisopname	12291	14.7	73	-1	72
Overleden[5]	6256	7.5	13	0	13

[1] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.

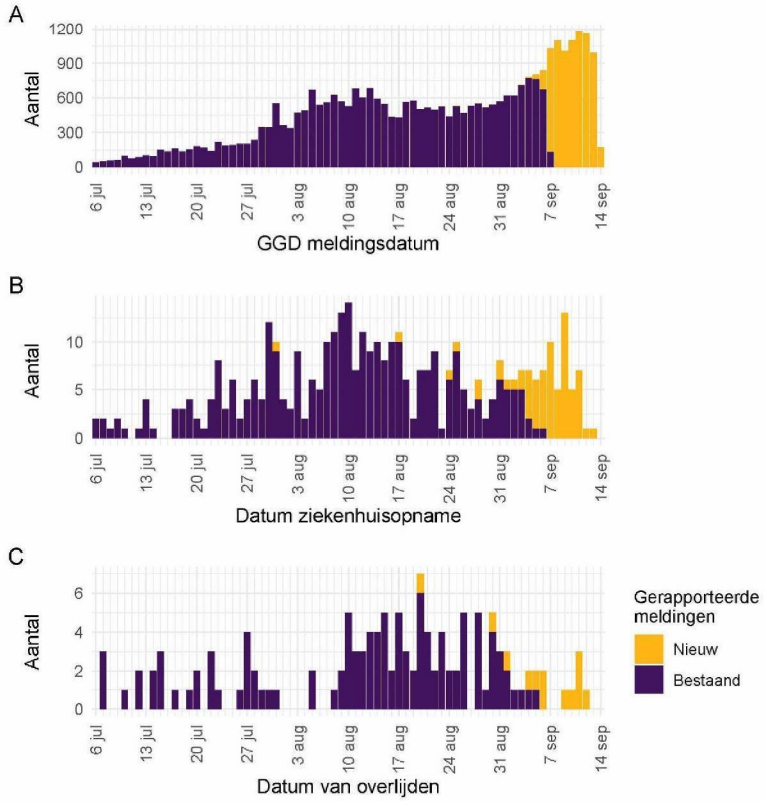
[2] Meldingen die tussen 7 september 10:00 en 14 september 10:00 aan het RIVM zijn gemeld. Dit betreft het aantal meldingen, opnames en overlijdens die in de afgelopen week nieuw aan het RIVM zijn gerapporteerd. Datum van melding aan de GGD, ziekenhuisopname of overlijden kan echter in een andere week vallen. Bij overige tabellen en figuren in dit rapport wordt de datum van melding, ziekenhuisopname of overlijden gebruikt. Deze cijfers zijn dus niet hetzelfde.

[3] Meldingen die gewist of herzien zijn tussen 7 september 10:00 en 14 september 10:00. Behalve dat er nieuwe meldingen worden ontvangen, worden eerdere meldingen soms aangepast; de aantallen meldingen per dag kunnen daardoor variëren.

[4] Het verschil tussen de cumulatieve meldingen t/m 14 september 10:00 ten opzichte van 7 september 10:00.

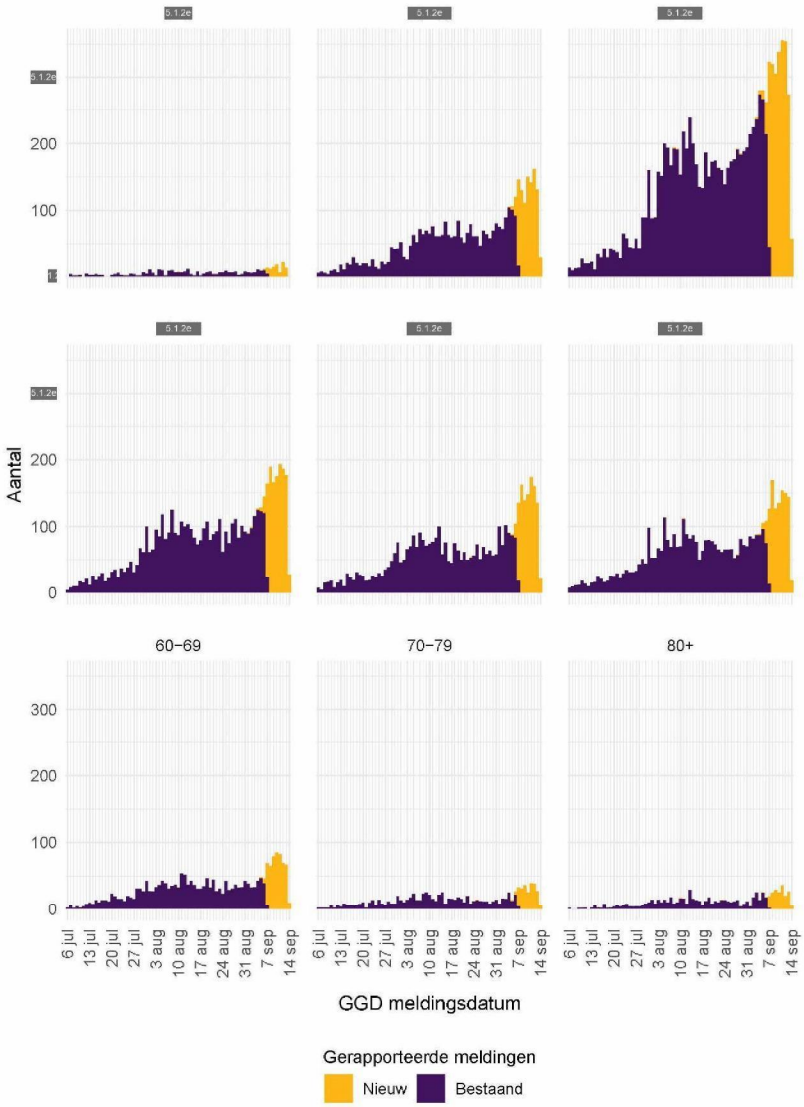
[5] Voor 83 sterfgevallen is aangegeven dat COVID-19 niet de directe oorzaak van overlijden is

2 COVID-19 meldingen aan de GGD'en vanaf 6 juli 2020

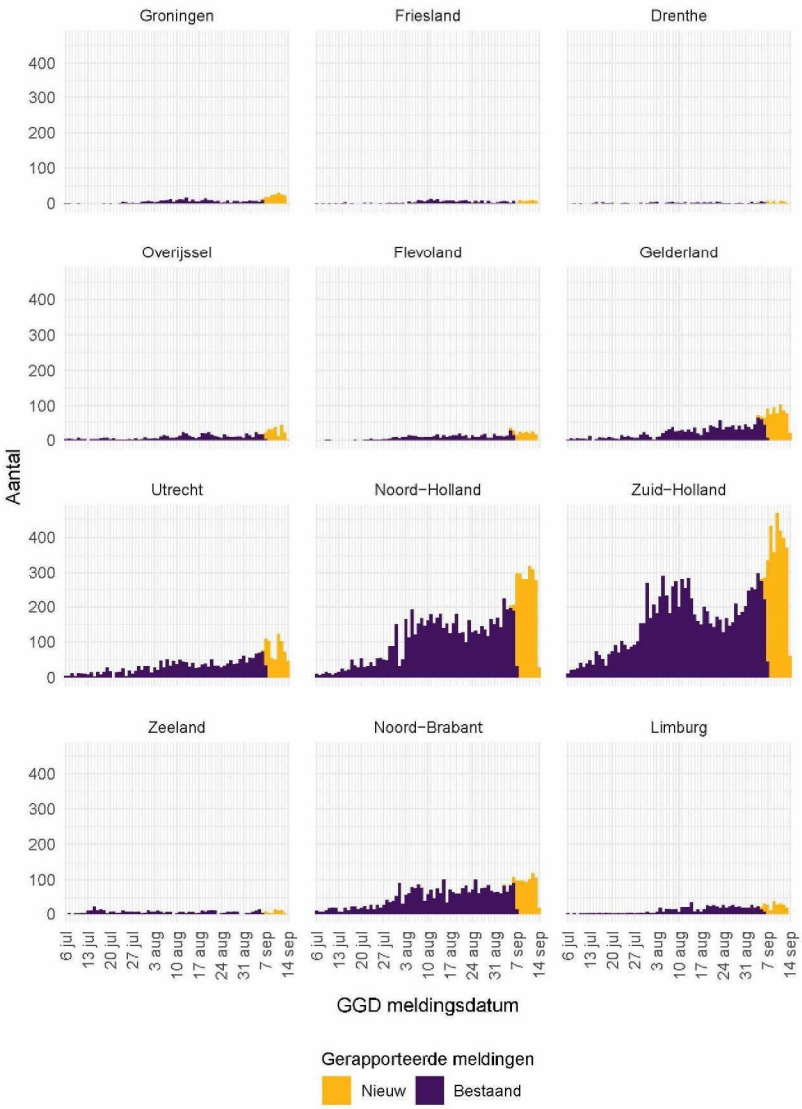


Figuur 1: Aantal aan de GGD'en gemelde COVID-19 patiënten vanaf 6 juli 2020. (A) Aantal aan de GGD'en gemelde COVID-19 patienten, naar meldingsdatum. (B) Aantal aan de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten, naar datum van ziekenhuisopname. (C) Aantal aan de GGD'en gemelde overleden COVID-19 patiënten, naar datum van overlijden.

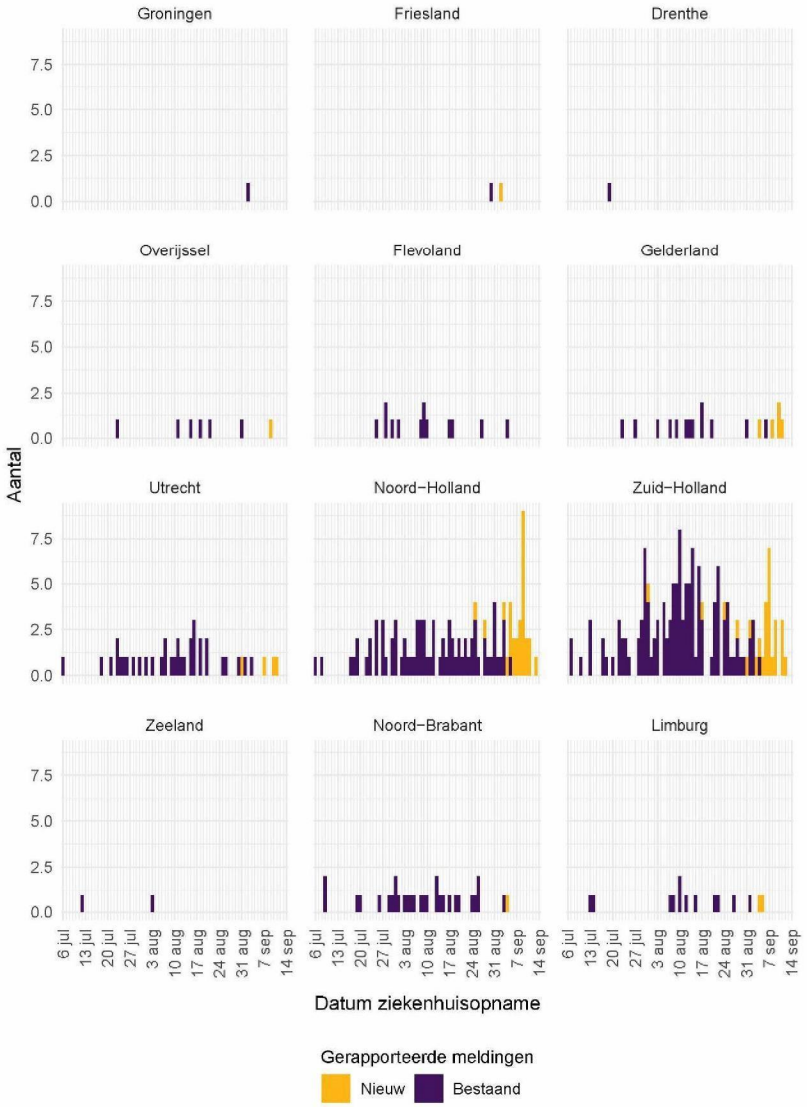
Meldingen aan het RIVM van 6 juli t/m 7 september 10:00 uur zijn in deze grafieken weergegeven in paars. Meldingen van 7 september 10:01 uur t/m 14 september 10:00 uur zijn weergegeven in geel. Sinds 1 juni kan iedereen zich met klachten laten testen. Toch is het aannemelijk dat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier weergegeven worden. Van enkele patiënten is de datum van opname en/of de datum van overlijden niet bekend. Deze kunnen daarom niet worden weergegeven in deze figuren.



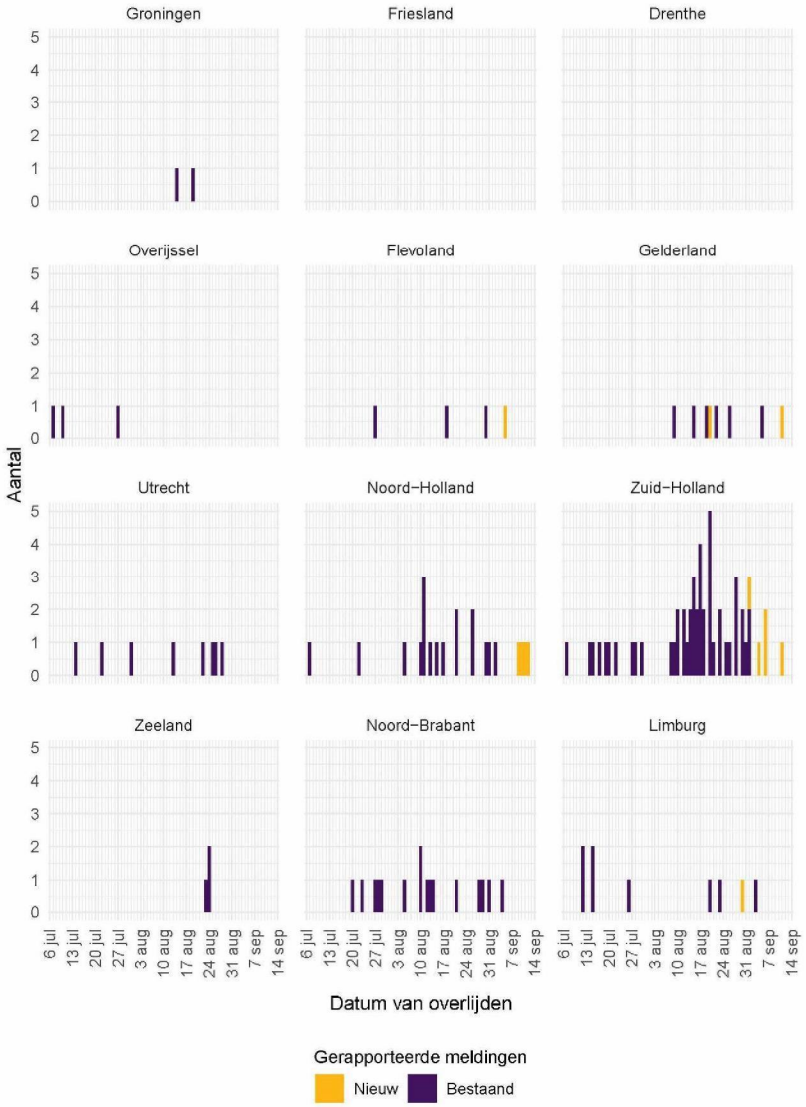
Figuur 2: Aantal bij de GGD'en gemeldeCOVID-19 patiënten vanaf 6 juli 2020,per leeftijdsgroep. Voor de epidemiologische curves met data vanaf 27 februari, zie Figuur 26.



Figuur 3: Aantal bij de GGD'en gemelde COVID-19 patiënten vanaf 6 juli 2020, per provincie. Voor de epidemiologische curves met data vanaf 27 februari, zieFiguur 29.



Figuur 4: Aantal bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten vanaf 6 juli 2020per provincie. Voor de epidemiologische curves met data vanaf 27 februari, zie Figuur 30.



Figuur 5: Aantal bij de GGD'en gemelde overleden COVID-19 patiënten vanaf 6 juli 2020, per provincie. Voor de epidemiologische curves met data vanaf 27 februari, zie Figuur 31.

