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

Meningococcal disease serogroup B

Updated information for the Dutch Health Council

This report contains an erratum d.d. 13-05-2022 on page 47

This report contains a second erratum d.d. 19-07-2022 on page 48

RIVM letter report 2022-0046

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Synopsis

Meningococcal disease serogroup B
Updated information for the Dutch Health Council

Meningococcal disease is a very serious infectious disease that can be caused by several types of meningococcal bacteria (serogroups). These types are indicated by letters. In the Netherlands, children are vaccinated against meningococcal disease caused by types A, C, W and Y. There is also a vaccine against meningococcal disease caused by type B. In 2018, the Health Council of the Netherlands advised against including vaccination against meningococcal B disease in the National Immunisation Programme. The Health Council found the effectiveness and safety of the vaccine still too uncertain and the costs to prevent one sick child were high.

Meanwhile, more has become known about how well the vaccine works and about its safety. The Health Council will therefore make a new recommendation on meningococcal B vaccination. To this end, RIVM has collected background information and recent data on meningococcal B disease in the Netherlands.

Experiences from abroad confirm that the meningococcal B vaccine can prevent serious meningococcal disease. There are several meningococcal B bacteria and the vaccine does not protect against all of these. Which bacteria and how many children fall ill differ between countries and per year. In at least 70% of the children that receive one of the two current meningococcal B vaccines, the vaccine works well. In these children, the vaccine protects against 75 per cent of the various meningococcal B bacteria that can make them ill in the Netherlands.

The meningococcal B vaccination can cause a high fever in babies, especially if they receive it at the same time as other vaccinations. If a baby is given paracetamol on the day of the meningococcal B vaccination, this is 50 per cent less common.

The experience also shows that three vaccinations per child are enough, instead of the four that were previously thought to be needed. In recent years, fewer people have become ill with meningococcal B disease. That was also the case in the year before the coronavirus pandemic. The cause of this is not clear. Because of this decrease, the costs per child to prevent them from getting meningococcal B disease are likely not much lower than in 2018.

Keywords: meningococcus, meningococcal disease, vaccination, incidence, safety, cost-effectiveness, meningococcal serogroup B

Publiekssamenvatting

Meningokokkenziekte serogroep B
Actuele informatie voor de Gezondheidsraad

Meningokokkenziekte is een levensbedreigende ziekte die door verschillende soorten meningokokkenbacteriën (serogroepen) wordt veroorzaakt. Deze soorten worden aangegeven met letters. In Nederland worden kinderen gevaccineerd tegen meningokokken A, C, W en Y. Er bestaat ook een vaccin tegen meningokokken B. In 2018 heeft de Gezondheidsraad geadviseerd om vaccinatie tegen meningokokken B niet in te voeren in het Rijksvaccinatieprogramma. De Gezondheidsraad vond de werking en de veiligheid van het vaccin nog te onzeker. Ook waren de kosten om te voorkomen dat één kind ziek wordt van meningokokken B hoog.

Ondertussen is er meer bekend geworden over hoe goed het vaccin werkt en over de veiligheid ervan. De Gezondheidsraad gaat daarom opnieuw een advies uitbrengen. Als ondersteuning van dit advies heeft het RIVM achtergrondinformatie verzameld over vaccinatie tegen meningokokken B-ziekte en hoe vaak het in Nederland voorkomt.

Ervaringen uit het buitenland bevestigen dat de meningokokken B-vaccins ernstige meningokokkenziekte kunnen voorkomen. Er zijn verschillende meningokokken B-bacteriën en het vaccin beschermt niet tegen alle B-varianten. Het verschilt tussen landen en per jaar hoeveel kinderen ziek worden van welke variant. Het huidige vaccin werkt bij 70 procent of meer van de gevaccineerde kinderen goed. Bij deze kinderen beschermt het vaccin tegen ongeveer 75 procent van de verschillende meningokokkenbacteriën waar zij nu in Nederland ziek van kunnen worden.

De meningokokken B-vaccinatie kan bij baby’s regelmatig hoge koorts veroorzaken, vooral als ze deze tegelijk met andere vaccinaties krijgen. Als baby’s op de dag van de meningokokken B-vaccinatie paracetamol krijgen, komt dit 50 procent minder vaak voor.

De ervaringen laten ook zien dat 3 vaccinaties per kind genoeg zijn, in plaats van de 4 waar eerder van was uitgegaan. De afgelopen jaren zijn minder mensen ziek geworden door meningokokken B; ook al voor de uitbraak van het coronavirus. De oorzaak daarvan is niet duidelijk. Vanwege deze daling zijn de kosten per kind om te voorkomen dat het ziek wordt van de meningokokken B-bacterie, waarschijnlijk niet veel lager dan in 2018.

Kernwoorden: meningokok, meningokokkenziekte, vaccinatie, incidentie, veiligheid, kosteneffectiviteit, meningokokken B

Contents

Summary

The licensed meningococcal serogroup B (MenB) vaccines are immunogenic. After the primary series of 2 doses with the multicomponent MenB vaccine 4CMenB, around 95% of infants seroconvert. Waning occurs, but after the booster, around 95% had antibody levels above the correlate of protection. In adolescents, after vaccination with the 2 doses of 4CMenB or 2 doses of the bivalent MenB vaccine MenB-fHbp this proportion is slightly lower.

4CMenB has a vaccine effectiveness against invasive meningococcal disease (IMD) of above 70% against covered serotype B strains in infants.

The strain coverage of MenB vaccines among the IMD-B cases in the Netherlands is above 75%, but is slightly lower for younger age groups (77-79% among < 5 years old: 4CMenB) than for adolescents (around 85-92%).

Based on the current Dutch strains, 4CMenB may also prevent >50% of IMD cases caused by serogroup W (IMD-W), with an estimated vaccine effectiveness of 88% after three doses. MenB-fHbp may only prevent 14% of IMD-W cases (in the licenced age group 10-24 year olds).

MenB vaccines do not prevent meningococcal carriage. It is therefore unlikely that MenB vaccination will prevent IMD in unvaccinated age-groups, i.e. no herd protection can be expected.

No safety issues with large scale use of MenB vaccination have been reported; reported rates of Kawasaki disease and sudden death were as reported in control years. Slightly higher rates than expected of seizures (incidence ratios of 1.43 (95%CI: 1.02-2.02) and febrile seizures (1.72 (95%CI: 1.08-2.75)) were observed.

High fever in infants after 4CMenB is more common than for several other vaccines, and most common in the youngest age groups. The odds for high fever nearly doubles when vaccination is administered concomitant with other vaccines. Administration of ≥2 doses antipyretic prophylaxis reduces the odds of fever by a third to a half, depending on the age group, without loss of antibody response. With paracetamol, reported rates seem similar to those reported after other NIP vaccinations at similar age.

The overall IMD incidence caused by serogroup B decreased from around 0.45 per 100,000 individuals between 2011-2019 to 0.18 per 100,000 in 2021, at least partially due to the COVID19-control measures. Pre-COVID (in 2019), the incidence in children <5 years of age was 2.5/100,000 (n=22) and in those aged 15-24 years 0.9/100,000 (n=20).

The incremental cost-effectiveness ratio (ICER) of the, at that time recommended, four-dose MenB vaccination scheme for infants in the

Netherlands was estimated at €244.000 per QALY gained in 2013. Because of the decrease of the IMD-B incidence since then, it is unlikely that the cost-effectiveness of vaccination has improved substantially, even when a three-dose schedule and higher disease costs than in 2013 are used, and spill-over effects to relatives are included in the model.

1 Introduction to this document

This document builds on the report that was provided to the Dutch Health Council in preparation for the decision on vaccination against meningococcal disease in 2018 (1), but only focusses on meningococcal serogroup B (MenB). The document mainly describes data and literature that is new since the previous report; references with new insights or updated information are indicated in bold.

