



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



**Meningococcal disease serogroup B**  
Updated information for the Dutch Health Council

RIVM letter report 2025-0043

## Colophon

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DOI 10.21945/RIVM-2025-0043

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This study was commissioned by the Ministry of Health, Welfare and Sports and the Dutch Health Council in the context of V/151103/25/RV, surveillance of the National Immunisation Programme

Published by:  
**National Institute for Public Health  
and the Environment, RIVM**  
PO Box 1 | 3720 BA Bilthoven  
The Netherlands  
[www.rivm.nl/en](http://www.rivm.nl/en)

## Synopsis

### **Meningococcal disease serogroup B**

Updated information for the Dutch Health Council

Meningococcal disease is a life-threatening disease caused by different types of meningococcal bacteria (serogroups). These serogroups are distinguished by different letters. In the Netherlands, children are vaccinated against meningococcal disease caused by serogroups A, C, W and Y. There are also vaccines for another serogroup, B. In 2022, the Health Council of the Netherlands advised against the introduction of serogroup B vaccination in the National Immunisation Programme.

Since 2022, the number of people in the Netherlands who become ill with meningococcal disease as a result of an infection with serogroup B has crept up gradually. In 2024, the number of meningococcal disease serogroup B patients stood at 118, 34 of which were children under the age of five and 30 of which were young adults (aged from 15 to 24). The Health Council will therefore issue a new advisory report on vaccination against meningococcal disease serogroup B for the Ministry of Health, Welfare and Sport. As input for this advisory report, RIVM has collated information about serogroup B vaccination and the incidence of meningococcal serogroup B disease in the Netherlands. This report will also address the costs and effects of vaccination.

There are various strains of meningococcal serogroup B bacteria. Which strains are the most common causes of disease differs from country to country and from year to year. While the vaccines do not protect against all strains, they appear effective in the European countries that use them.

If serogroup B vaccination is to be added to the National Immunisation Programme's vaccine scheme, additional vaccination moments will be required. There are vaccines that combine protection against serogroup B with protection against serogroups A, C, W and Y, but these are not currently available in Europe.

Keywords: meningococcus, meningococcus serogroup B, vaccination, Health council, serogroups, strains, disease, meningitis, cost effectiveness, national immunisation programme



## Publiekssamenvatting

### **Meningokokkenziekte serogroep B**

Actuele informatie voor de Gezondheidsraad

Meningokokkenziekte is een levensbedreigende ziekte die door verschillende typen meningokokkenbacteriën (serogroepen) wordt veroorzaakt. Deze serogroepen zijn met letters aangegeven. In Nederland worden kinderen gevaccineerd tegen meningokokken A, C, W en Y. Er is ook een type B waartegen vaccins bestaan. In 2022 heeft de Gezondheidsraad geadviseerd om de vaccinatie tegen meningokokken B niet in te voeren in het Rijksvaccinatieprogramma.

Sinds 2022 zijn in Nederland elk jaar iets meer mensen ziek geworden van een besmetting met meningokokken B. In 2024 waren er 118 meningokokken B patiënten, van wie 34 kinderen onder de vijf jaar en 30 jongvolwassenen (15-24 jaar). De Gezondheidsraad gaat het ministerie van VWS opnieuw adviseren over vaccinatie tegen meningokokken B. Als ondersteuning van dit advies heeft het RIVM informatie samengevoegd over deze vaccinatie en hoe vaak ziekte door meningokokken B in Nederland voorkomt. Dit document gaat ook in op kosten en effecten van vaccinatie.

Er zijn verschillende stammen van meningokokken B. Het verschilt per land en per jaar welke stammen het meeste ziekte veroorzaken. De vaccins beschermen niet tegen alle stammen, maar lijken goed te werken in Europese landen die ze gebruiken.

Om een vaccinatie tegen meningokokken B toe te voegen aan het prikschema van het Rijksvaccinatieprogramma, zouden extra vaccinatiemomenten nodig zijn. Er bestaan vaccins waarin de serogroep B is gecombineerd met het bestaande ACWY-vaccin. Deze vaccins zijn nu niet verkrijgbaar in Europa.