3 Regionale overzichten van COVID-19 meldingen aan de GGD'en

3.1 Aantal COVID-19 meldingen per provincie in de afgelopen week

Tabel 2: Aantal COVID-19 patiënten bij de GGD'en gemeld, in het ziekenhuis opgenomen en overleden per provincie in de afgelopen week, totaal en per 100.000 inwoners[1,2,3]

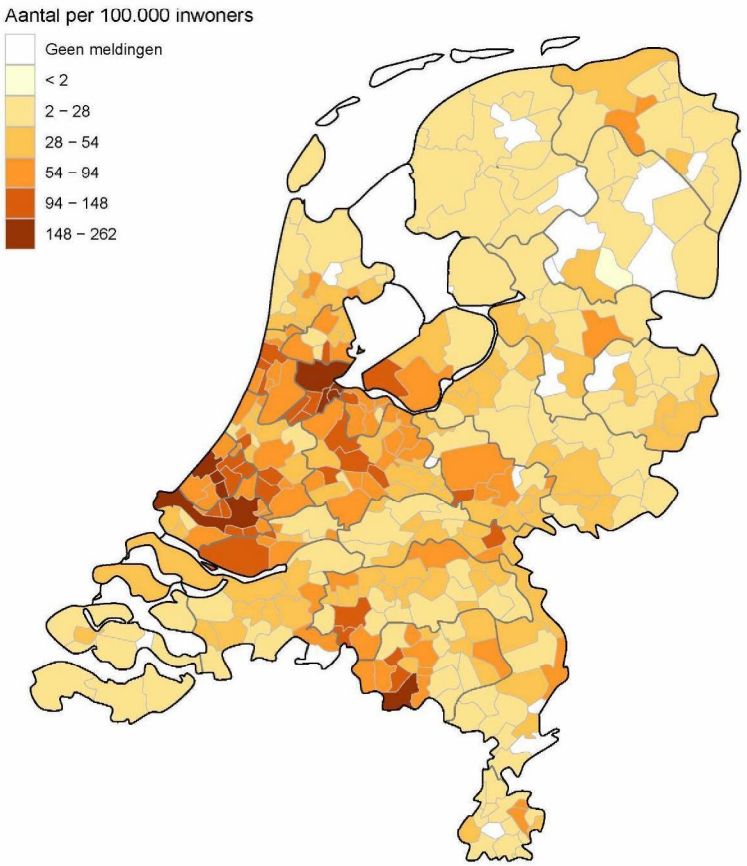
Provincie	Totaal gemeld	/100.000	Ziekenhuisopname	/100.000	Overleden	/100.000
Totaal gemeld	7739	44.5	43	0.2	6	0.0
Groningen	164	28.0	0	0.0	0	0.0
Friesland	46	7.1	0	0.0	0	0.0
Drenthe	30	6.1	0	0.0	0	0.0
Overijssel	193	16.6	1	0.1	0	0.0
Flevoland	138	32.6	0	0.0	0	0.0
Gelderland	627	30.1	4	0.2	1	0.0
Utrecht	656	48.4	3	0.2	0	0.0
Noord-Holland	2084	72.4	19	0.7	4	0.1
Zuid-Holland	2838	76.5	16	0.4	1	0.0
Zeeland	48	12.5	0	0.0	0	0.0
Noord-Brabant	728	28.4	0	0.0	0	0.0
Limburg	187	16.7	0	0.0	0	0.0

[1] Betreft het aantal COVID-19 patiënten met een datum van melding aan de GGD, opnamedatum of datum van overlijden in de periode van 7 september 10:01 t/m 14 september 10:00 uur.

[2] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.

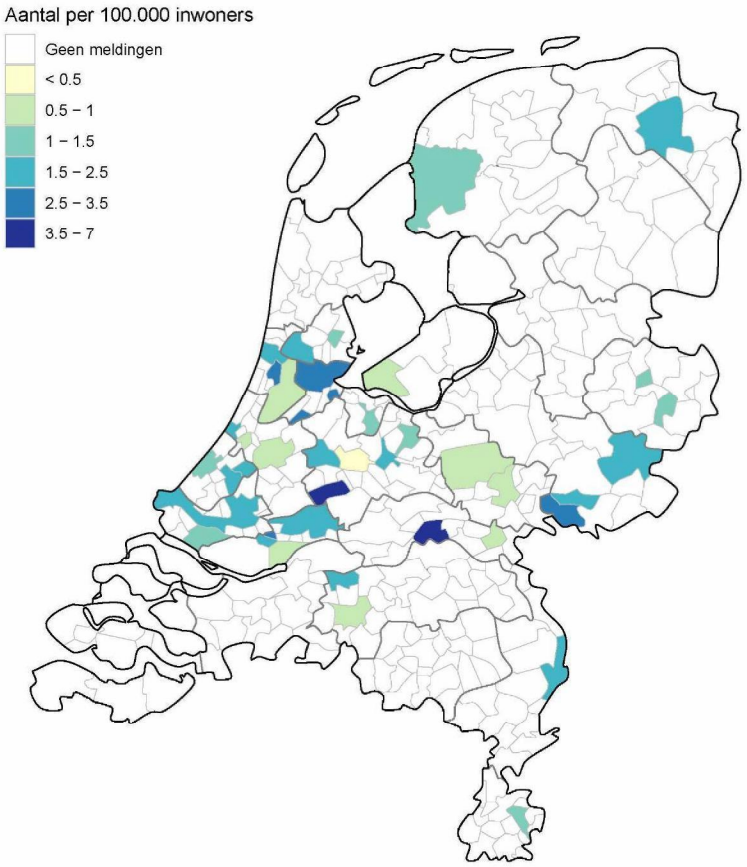
[3] Per 20 mei is de indeling naar provincie gebaseerd op woonlocatie van de patiënt in plaats van meldende GGD. Wanneer woonlocatie onbekend is, is de indeling gebaseerd op meldende GGD.

3.2 Kaarten met COVID-19 meldingen per gemeente in de afgelopen twee weken



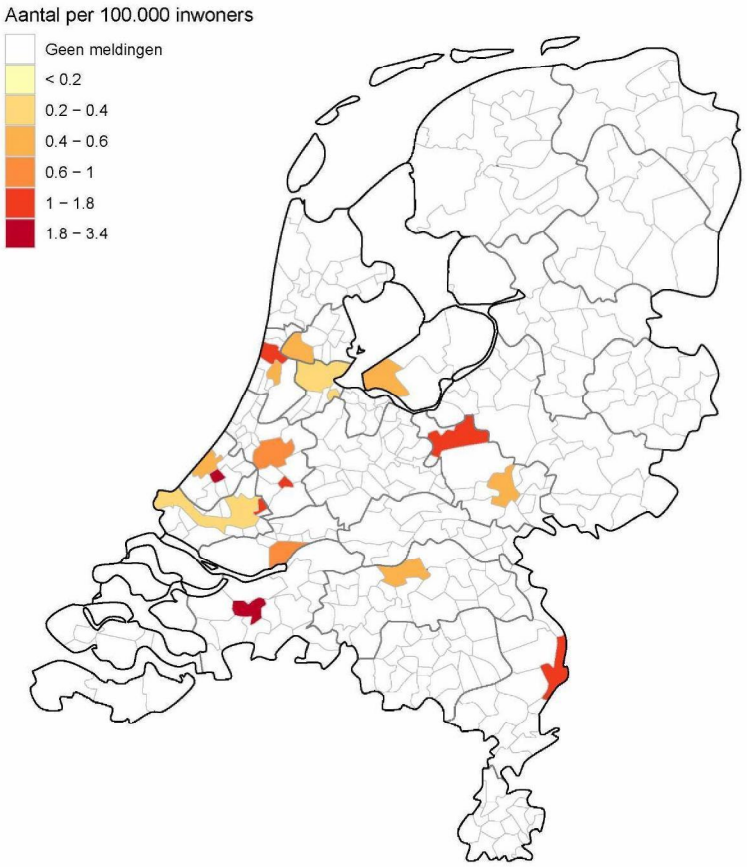
Figuur 6: Aantal in de afgelopen twee weken bij de GGD'en gemelde COVID-19 patiënten per 100.000 inwoners per gemeente met GGD meldingsdatum van 31 augustus t/m 14 september 10:00 uur. De grijze lijnen geven de grenzen van de GGD-regio's weer.

Iedere dinsdag wordt de kleurindeling van de kaart aangepast zodat het contrast tussen gemeenten duidelijker weergegeven wordt.



Figuur 7: Aantal bij de GGD'en gemelde in de afgelopen twee weken in het ziekenhuis opgenomen COVID-19 patiënten per 100.000 inwoners per gemeente met datum van ziekenhuisopname van 31 augustus t/m 14 september 10:00 uur. De grijze lijnen geven de grenzen van de GGD-regio's weer.

Iedere dinsdag wordt de kleurindeling van de kaart aangepast zodat het contrast tussen gemeenten duidelijker weergegeven wordt.



Figuur 8: Aantal bij de GGD'en gemelde in de afgelopen twee weken overleden COVID-19 patiënten per 100.000 inwoners per gemeente met overlijdensdatum van 31 augustus t/m 14 september 10:00 uur. De grijze lijnen geven de grenzen van de GGD-regio's weer .

Iedere dinsdag wordt de kleurindeling van de kaart aangepast zodat het contrast tussen gemeenten duidelijker weergegeven wordt.

4 Leeftijdsverdeling en man-vrouwverdeling van bij GGD'en gemelde COVID-19 patiënten in de afgelopen week

Tabel 3: Leeftijdsverdeling van aan de GGD'en gemelde COVID-19 patiënten, van in het ziekenhuis opgenomen COVID-19 patiënten en van overleden COVID-19 patiënten in de afgelopen week[1,2]

Leeftijdsgroep	Totaal gemeld	%	Ziekenhuisopname	%	Overleden	%
Totaal gemeld	7739		43		6	
0-4	23	0.3	0	0.0	0	0.0
5-9	73	0.9	0	0.0	0	0.0
10-14	244	3.2	0	0.0	0	0.0
15-19	755	9.8	0	0.0	0	0.0
20-24	1432	18.5	2	4.7	0	0.0
25-29	892	11.5	1	2.3	0	0.0
30-34	698	9.0	3	7.0	0	0.0
35-39	580	7.5	0	0.0	0	0.0
40-44	500	6.5	2	4.7	0	0.0
45-49	574	7.4	2	4.7	0	0.0
50-54	545	7.0	0	0.0	0	0.0
55-59	478	6.2	2	4.7	0	0.0
60-64	330	4.3	7	16.3	0	0.0
65-69	195	2.5	6	14.0	0	0.0
70-74	144	1.9	6	14.0	0	0.0
75-79	91	1.2	5	11.6	1	16.7
80-84	75	1.0	5	11.6	1	16.7
85-89	54	0.7	0	0.0	2	33.3
90-94	39	0.5	1	2.3	2	33.3
95+	16	0.2	1	2.3	0	0.0
Niet vermeld	1	0.0	0	0.0	0	0.0

[1] Betreft het aantal COVID-19 patiënten met een datum van melding aan de GGD, opnamedatum of datum van overlijden in de periode van 7 september 10:01 t/m 14 september 10:00 uur.

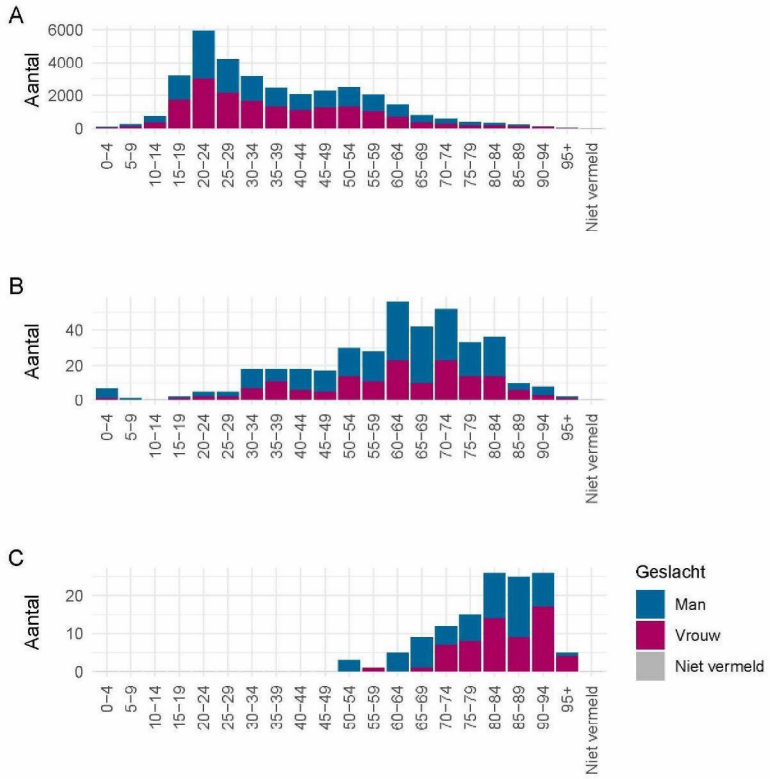
[2] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.

Tabel 4: Man-vrouwverdeling van aan de GGD'en gemelde COVID-19 patiënten, van in het ziekenhuis opgenomen COVID-19 patiënten en van overleden COVID-19 patiënten in de afgelopen week[1,2]

Geslacht	Totaal gemeld	%	Ziekenhuisopname	%	Overleden	%
Totaal gemeld	7739		43		6	
Man	3661	47.3	23	53.5	4	66.7
Vrouw	4078	52.7	20	46.5	2	33.3
Niet vermeld	0	0.0	0	0.0	0	0.0

[1] Betreft het aantal COVID-19 patiënten met een datum van melding aan de GGD, opnamedatum of datum van overlijden in de periode van 7 september 10:01 t/m 14 september 10:00 uur.

[2] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.



Figuur 9: Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde COVID-19 patiënten vanaf 6 juli 2020. (A) Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde COVID-19 patiënten. (B) Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten. (C) Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde overleden COVID-19 patiënten.

5 Reishistorie van bij GGD'en gemelde COVID-19 patiënten vanaf 6 juli 2020 en in de afgelopen week

Tabel 5: Aantal aan de GGD'en gemelde COVID-19 patiënten die in de 14 dagen voor aanvang van de ziekte in het buitenland zijn geweest[1]

	Vanaf 6 juli		Afgelopen week[2]	
	Aantal	%	Aantal	%
Totaal gemeld	32976		7858	
Reishistorie	5190	15.7	448	5.7
Geen reishistorie	21668	65.7	4540	57.8
Niet vermeld	6118	18.6	2870	36.5

[1] Of een COVID-19 patiënt wel of geen reishistorie heeft, wordt vanaf week 36 bepaald door de volgende criteria: a) De patiënt heeft bij de GGD hebben aangegeven een reishistorie te hebben en b) er zit maximaal 14 dagen tussen de terugkomstdag en de eerste ziektedag van de patiënt.
[2] Meldingen die tussen 7 september 10:00 en 14 september 10:00 aan het RIVM zijn gemeld.

Tabel 6: Aantal aan de GGD'en gemelde COVID-19 patiënten die in de 14 dagen voor aanvang van de ziekte in het buitenland zijn geweest naar verblijfplaats

	Vanaf 6 juli		Afgelopen week[1]	
Land van verblijf	Aantal	%	Aantal	%
Spanje	1121	21.6	46	10.3
Frankrijk	942	18.2	71	15.8
Turkije	601	11.6	79	17.6
Duitsland	512	9.9	65	14.5
België	426	8.2	41	9.2
Griekenland	342	6.6	36	8.0
Hongarije	236	4.5	14	3.1
Italië	187	3.6	26	5.8
Malta	162	3.1	1	0.2
Tsjechië	135	2.6	20	4.5
Oostenrijk	131	2.5	10	2.2
Kroatië	96	1.8	5	1.1
Polen	81	1.6	4	0.9
Aruba	65	1.3	0	0.0
Portugal	64	1.2	9	2.0
Overig	730	14.1	66	14.7

[1] Meldingen die tussen 7 september 10:00 en 14 september 10:00 aan het RIVM zijn gemeld.

6 Setting van mogelijke besmetting van bij GGD'en gemelde COVID-19 patiënten vanaf 6 juli 2020 en in de afgelopen week

In het brononderzoek door de GGD wordt bij COVID-19 patiënten nagegaan of er gerelateerde ziektegevallen zijn. Als dit het geval is wordt vermeld in welke setting de besmetting mogelijk heeft plaatsgevonden.