In 2018, the Health Council advised not to include MenB vaccination in the national immunisation programme (NIP) at that moment. The advice was based on the uncertainties concerning its effectiveness and the duration of the effectiveness as well as the unfavourable cost-effectiveness ratio. Because of the mentioned uncertainties, the Health Council did not weigh the common adverse event of vaccination, i.e., high fever in very young children leading to hospital admissions, against the benefits (2). However, the committee recommended a re-evaluation of the advice as soon as more information would become available, which they expected to be the case after three years. This report is aimed to provide the updated background for that evaluation.

2 Epidemiology of meningococcal disease in the Netherlands

A note before presenting the epidemiology of invasive meningococcal disease (IMD) in the Netherlands: the numbers for the calendar years 2020-2021 are very likely affected (lower) by the control measures that have been implemented to counter the COVID-19 pandemic **(3, 4)**. Furthermore, vaccination against serogroups A, C, W, and Y (MenACWY) has been introduced for 14 month and 14-year-old children with a catch-up campaign (15-18 year olds) in 2018-2019 **(5)**. Consequently, the overall IMD numbers have also decreased as a result of this campaign **(6)**. This has affected the *proportion* of IMD cases that are caused by MenB. We will hence focus on the time period 2019-2021 in this overview of the IMD epidemiology in the Netherlands, whereby 2019 reflects the pre-covid period.

2.1 Incidence of invasive meningococcal disease

Overall, IMD is uncommon in the Netherlands, with 157 cases in 2019, 68 in 2020 and 37 cases in 2021. Serogroup B is the most prevalent serogroup causing IMD (n=31 in 2021, **Figure 1**). The incidence of serogroup B IMD (IMD-B) has been declining between 1999 and 2011 and was subsequently relatively stable until 2019 at around 0.45 per 100,000 individuals (n= 74 cases on average yearly). The incidence decreased to 0.18 per 100,000 in 2021 most likely due to the COVID19 control measures. The cause of the large decline in IMD-B from 1999-2011 is unknown, however, other countries report the same decrease (7). As reported previously, life style changes including the smoking ban from public places may have contributed to this decline (8). Despite the decline in absolute number of cases, the *proportion* of IMD cases caused by serogroup B has increased in recent years to 86% in 2021. This proportional increase is at least partly the result of the recent introduction of MenACWY vaccination, thereby preventing IMD caused by those serogroups **(6)**.

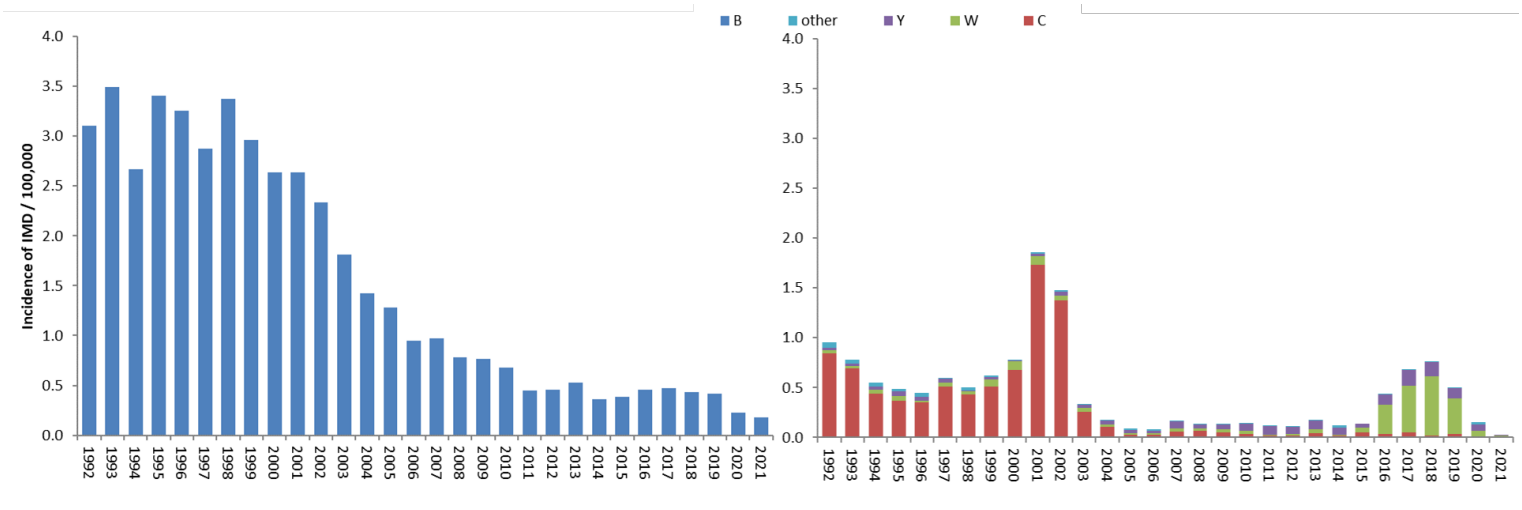

Figure 1 The incidence of invasive meningococcal disease (IMD) cases per 100,000 population by serogroup for the period 1992-2021; all age groups are

included: left, IMD-B, right, IMD caused by serogroups C, W, Y and other serogroups.

The IMD-B incidence has been highest in young children and, to a lesser extent, adolescents and young adults (**Figure 2**). Pre-covid (in 2019), the incidence in children younger than 5 years old was 2.5/100,000 (n= 22) and in those aged 15-24 years, the incidence was 0.9/100,000 (n=20). In 2021, incidences decreased to 1.6/100,000 (n=14) and 0.5/100,000 (n=10), respectively. The incidence has been fluctuating over several years (Figure 2), but the recent decrease will also have been due to the COVID-19 control measures.

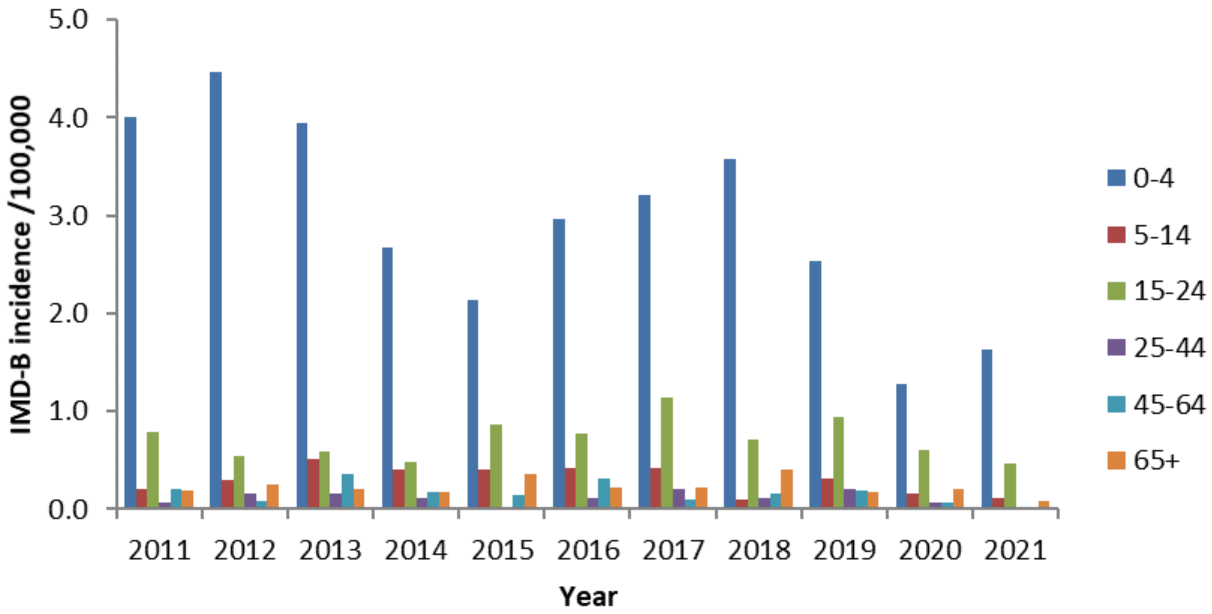

Figure 2 The incidence of invasive meningococcal disease serogroup B (IMD-B) cases per 100,000 population per age-group for the period 2011-2021.