**Kernwoorden:** meningokok, meningokokken B, vaccinatie, Gezondheidsraad, serogroepen, stammen, ziekte, meningitis, kosteneffectiviteit, rijksvaccinatieprogramma



## Contents

### **Summary — 9**

#### **1 Introduction — 11**

#### **2 Epidemiology of meningococcal disease in the Netherlands — 13**

- 2.1 Incidence of invasive meningococcal disease — 13
- 2.2 Mortality and morbidity — 15
- 2.3 Clustering of IMD-B isolates — 16
- 2.4 Meningococcal carriage — 17

#### **3 Meningococcal B vaccination — 19**

- 3.1 Use of MenB vaccines — 19
  - 3.1.1 Vaccine acceptance — 19
- 3.2 Genomic analyses (strain coverage by the MenB vaccines) — 20
- 3.3 Immunogenicity — 21
  - 3.3.1 MenB vaccines — 21
  - 3.3.2 MenABCWY vaccines — 24
- 3.4 Vaccine effectiveness — 25
  - 3.4.1 Protection against MenB carriage — 25
  - 3.4.2 Protection against IMD-B — 26
  - 3.4.3 Duration of protection — 27
  - 3.4.4 Protection against gonorrhoea — 27
- 3.5 Vaccine impact — 31
- 3.6 Reactogenicity / side effects — 32

#### **4 Cost-effectiveness of meningococcal B vaccines — 35**

- 4.1 Methods — 35
  - 4.1.1 Transition probabilities — 36
  - 4.1.2 Uncertainty assessment — 37
  - 4.1.3 Validation — 37
- 4.2 Results — 37
  - 4.2.1 Public health gains — 37
  - 4.2.2 Cost-effectiveness results — 38
  - 4.2.3 Uncertainty assessment — 39

#### **5 Aspects of implementation — 43**

- 5.1 Infant vaccination — 43
- 5.2 Adolescent vaccination — 44

### **Acknowledgements — 47**

### **References — 49**



## Summary

In 2022, the Health Council advised against introducing meningococcal serogroup B (MenB) vaccination into the national immunisation programme of the Netherlands. Reasons for this advice included low incidence, unfavourable cost-effectiveness and a relatively high number of transient adverse events. The current report builds on the previous report from 2022, providing updated information for the Health Council on the epidemiology of invasive meningococcal serogroup B disease (IMD-B), the immunogenicity and (cost-)effectiveness of (new) MenB vaccines and implementation aspects.

After a decrease in IMD-B during the COVID-19 pandemic, an increase of IMD-B cases was observed in young children and adolescents in 2023 and 2024 to levels higher than pre-pandemic. In 2024, 134 IMD-B cases were reported, of which 34 among children aged <5 years and 30 among 15-24 year-olds. Between 2019 and 2024, nine <5 year-olds and five 15-24 year-olds died of IMD-B. Most IMD-B cases occur in previously healthy individuals (87%).

For infants, one MenB vaccine is registered (4CMenB) which can be administered in a 2+1 schedule. Post-implementation studies from several European countries show high vaccine effectiveness of 4CMenB against IMD-B in their infant programmes (71-96%). There is still little data on the duration of this protection, but antibody levels were shown to decline considerably within one year after vaccination.

For adolescents, two MenB vaccines are registered (4CMenB and MenB-fHbp). Two MenABCWY (Penbraya and Penmenvy) have been developed. Penbraya was registered by the European Medicine Agency in November 2024, but in January 2025 the market authorization was withdrawn by the EMA at the request of the manufacturer because of commercial reasons. Penmenvy is not registered by the European Medicines Agency, but has been registered by the FDA since February 2025. There is very little data on vaccine effectiveness of the two MenB vaccines in adolescents; one study on 4CMenB showed ~85% effectiveness against IMD-B. Immunogenicity data of MenB and MenABCWY vaccines shows high responses shortly after vaccination but considerable declines in antibody levels within one year after vaccination.