Tabel 7: Aantal aan de GGD'en gemelde COVID-19 patiënten naar aanwezigheid van gerelateerde ziektegevallen[1]

	Vanaf 6 juli		Afgelopen week[2]	
Gerelateerde ziektegevallen aanwezig	Aantal	%	Aantal	%
Totaal gemeld	32979		7858	
Ja, setting vermeld	12047	36.5	1992	25.3
Ja, setting niet vermeld	2847	8.6	765	9.7
Ja, setting onbekend	195	0.6	50	0.6
Nee	10587	32.1	2045	26.0
Niet vermeld	7303	22.1	3006	38.3

[1] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijk dat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden.

[2] Meldingen die tussen 7 september 10:00 en 14 september 10:00 aan het RIVM zijn gemeld.

Tabel 8: Vermelde mogelijke settings van besmetting van aan de GGD'en gemelde COVID-19 patiënten waarbij sprake is van gerelateerde gevallen[1,2]

	Vanaf 6 juli		Afgelopen week[3]	
Setting	Aantal	%	Aantal	%
Thuissituatie (huisgenoten)	6436	53.4	1115	56.0
Overige familie	1747	14.5	194	9.7
Partner, niet samenwonend[4]	42	0.3	9	0.5
Kennissen en vrienden[4]	929	7.7	116	5.8
Werksituatie	1156	9.6	207	10.4
School en kinderopvang	110	0.9	53	2.7
Medereiziger / reis / vakantie[4]	857	7.1	29	1.5
Vlucht[4]	37	0.3	1	0.1
Horeca[5]	556	4.6	107	5.4
Feest / verjaardag / borrel[4]	319	2.6	29	1.5
Studentenvereniging/-activiteiten[4]	144	1.2	35	1.8
Vrijetijdsbesteding, zoals sportclub	256	2.1	66	3.3
Religieuze bijeenkomsten	33	0.3	5	0.3
Koor	5	0.0	3	0.2
1e lijn gezondheidszorg / huisarts	38	0.3	6	0.3
2e lijn gezondheidszorg / ziekenhuis	80	0.7	16	0.8
Overige gezondheidszorg	38	0.3	7	0.4
Verpleeghuis	750	6.2	181	9.1
Woonzorgcentrum voor ouderen	171	1.4	34	1.7
Woonvoorziening voor verstandelijk beperkten	46	0.4	21	1.1
Woonvoorziening voor lichamelijk beperkten	8	0.1	6	0.3
Overige woonvoorziening	44	0.4	3	0.2
Dagopvang voor ouderen	3	0.0	1	0.1
Dagopvang voor verstandelijk beperkten	4	0.0	1	0.1
Dagopvang voor lichamelijk beperkten	1	0.0	0	0.0
Overige dagopvang	7	0.1	0	0.0
Hospice	3	0.0	1	0.1
Uitvaart[4]	20	0.2	1	0.1
Overig	297	2.5	48	2.4

[1] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijk dat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden.

[2] Per patiënt kunnen meerdere settings gerapporteerd zijn. De percentages in Tabel 8 worden berekend ten opzichte van het aantal patiënten waarbij sprake is van gerelateerde gevallen en tenminste één setting is vermeld (Tabel 7).

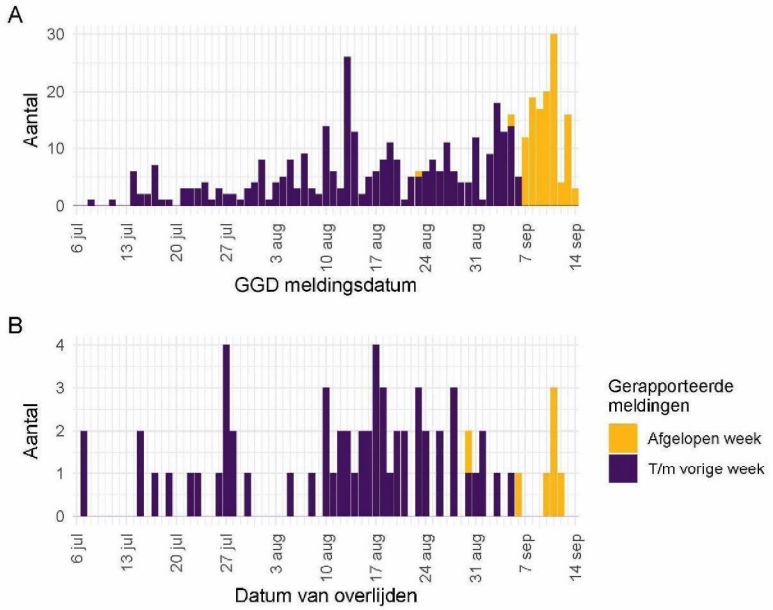
[3] Meldingen die tussen 7 september 10:00 en 14 september 10:00 aan het RIVM zijn gemeld.

[4] 'Tot 6 augustus werden deze settings geregistreerd als 'overige setting'. Vanaf 6 augustus is de GGD gevraagd deze overige settings nader te specificeren.

[5] Vanaf 1 juli is deze setting gestructureerd nagevraagd.

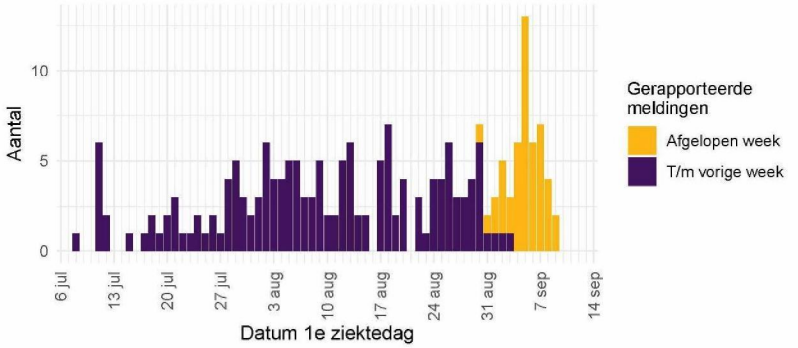
7 Surveillance van COVID-19 in verpleeghuizen en woonzorgcentra vanaf 6 juli 2020

Via een samenwerking tussen artsen, laboratoria en de GGD'en wordt informatie verzameld over personen (patiënten) met een positieve COVID-19 testuitslag (zie pagina 1). Vanaf 1 juli is gestructureerd nagevraagd of een persoon in een verpleeghuis of woonzorgcentrum woont. Vanaf 8 september wordt deze informatie gebruikt om het aantal COVID-19 patiënten woonachtig in een verpleeghuis of woonzorgcentrum, en het aantal bewoners met COVID-19 die overleden zijn, te monitoren.



Figuur 10: Aantal verpleeghuis- en woonzorgcentrumbewoners met COVID-19 gemeld aan de GGD'en vanaf 6 juli 2020. (A) Aantal gemelde verpleeghuis- en woonzorgcentrumbewoners, naar meldingsdatum. (B) Aantal overleden verpleeghuis- en woonzorgcentrumbewoners, naar datum van overlijden.

Meldingen aan het RIVM t/m 7 september 10:00 uur zijn in deze grafieken weergegeven in paars. Meldingen van 7 september 10:01 uur t/m 14 september 10:00 uur zijn weergegeven in geel. De werkelijke aantallen COVID-19 patiënten en overleden COVID-19 patiënten zijn hoger dan zoals hier weergegeven omdat waarschijnlijk niet alle mogelijk besmette personen getest worden.



Figuur 11: Aantal nieuwe verpleeghuis- en woonzorgcentrumlocaties met COVID-19 vanaf 6 juli 2020. Aantal nieuwe verpleeghuis- en woonzorgcentrumlocaties waar sprake is van tenminste één COVID-19 besmetting op basis van een positieve test. Een verpleeghuis of woonzorgcentrum wordt meegeteld als 'nieuwe locatie' wanneer er tenminste 28 dagen vóór de positieve test geen nieuwe patiënten zijn gemeld.

Meldingen aan het RIVM t/m 7 september 10:00 uur zijn in deze grafieken weergegeven in paars. Meldingen van 7 september 10:01 uur t/m 14 september 10:00 uur zijn weergegeven in geel.

8 Bron- en contactonderzoek van COVID-19 meldingen aan de GGD'en

8.1 Resultaten uit bron- en contactonderzoek

Wanneer iemand besmet is met het nieuwe coronavirus start de GGD met bron- en contactonderzoek (BCO) volgens een landelijk protocol, met als doel om verdere verspreiding van het virus te voorkomen. Het contactonderzoek richt zich op personen met wie de besmette persoon de afgelopen tijd in contact is geweest. Nauwe contacten zijn mensen waarmee langer dan 15 minuten op minder dan 1,5 meter afstand contact is geweest tijdens de besmettelijke periode, waarbij onderscheid wordt gemaakt tussen huisgenoten en overige nauwe contacten. Andere (niet nauwe) contacten van de besmette persoon zijn mensen die langer dan 15 minuten met de persoon in dezelfde ruimte waren, maar waar wel 1,5 meter afstand was.

De GGD neemt contact op met de nauwe contacten van de besmette persoon en adviseert hen tot 10 dagen na het laatste contact met de besmette persoon thuis in quarantaine te blijven. De andere (niet nauwe) contacten krijgen een brief of e-mail. Contacten moeten zich bij de eerste klachten zo snel mogelijk laten testen. Nauwe contacten worden op individuele basis geregistreerd, indien zij gelinkt zijn aan meerdere besmette personen worden ze niet dubbel in de rapportage meegenomen. Niet nauwe contacten worden pas individueel geregistreerd als ze zich bij de GGD melden met klachten.

Tabel 9: Aantallen aan de GGD'en gemelde COVID-19 patiënten, aantallen gevonden in het kader van bron- en contactonderzoek en aantallen waarbij contactinventarisatie is uitgevoerd[1]

		Gevonden ihkv BCO[2]		Contactinventarisatie uitgevoerd	
Week	Nieuwe meldingen	Aantal	%	Aantal	%
27	435	—	—	400	92.0
28	469	125	26.7	440	93.8
29	929	266	28.6	912	98.2
30	1285	359	27.9	1261	98.1
31	2378	573	24.1	2269	95.4
32	3923	717	18.3	3558	90.7
33	4063	661	16.3	3783	93.1
34	3605	525	14.6	3433	95.2
35	3573	597	16.7	3395	95.0
36	4944	762	15.4	4601	93.1
37	7567	907	12.0	5041	66.6

[1] Contactinventarisatie houdt in dat de GGD voor elke nieuwe COVID-19 melding in kaart brengt welke contacten deze patiënt heeft gehad tijdens de besmettelijke periode, die twee dagen voor de start van de klachten begint.
[2] Geen volledige gegevens over week 27.

Tabel 10: Resultaten uit het bron- en contactonderzoek van de bij de GGD'en gemelde COVID-19 patiënten[1]

Soort contact[2,3]	Week-nummer[4]	Contacten	Gemiddeld aantal contacten per nieuwe COVID-19 melding[5]	Positief geteste contacten	% Positief geteste contacten[6]
Totaal	27	1546	3.9	100	6.5
	28	1693	3.8	167	9.9
	29	3277	3.6	376	11.5
	30	4129	3.3	378	9.2
	31	6298	2.8	639	10.1
	32	7023	2.0	642	9.1
	33	7513	2.0	444	5.9
	34	8806	2.6	560	6.4
	35	10226	3.0	723	7.1
	36	13265	2.9	1114	8.4
	37	12872	2.6	496	3.9
Huisgenoten	27	612	1.5	72	11.8
	28	611	1.4	88	14.4
	29	1211	1.3	230	19.0
	30	1544	1.2	217	14.1
	31	2415	1.1	396	16.4
	32	2745	0.8	401	14.6
	33	2695	0.7	237	8.8
	34	3487	1.0	294	8.4
	35	4124	1.2	398	9.7
	36	5721	1.2	698	12.2
	37	5981	1.2	355	5.9
Overige nauwe contacten	27	911	2.3	28	3.1
	28	1069	2.4	78	7.3
	29	2050	2.2	144	7.0
	30	2563	2.0	158	6.2
	31	3866	1.7	240	6.2
	32	4258	1.2	238	5.6
	33	4784	1.3	206	4.3
	34	5274	1.5	264	5.0
	35	6071	1.8	324	5.3
	36	7471	1.6	415	5.6
	37	6824	1.4	138	2.0

[1] Vanwege onvolledige registratie bij een aantal GGD'en in week 32, 33 en 34 zijn de gegevens over deze weken niet volledig.
[2] Andere, niet nauwe contacten zijn niet meegenomen in Totaal.
[3] Van enkele nauwe contacten is niet bekend wat voor soort contact ze zijn.
[4] Het weeknummer is gebaseerd op de datum van registratie bij de GGD.
[5] Hierbij worden alleen de nieuwe COVID-19 meldingen meegenomen waarvoor contactinventarisatie is uitgevoerd, zie Tabel 9.
[6] In verband met de monitorperiode van 14 dagen zijn de gegevens over het aantal en percentage positief geteste contacten niet volledig voor week 36 en 37.

9 SARS-CoV-2 testen afgenomen door de GGD'en vanaf 1 juni

Vanaf 1 juni kunnen alle personen met klachten passend bij SARS-CoV-2 infectie (COVID-19) zich laten testen door de GGD, bijvoorbeeld in de teststraten. Voor 1 juni is in alle GGD regio's het afspraken- en uitslagensysteem CoronIT geïmplementeerd. Onderstaande rapportage is gebaseerd op CoronIT data van voorbije volledige kalenderweken vanaf 1 juni 2020, geëxporteerd op 13 september 2020.

Sinds 12 augustus is er een teststraat op Schiphol, waar terugkerende reizigers uit risicogebieden zich kunnen laten testen, ook wanneer zij asymptomisch zijn. In sectie 9.1 zijn het totaal aantal uitgevoerde testen in Nederland, exclusief testlocatie Schiphol, opgenomen. In sectie 9.2 zijn enkel de gegevens van testlocatie Schiphol opgenomen. Totale aantallen uitslagen zijn gebaseerd op alleen positieve en negatieve uitslagen, testen met uitslag heranalyse of onbeoordeelbaar zijn geëxcludeerd. Omdat alleen geboortejaar beschikbaar is om de leeftijd van patiënten te bepalen, is 2020 minus het geboortejaar gebruikt om de leeftijd toe te kennen. Dit betekent dat ongeveer de helft van de patiënten een jaar te oud is ingeschat.

9.1 SARS-CoV-2 testen afgenomen door de GGD'en in heel Nederland (exclusief testlocatie Schiphol) vanaf 1 juni

Tabel 11: Aantal testen uitgevoerd door de GGD'en, met bekende uitslag

Weeknummer	Totaal aantal testen met uitslag	Aantal positief	Percentage positief
23	48812	986	2.0
24	57013	841	1.5
25	61604	567	0.9
26	61222	426	0.7
27	67248	375	0.6
28	74919	463	0.6
29	88508	925	1.0
30	111416	1195	1.1
31	101471	2411	2.4
32	98621	3681	3.7
33	102921	3719	3.6
34	135723	3398	2.5
35	156298	3420	2.2
36	176599	5163	2.9
37[1]	64761	2169	3.3
Totaal	1407136	29739	2.1

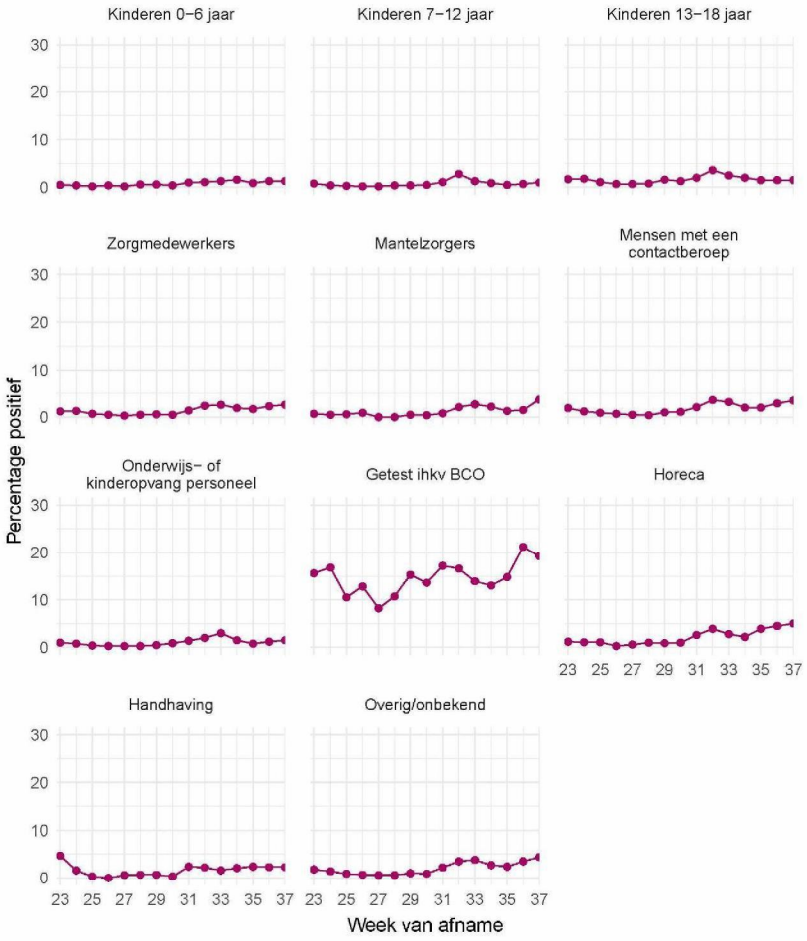
[1] De gegevens van week 37 zijn nog niet volledig.