It is uncertain how the numbers of IMD-B cases will develop when COVID-19 control measures are lifted. In the UK, an increase in IMD-B was observed in autumn 2021 in those aged 15-19 years after removal of all mitigations mid-July **(9)**. In the period September-November 2021, 47 IMD-B cases occurred, of which 22 were aged 15-19 years. Although the overall number of IMD-B cases was not higher than in pre-COVID years, the number among the 15-19 year olds was higher compared to 2018 (n=16) and 2019 (n=19). In other age groups, the number of cases were lower than in pre-COVID years. It was hypothesized that the lock-down and correspondingly the absence of MenB carriage and transmission may have caused an immunity dept that can have resulted in an increased number of susceptible individuals in the population. The age-group specific increase may be due to high carriage and transmission rates in that particular age group and protection of infants through vaccination against MenB since autumn 2015. Whether there was a substantial decrease in meningococcal carriage during the COVID-pandemic and a subsequent immunity dept has not been determined. It is unknown how much of the increase may

be explained by the increase in social contacts and possibly in co-infections (10).

2.2 Mortality and morbidity

For 97% of the cases reported to the National Reference Laboratory for Bacterial Meningitis (NRLBM) in the period 2015-2021, the information could be linked to the notifications of the Municipal Health Services. For IMD-B cases, clinical data on mortality, clinical presentation, and underlying diseases are available for 100%, 99.5%, and 78%, respectively. The IMD-B case-fatality rate was 5% (n=20/430) in this period. In those aged <5 years, the case-fatality rate was 5% (n=7/147 in 2015-2021) and in 5-24 year olds, 3% (n=4/153). The IMD-B case-fatality rate was highest in patients of 65 years or older (10%) and among patients with comorbidities (13% versus 4% for those without comorbidity). Overall, the IMD-B case-fatality has been lower than for IMD caused by serogroups C, W, and Y (overall 13%; n=59/382). Detailed clinical information, obtained through retrospective chart review, of IMD-B cases from July 2011-May 2020 in the Netherlands showed that 40% of the patients were hospitalised for a minimum of 10 days, 37% required admission to the intensive care unit, of which 47% needed intensive care for at least four days **(11); Table 1**. Two percent of the IMD-B cases died, which corresponds to the numbers found in the notified data, but which is lower than found in recent data from Denmark (7% **(12)**). Of the 278 cases that were included in the Dutch study, 42% had sequelae at discharge, 24% still had mild sequelae after one year and 2.4% still had severe sequelae after one year (Table 2). As described in (13), severe sequela included among others mental retardation, necrosis requiring skin transplantation or amputation, deafness requiring cochlear implant(s), renal or adrenal gland insufficiency and epilepsy, or peripheral paralysis/paresis). Mild sequela included the other sequelae, including other forms of hearing loss. Note that the Dutch data were obtained from nine sentinel clinical laboratories across the Netherlands that serve twenty hospitals of which 18 participated, including one academic hospital. The percentage of all cases that was treated in an academic hospital was slightly lower compared to national data, which may have led to a slight underestimation of the proportion with (long-term) sequelae. The percentage of IMD-B cases with sequelae was, nevertheless, similar to those found in Denmark (25% **(12)**).

The associations between serogroup (B, C, W, and Y) and disease course and outcome were determined using logistic regression, which results in odds ratio's (OR) that indicate whether the different variables differ per serogroup, when correcting for age (Table 1). The same was done for sequelae and their duration (Table 2). IMD-B was used as reference group; an OR above 1 means that for IMD caused by that serogroup, the duration/hospitalisation/case-fatality etc was longer/higher compared to IMD-B. The other way around, if the OR was lower than 1, it means that the variables were shorter/lower for that serogroup compared to IMD-B. When correcting for age, no difference in hospitalisation duration or ICU admission was observed between the serogroups, but the case fatality rate was lowest for IMD-B. The sequelae at discharge and the sequelae ≥ 1 year after discharge did not differ significantly between the

serogroups, but there was a non-significant trend of fewer sequelae ≥1 year after discharge for IMD-B.

Table 1 Disease course and outcome of invasive meningococcal disease by serogroup (n=278)

	Hospitalisation duration (% 10 days or more)[a]	**Odds ratio[a,b] CI**	**ICU admittance (% yes)[c]**	**Odds ratio[b,c] CI**	**ICU duration (% 4 days of more)[d]**	**Odds ratio [b,d] CI**	**Case-fatality (% yes)**	**Odds ratio[b] CI**
Serogroup B	57 / 141 (40.4%)	1.0	55 / 148 (37%)	1.0	24 / 51 (47%)	1.0	3 / 152 (2.0%)	1.0
Serogroup C	8 / 13 (62%)	1.6 (0.45-5.7)	6 / 13 (46%)	1.1 (0.32-3.5)	2 / 6 (33%)	0.61 (0.10-3.7)	1 / 13 (7.7%)	2.2 (0.21-24)
Serogroup W	39 / 73 (53%)	0.99 (0.50-2.0)	40 / 76 (53%)	1.35 (0.72-2.6)	17 / 38 (45%)	0.99 (0.41-2.4)	10 / 76 (13%)	3.9 (0.99-15)
Serogroup Y	17 / 35 (49%)	0.62 (0.26-1.5)	16 / 37 (43%)	0.83 (0.37-1.9)	5 / 14 (36%)	0.68 (0.19-2.4)	5 / 37 (14%)	3.7 (0.78-18)
Total	121 / 262 (46%)	NA	117 / 274 (43%)	NA	48 / 109 (44%)	NA	19 / 278 (6.8%)	NA
P Value [e]	0.19	0.52	0.17	0.65	0.83	0.89	<0.01	0.18

Abbreviations: CI, 95% confidence interval; ICU, intensive care unit; NA, not applicable.
[a] Among 262 patients, as for 16 patients, the hospitalisation duration was unknown.
[b] Odds Ratio compared to reference category (1.0) in logistic regression analysis with adjustment for age.
[c] Among 274 patients, as 4 patients had missing data for ICU admission.
[d] Among 109 patients, as 8 patients had missing data for IC duration among patients admitted to the ICU.
[e] Overall p-values of the effect of serogroup on the outcome measure in the crude (left) and adjusted (right) analysis. P-value < 0.05 was considered statistically significantly different between serogroups.

Table 2 Sequelae of invasive meningococcal disease by serogroup (n=278)

	Sequelae at discharge mild, n (%)[a]	**Sequelae at discharge severe, n (%)[a]**	**Total, n(%) [a]**	**Odds Ratio [a,b] CI**	**Sequelae ≥1 year after discharge mild, n (%)[c]**	**Sequelae ≥1 year after discharge severe, n (%)[c]**	**N / Total (%)[c]**	**Odds Ratio[b,c] CI**
Serogroup B	57 (42%)	8 (5.7%)	65 / 137 (46%)	1.0	30 (24%)	3 (2 .4%)	33 / 123 (27%)	1.0
Serogroup C	6 (46%)	1 (7.7%)	7 / 12 (54%)	1.32 (0.38-4.5)	2 (18%)	1 (9.1%)	3 / 11 (27%)	1.61 (0.38-6.9)
Serogroup W	23 (32%)	14 (19%)	36 / 63 (51%)	1.28 (0.65-2.5)	13 (22%)	4 (6.8%)	17 / 59 (29%)	1.82 (0.80-4.1)
Serogroup Y	14 (39%)	4 (11%)	18 / 31 (50%)	1.20 (0.50-2.9)	6 (25%)	2 (8.3%)	8 / 24 (33.3%)	2.43 (0.82-7.2)
Total	100 (38%)	26 (11%)	126 / 243 (52%)	NA	51 (24%)	10 (4.6%)	61 / 217 (28%)	NA
P-value [d]			0.48	0.90			0.93	0. 35

Abbreviations: CI, confidence interval; ICU, intensive care unit; NA, not applicable.
[a] Among 243 surviving patients without missing information at discharge.
[b] Odds Ratio compared to reference category (1.0) in logistic regression analysis with adjustment for age.
[c] Among 217 patients who survived their hospitalisation, did not died due to other reasons one year after discharge, and were still registered in the hospital of admission.
[d] Overall P-values of the effect of serogroup on the outcome measure in the crude (left) and adjusted (right) analysis. P-value < 0.05 was considered statistically significant.