The actual effectiveness of infant and adolescent MenB vaccination that could be expected in the Netherlands is uncertain, because of uncertainty around strain coverage (i.e., how well vaccine components match the genetic variants of the circulating strains). This ranges between 34-95% for children <5 years and between 29-97% for adolescents.

MenB vaccines are more reactogenic than other childhood vaccines, although prophylactic paracetamol has been shown to reduce fever after vaccination. In clinical studies, reactogenicity of MenABCWY vaccines was similar to MenB vaccines but higher than for MenACWY vaccines.

Cost-effectiveness was estimated for different scenarios of infant or adolescent MenB or MenABCWY vaccination. Despite the higher incidence of IMD-B in infants and adolescents in 2023 and 2024, cost-

effectiveness estimates are still well above currently used thresholds for cost-effectiveness.

As generally no more than two injections are given per visit in the Dutch NIP, introduction of MenB vaccination would require extra visits. For infants this could be at 2 and 4 months of age with a booster at 13-15 months. For adolescents the two MenB doses could be given at 13-15 years, as the IMD-B incidence starts to increase in adolescents at age 15.

## 1 Introduction

This document builds on the report that was provided to the Dutch Health Council for the advice on vaccination against invasive meningococcal serogroup B disease (IMD-B) in 2022 (1). The document mainly describes data and literature that was not yet available at the time of the previous report.

In 2022, the Health Council advised not to include meningococcal serogroup B (MenB) vaccination in the national immunisation programme (NIP) at that moment (2). In the report the Health Council mentioned several arguments for their advice not to include MenB vaccination. The number of cases with IMD-B was relatively low. There was uncertainty around the actual effectiveness of the vaccination because IMD-B is a very rare disease. The vaccine does not provide herd protection. The cost-effectiveness was likely unfavourable, because of the low number of cases, the high costs of the vaccine and multiple doses that are needed. Furthermore, MenB vaccination relatively often results in transient adverse events, including high fever among infants possibly leading to hospitalization and medical interventions.

New developments, e.g. an increase in the number of cases or availability of a new vaccine, would be reasons for the Health Council to re-evaluate their advice. This report provides updated information on IMD-B and MenB vaccination for the Health Council.