Tabel 12: Aantal testen en percentage positief per doelgroep uitgevoerd door de GGD'en.

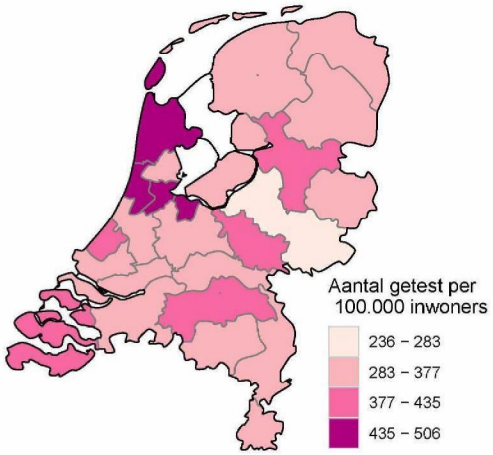
Groep	Vanaf 1 juni			Afgelopen kalender week[1]		
	Aantal positief	Aantal getest	Percentage positief	Aantal positief	Aantal getest	Percentage positief
Getest ihkv BCO[2]	2351	15521	15.1	81	422	19.2
Kinderen 0-6 jaar	93	13317	0.7	6	457	1.3
Kinderen 7-12 jaar	379	61456	0.6	45	4532	1.0
Kinderen 13-18 jaar	1299	75466	1.7	103	6700	1.5
Zorgmedewerkers	1262	89265	1.4	119	4553	2.6
Onderwijs/kinderopvang	635	71011	0.9	111	7427	1.5
Mantelzorgers	36	3001	1.2	5	136	3.7
Contactberoep	2813	138595	2.0	280	7927	3.5
Horeca	782	27602	2.8	82	1639	5.0
Handhaving[3]	129	7777	1.7	12	530	2.3
Overig/onbekend	19960	904125	2.2	1325	30438	4.4
Totaal	29739	1407136	2.1	2169	64761	3.3

[1] Van 7 september tot en met 13 september.
[2] Voor deze personen is geregistreerd dat zij getest zijn in het kader van bron- en contactonderzoek (BCO). Het werkelijk aantal geteste personen vanwege BCO is waarschijnlijk hoger.
[3] Onder handhaving vallen medewerkers bij politie, BOA, marechaussee, brandweer en Dienst Justitiële Inrichtingen.

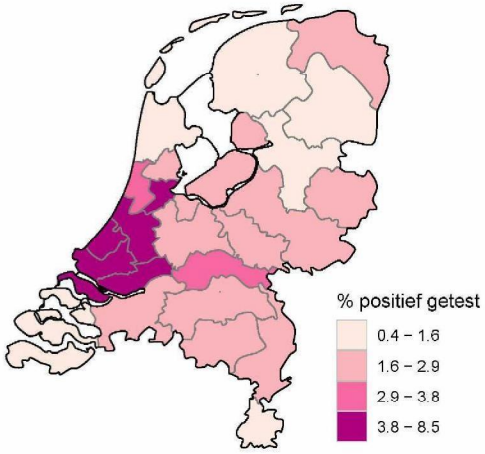
Figuur 12: Aantal positieve en negatieve testen per week en per doelgroep vanaf 1 juni. NB: De reikwijdtes van de y-assen verschillen.



Figuur 13: Percentage positieve testen per doelgroep en per kalenderweek vanaf 1 juni.



Figuur 14: Aantal testen per 100.000 inwoners per GGD regio waar de patiënt woont in de afgelopen kalenderweek (van 7 september tot en met 13 september). De grijze lijnen geven de grenzen van de GGD-regio's weer.



Figuur 15: Percentage positieve testen per GGD regio waar de patiënt woont in de afgelopen kalenderweek (van 7 september tot en met 13 september). De grijze lijnen geven de grenzen van de GGD-regio's weer.

Tabel 13: Aantal positieve en negatieve testen vanaf 1 juni per leeftijdsgroep en geslacht.

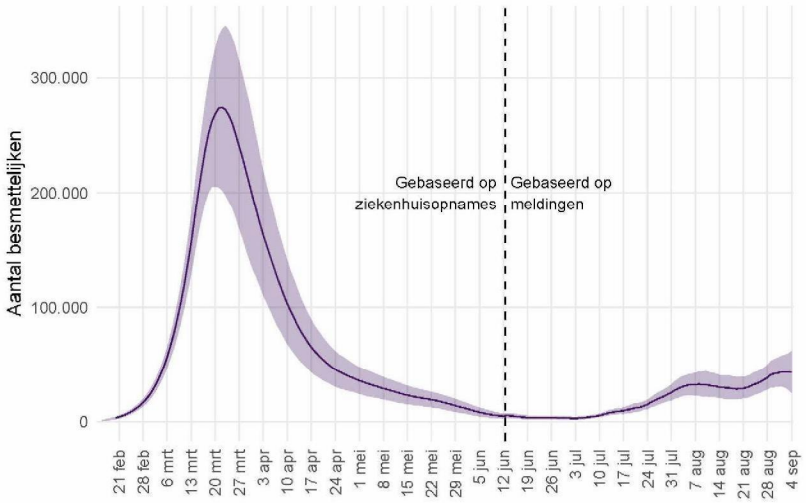
	Mannen			Vrouwen		
Leeftijdsgroep	Aantal positief	Aantal getest	Percentage positief	Aantal positief	Aantal getest	Percentage positief
0-4	55	4780	1.2	45	3839	1.2
5-9	116	17666	0.7	132	15170	0.9
10-14	329	38524	0.9	335	32095	1.0
15-19	1151	46506	2.5	1428	52396	2.7
20-24	2713	60098	4.5	2657	79675	3.3
25-29	1999	59818	3.3	2039	86490	2.4
30-34	1453	64285	2.3	1567	94814	1.7
35-39	1096	60546	1.8	1235	84617	1.5
40-44	876	49104	1.8	1068	66144	1.6
45-49	932	40652	2.3	1098	54757	2.0
50-54	1087	38530	2.8	1229	51734	2.4
55-59	967	34498	2.8	923	48092	1.9
60-64	676	31582	2.1	662	43019	1.5
65-69	366	25809	1.4	331	30943	1.1
70-74	225	20100	1.1	233	21450	1.1
75-79	115	10593	1.1	118	11280	1.0
80-84	66	5621	1.2	85	5915	1.4
85-89	24	2250	1.1	32	2434	1.3
90-94	11	543	2.0	8	780	1.0
95+	1	91	1.1	2	146	1.4
Niet vermeld	0	0	0.0	0	0	0.0
Totaal	14258	611596	2.3	15227	785790	1.9

10 Schattingen en berekeningen

10.1 Schatting van het aantal besmettelijke personen gebaseerd op gegevens t/m 4 september 2020

Als iemand het coronavirus oploopt, is hij/zij een tijd lang besmettelijk voor anderen. Hoe lang dit duurt, verschilt van persoon tot persoon. Op basis van verschillende gegevensbronnen over hoeveel mensen het coronavirus opgelopen hebben in een bepaalde periode, kan een inschatting worden gemaakt van het aantal besmettelijke personen in de algemene bevolking. Deze schatting gaat gepaard met onzekerheid: het exacte aantal is onbekend, maar we kunnen door berekeningen aangeven tussen welke waarden het zich waarschijnlijk bevindt. Op 4 september lag het geschatte aantal besmettelijken tussen 25242 en 62381 personen.

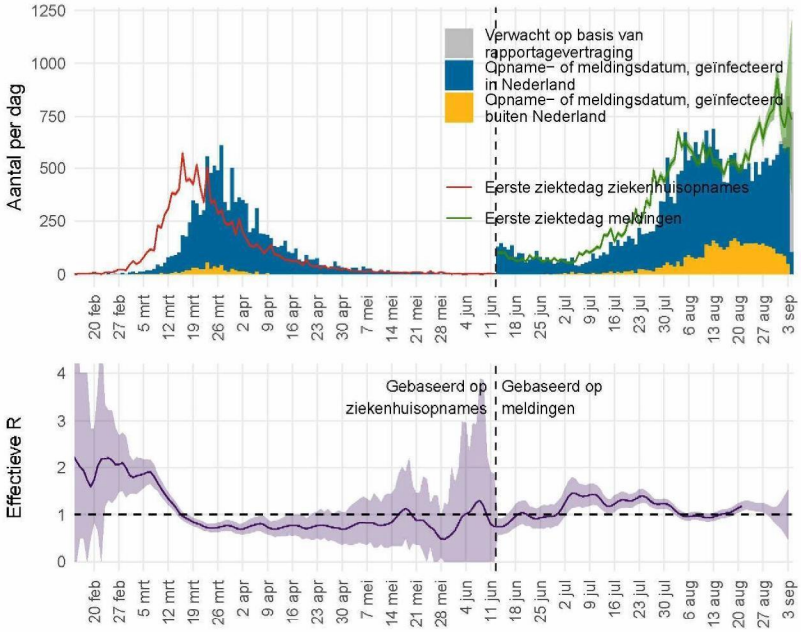
De methode is nog in ontwikkeling. Eerder baseerden we een schatting van het aantal besmettelijke personen op basis van intensive care (IC) opnames. Omdat het aantal mensen dat met COVID-19 op een IC is opgenomen heel laag kan zijn, baseren we de schattingen voor aantal besmettingen in de periode van februari tot 12 juni 2020 op basis van ziekenhuisopnames. Vanaf 12 juni berekenen we het aantal besmettelijke personen op basis van het aantal meldingen van COVID-19 patiënten omdat het aantal ziekenhuisopnames laag is. Dit aantal meldingen wordt bijgehouden door de GGD'en.



Figuur 16: Het geschat aantal besmettelijke personen voor Nederland. De figuur geeft het aantal besmettelijke personen op basis van het aantal ziekenhuisopnames tot 12 juni, links van de verticale stippellijn, en het aantal besmettelijke personen op basis van het aantal meldingen vanaf 12 juni, rechts van de stippellijn. We definiëren besmettelijke personen hier als mensen die een infectie hebben, en die ook in redelijke mate besmettelijk zijn, waarbij uiteindelijk aantoonbare antistoffen worden gevormd na deze infectie.

10.2 Het reproductiegetal R gebaseerd op gegevens t/m 4 september 2020

Het reproductiegetal R geeft het gemiddeld aantal mensen dat besmet wordt door een persoon met COVID-19. Voor de schatting van dit reproductiegetal gebruiken we het aantal gemelde COVID-19 ziekenhuisopnames per dag in Nederland. Omdat een ziekenhuisopname van een COVID-19 patiënt met enige vertraging doorgegeven wordt in het rapportagesysteem, corrigeren we de aantallen ziekenhuisopnames voor deze vertraging[1]. Voor een groot deel van de gemelde patiënten is de eerste ziektedag bekend. Deze informatie wordt gebruikt om de eerste ziektedag voor de overige patiënten te schatten. Door het aantal in het ziekenhuis opgenomen patiënten per datum van eerste ziektedag weer te geven is direct te zien of het aantal infecties toeneemt, piekt of afneemt. Voor de berekening van het reproductiegetal is het ook nodig te weten wat de tijdsduur is tussen de eerste ziektedag van een COVID-19 patiënt en de eerste ziektedag van zijn of haar besmetter. Deze tijdsduur is gemiddeld 4 dagen, berekend op basis van COVID-19 meldingen aan de GGD. Als het aantal nieuwe ziekenhuisopnames laag is, berekenen we het reproductiegetal R op basis van het aantal meldingen van COVID-19 patiënten. Dit aantal meldingen wordt bijgehouden door de GGD'en. Met deze informatie wordt de waarde van het reproductiegetal berekend zoals beschreven in Wallinga & Lipsitch 2007[2].



Figuur 17: Het effectief reproductiegetal R voor Nederland.

[1] van de Kassteele J, Eilers PHC, Wallinga J. Nowcasting the Number of New Symptomatic Cases During Infectious Disease Outbreaks Using Constrained P-spline Smoothing. Epidemiology. 2019;30(5):737-745. doi:10.1097/EDE.0000000000001050.

[2] Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc Biol Sci. 2007;274(1609):599-604. doi:10.1098/rspb.2006.3754.

Figuur 17 geeft links van de stippellijn in blauw het aantal in Nederland voor COVID-19 in het ziekenhuis opgenomen patiënten naar opnamedatum, zoals gemeld aan de GGD'en. In grijs is het verwachte extra aantal opnames weergegeven, op basis van correctie voor rapportagevertraging. Het aantal in het ziekenhuis opgenomen patiënten per datum van eerste ziektedag is weergegeven in rood. Bij patiënten waar de eerste ziektedag niet bekend is, is deze geschat. Op basis van deze eerste ziektedag voor in het ziekenhuis opgenomen patiënten wordt het reproductiegetal berekend. Als het aantal nieuwe ziekenhuisopnames laag is, berekenen we het reproductiegetal R op basis van het aantal meldingen van COVID-19 patiënten. Rechts van de stippellijn is het aantal meldingen naar meldingsdatum weergegeven in blauw. De eerste ziektedag van deze patiënten is weergegeven in groen. De meest aannemelijke waarde van het reproductiegetal is weergegeven als paarse lijn in de onderste figuur. Wanneer de rode of groene lijn in de bovenste figuur een stijgende trend heeft is het reproductiegetal groter dan 1, wanneer de rode of groene lijn een dalende trend heeft is het reproductiegetal kleiner dan 1. De onzekerheidsmarge van een reproductiegetal is groter als er weinig ziekenhuisopnames of als er weinig meldingen zijn (paars, het 95% betrouwbaarheidsinterval). Bij lage aantallen ziekenhuisopnames wordt de onzekerheid van het reproductiegetal groter en kan deze meer schommelen. Als de schatting boven de waarde 1 komt, moet eerst naar de bandbreedte worden gekeken voordat er conclusies kunnen worden getrokken. De rapportagevertragingen en de tijdsduur tussen opeenvolgende infecties betekenen in Nederland dat we betrouwbare schattingen kunnen maken van de waarde van het reproductiegetal R langer dan 14 dagen geleden. Voor schattingen van R meer recent dan 14 dagen geleden is de betrouwbaarheid niet groot, en voor deze periode wordt de meest aannemelijke waarde weggelaten. Op 21 augustus was het reproductiegetal R gemiddeld 1.17 (1.08 – 1.27, 95% betrouwbaarheidsinterval).

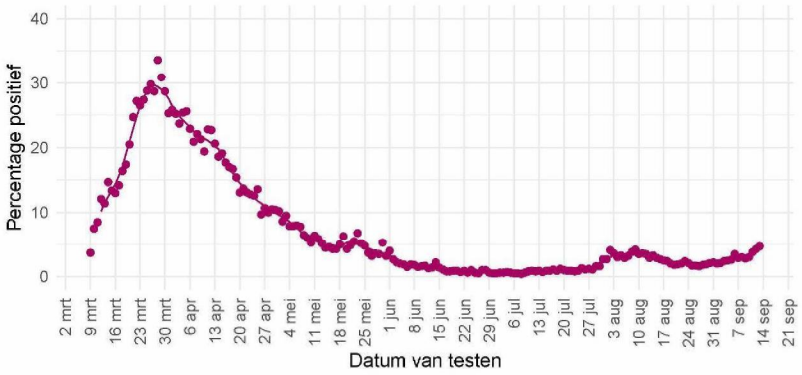
11 COVID-19 gegevens uit overige bronnen

11.1 SARS-CoV-2 laboratoriumtests op basis van de virologische dagstaten

Om zicht te houden op het aantal geteste personen en het aantal positief geteste personen op het SARS-CoV-2 virus in Nederland, is alle laboratoria in Nederland die diagnostiek voor SARS-CoV-2 uitvoeren gevraagd om vanaf 9 maart deze data dagelijks te melden. De laboratoria rapporteren op maandag voor 12 uur over de voorgaande week. Het aantal personen met een positieve uitslag wijkt af van het aantal patiënten gemeld door GGD'en omdat sommige personen mogelijk vaker getest worden en omdat positieve laboratorium uitslagen sneller gerapporteerd kunnen worden.