2.3 Carriage

Generally, meningococcal carriage is relatively low in young children (4.5%) but increases during childhood with a peak of 24% in 19 year olds (14). Subsequently, carriage decreases to about 8% in 50-year olds and to a slightly lower prevalence in older ages (14). A study performed among Dutch students in 2018, just before the MenACWY vaccine introduction, reported that 25% of the students carried meningococci **(15)**; this percentage was independent of serogroup or pathogenicity of the carried strains. The carriage prevalence of group B meningococci in this group was 9%. It has now become clear that MenB vaccines do not prevent MenB carriage **(16, 17)**; it is therefore unlikely that MenB vaccines will decrease meningococcal B transmission.

3 Meningococcal B vaccination

Currently, two MenB protein vaccines are licenced and available in the Netherlands: the multicomponent vaccine 4CMenB (Bexsero) is approved for use in individuals of 2 months of age and older, and the bivalent rLP2086 vaccine MenB-fHbp (Trumenba), is approved for use in adolescents 10-25 years of age. Two pentavalent vaccines combining the protein-based MenB and polysaccharide conjugate MenACWY components targeted at protection against IMD-A, B, C, W and Y are being developed (phase III) but are not yet available **(4)**.

3.1 Use of MenB vaccines

In the Netherlands, the MenB vaccines are available for private use but use is limited. Around 8,000 doses of 4CMenB have been administered between October 2018 and December 2021 **(18)**. 4CMenB has mainly been used by those aged 10 years or younger, but given the number of administered vaccines, the coverage in that age-group is still low in the Netherlands. Private use of MenB-fHbp has been very limited with overall around 140 doses sold since 2020 **(18)**.

Several countries have introduced MenB vaccination in their childhood vaccination programmes or have used MenB privately at a relatively high coverage, including Austria, Canada, Italy, Lithuania, Malta, Portugal, South Australia, Spain, UK **(19, 20).** Most countries use MenB only in infants but in South Australia, MenB is introduced as toddler and adolescents (15-17 years of age) vaccines in their NIP **(21)**. Some countries recommend MenB vaccination only for risk groups (Greece, Luxembourg, Czechia) **(19)**. In infants, either a 2+1 schedule with two primary vaccinations at the age of 2-5 months and a booster vaccination at the age of 12-15 months (UK, Lithuania, Malta), or a 3+1 schedule (Austria, Italy) with similar timings have been used **(19)**. For adolescents, one primary and one booster is recommended. During the COVID-19 pandemic, France also decided to implement infant MenB vaccination in the NIP **(22)**. One of the reasons for this decision is the concern for a possible epidemic resurgence after returning to normal social life, as there may be an immunity gap due to reduced circulation of meningococci in the population during the COVID-19 pandemic. Note that in France, only MenC vaccination is used in the NIP. Cross-protection against IMD-W may therefore be anticipated.

3.1.1 Vaccine acceptance

The uptake of infant 4CMenB has been good in the UK, where 4CMenB is used in the NIP since September 2015; 93% has received 2 doses at the age of 1 year, and 88% all 3 doses **(23)**. Furthermore, the addition of 4CMenB to the routine infant immunisation schedule did not seem to have had an adverse effect on compliance with other vaccinations **(24)**. In Italy, where 4CMenB was introduced separately per region, the coverage in 2019 varied between 47% and 91%, with overall 69% in Italy among children born in 2017 **(25)**.

3.2 Genomic analyses (strain coverage by the vaccines)

Because of the nature of the MenB vaccines, being protein-based instead of polysaccharide-based, protection depends among others on the coverage of the strains circulating within a country, as the components of the vaccine need to cover the circulating MenB clones to provide protection. For the Netherlands, the overall strain coverage of 4CMenB was estimated at around 73% for all isolates in the years 2017-2019. However, the strain coverage was 58% coverage for children aged 0-4 years **(26)**. More recent Dutch surveillance data (2019-2021) showed a strain coverage for 4CMenB for IMD-B of 77-79% among those younger than 5 years old (n=24 sequenced isolates), 75-92% for those aged 5-14 years (n=6, more uncertainty) and 87-91% for 15-24 years olds (n=23). For MenB-fHbp, the strain coverage in 2019-2021 in the age groups for which the vaccine is licensed was estimated at 69% for those aged 10-17 years old and 85% for the 18-25 years olds. To determine the strain coverage for 4CMenB, 50% of the unpredictable strains are standard added to the coverage. If the same is done for MenB-fHbp, the coverage was estimated at 85% and 92% for the 10-17 years and 18-25 years olds. A lower strain coverage in the youngest age groups is seen in several countries **(26-29)** including in the Netherlands. This is likely caused by a larger strains diversity in this age group, especially with strains that rarely cause disease in adolescents or (younger) adults **(30)**. In contrast to the Dutch surveillance data, for several countries, the strain coverage for IMD-B decreased in recent years **(27, 31)**. After 4CMenB implementation in the NIP in the UK, the number of vaccine-covered strains decreased among vaccinees, but importantly, during the study period, there was no increase among children <4 years in the absolute numbers of cases that were infected with a poorly covered strain **(30)**.

Because the vaccine-proteins are (partly) shared between serogroups and bacterial species, MenB vaccines can also partially protect against IMD caused by other serogroups as well as against *Neisseria gonorrhoea* **(32, 33)**. For IMD-W, data from Switzerland showed that clonal complex (cc)22 IMD-W strains were covered by 4CMenB. In contrast, coverage could not be predicted for cc11 IMD-W strains based on whole genome sequencing **(31)**. These data are in line with Dutch results. 4CMenB coverage for cc11 IMD-W is unpredictable because immunoassays, which provide input to predict coverage, give variable results for this meningococcal type. Cc11 is dominant among IMD-W strains in the Netherlands, but the incidence has decreased drastically as a result of the MenACWY vaccination campaign. For the Netherlands for the period 2017-2018, most IMD-W strains had an unpredictable coverage; potentially up to 52% of IMD-W cases were covered by 4CMenB. For 2019-2021, limited surveillance data of other serogroups (mainly W and Y) was available for children and adolescents because of the low incidence. The estimated coverage of 4CMenB for other serogroups for <5 years was 50-80% (based on 6 isolates) and 50-77% for 15-24 years (13 isolates). For MenB-fHbp, the strain coverage of non-B serotypes is much lower (14% for 10-24 year olds) than for 4CMenB because of the more narrow selection of antigens that are included in MenB-fHbp.