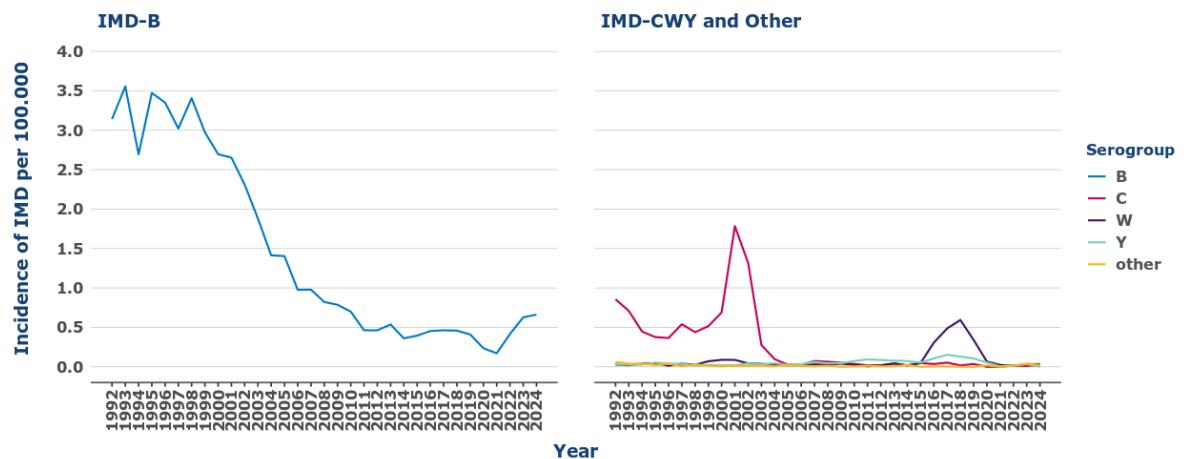


## 2 Epidemiology of meningococcal disease in the Netherlands

### 2.1 Incidence of invasive meningococcal disease

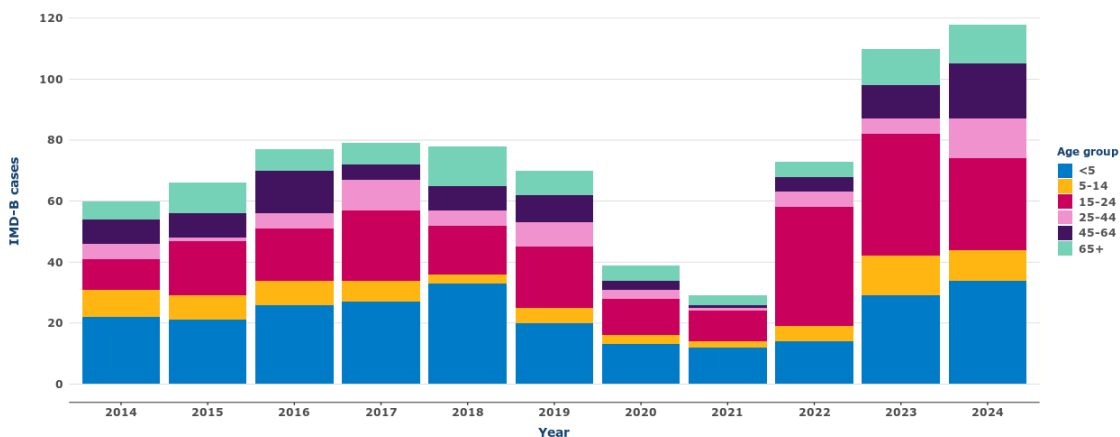
In 2024, there were 134 cases of IMD in the Netherlands, of which the vast majority was caused by serogroup B (n=118 in 2024, 88%, Figure 1). The incidence of IMD-B was 3.0-3.5/100,000 (~495 cases annually) in the period 1992 to 1999. It declined between 1999 and 2011 without a specific reason, showing natural fluctuation in IMD-B incidence. The IMD-B incidence was relatively stable between 2011 and 2019 at around 0.45 per 100,000 individuals (n=75 cases on average yearly). The incidence decreased to 0.17 per 100,000 (n=30 cases) in 2021 most likely due to the COVID-19 control measures (3). After the control measures were lifted, the incidence increased to 0.63 and 0.66 per 100,000 in 2023 (n=112) and 2024 (n=119), respectively, which was higher than the pre-pandemic average. The incidence of IMD caused by other serogroups than B was very low in 2024 (0.08 per 100,000, n=14, Figure 1). This is at least partly the result of the introduction of MenACWY vaccination in 2018, thereby preventing IMD caused by those serogroups (4).

Figure 1 Incidence of IMD per 100,000 population by serogroup for the period 1992-2024, the Netherlands.



Left: IMD-B; right: IMD caused by serogroups C, W, Y and other serogroups.

Figure 2 Number of IMD-B cases by year and age group for the period 2014-2024, the Netherlands.



The IMD-B incidence is highest in children <5 years of age; 29% of the IMD-B cases occurred in that age group in 2024. In 2024, the incidence was 3.9 per 100,000 (n=34, Figure 2 and 3), which was slightly higher than the average in the pre-pandemic years 2014-2019 (average: 2.8 per 100,000, 25 cases). In the age group 15-24 years, the incidence of IMD-B is also relatively high, with an incidence of 1.4 per 100,000 (n=30) in 2024 (Figure 2 and 3). In the post-pandemic years 2022-2024, the incidence in this age group was higher than in the pre-pandemic years (average: 1.7 per 100,000 vs. 0.8 per 100,000). An immunity gap caused by decreased exposure due to social distancing and self-isolation measures may explain this increase after the pandemic (5). Like in the Netherlands, an increase in IMD-B incidence in adolescents was observed in England (Figure 4), with 84 and 117 cases in 2021-2022 and 2022-2023 compared to a pre-pandemic average of 71 yearly cases (2015-2019) (6). A rebound of the number of IMD cases after the COVID-19 pandemic was also reported in France in 2022, with IMD-B cases among adolescents increasing to above pre-pandemic numbers (7).