Tabel 14: Aantal geteste personen en aantal SARS-CoV-2 positief geteste personen in Nederland, gemeld door laboratoria, per week.

Datum van - tot	Aantal labs	Aantal geteste personen	Aantal personen met positieve uitslag	% positief
2020-03-09 - 2020-03-15	30	17080	1529	9.0
2020-03-16 - 2020-03-22	35	21338	3953	18.5
2020-03-23 - 2020-03-29	37	24745	7232	29.2
2020-03-30 - 2020-04-05	40	29098	7424	25.5
5.1.2e - 5.1.2e	41	38960	8391	21.5
2020-04-13 - 2020-04-19	42	40102	7140	17.8
2020-04-20 - 2020-04-26	43	38395	4947	12.9
2020-04-27 - 2020-05-03	44	28954	2906	10.0
2020-05-04 - 2020-05-10	46	29006	2072	7.1
2020-05-11 - 2020-05-17	49	32687	1678	5.1
2020-05-18 - 2020-05-24	52	28836	1578	5.5
2020-05-25 - 2020-05-31	52	33871	1302	3.8
5.1.2e - 5.1.2e	53	58956	1224	2.1
5.1.2e - 5.1.2e	53	63778	1004	1.6
5.1.2e - 5.1.2e	53	65541	619	0.9
5.1.2e - 5.1.2e	53	64140	493	0.8
5.1.2e - 5.1.2e	53	69658	408	0.6
5.1.2e - 5.1.2e	54	79309	520	0.7
2020-07-13 - 2020-07-19	53	89783	858	1.0
2020-07-20 - 2020-07-26	53	113744	1099	1.0
2020-07-27 - 2020-08-02	54	122021	2403	2.0
2020-08-03 - 2020-08-09	55	118058	3950	3.3
2020-08-10 - 2020-08-16	54	121253	3900	3.2
2020-08-17 - 2020-08-23	54	161406	3416	2.1
2020-08-24 - 2020-08-30	54	183218	3296	1.8
2020-08-31 - 2020-09-06	54	180822	4433	2.5
2020-09-07 - 2020-09-13	50	143976	4710	3.3



Figuur 18: Percentage van personen die getest zijn op SARS-CoV-2 waarbij de testuitslag positief was, gemeld door de virologische laboratoria. De stippen geven het percentage per dag aan; de lijn een 7-daags lopend gemiddelde.

Tabel 15: Aantal geteste personen en aantal SARS-CoV-2 positief geteste personen in Nederland, gemeld door virologische laboratoria, uitgesplitst naar aanvrager[1]. De gegevens van de laatste vier kalenderweken (van 17 augustus t/m 13 september) zijn weergegeven per week. De gegevens van de periode daarvoor, vanaf 15 juni, zijn samengevoegd.

Aanvrager	Datum van - tot	Aantal labs	Aantal geteste personen	Aantal personen met positieve uitslag	Percentage positief
Ziekenhuis	5.12e - 5.12e	41	45490	433	1.0
	2020-08-17 - 2020-08-23	34	6039	105	1.7
	2020-08-24 - 2020-08-30	34	6986	107	1.5
	2020-08-31 - 2020-09-06	34	7553	133	1.8
	2020-09-07 - 2020-09-13	33	7906	186	2.4
Verpleeghuis	5.12e - 5.12e	41	7669	107	1.4
	2020-08-17 - 2020-08-23	34	1410	30	2.1
	2020-08-24 - 2020-08-30	34	1759	31	1.8
	2020-08-31 - 2020-09-06	34	2293	95	4.1
	2020-09-07 - 2020-09-13	33	1989	67	3.4
GGD	5.12e - 5.12e	41	398945	6675	1.7
	2020-08-17 - 2020-08-23	34	81866	1767	2.2
	2020-08-24 - 2020-08-30	34	93755	1668	1.8
	2020-08-31 - 2020-09-06	34	95097	1993	2.1
	2020-09-07 - 2020-09-13	33	65583	1882	2.9
Overig	5.12e - 5.12e	41	37354	385	1.0
	2020-08-17 - 2020-08-23	34	9276	91	1.0
	2020-08-24 - 2020-08-30	34	8696	65	0.7
	2020-08-31 - 2020-09-06	34	11222	158	1.4
	2020-09-07 - 2020-09-13	33	14510	322	2.2

[1] In bovenstaande cijfers zijn alleen gegevens meegenomen van laboratoria die deze hebben uitgesplitst naar aanvrager, dit betreft een deel van de laboratoria.

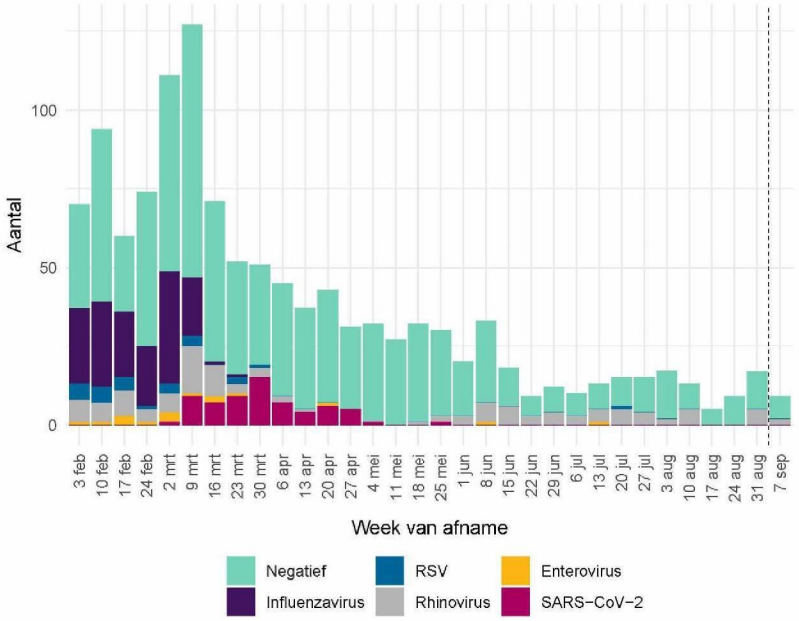
Tabel 16: Aantal geteste personen en aantal SARS-CoV-2 positief geteste ziekenhuismedewerkers en -patiënten in Nederland, gemeld door virologische laboratoria[1]. De gegevens van de laatste vier kalenderweken (van 17 augustus t/m 13 september) zijn weergegeven per week. De gegevens van de periode daarvoor, vanaf 15 juni, zijn samengevoegd.

Aanvrager	Datum van - tot	Aantal labs	Aantal geteste personen	Aantal personen met positieve uitslag	Percentage positief
Medewerkers	5.1.2e - 5.1.2e	41	14240	145	1.0
	2020-08-17 - 2020-08-23	34	2283	28	1.2
	2020-08-24 - 2020-08-30	34	3298	55	1.7
	2020-08-31 - 2020-09-06	34	3898	48	1.2
	2020-09-07 - 2020-09-13	33	4390	109	2.5
Patiënten	5.1.2e - 5.1.2e	41	26850	268	1.0
	2020-08-17 - 2020-08-23	34	3384	73	2.2
	2020-08-24 - 2020-08-30	34	3370	50	1.5
	2020-08-31 - 2020-09-06	34	3289	80	2.4
	2020-09-07 - 2020-09-13	33	3163	70	2.2

[1] In bovenstaande cijfers zijn alleen gegevens meegenomen van laboratoria die deze hebben uitgesplitst naar doelgroep, dit betreft een deel van de laboratoria.

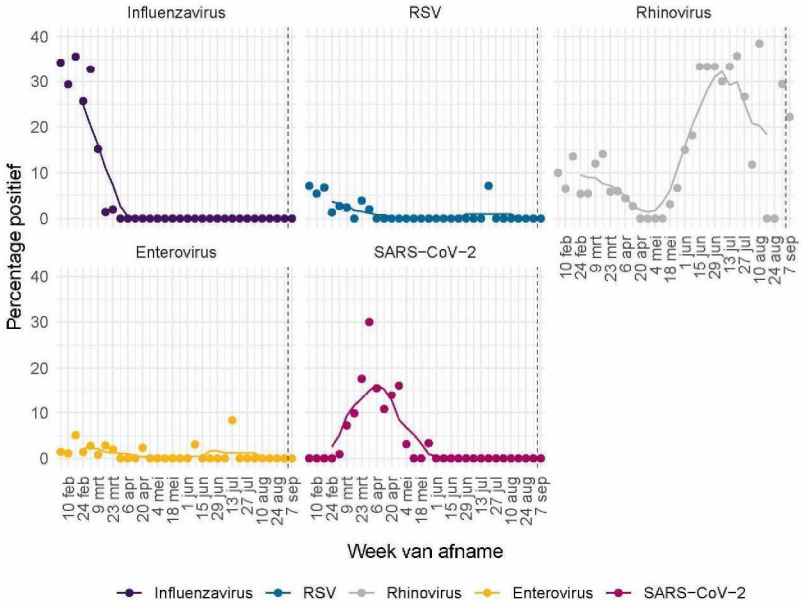
11.2 Nivel/RIVM huisartsen peilstation surveillance: respiratoire infecties bij personen met griepachtige klachten of acute luchtweginfecties.

De aantallen mensen met COVID-19 in de steekproef van de Peilstations kunnen niet vergeleken worden met de resultaten van de GGD'en. Bij een steekproef van de personen die de huisarts consulteren met griepachtige klachten of acute luchtweginfecties, worden monsters afgenomen voor de landelijke respiratoire surveillance. Dit wordt gedaan door ongeveer 40 huisartsenpraktijken die deelnemen aan de Peilstations van Nivel Zorgregistraties Eerste Lijn. Momenteel worden de meeste mensen met griepachtige klachten getest door de GGD'en. De resultaten van de Peilstations zijn gebaseerd op mensen die op consult komen bij de huisarts.



Figuur 19: Aantal patiënten met griepachtige klachten of een acute respiratoire infectie dat positief getest is op Influenzavirus, RSV, Rhinovirus, Enterovirus of SARS-CoV-2 of dat negatief getest is op deze virussen. Gegevens van de afgelopen week (rechts van de stippellijn) zijn incompleet omdat nog niet alle testresultaten bekend zijn.

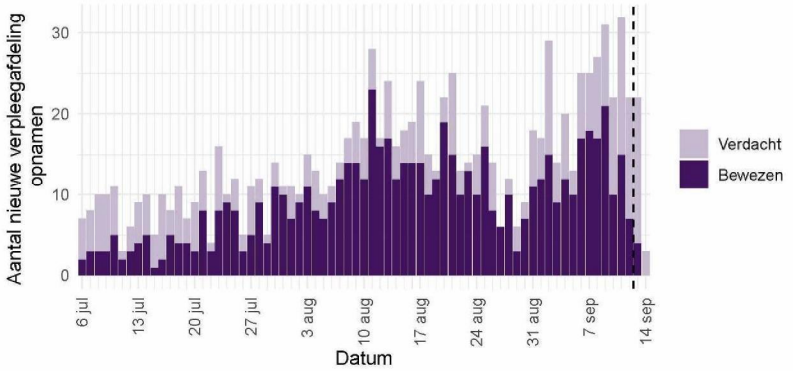
Aanwezigheid van andere virussen in de groep negatief is niet uit te sluiten, omdat er slechts op een beperkt aantal virussen getest wordt. Dubbelinfecties kunnen voorkomen. Hierdoor kunnen het aantal positieve testen hoger zijn dan het aantal positieve monsters.



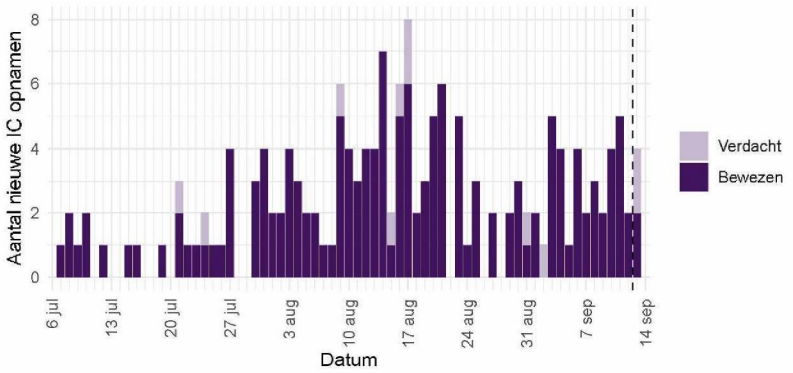
Figuur 20: Percentage patiënten met griepachtige klachten of een acute respiratoire infectie dat positief getest is op Influenzavirus, RSV, Rhinovirus, Enterovirus of SARS-CoV-2. De stippen geven het aantal per dag aan; de lijn een 7-daags lopend gemiddelde.

11.3 COVID-19 opnames op de verpleegafdeling en de intensive care

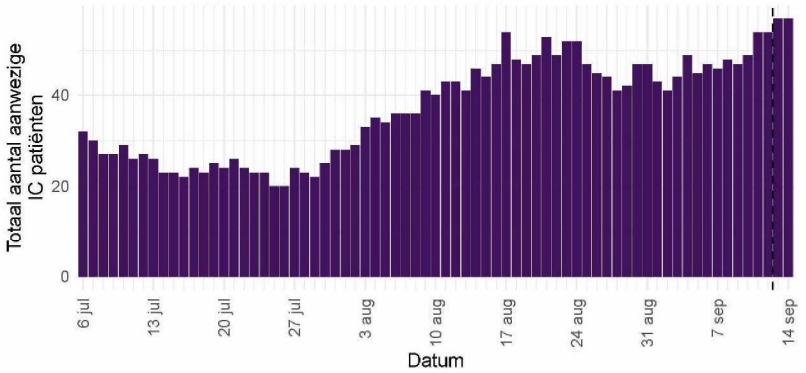
De Stichting NICE rapporteert dagelijks het aantal COVID-19 patiënten dat opgenomen is op de verpleegafdeling en de intensive care. In de afgelopen week zijn er 123 nieuwe bewezen COVID-19 verpleegafdeling opnames geregistreerd door NICE (ten opzichte van 80 in de week ervoor) en 25 nieuwe bewezen COVID-19 IC opnames (ten opzichte van 13 in de week ervoor). Er is mogelijk een vertraging van 2 a 3 dagen in de data-aanlevering. Gegevens rechts van de stippellijn worden momenteel nog aangevuld door de IC's.



Figuur 21: Aantal nieuwe verdachte en bewezen COVID-19 patiënten per dag op Nederlandse[1] verpleegafdelingen.



Figuur 22: Aantal nieuwe verdachte en bewezen COVID-19 patiënten per dag op Nederlandse[1] intensive care afdelingen.



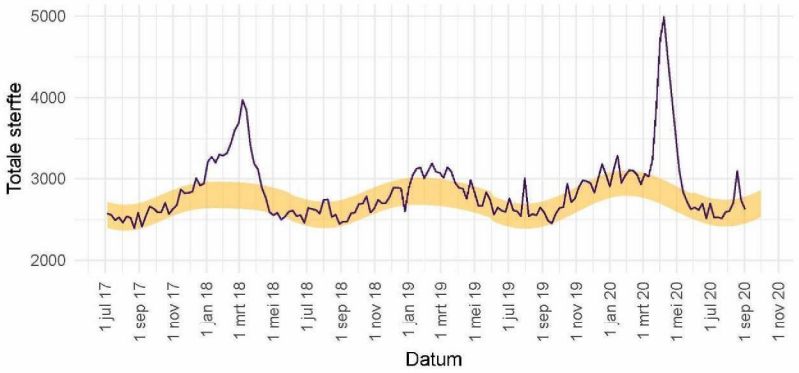
Figuur 23: Totaal aantal bewezen COVID-19 patiënten opgenomen per dag op Nederlandse[1] intensive care afdelingen.

[1] Inclusief opnames op Duitse IC's ten tijde van de overbezette Nederlandse IC's.