3.3 Immunogenicity, vaccine effectiveness and vaccine impact

3.3.1 Protection against IMD-B

The immunogenicity data for MenB vaccines has been based on the serum bactericidal antibody assay (SBA) with rabbit or human complement (hSBA) as serocorrelate of protection against IMD; an hSBA titre of at least 4 is defined as correlate of protection or seroconversion (34) however, different cut offs are used depending on the study. Recent data confirm the good immunogenicity results that were presented in the previous report for the Health Council. As the strain coverage differs between isolates, the proportion of individuals that seroconvert also differ depending on the used strains in the different studies. E.g., an open-label randomised control trial included about 100 infants per arm that received a 2+1 schedule with 4CMenB (both arms) as well as, either a 1+1 schedule or a 2+1 schedule of the 13-valent pneumococcal conjugate vaccine (PCV13) **(35)**. They showed that at least 95% of infants had a hSBA titre against the vaccine-matched strain of at least 4 after the two primary doses and at least 92% after the booster dose. Similar results were observed in another trial in the UK of similar size, which compared 4CMenB vaccination in infants administered together with routine immunizations (test group) at 2, 4, and 12 months or 4CMenB administered alone at 6, 8, and 13 months of age (control group) **(36)**. This study showed that 97% (95%CI: 91-100) of the infants of the test group had an hSBA titre of at least 4 after the primary series; the percentage remained the same after the booster vaccination. Between the primary series and the booster, the percentage of infants with sero-protective titres decreased.

In persons 10-25 years of age, MenB-fHbp was immunogenic after using either a 2-dose (0 and 6 months) or a 3-dose (0, 1-2 and 6 months) series **(37)**. In around 1,000 persons, 74% (95%CI: 71-77) seroconverted after the second dose. A review on the immunogenicity of MenB-fHbp in individuals aged 18-25 years showed that 83%-85% had hSBA titres indicative for protection against the four primary MenB test strains combined (i.e. composite responses) **(38)**. When using 4CMenB in individuals aged 10-25 years (n=94 per arm) receiving 2 doses at two months apart, approximately similar percentages of seroconversion were observed (seroconversion for fHbp, NadA, PorA, NHBA of 83%, 100%, 79%, 81%, respectively) **(39)**. In the summary of product characteristics, 100%, 99%, 100% and 100% per antigen are presented (76).

Because of the novelty of the vaccines, little data is available on long-term persistence of antibodies. The maximum follow-up, as published so far, has been a study determining the post-primary responses 4 years and 7.5 years after adolescent vaccination **(40)**. Recipients were aged 11-17 years at time of vaccination, which occurred in Australia, Canada and Chili. At the age of 15-24 years, four years after 2-dose 4CMenB vaccination, the percentage of individuals with an hSBA titers ≥4 were 30%, 84%, 9% and 75% for the four vaccine components (fHbp, NadA, PorA and NHBA, respectively). In individuals that received their vaccination 7.5 year before, the percentages were 44%, 84%, 29% and 81%, respectively. Another extension study followed-up 391 children vaccinated in Hungary and Spain at 2–10 years for 24–36 months after

vaccination completion **(41)**. They found that, in all age groups and for both a 3+1 and a 2+1 schedule, the percentage with hSBA titres ≥4 and the geometric mean titres (GMT) tended to be higher than in age-matched vaccine-naïve groups for fHbp, NadA and PorA, but not for NHBA. In those having received 4CMenB at 3.5, 5 and 11 months of age, still 53%, 88%, 38% and 38% had hSBA titres ≥4 for fHbp, NadA, PorA and NHBA, respectively, at 24–36 months post-primary series.

A summary of vaccine effectiveness data can be found in Table 3. In the previous report (1), vaccine effectiveness (VE) estimates were reported from the infant MenB vaccination programme in the UK as determined within one year after introduction. A VE against all IMD-B after 2 doses of 83% (95%CI: 24-95) was estimated using the screening method, i.e., using cases and the vaccine coverage in the country (42). When adjusted for the strain coverage, the VE was 94%. Using the indirect screening method three years after vaccine introduction, a VE against all IMD-B of 53% (95%CI: -34-83) was found among children receiving 2-doses **(23)**. Among children who received three doses, the VE was 59% (95%CI: -31-87). The estimates slightly increased to 64% and 71%, respectively, when they only included cases infected by strains that are covered by 4CMenB. Authors affiliated to the manufacturer of the vaccine (GSK) re-analysed the UK data; there was an increasing trend in IMD-B observed among non-vaccinated individuals during the study period, which they included in the in the analysis **(43)**. The corrected estimate of the was VE of 79% (95%CI: 72-85) after 2 doses and 80% (95%CI: 70-87) after 3 doses.
Recent studies from other countries report quite similar VE estimates in infants. A Portuguese matched case control study in children younger than five years old found a VE of 79% (95%CI: 45-92) based on 69 cases (5 fully vaccinated children) and 142 controls (33 fully vaccinated **(44)**. In Italy, where MenB vaccination for infants is implemented in several regions at different timepoints, a comparison was made of Tuscany and Venice. In Tuscany, MenB vaccination was introduced in 2014 with a 3+1 schedule and in Venice in 2015 with a 2+1 schedule in infants. The estimated VEs were 94% (95%CI: 55-99) and 91.0% (95%CI: 60-98), respectively **(45)**.
In Canada, 4CMenB was used in 2014 in a successful mass-vaccination campaign directed at individuals aged 2 months to 20 years of age to control a long-lasting outbreak of IMD-B **(46)**. Four years after the campaign, the estimated VE was 79% (95%CI: -231%-99%) based on only one vaccinated case, one unvaccinated young adult and three unvaccinated elderly **(47)**. Limited data is available otherwise on product-specific VE in adolescents, but outbreak response data from the US indicate good protection based on the absence or limited number of cases after vaccine campaigns **(48, 49)**. A state-wide trial with 4CMenB in Australia reported no IMD-B cases after vaccination; a VE could not be calculated **(50)**.

Table 3 Vaccine effectiveness of 4CMenB against IMD-B, the incidence at vaccine introduction and the strain coverage in the country.

Target population	***Country***	***Country***	***Schedule***	***Incidence at vaccine introduction***	***Strain coverage***	***Estimated vaccine effectiveness against IMD-B***	***Corrected VE***	***Reference***
Infants in NIP	UK	UK	2 dose (booster was not yet administered)	4.5/100,000 in 1-4 year olds (from (7))	73% pre vaccine introduction	83% (95%CI 24-95).	For covered strains 94%	(42)
Infants in NIP	UK	UK	2+1	4.5/100,000 in 1-4 year olds (from (7))	73% pre vaccine introduction	53% (95%CI -34-83) for 2 doses, 59% (95%CI -31-87) for 3 doses.	For covered strains 64.4% (2 doses) and 71% (3 doses)	**(23)**
Infants in NIP	UK	UK	2+1	4.5/100,000 in 1-4 year olds (from (7))	73% pre vaccine introduction		Corrected for IMD-B trend in unvaccinated individuals independent of strain coverage: 79% (95%CI 72-85) after 2 doses and 80% (95%CI 71-87) after 3 doses	**(43)**
Children and adolescents	Portugal	Portugal	2-4 doses, depending on age	2.63/100,000 in 1-4 year olds (from (7))	Not provided at population level	79% (95%CI 45-92)		**(44)**
0-4 years	Italy - Tuscany	Italy - Tuscany	3+1	1.96/100,000 in 0-4 years	Not known	94% (95%CI 55-99)		**(45)**

Target population	*Country*	*Country*	*Schedule*	*Incidence at vaccine introduction*	*Strain coverage*	*Estimated vaccine effectiveness against IMD-B*	*Corrected VE*	*Reference*
0-5 years	Italy - Veneto	Italy - Veneto	2+1	1.94/100,000 in 0-5 years	Not known	91% (95%CI 60-98)		**(45)**
0-20 years	Canada	Canada	2-4 doses are, depending on age	11.4/100,000 person-years in 0-20 years	85% in 2006-2009	no IMD-B cases had occurred		**(46)**
0-20 years	Canada	Canada	2-4 doses are, depending on age	11.4/100,000 person-years in 0-20 years	85% in 2006-2009	79% (95%CI: -231%-99%)		**(47)**
Adolescents (school-based)	South Australia	South Australia	1+1	2.8/ 100,000 population in 0-25 years	90%	no IMD-B cases had occurred		**(50)**

The impact of vaccination includes the overall effect of the vaccine in the target population, so including the direct effect in vaccinees and the effect in the non-vaccinated individuals. However, because MenB vaccines do not affect carriage, the impact is a combination of the vaccine effectiveness and the vaccine coverage. In Canada, the vaccine coverage of the campaign was 82% in the targeted age groups and had direct impact; no IMD-B cases occurred in the targeted age group in the 2.5 years following the campaign **(46)**. Four years after the vaccination campaign, the overall vaccine campaign impact, estimated by taking into account the decrease in IMD-B incidence, was a 86% (95%CI: -2%-98%) decrease in IMD-B risk **(47)**. The impact was mainly seen in the targeted age group suggesting no herd protection. In the UK, three years after implementation of 4CMenB in infants in the NIP, there was a reduction of 75% (95%CI: 64-81) in IMD-B **(23)**. In Italy, the overall impact of vaccine implementation in children was larger in Tuscany where a 3+1 schedule is used since 2014 (68%, 95%CI: 10-89) compared to Venice where a 2+1 schedule is used since 2015 (31%, 95%CI: −56-69) **(45)**.