Figure 3 Incidence of IMD-B per 100,000 population by age group for the period 2014-2024, the Netherlands.

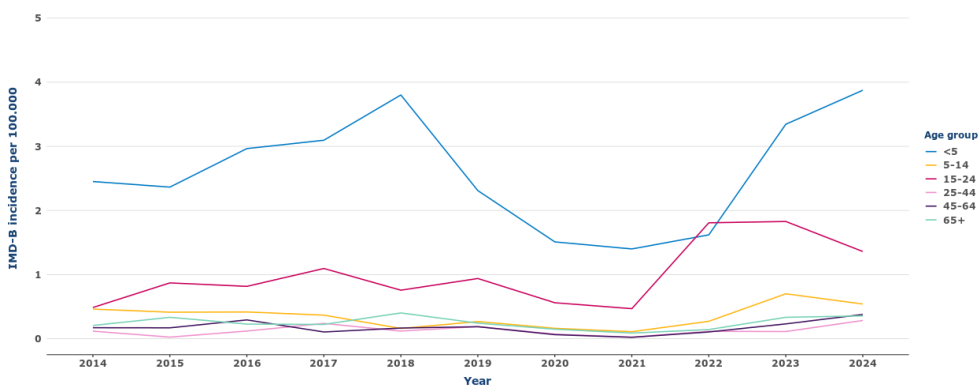
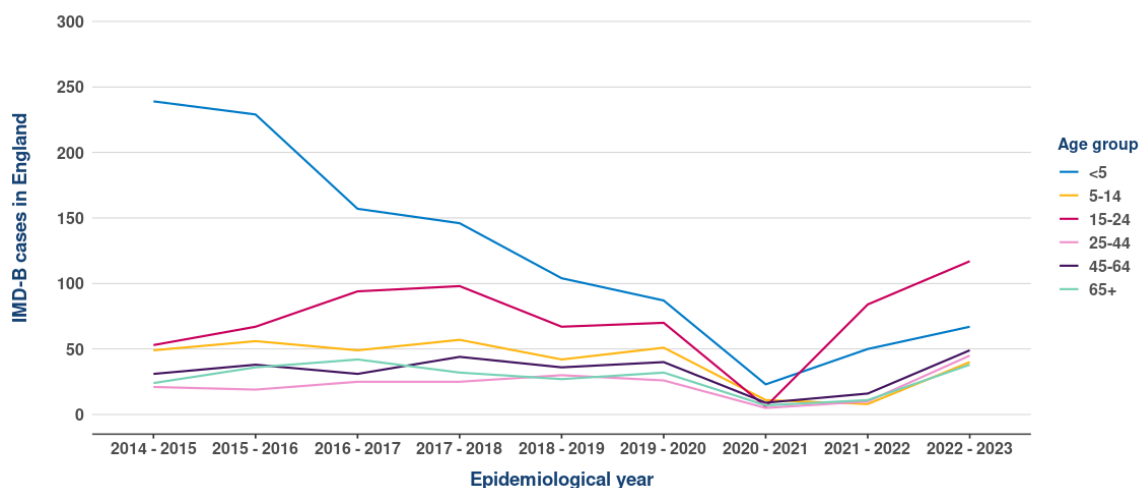


Figure 4 Number of IMD-B cases by epidemiological year and age group for the period 2014-2015 to 2022-2023, England (6).



Of note, the number of cases of IMD-B among <5 years of age have been declining in England, at least partly because of implementation of MenB vaccination in the NIP since 2015.