Bron: Nationale Intensive Care Evaluatie – NICE. Gegevens bijgewerkt op 14 september, 10:50 uur Voor uitgebreider en nog actuelere informatie zie Stichting NICE

11.4 Totale sterfte in Nederland t/m 2 september 2020

Sinds de grieppandemie van 2009 gebruikt het RIVM gegevens van het Centraal Bureau voor de Statistiek (CBS) om het totaal aantal overleden mensen wekelijks te bewaken. Hierdoor wordt de impact van koude- of hittegolven, uitbraken en epidemieën op sterfte in beeld gebracht. Niet bij alle mensen die overlijden aan COVID-19 is een laboratoriumtest gedaan, waardoor ze niet in de COVID-19 meldingsgegevens worden opgenomen. De totale sterfte in 2020 die in beeld gebracht wordt door deze grafiek geeft mogelijk een completer beeld van sterfte door COVID-19. Deze grafiek geeft de totale sterfte weer t/m 2 september.

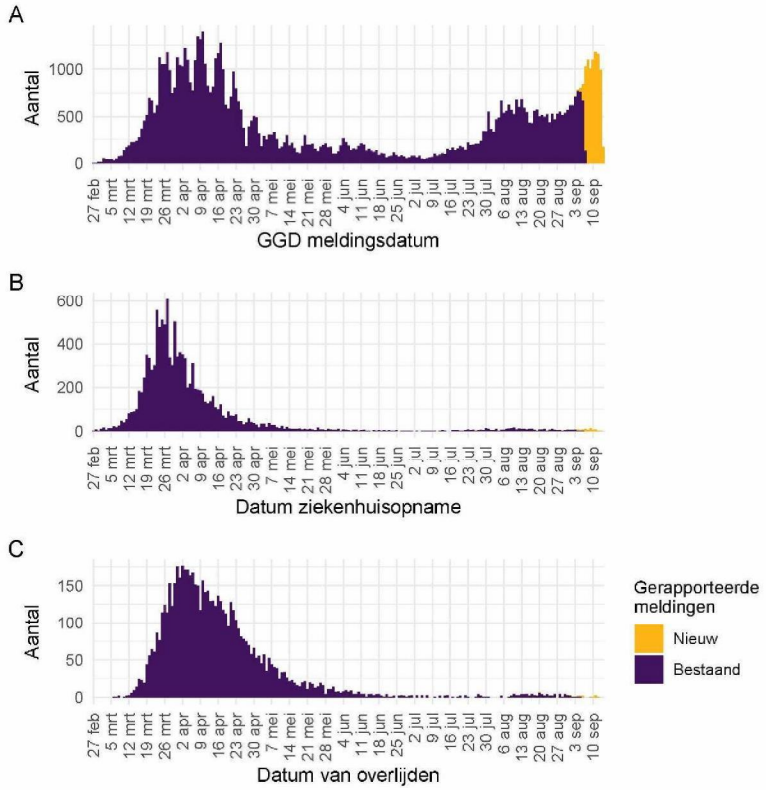


Figuur 24: Totale sterfte in Nederland t/m 2 september. De waargenomen sterfte wordt vergeleken met het aantal overlijdens dat wordt verwacht op basis van voorgaande jaren. Het gele lint in de grafiek toont de sterfte die op dat moment in het jaar wordt verwacht. Binnen 2 weken zijn circa 97% van alle sterfgevallen bekend bij het CBS.

Voor gedetailleerde informatie zie: RIVM - Monitoring Sterftecijfers en CBS. Zie EuroMOMO voor een Europees overzicht.

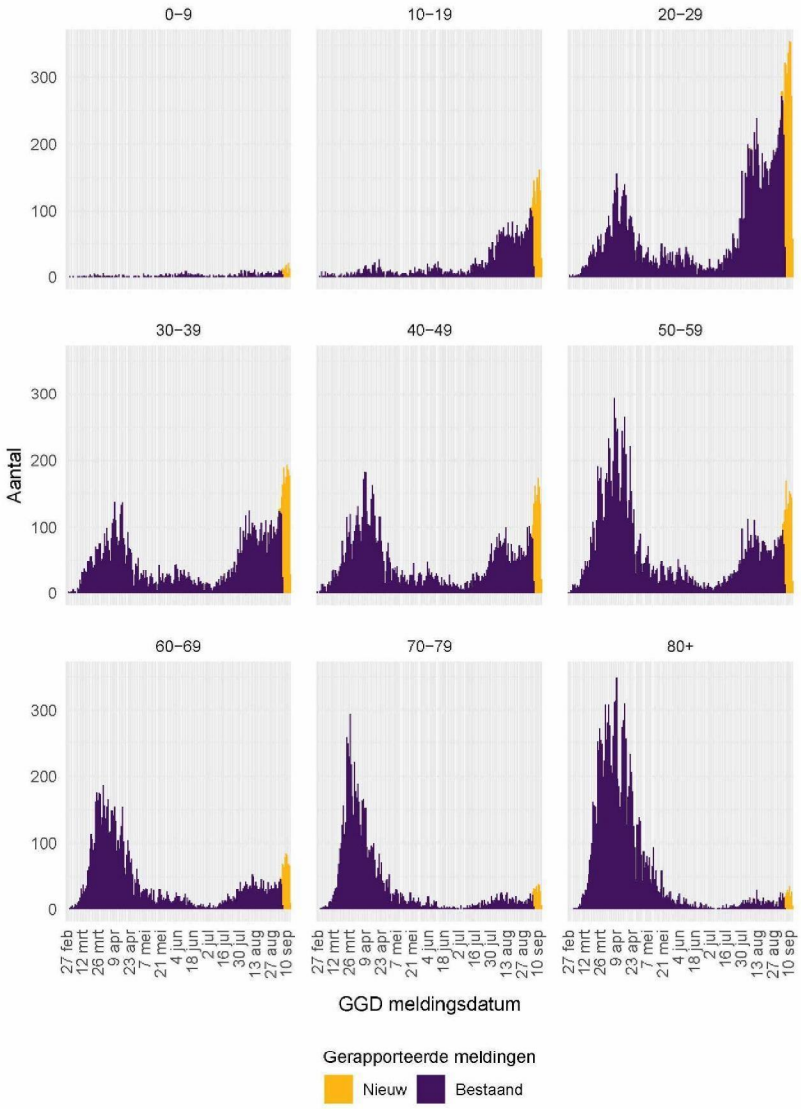
12 COVID-19 meldingen vanaf 27 februari 2020

12.1 COVID-19 meldingen aan de GGD'en vanaf 27 februari 2020

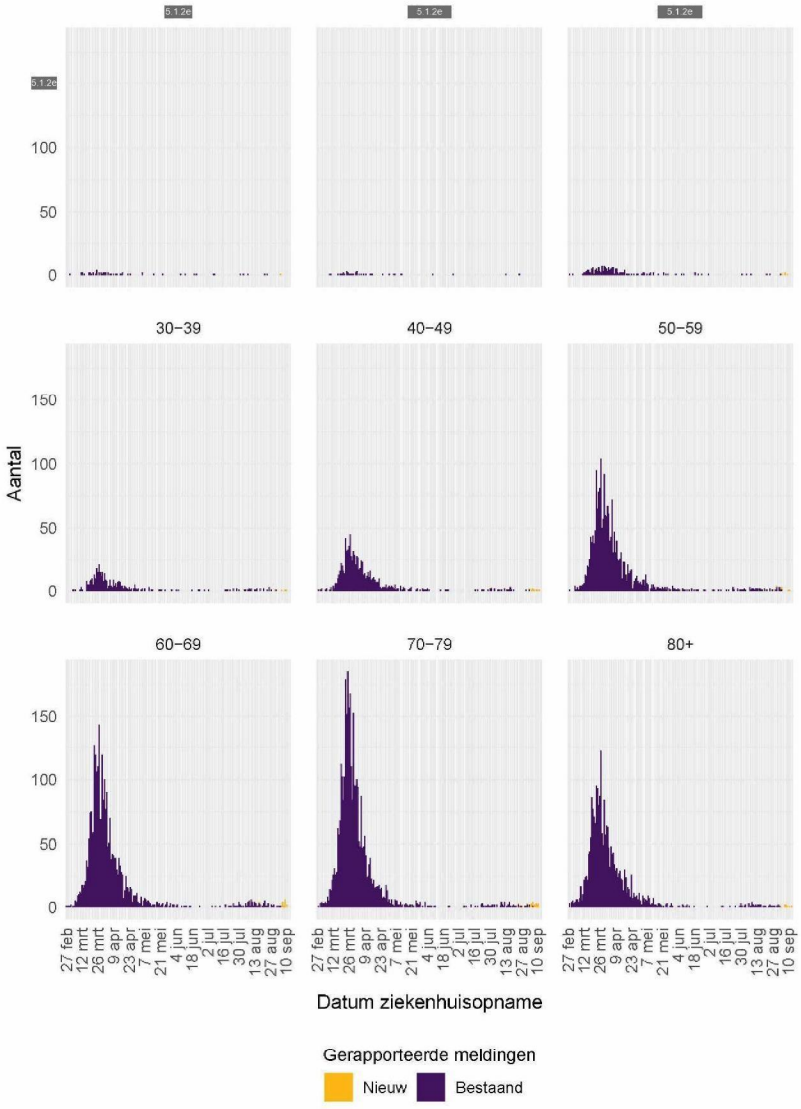


Figuur 25: Aantal bij de GGD'en gemelde COVID-19 patiënten vanaf 27 februari 2020. (A) Aantal bij de GGD'en gemelde COVID-19 patienten, naar meldingsdatum. (B) Aantal bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten, naar datum van ziekenhuisopname. Van 5% van de in het ziekenhuis opgenomen COVID-19 patiënten is de datum van ziekenhuisopname (nog) niet gemeld. (C) Aantal bij de GGD'en gemelde overleden COVID-19 patiënten, naar datum van overlijden. Van enkele overleden COVID-19 patiënt is de datum van overlijden (nog) niet gemeld.

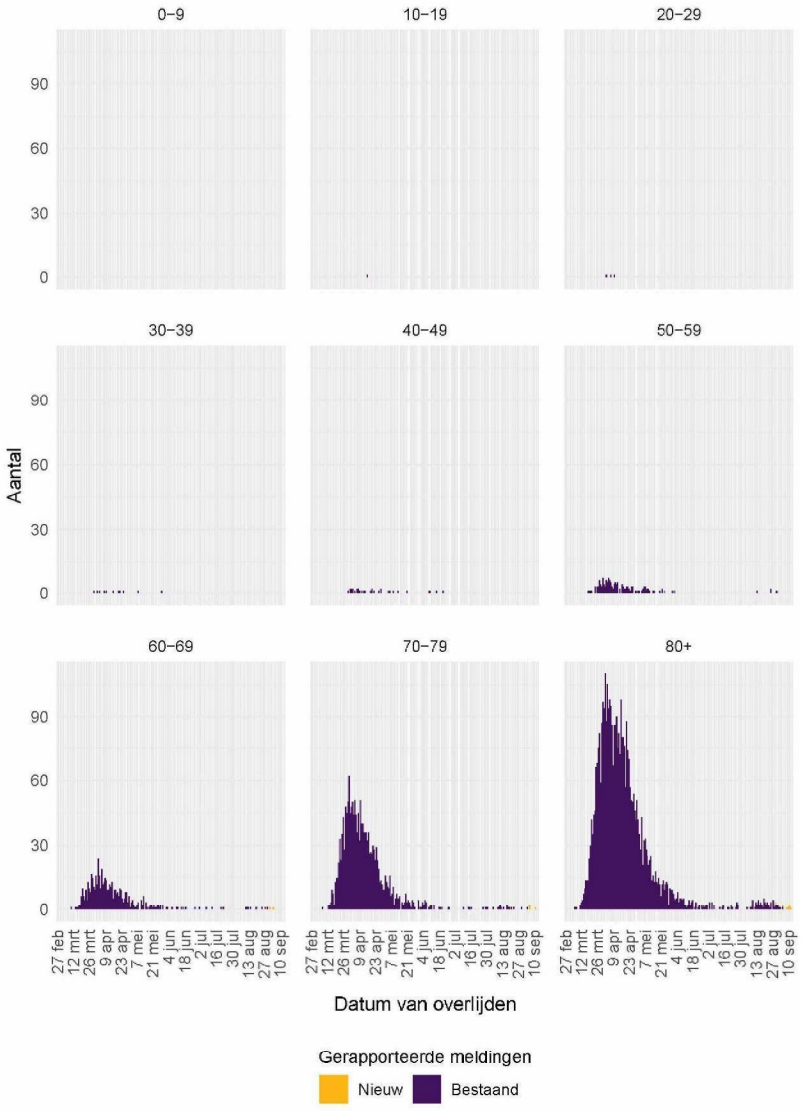
Meldingen aan het RIVM t/m 7 september 10:00 uur zijn in deze grafieken weergegeven in paars. Meldingen van 7 september 10:01 uur t/m 14 september 10:00 uur zijn weergegeven in geel. Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijk dat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden.



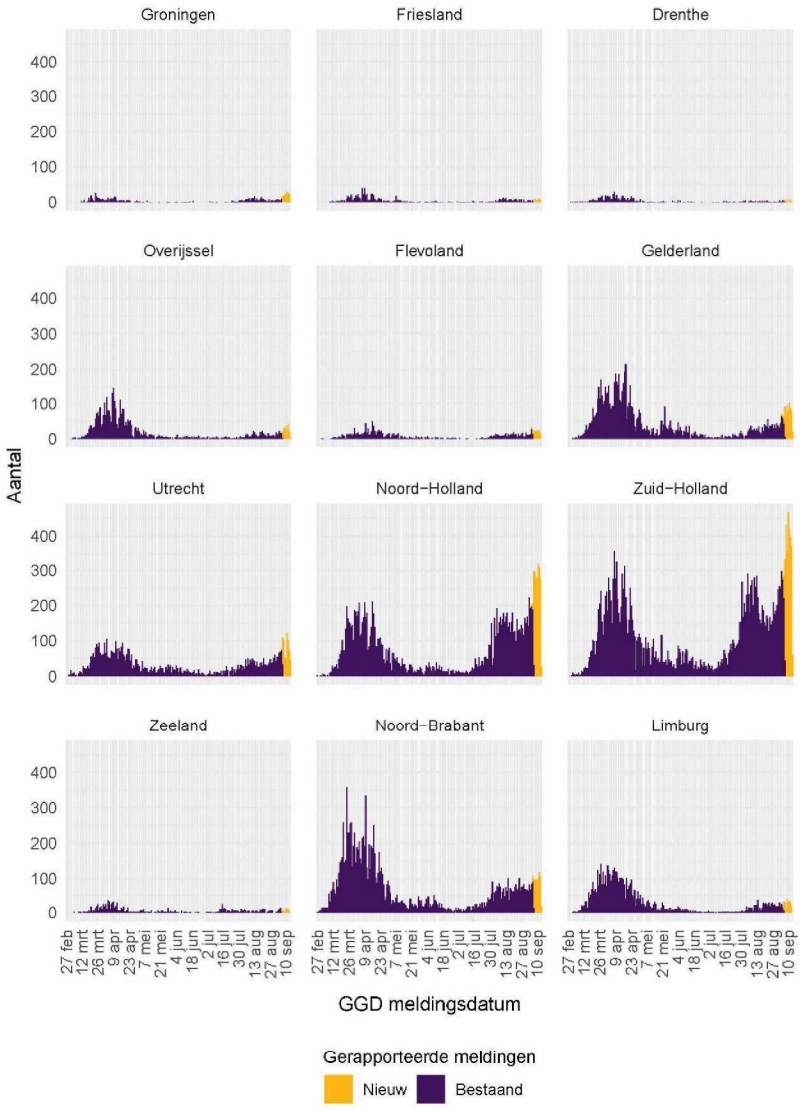
Figuur 26: Aantal bij de GGD'en gemelde COVID-19 patiënten, per leeftijdsgroep.