3.3.2 Protection against IMD caused by other serogroups

In the previous report (1), no data was available yet on the effectiveness or immunogenicity of MenB against other meningococcal serogroups. Still, few data of MenB vaccination against other serogroups are available. In a small study (n=147) testing Brazilian and European isolates, up to 62% of non-MenB isolates were lysed (hSBA titre ≥4) following vaccination with 2 doses of 4CMenB **(51)**. Per serogroup, the percentage of isolates that were lysed were 55% for MenC, 74% for MenW, and 66% for MenY. UK IMD surveillance data of the 4 years before and 4 years after implementation were used to estimate direct protection against IMD-W. The study estimated 69% (adjusted incidence rate ratio, 95%CI: 33-80) fewer IMD-W cases aged 12 years or younger than predicted in fully-eligible age cohorts and 52% (95%CI: 19-72) fewer cases among partly-eligible age-cohorts **(52)**. These results indicate effective protection of MenB against IMD caused by the locally circulating serogroup W strains (vaccine effectiveness after 2 doses: 34% (95%CI: -472%-83%, after three doses: 88% (95%CI: -29%-98%)). During the study period (2011-2019), 89% (185/207) with available information were caused by MenW:cc11, which is the same cc that is dominant in the Netherlands.

3.4 Reactogenicity / side effects

As presented in the previous report (1), MenB vaccines have acceptable safety profiles, although local reactions including pain, redness, swelling and fever are commonly reported. Data from the UK after more than 3 million doses of 4CMenB administered to infants in the NIP have shown no new safety concerns **(21)**.

A proactive nationwide surveillance study of the UK investigated suspected adverse reactions of 4CMenB in children up to age 18 months, with focus on fever, local reactions, Kawasaki disease, seizures, and sudden death, and compared the number of spontaneous reports with the expected number of events **(24)**. The children have received their 4CMenB at the age of 8 weeks (or a small proportion at 12 weeks). For all children, it is advised to use three doses of prophylactic paracetamol;

the first dose of paracetamol to be administered around the time of vaccination with two additional doses at 4–6 hour intervals. Children simultaneously received DTaP/IPV/Hib, PCV13, and oral rotavirus vaccination. In approximately two years and after 1.3 million vaccinated children, 902 reports of suspected adverse reactions were received. Forty-one percent was related to local reactions and 40% to fever. It was unknown whether the children with high fever had received prophylactic paracetamol. The reported rates of Kawasaki disease, seizures, and sudden death were not different from expected based on the background incidence and the number of vaccinated children but this may have been due to low power. A study in the same population but with a longer time study period and a different data source (The Health Improvement Network covering 5% of the population) found that seizures and its sub-set febrile seizures occurred slightly more often in the infants than expected (incidence ratios in a self-controlled case series of 1.4 (95%CI: 1.0-2.0) for seizures and 1.7 (95%CI: 1.1-2.8) for febrile seizures) **(53)**. Kawasaki disease was not different from the background incidence. A signal of increased incidence of nephrotic syndrome (NS) after the mass-vaccination campaign in Canada was published based on the identification of three cases in whom NS was diagnosed after their second 4CMenB dose **(54)**. After active searching, another NS case was found. All were vaccinated children at 2–5-years-old with onset of NS several months post-vaccination. The incidence of NS was 4-8 times higher than in the control situations. A signal of increased incidence of NS post-4CMenB vaccination has not been reported in other countries.

(High) fever after 4CMenB vaccination in infants has been an issue from the start and MenB vaccination is therefore often implemented with the advice to use prophylactic paracetamol in infants when receiving the MenB vaccine and routine vaccines concomitantly. Still, the implementation of 4CMenB in the NIP has led to increased fever-related hospitalisation within three days post-vaccination (incidence of attributable cases: 128 (93-165)/100,000 after dose 1 and 67 (95%CI: 43-94)/100,000 after dose 3, no increase after dose 2 (55); paracetamol use was unknown for the hospitalised infants in the study). Data from the mass-vaccination campaign in Canada showed the distribution of fever among age groups and the effect of antipyretic prophylaxis and coadministration of other vaccines **(56)**. The study showed that fever was highest on days 1-2 and was most common in the children aged <2 years (18-22% for primary series, 14% after dose 4) and the incidence decreased with higher age. Only 0.6% of those <2 years old reported a temperature of ≥40°C. Note that this percentage of high fever is lower compared to what was reported in some clinical trials, likely because of non-systematic temperature measurement and the use of antipyretic prophylaxis. In a clinical trial comparing 4CMenB and MenC when given together with DTaP-HBV-IPV/Hib and PCV7 but without prophylactic paracetamol, fever was more common after 4CMenB (21% ≥39°C after first dose) than after MenC vaccination (1% ≥39°C after first dose) (57). The percentage with fever (when using prophylactic paracetamol) was slightly lower or similar to what was found in the Netherlands after routine PCV10 or DTaP-IPV(-HepB) vaccination without prophylactic paracetamol **(58)**.

In the Canadian study, use of antipyretic prophylaxis had largest effect in this youngest population, and did not have any affect in vaccinees older than nine years old **(56)**. Among the <2 years old, fever was associated with the number of acetaminophen doses and coadministration of other vaccines; compared with not using acetaminophen prophylaxis, taking ≥2 doses reduced the odds of fever by half to a third, depending on the age group (overall <2 years: OR=0.35; 95%CI: 0.2-0.6). Coadministration of other vaccines nearly doubled the odds of fever in those <2 years when corrected for age at immunisation, sex, dose and interval to acetaminophen initiation (OR for fever at the age of 2–6 months: 2.7 (95%CI: 1.7–4.4), of 12–14 month: 1.95 (95%CI: 1.1–3.6) and of 18–23 month: 1.8 (95%CI: 1.1–3.6)). In pre-term infants, paracetamol administration also reduced fever post-vaccination **(59)**.

In a study that analysed data from the national passive surveillance system for adverse events in the US, vaccination of individuals aged 10-25 years that were vaccinated with 4CMenB also revealed no new safety concerns **(60)**. Similarly, in the same population and surveillance system, vaccination with MenB-fHbp did not show new safety concerns; headache, pyrexia, chills, and myalgia were most commonly reported which is consistent with adverse effects identified in clinical trials **(61)**. In a large post-licensure study in South Australia, spontaneous reporting of adverse events following 4CMenB of 30,522 students were analysed. Overall, 0.32% (95%CI: 0.28-0.39%) reported adverse events, of which mainly injection site reaction, headache and nausea. Reported adverse events were more common after the first dose and declined with increasing age **(62)**.