## 2.2 Mortality and morbidity

For 85% of the cases for which meningococcal isolates were sent in to the National Reference Laboratory for Bacterial Meningitis (NRLBM) in the period 2019-2024, the information could be linked to the notifications of the Municipal Health Services. Additionally, four notified cases were included in this analysis for which no meningococcal isolate was present at the NRLBM, but either a clear link with another IMD-B case was present or PCR confirmation was performed. For the included notifications, clinical data on mortality, clinical presentation, and underlying diseases were available for 96%, 98%, and 88%, respectively, during this period.

Most cases of IMD-B occurred in individuals who were previously healthy. Overall, 87% ( $n = 380/439$ ) of the IMD-B cases had no known comorbidities. Among those under 5 years old this was 98%, and among 15-24 year-olds 91% had no known comorbidities. Of the 59 cases with comorbidities, 22% were immunosuppressed. Case fatality rates are shown in Table 1. In 2019-2024 the overall case fatality rate for IMD-B was 5.5% (23/422). The case fatality rate was highest among <5 and 5-14 year-olds (both 8%; 9/117 and 3/38) and those aged 65 or older (7%; 3/43). In 15-24 year olds, the case fatality rate was 3% ( $n=5/146$ ). Case fatality rates were similar for cases with and without comorbidities (3% and 5%, respectively). Fatalities among cases with comorbidities were similar in immunosuppressed and non-immunosuppressed individuals, though the group size is small (both groups had one fatality). Overall, the IMD-B case fatality rate has been lower than for IMD caused by serogroups C, W, and Y (13%; 17/135), which corresponds with previous reports (8).

Clinical presentation of IMD-B cases is shown in Table 2. Among young children and adolescents, meningitis without septicaemia was most common with 49% (n=60) and 68% (n=102), respectively. Septicaemia without meningitis was more common among young children (30%, n=37) than adolescents (9%, n=14). Among older adults, a clinical presentation without septicaemia or meningitis was more common (35%).

*Table 1 Case fatality rates and comorbidity status of IMD-B cases by age group for the period 2019-2024, the Netherlands.*

|                      | <b>Case fatality rate<br/>% (n)</b> |
|----------------------|-------------------------------------|
| <b>Age group</b>     |                                     |
| <5                   | 8% (9/117)                          |
| 5-14                 | 8% (3/38)                           |
| 15-24                | 3% (5/146)                          |
| 25-64                | 4% (3/78)                           |
| 65+                  | 7% (3/43)                           |
| Total                | 5% (23/422)                         |
| <b>Comorbidities</b> |                                     |
| No                   | 5% (16/326)                         |
| Yes                  | 3% (2/59)                           |
| Total                | 5% (18/385)                         |

*Table 2 Clinical presentation of IMD-B cases by age group for the period 2019-2024, the Netherlands.*

| <b>Clinical presentation</b>   | <b>&lt;5<br/>% (n)</b> | <b>5-14<br/>% (n)</b> | <b>15-24<br/>% (n)</b> | <b>25-64<br/>% (n)</b> | <b>65+<br/>% (n)</b> |
|--------------------------------|------------------------|-----------------------|------------------------|------------------------|----------------------|
| Meningitis with septicaemia    | 7% (9)                 | 11% (4)               | 10% (15)               | 5% (4)                 | 4% (2)               |
| Meningitis without septicaemia | 49% (60)               | 68% (26)              | 68% (102)              | 60% (49)               | 26% (12)             |
| Septicaemia without meningitis | 30% (37)               | 13% (5)               | 9% (14)                | 22% (18)               | 30% (14)             |
| No septicaemia or meningitis   | 10% (12)               | 8% (3)                | 11% (16)               | 11% (9)                | 35% (16)             |
| No information                 | 3% (4)                 | 0% (0)                | 3% (4)                 | 1% (1)                 | 4% (2)               |