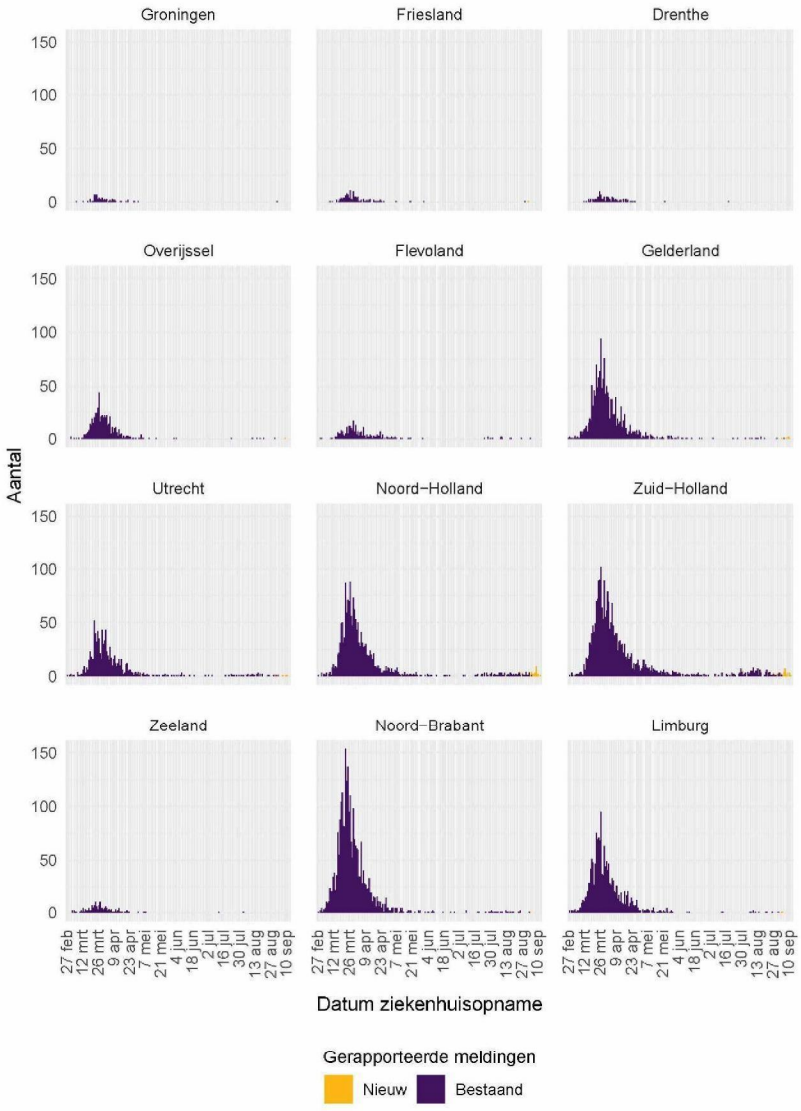
Figuur 27: Aantal bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten, per leeftijdsgroep.



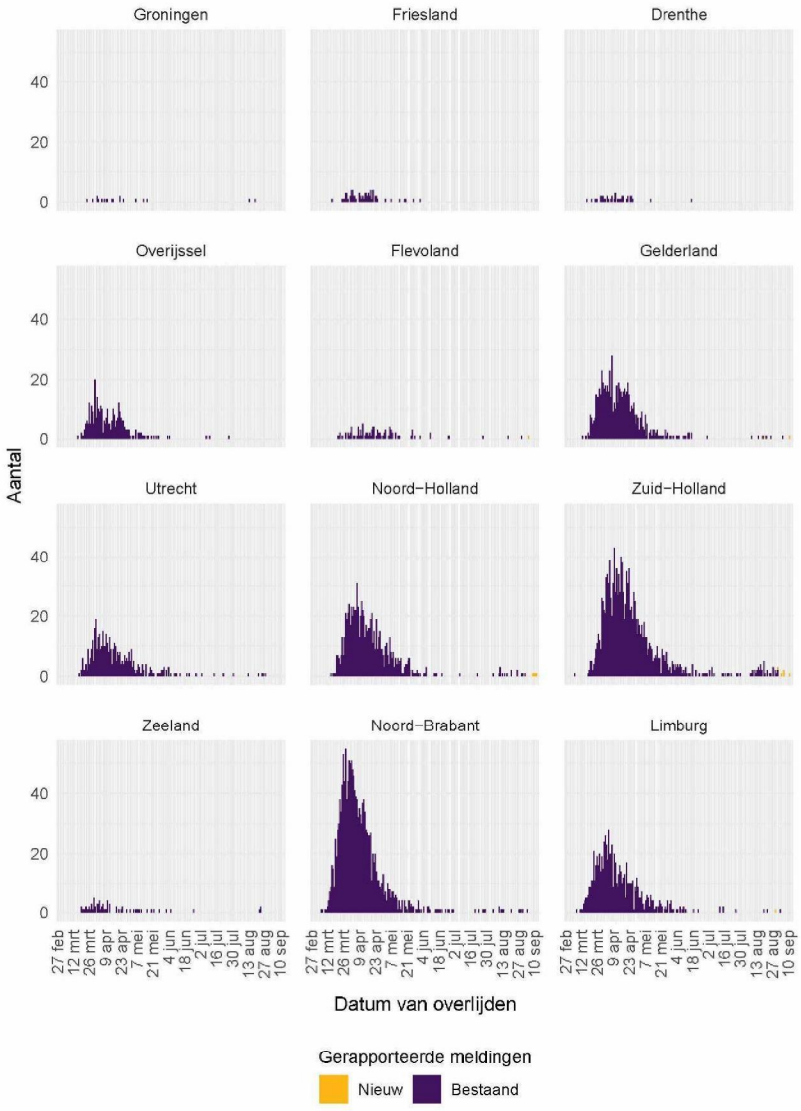
Figuur 28: Aantal bij de GGD'en gemelde overleden COVID-19 patiënten, per leeftijdsgroep.



Figuur 29: Aantal bij de GGD'en gemelde COVID-19 patiënten, per provincie.



Figuur 30: Aantal bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten, per provincie.



Figuur 31: Aantal bij de GGD'en gemelde overleden COVID-19 patiënten, per provincie.

12.2 Regionale overzichten van COVID-19 meldingen vanaf 27 februari 2020

12.2.1 Aantallen COVID-19 meldingen per provincie vanaf 27 februari 2020

Tabel 17: Aantal COVID-19 patiënten bij de GGD'en gemeld, in het ziekenhuis opgenomen en overleden per provincie, totaal aantal patiënten en aantal patiënten per 100.000 inwoners[1,2,3]

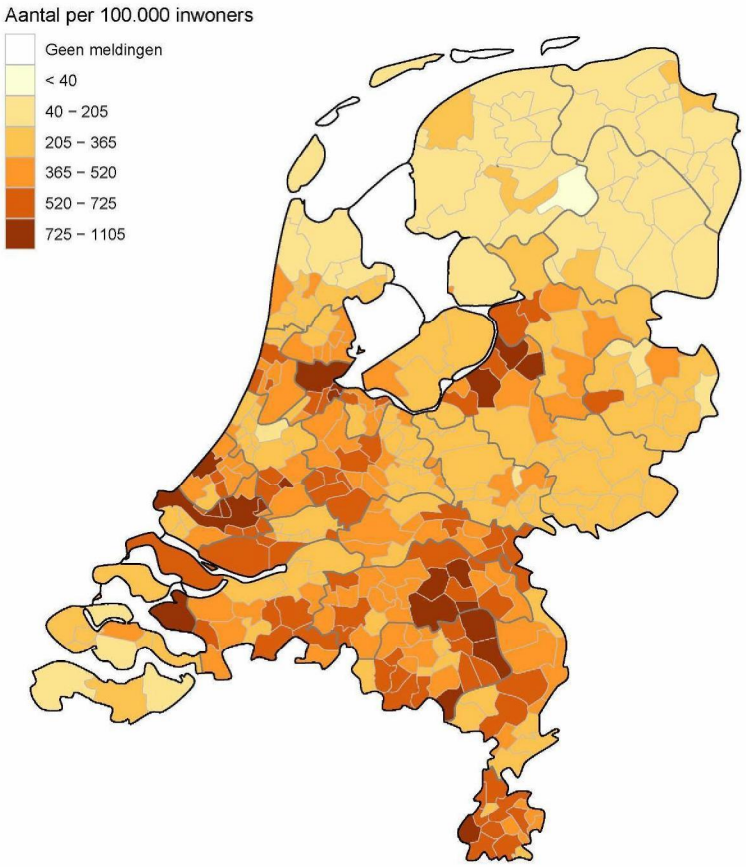
Provincie	Totaal gemeld	/100.000	Ziekenhuisopname	/100.000	Overleden	/100.000
Totaal gemeld	83399	479.1	12291	70.6	6256	35.9
Groningen	817	139.5	76	13.0	19	3.2
Friesland	904	139.1	133	20.5	69	10.6
Drenthe	657	133.1	119	24.1	41	8.3
Overijssel	3807	327.5	555	47.7	315	27.1
Flevoland	1591	376.1	278	65.7	96	22.7
Gelderland	8585	411.6	1535	73.6	694	33.3
Utrecht	6575	485.3	928	68.5	437	32.3
Noord-Holland	15853	550.5	1753	60.9	836	29.0
Zuid-Holland	23969	646.3	2372	64.0	1361	36.7
Zeeland	1144	298.3	154	40.2	73	19.0
Noord-Brabant	13674	533.5	2807	109.5	1554	60.6
Limburg	5823	521.2	1581	141.5	761	68.1

[1] Betreft het aantal COVID-19 patiënten met een datum van melding aan de GGD, opnamedatum of datum van overlijden in de periode van 7 september 10:01 t/m 14 september 10:00 uur.

[2] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.

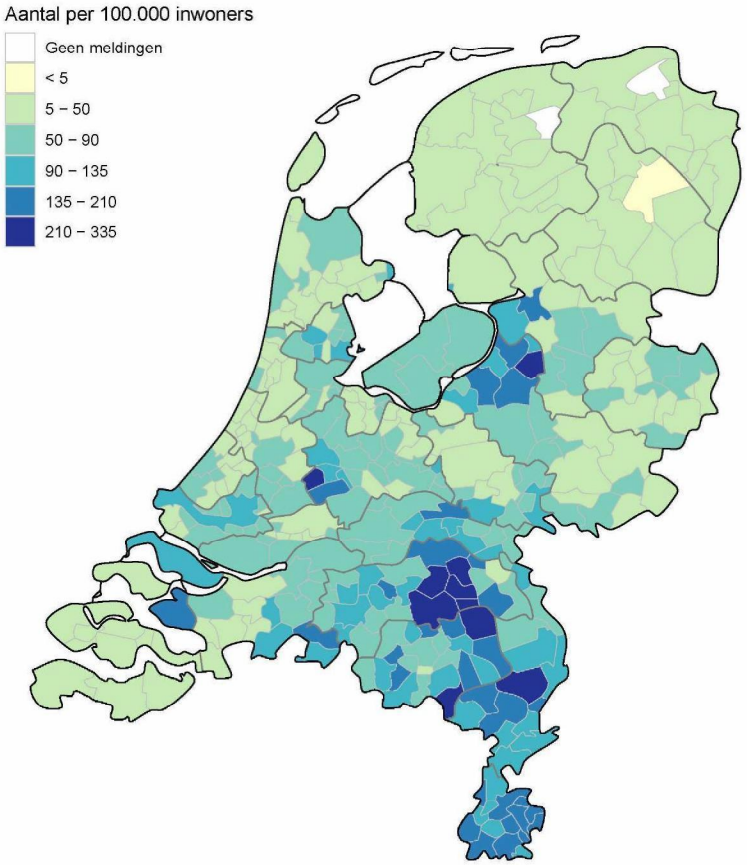
[3] Per 20 mei is de indeling naar provincie gebaseerd op woonlocatie van de patiënt in plaats van meldende GGD. Wanneer woonlocatie onbekend is, is de indeling gebaseerd op meldende GGD.

12.2.2 Kaarten met COVID-19 meldingen per gemeente vanaf 27 februari 2020



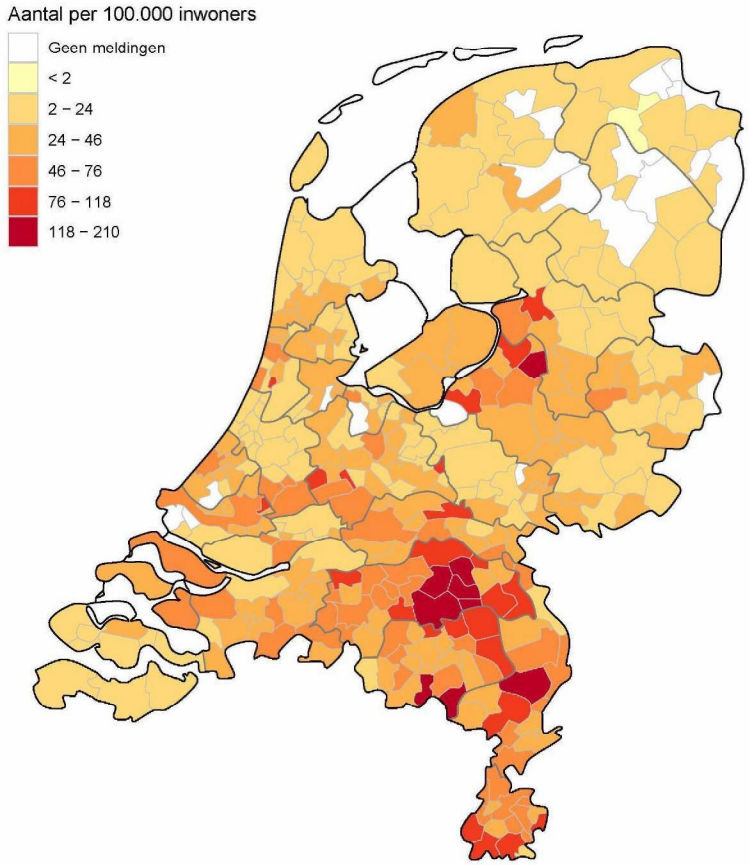
Figuur 32: Totaal aantal bij de GGD'en gemelde COVID-19 patiënten per 100.000 inwoners per gemeente t/m 14 september 10:00 uur. De grijze lijnen geven de grenzen van de GGD-regio's weer.

Iedere dinsdag wordt de kleurindeling van de kaart aangepast zodat het contrast tussen gemeenten duidelijker weergegeven wordt.



Figuur 33: Totaal aantal bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten per 100.000 inwoners per gemeente t/m 14 september 10:00 uur. De grijze lijnen geven de grenzen van de GGD-regio's weer.

Iedere dinsdag wordt de kleurindeling van de kaart aangepast zodat het contrast tussen gemeenten duidelijker weergegeven wordt.



Figuur 34: Totaal aantal bij de GGD'en gemelde overleden COVID-19 patiënten per 100.000 inwoners per gemeente t/m 14 september 10:00 uur. De grijze lijnen geven de grenzen van de GGD-regio's weer.

Iedere dinsdag wordt de kleurindeling van de kaart aangepast zodat het contrast tussen gemeenten duidelijker weergegeven wordt.

12.3 Leeftijdsverdeling en man-vrouwverdeling van COVID-19 patiënten vanaf 27 februari 2020

Tabel 18: Leeftijdsverdeling van bij de GGD'en gemelde COVID-19 patiënten, van in het ziekenhuis opgenomen COVID-19 patiënten en van overleden COVID-19 patiënten[1]

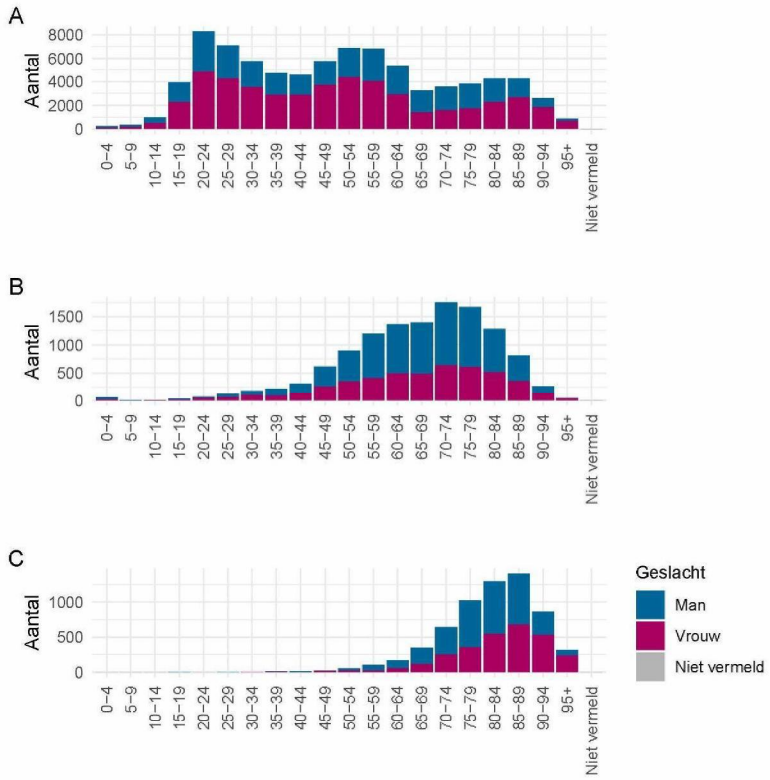
Leeftijdsgroep	Totaal gemeld	%	Ziekenhuisopname	%	Overleden	%
Totaal gemeld	83399		12291		6256	
0-4	261	0.3	58	0.5	0	0.0
5-9	373	0.4	3	0.0	0	0.0
10-14	980	1.2	8	0.1	0	0.0
15-19	3932	4.7	34	0.3	1	0.0
20-24	8289	9.9	69	0.6	0	0.0
25-29	7109	8.5	124	1.0	3	0.0
30-34	5784	6.9	178	1.4	4	0.1
35-39	4729	5.7	217	1.8	7	0.1
40-44	4574	5.5	308	2.5	7	0.1
45-49	5777	6.9	617	5.0	24	0.4
50-54	6897	8.3	900	7.3	50	0.8
55-59	6799	8.2	1192	9.7	100	1.6
60-64	5310	6.4	1363	11.1	167	2.7
65-69	3262	3.9	1395	11.3	345	5.5
70-74	3580	4.3	1752	14.3	640	10.2
75-79	3807	4.6	1669	13.6	1022	16.3
80-84	4242	5.1	1279	10.4	1297	20.7
85-89	4246	5.1	816	6.6	1411	22.6
90-94	2588	3.1	262	2.1	864	13.8
95+	853	1.0	47	0.4	314	5.0
Niet vermeld	7	0.0	0	0.0	0	0.0

[1] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.