4 Cost-effectiveness

The previous document for the Health Council (1) reported on a cost-effectiveness analysis for the Netherlands that was performed in 2013 by Pouwels et al. (63) as well as several analyses from other countries. Pouwels et al. used a single-cohort model and concluded that introduction of routine infant vaccination against IMD-B would unlikely be cost-effective in the Netherlands (incremental cost-effectiveness ratio (ICER) in the range of €220,000-250,000 per quality adjusted life years (QALY) gained, depending on vaccination schedule). Only if the IMD-B incidence would increase or the vaccine price would be substantially lower than €40, MenB vaccination was estimated to be cost-effective at €50,000 per quality adjusted live year (QALY). Pouwels used the incidence in 2005-2009, which was 1.07/100,000 compared to 0.42/100,000 in recent pre-COVID years. The main scenario in the earlier cost-effectiveness analysis included a 3+1 schedule. However, reduced schedules (2+1) have been shown to be effective, which will result in lower vaccination costs per child. Furthermore, several other factors that affect the cost-effectiveness analysis have recently been implemented in different analyses.

There are still uncertainties around the costs of IMD(-B) such as the rate and costs of (long-term) sequelae after having suffered from IMD(-B). The costs of sequalae have been estimated to be around 70-81% of the overall costs of IMD-B **(64, 65)**. Changes in these values will therefore have an effect on the cost-effectiveness results. A Dutch cost-of-illness analysis for IMD-B with GSK authors shows higher direct and indirect costs from a societal perspective compared to what was included by Pouwels etal.; the costs varied between €40,000 and €123,000 per case, depending on the scenario and the included factors **(66)**. The higher direct costs result among others from additional sequelae and the fact that these occur among the (very) young. Higher costs per case will lead to a more beneficial cost-effectiveness analysis. Note, however, that the used percentage of survivors with long-term sequelae was higher in Zeevat etal. **(11)** than found in the detailed clinical information of Dutch IMD-B cases of 2011-2020 by the RIVM (**Table 2**).

Recently, cost-effectiveness studies for England and Germany have been published that used the same DYCE (DYnamic Cost Effectiveness), i.e., a multi-cohort model, and were funded by GSK. Multi-cohort models are generally recommended when indirect effects are expected or when the intervention impacts subsequent cohorts differently (67). Furthermore, these can be used when cross-protection is expected. The study from England shows that the inclusion of some aspects that are not (yet) routinely included in cost-effectiveness analysis in England had a huge impact on the ICER. In more detail, more types of long-term sequelae, the impact of IMD-B on the quality of life of family members and caregivers (spill-over effects), the costs beyond direct medical costs, a factor to account for the societal preference to prevent severe diseases with long-term sequalae of IMD-B in children (QALY losses of long-term sequelae x 3), and a lower discount rate to give more value to the long-term impact of IMD, reduced the ICER stepwise from £361.000/QALY to

£18.600/QALY **(68)**. So, only when the additional factors were included in the multicohort model, MenB vaccination could be cost-effective in the UK. Note, however, that the used IMD-B incidence in this English study (base case 1.83/100,000, high 2.55/100,000, low 0.77/100,000) is substantially higher than the incidence in the Netherlands, even in the pre-COVID period (2011-2019; on average 0.44/100,000; Figure 1).

So far, spill-over effects and the adjustment factor to account for the long-term sequelae are not commonly included in cost-effectiveness analyses of vaccines in the Netherlands. Specifically, the adjustment factor, so, the choice to assign a heavier weight to QALYs lost or due to long-term sequelae, which resembles increasing the cut off for costs per QALY gained for cost-effectiveness, would more be a responsibility for the Health Council to decide on. Furthermore, for MenB vaccination, no indirect protection is expected because of the lack of protection against carriage, and the impact of vaccination is expected to be equal for different cohorts. Cross-protection of MenB vaccination against e.g. IMD-W has been shown **(52)**. Note, however, that cross-protection of MenB vaccination against IMD-W would have the largest direct effect if no (infant) MenACWY is used in the NIP. In UK, MenACWY vaccination is offered to adolescents but not to infants in the NIP and in Germany, MenC vaccination is offered to infants and adolescents (19).
The analysis for Germany estimated that implementation of MenB vaccination in the NIP would rapidly produce health benefits, but at around €190,000 per QALY gained. The ICER decreased to around €78,000, when a factor for societal preferences to prevent this severe disease that can cause long-term sequelae was included and when they corrected for IMD underreporting **(69)**. The incidence of IMD-B in Germany has been quite similar to the Netherlands pre-COVID **(70)**. In the German analysis, differential discount rates of 3% for costs and 1% for QALYs was used over a time horizon of 100 years. Discounting is used to adjust future costs and QALY gains of health-care interventions to the "present value" (71). In a multi-cohort model with a higher discount rate for costs than for QALYs, vaccination costs become lower for each newly vaccinated cohort relative to the QALY gains of that cohort, thereby improving the ICER over time. The Netherlands also recommends to use differential discount rates of 4% for costs and 1.5% for QALYs.

For the Netherlands, taking into account the fact that MenB vaccination does not affect carriage and thus indirect effects are not expected and that infants are vaccinated against MenACWY, a single-cohort model like Pouwels et al. still seems adequate. The incidence of MenB has decreased since the cost-effectiveness analysis of Pouwels etal. in 2013. Therefore, it is unlikely that the cost-effectiveness of Men B vaccination has substantially improved since then, even when a three-dose schedule and higher disease costs are used, and spill-over effects to relatives are included in the model.

5 Aspects of implementation

As described above, there are two vaccines available: 4CMenB (Bexsero), which can be used from infant age, and MenB-fHbp (Trumenba), which can be used in adolescents. Note that the vaccines do not prevent carriage so the health impact will only be dependent on the IMD-B incidence, strain coverage, vaccine coverage and vaccine effectiveness, and no indirect protection can be expected.

5.1 Infants vaccination

4CMenB is licenced for infants from 2 months of age. Three primary doses and a booster (3+1) are originally advised when starting at 2 months. If starting at three months, a 2+1 schedule can be used (see also **(72)**). Between the primary series and the booster there should be at least six months and the booster should not be given before 12 months of age. Note that in the UK, a (reduced) 2+1 schedule has been used in the NIP starts at 2 month old (vaccinations at 2, 4 and 12 months). The 2+1 schedule effectively prevents IMD-B in the target group **(23)**.

The age of the IMD-B cases younger than 5 years in 2015-2021 is presented in **Figure 3**. The youngest case during that period was 0 months old, followed by four cases at one month old and ten cases aged two months. Because of the development of the immune system, the vaccine is licenced for use in infants from 2 months of age and cases before that age can therefore not be prevented through vaccination. If implemented, it is, however, desirable to vaccinate children as early as possible.

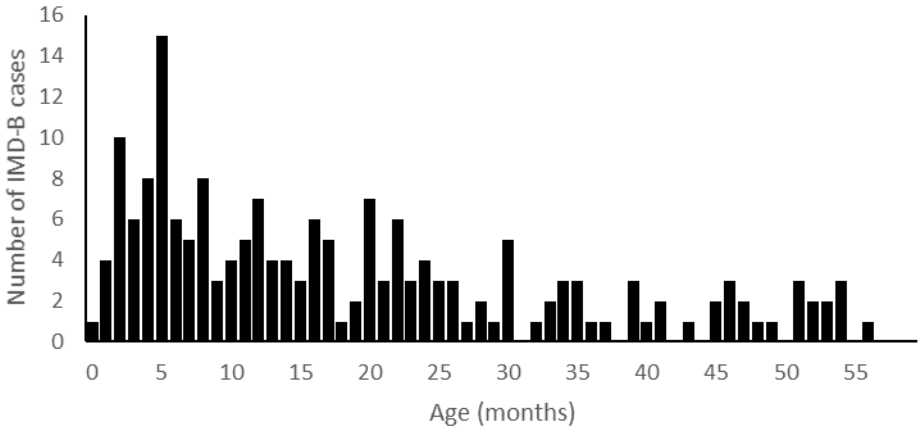

Figure 3 The number of invasive meningococcal disease serogroup B (IMD-B) cases aged younger than 5 years, per age in month in the period 2015-2021.