### 2.3 Clustering of IMD-B isolates

All invasive meningococcal isolates are routinely finetyped in the Netherlands, i.e., DNA-sequencing of the variable regions of two outer membrane proteins (porA and fetA) is performed. The finetype is used to determine whether two or more cases are a likely cluster and may indicate an outbreak of IMD. A recent analysis determined spatiotemporal clustering of IMD-B cases based on finetype, over a period of 2005-2023 including 1642 cases (9). Overall, 453 distinct finetypes were observed, of which 68% occurred only once. The analysis confirmed the large finetype diversity among meningococcal isolates causing IMD-B, which did not differ over time. Furthermore, it showed that IMD-B clusters were rare. The clusters that were identified had a median size of two cases with an interquartile range of 2-3. The range of the number of clusters that was observed per unique finetype was 1-3; with a median of one cluster per finetype. Overall, these results confirmed that, with the currently employed control measures (10), IMD-B cases are generally sporadic cases, i.e. not causing secondary cases.

## 2.4 Meningococcal carriage

Generally, meningococcal carriage is relatively low in young children (4.5%) and increases during childhood with a peak of 24% in 19-year-olds (11). Subsequently, carriage decreases to about 8% in 50-year-olds and to a slightly lower prevalence in older ages (11). A study among students in Utrecht, the Netherlands, performed in 2018, just before the MenACWY vaccine introduction, reported MenACWY and MenB carriage (12). This study was repeated in 2022 (13). Meningococcal isolates from asymptomatic carriers (n=68 in 2018, n=146 in 2022) were serogrouped and subjected to whole genome sequencing for further typing. The carriage prevalence of serogroup ACWY meningococci declined from 4.3% in 2018 to 0.2% in 2022, the serogroup B carriage remained constant (4.3% in 2018 and 4.7% in 2022) and carriage of serogroup E increased from 0% to 3.3% (14). Whole genome sequencing of the isolated strains revealed that the carried serogroup B strains predominantly belonged to clonal complexes ST-32, ST-41/44, and ST-213, with no significant genetic shifts between the period before and after introduction of MenACWY in the NIP.



### 3 Meningococcal B vaccination

Currently, two MenB protein vaccines are licenced and available in the Netherlands: the multicomponent, outer membrane vesicle (OMV)-based vaccine 4CMenB (Bexsero) is approved for use in individuals of 2 months of age and older with a 2+1 or 3+1 dose schedule for infants aged 2-5 months, a 2+1 for children aged 6-23 months and a 2-dose schedule for those 2 years or older (15), and the bivalent, not OMV-based, rLP2086 vaccine MenB-fHbp (Trumenba) is approved for use in persons 10 years or older as a 2- or 3-dose schedule (16). The MenB protein vaccines can prevent IMD-B but do not prevent carriage of meningococci (17, 18).

A pentavalent vaccine (Penbraya, Pfizer) combining the MenB-fHbp vaccine and a MenACWY-TT vaccine (Nimenrix) has been authorized for use by the European Medicines Agency (EMA) in November 2024, but in January 2025 the market authorization was withdrawn by the EMA at the request of the manufacturer because of commercial reasons (19). This vaccine is indicated for those 10 years of age and older. Two doses given 6-12 months apart are needed for protection against IMD-B. Another pentavalent vaccine (Penmenvy, GSK) combining the 4CMenB vaccine and another MenACWY vaccine (Menveo) has been authorized for use by the US Food and Drug Administration (FDA) in February 2025 (20).

#### 3.1 Use of MenB vaccines

In the Netherlands, the MenB vaccines are available for private use but use is limited. Furthermore, MenB vaccination is recommended for those with increased risk at (complicated) IMD, including those with certain innate complement disorders, persons using eculizumab and those with (functional) asplenia (21). Costs for 4CMenB are only reimbursed for the abovementioned medical risk groups. Dispensing data collected by the Dutch Foundation for Pharmaceutical Statistics (SFK) from public pharmacies show that around 13,000 doses of 4CMenB have been administered between October 2018 and October 2024 (22). 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. Private use of MenB-fHbp has been very limited with overall around 380 doses dispensed between January 2020 and October 2024 (22).