Tabel 19: Man-vrouwverdeling van bij de GGD'en gemelde COVID-19 patiënten, van in het ziekenhuis opgenomen COVID-19 patiënten en van overleden COVID-19 patiënten[1]

Geslacht	Totaal gemeld	%	Ziekenhuisopname	%	Overleden	%
Totaal gemeld	83399		12291		6256	
Man	34742	41.7	7521	61.2	3436	54.9
Vrouw	48565	58.2	4762	38.7	2820	45.1
Niet vermeld	92	0.1	8	0.1	0	0.0

[1] Sinds 1 juni kan iedereen met klachten zich laten testen. Toch is het aannemelijkdat niet alle COVID-19 patiënten getest worden. De werkelijke aantallen in Nederland zijn daarom waarschijnlijk hoger dan de aantallen die hier genoemd worden. Het werkelijke aantal COVID-19 patiënten opgenomen in het ziekenhuis of overleden is hoger dan het aantal opgenomen of overleden patiënten gemeld in de surveillance, omdat de surveillance gebaseerd is op de informatie op het moment van melding. Aan het RIVM wordt niet gemeld wie hersteld is.



Figuur 35: Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde COVID-19 patiënten vanaf 27 februari 2020. (A) Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde COVID-19 patiënten. (B) Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde in het ziekenhuis opgenomen COVID-19 patiënten. (C) Leeftijdsverdeling en man-vrouwverdeling van bij de GGD'en gemelde overleden COVID-19 patiënten.

12.4 Onderliggende aandoeningen en/of zwangerschap bij overleden COVID-19 patiënten jonger dan 70 jaar vanaf 27 februari 2020

Tabel 20: Aantal overleden COVID-19 patiënten jonger dan 70 jaar met onderliggende aandoeningen en/of zwangerschap[1]

	Overleden	%
Totaal gemeld	708	
Onderliggende aandoening en/of zwangerschap	492	69.5
Geen onderliggende aandoening	70	9.9
Niet vermeld	146	20.6

[1] Het werkelijke aantal overleden COVID-19 patiënten jonger dan 70 jaar is hoger dan het aantal overleden patiënten gemeld in de surveillance omdat niet alle personen met COVID-19 worden getest en de surveillance is gebaseerd op de informatie op het moment van melding.

Tabel 21: Gerapporteerde onderliggende aandoeningen en/of zwangerschap van overleden COVID-19 patiënten jonger dan 70 jaar[1,2]

	Overleden	%
Zwangerschap	0	0.0
Postpartum	0	0.0
Cardio-vasculaire aandoeningen en hypertensie	216	43.9
Diabetes	129	26.2
Leveraandoening	18	3.7
Chronische neurologische of neuromusculaire aandoeningen	72	14.6
Immuundeficiëntie	8	1.6
Nieraandoening	42	8.5
Chronische longaandoeningen	116	23.6
Maligniteit	77	15.7
Obesitas[3]	36	7.3
Dementie/Alzheimer[3]	29	5.9
Parkinson[3]	5	1.0
Overig	122	24.8

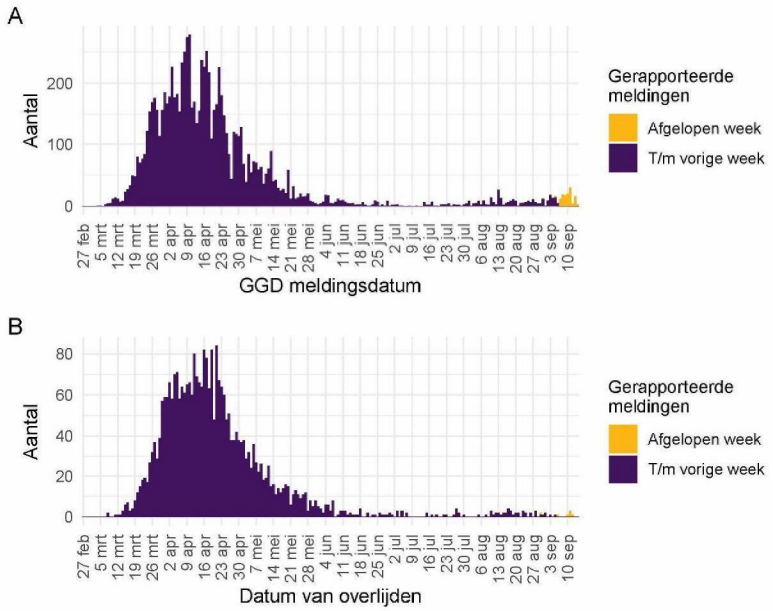
[1] Het werkelijke aantal overleden COVID-19 patiënten jonger dan 70 jaar is hoger dan het aantal overleden patiënten gemeld in de surveillance omdat niet alle personen met COVID-19 worden getest en de surveillance is gebaseerd op de informatie op het moment van melding.

[2] Per patiënt kunnen meerdere onderliggende aandoeningen gerapporteerd zijn. De percentages in Tabel 21 worden berekend vanuit het aantal overleden patiënten jonger dan 70 jaar voor wie tenminste één onderliggende aandoening is vermeld (Tabel 20).

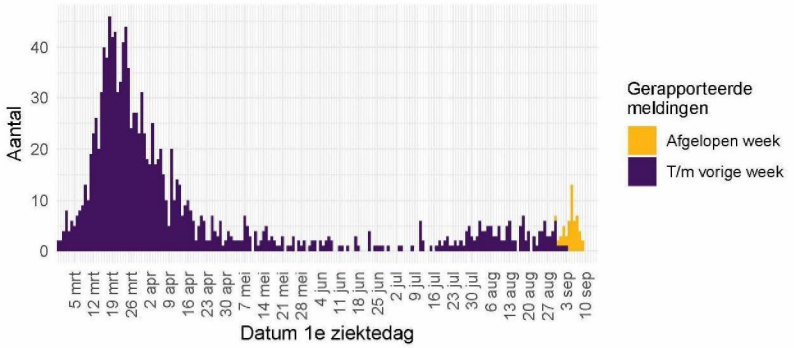
[3] Vanaf 11 april zijn deze onderliggende aandoeningen gestructureerd nagevraagd.

12.5 Surveillance van COVID-19 in verpleeghuizen in Nederland

Voor een uitleg over hoe deze grafieken tot stand zijn gekomen, zie pagina 18.



Figuur 36: Aantal verpleeghuisbewoners met COVID-19 vanaf 27 februari 2020. (A) Aantal gemelde verpleeghuisbewoners, naar meldingsdatum. (B) Aantal overleden verpleeghuisbewoners, naar datum van overlijden.
newline{}Meldingen aan het RIVM t/m 7 september 10:00 uur zijn in deze grafieken weergegeven in paars. Meldingen van 7 september 10:01 uur t/m 14 september 10:00 uur zijn weergegeven in geel. De werkelijke aantallen COVID-19 patiënten en overleden COVID-19 patiënten zijn hoger dan zoals hier weergegeven omdat waarschijnlijk niet alle mogelijk besmette personen getest worden.



Figuur 37: Aantal nieuwe verpleeghuislocaties met COVID-19 vanaf 27 februari 2020. Aantal nieuwe verpleeghuislocaties waar sprake is van tenminste één COVID-19 besmetting op basis van een positieve test. Een verpleeghuis wordt meegeteld als 'nieuwe locatie' wanneer er tenminste 28 dagen vóór de positieve test geen nieuwe patiënten zijn gemeld.

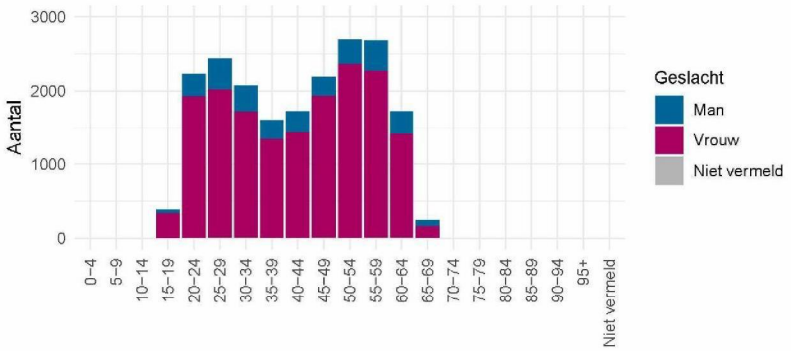
Meldingen aan het RIVM t/m 7 september 10:00 uur zijn in deze grafieken weergegeven in paars. Meldingen van 7 september 10:01 uur t/m 14 september 10:00 uur zijn weergegeven in geel.

12.6 Surveillance van COVID-19 onder zorgmedewerkers

Tot en met 14 september 10.00 uur zijn 19996 zorgmedewerkers in de leeftijd van 18 t/m 69 jaar met COVID-19 gemeld. Dit betreft zorgmedewerkers binnen en buiten het ziekenhuis. Het is niet bekend of te achterhalen of de zorgmedewerkers het virus tijdens hun werk hebben opgelopen of daarbuiten. Van hen zijn 542 gemeld als opgenomen in het ziekenhuis, dit is 3% van het totaal aantal positief op COVID-19 geteste zorgmedewerkers. Van 13 zorgmedewerkers is gerapporteerd dat zij zijn overleden. Zij hadden een leeftijd tussen de 40 en 69 jaar.

De leeftijdsverdeling en man-vrouwverdeling van zorgmedewerkers zijn duidelijk anders dan die van overige COVID-19 patiënten. Zorgmedewerkers zijn gemiddeld jonger en vaker vrouw, zoals te zien in onderstaande figuur.

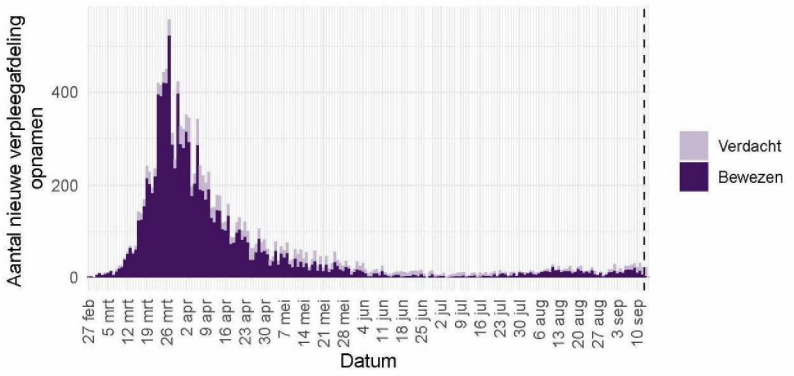
Vanaf 1 juni kan iedereen met klachten zich laten testen op het nieuwe coronavirus. Tot die tijd was het testbeleid voornamelijk gericht op mensen met een verhoogd risico op een ernstig beloop van de ziekte of patiënten opgenomen in het ziekenhuis. Daarnaast werden zorgmedewerkers laagdrempelig getest bij (milde) klachten, daarom vormen zorgmedewerkers een groot deel van het totaal aantal gemelde COVID-19 patiënten. Van alle 61007 meldingen van bevestigde COVID-19 patiënten tussen de 18 en 69 jaar is 33% (19996) zorgmedewerker. Van alle met COVID-19 gemelde als in het ziekenhuis opgenomen patiënten in de leeftijd 18 t/m 69 jaar (6379) is 8% een zorgmedewerker. Van alle 708 gemelde overleden COVID-19 patiënten in de leeftijd van 18 t/m 69 jaar was 1.8% een zorgmedewerker. Van alle Nederlanders tussen de 18 en 69 jaar werkt zo'n 11% als zorgmedewerker (bron: CBS statline).



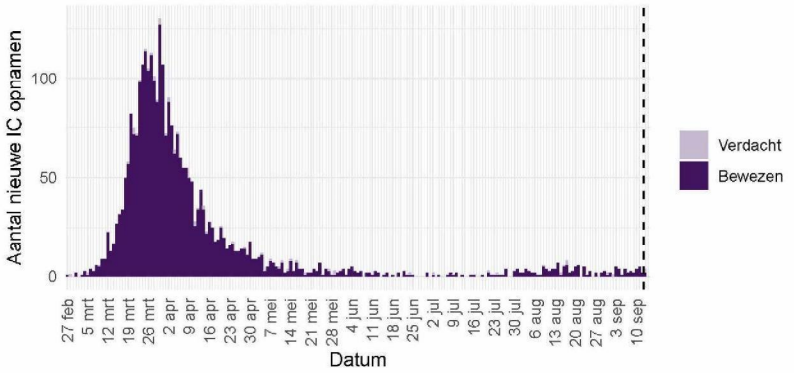
Figuur 38: Leeftijdsverdeling en man-vrouwverdeling van gemelde COVID-19 patiënten in de leeftijd 18-69 jaar die werkzaam zijn als zorgmedewerker.

12.7 COVID-19 opnames op de verpleegafdeling en de intensive care

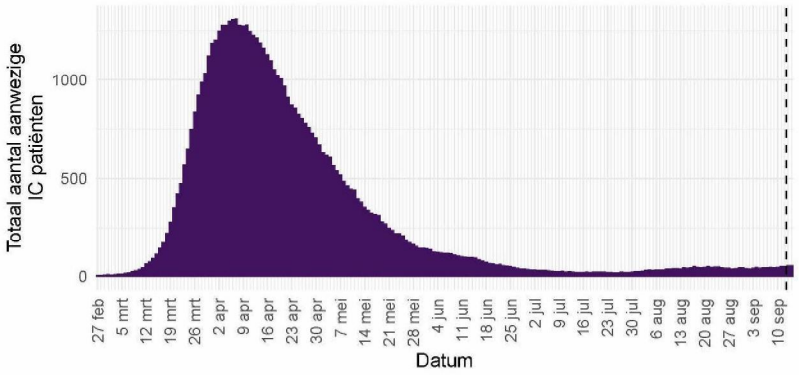
De Stichting NICE rapporteert dagelijks het aantal COVID-19 patiënten dat opgenomen is op de verpleegafdeling en de intensive care. In onderstaande grafieken zijn deze gegevens opgenomen. Er is mogelijk een vertraging van 2 a 3 dagen in de data-aanlevering. Gegevens rechts van de stippellijn worden momenteel nog aangevuld door de IC's.



Figuur 39: Aantal nieuwe verdachte en bewezen COVID-19 patiënten per dag op Nederlandse[1] verpleegafdelingen.



Figuur 40: Aantal nieuwe verdachte en bewezen COVID-19 patiënten per dag op Nederlandse[1] intensive care afdelingen.



Figuur 41: Totaal aantal bewezen COVID-19 patiënten opgenomen per dag op Nederlandse[1] intensive care afdelingen.

[1] Inclusief opnames op Duitse IC's ten tijde van de overbezette Nederlandse IC's.

Bron: Nationale Intensive Care Evaluatie – NICE. Gegevens bijgewerkt op 14 september, 10:50 uur Voor uitgebreider en nog actuelere informatie zie Stichting NICE