Generally, in the Netherlands, not more than two injections at one visit are administered. As cited in the previous report, it was shown that parents think that three vaccine injections per visit would be too much and that they rather prefer an additional visit instead of more injections at the same time (73). Furthermore, concomitant vaccination with the

MenB vaccine increases the risk of mild side effects including fever. Still, in UK, 4CMenB is administered together with DTaP-IPV-Hib, PCV13 and oral rotavirus vaccination without safety concerns **(24)**.

In the current schedule, two injections (DTaP-IPV-Hib-HepB and PCV10) are already offered at 3 and 5 month of age. Prematurely born children and children born from mothers that did not receive maternal pertussis vaccination during pregnancy are offered DTaP-IPV-Hib-HepB also vaccination at two months of age, i.e., one injection at that timepoint. If the current schedule would remain the same, MenB vaccination could be implemented at 2 months old. The second MenB dose should be given at least two months after the first dose. The second MenB dose could therefore be offered at 4 months. The booster should be offered between 12 and 15 months of age, but at least 6 months after the primary series. As, at 15 months, MMR and MenACWY are administered concomitantly in the current schedule, the third MenB dose could be offered at 12-14 months of age if the current schedule would remain unchanged.

For individuals with a complement disorder, those using eculizamab or with hypo/asplenia, MenB vaccination is recommended and reimbursed from 2 months of age and older (72). Depending on the age at primary vaccination, 1-3 primary doses and a booster are recommended. Children with these disorders could follow the same schedule as recommended for other children, if implemented in the NIP, although an additional primary dose may be needed, e.g. at six month, when starting the primary series at the age of two months (72), but no data is available for this risk group yet.

5.1.1 Use of antipyretics

Because of the risk on (high) fever (see chapter Reactogenicity / side effects), prophylactic paracetamol could be recommended at the day of MenB vaccination. In the UK and Canada, the advice is to take the first dose of paracetamol around the time of vaccination with two (or three) additional doses at 4–6 hour intervals **(24, 56)**. Prophylactic paracetamol can be extra relevant when several vaccinations are administered concomitantly. However, prophylactic paracetamol has been associated with lower antibody responses when used after vaccination with PCV10 co-administered with DTPa-HBV-IPV/Hib and oral human rotavirus vaccines (74) or other vaccinations (75). The clinical effect of the slightly reduced responses is not yet known though, as a high proportion of vaccine recipients seroconvert after using paracetamol. The blunting effect has only been seen after the primary series and not after booster doses. In a clinical trial using 4CMenB, immune responses were not decreased by the use of prophylactic paracetamol (57).

5.2 Adolescents vaccination

Both, 4CMenB and MenB-fHbp can be used in adolescents. For 4CMenB, from the age of 11 years, two vaccinations are needed, with at least one month in between (72, 76). For MenB-fHbp, which can be used at 10-25 years of age, also two vaccines are needed, administered at a 6 month interval (77). In the current schedule, MenACWY is offered at 14 years

old. 4CMenB can be offered together with MenACWY, without effect on the immunogenicity of either vaccine **(39)**. Co-administration of MenB-fHbp and MenACWY is also well tolerated in adolescents and induces protective antibody response **(37)**. MenB vaccines are more reactogenic than MenACWY, but the local adverse effects seemed unrelated to coadministration of other vaccines (78).

In **Figure 4**, the number of IMD-B cases among those aged 25 years or younger are shown. Among adolescents, the number of cases are highest among those aged 18 years (n=28); among those aged 16-19 years, the number of cases that occurred in the period 2015-2021 was 10 or more.

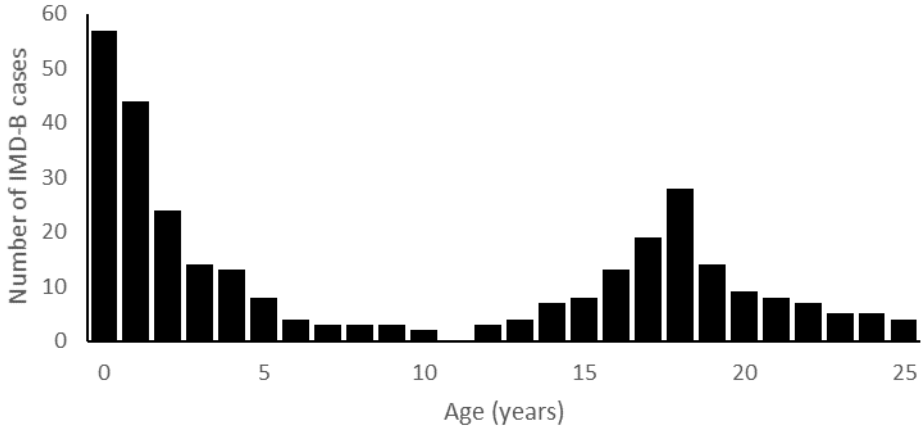

Figure 4 The number of invasive meningococcal disease serogroup B (IMD-B) cases aged younger than 25 years, per age in years in the period 2015-2021.

Based on the few studies that present immunological data from longer periods after vaccination indicate that antibodies wane over time. No studies are yet available on how the vaccine effectiveness changes over time.

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Conflicts of interest

Nina van Sorge received consultancy fees from Pfizer, MSD, and GSK outside the submitted work (fees paid to Amsterdam UMC); In addition, Nina van Sorge has a patent WO 2013/020090 A3 on *Streptococcus pyogenes* (GAS) vaccine development which is not related to this work, with royalties paid to University of California San Diego.

The main author and all other contributors report no potential conflicts of interest.

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Erratum report 2022-0046

Meningococcal disease serogroup B Updated information for the Dutch Health Council

Bilthoven: 13 May 2022
Subject: Erratum for report 2022-0046

In the RIVM report 2022-0046 with the title 'Meningococcal disease serogroup B, Updated information for the Dutch Health Council' a few corrections are made.

In the synopsis at page 3 and the Publiekssamenvatting at page 5 it says 'high fever is 50 per cent less common when paracetamol is used on the same day of meningococcal vaccination'. However, in the study that reported the referred results, fever (koorts) and not high fever (hoge koorts) was investigated. This is also the case for the results referred to at page 9 in the summary, where it says that 'the odds for high fever nearly doubles when vaccination is administered concomitant with other vaccines'. At these place 'high fever' should be replaced by 'fever'.

On page 33 it is written that 'If starting at three months, a 2+1 schedule can be used', referring to the GVS-advies of Zorginstituut Nederland. Since that publication, a 2+1 schedule has also been licensed for children aged two months old (reference SMPC for Bexsero).

On page 34 it is written that MMR and MenACWY are administered at 15 months. This is incorrect; these vaccines are administered at 14 months.

A. Steens

Second erratum rapport 2022-0046

Meningococcal disease serogroup B Updated information for the Dutch Health Council

Bilthoven: 19 July 2022
Subject: Second erratum for report 2022-0046

In Table 2 on page 18 of the RIVM report 2022-0046 with the title 'Meningococcal disease serogroup B, Updated information for the Dutch Health Council' a few corrections should be made. Some of the numbers of invasive meningococcal disease cases that had sequelae at discharge were not reported correctly.

The reported numbers should:

	Sequelae at discharge mild, n (%)	Sequelae at discharge severe, n (%)	Total, n(%)
Serogroup B	57 (42%)	8 (5.8%)	65 / 137 (47%)
Serogroup C	6 (50%)	1 (8.3%)	7 / 12 (58%)
Serogroup W	23 (37%)	13 (21%)	36 / 63 (57%)
Serogroup Y	14 (45%)	4 (13%)	18 / 31 (58%)
Total	100 (41%)	26 (11%)	126 / 243 (52%)

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