Several European countries have introduced 4CMenB vaccination for infants in their childhood vaccination programmes or have used 4CMenB vaccines privately at a relatively high coverage (23). In infants, mostly a 2+1 schedule with two primary vaccinations before the age of 6 months and a booster vaccination at the age of 12-15 months, is used (23). MenB vaccination with either 4CMenB or MenB-fHbp is recommended and reimbursed for adolescents 14-16 years in Czechia (23).

##### 3.1.1 Vaccine acceptance

Surveys conducted in 2013, 2022 and 2023 on vaccine acceptance in the Netherlands contained questions on whether parents would be inclined to vaccinate their children against several NIP candidates,

including vaccination against IMD-B, rotavirus (not included in NIP at time of survey), chickenpox, respiratory syncytial virus, influenza and hepatitis A (24, 25). Questions on attitude towards vaccination were measured on a 7-point likert scale. The percentage of parents reporting a positive attitude towards these NIP candidates was highest for vaccination against IMD-B. The intention to vaccinate their child against IMD-B increased from 47% of parents giving a positive score ( $\geq 6$ ) in 2013 to 64% in 2022 and 71% in 2023 (26). Intention was only measured for parents of young children, and the results may not be applicable for (parents of) adolescents.

### 3.2 Genomic analyses (strain coverage by the MenB vaccines)

Because MenB vaccines are protein-based, protection depends on how much the vaccine components match the genetic variants of the circulating strains within a country. Previously, the theoretical strain coverage in the Netherlands was determined using gMATS. As the ECDC-led project uses the BAST method to determine theoretical strain coverages, which is based on the MenDeVar test database (27), we used that same method here. The MenDeVar database includes *in vitro* data on the bactericidal activity of strains with specific genetic variation in the relevant genes. Strains are classified as being an exact match, cross-reactive or no match. To define covered strains, exact matching and cross-reactive strains are both included. As the used database is not exhaustive, the reactivity data misses for several gene variants (called 'insufficient result'). For those gene variants where no reactivity data is available, it is known that they are not an exact match. However, through cross-protection, immunity obtained from vaccination may still prevent infection by meningococci with those gene variants. In the calculation of the theoretical strain coverage, isolates classified as 'insufficient' are treated as being no match. The result is that the calculated strain coverage is likely an underestimation of the actual strain coverage. To be able to judge the potential proportion that may be covered by the vaccines, we also determined the 'maximal strain coverage' by assuming all 'insufficient' isolates to be covered through cross-protection. Although this calculation is not a method that is often used, it can be used to determine the maximal preventive potential of the vaccines. Of note, the previously used gMATS approach that was presented in the earlier report (1) included half of the 'insufficient' isolates as covered, leading to higher strain coverage estimates when using gMATs compared to BAST.

The strain coverage analysis included 167 isolates of IMD-B patients from the Netherlands with date of disease onset between January 2022-June 2024 (for 6 isolates, no results were available on the coverage of MenB-fHbp). The proportion of isolates categorised as covered, i.e. the theoretical strain coverage, was 34% for 4CMenB and 66% for MenB-fHbp (Table 3). However, because of the large proportion with insufficient data (53% for 4CMenB and 31% for MenB-fHbp), these values are likely an underestimation of the actual coverage and are at least uncertain. The overall 'maximal strain coverage', assuming that cross-protection takes place against all strains that were classified as 'insufficient', was 87% for 4CMenB and 96% for MenB-fHbp. Of note,

the low number of analyzed isolates, particularly for children aged 5-9 years, results in high uncertainty in the estimates.

*Table 3 Theoretical strain coverage for 4CMenB and MenB-FHbp by age group for strains of IMD-B cases for the period January 2022–June 2024, determined using the BAST method with the MenDeVar database, the Netherlands.*

| Age group   | IMD-B cases | Insufficient<br>% (n) |                        | Covered<br>% (n)    |                        |
|-------------|-------------|-----------------------|------------------------|---------------------|------------------------|
|             |             | 4CMenB <sup>1</sup>   | MenB-FHbp <sup>2</sup> | 4CMenB <sup>1</sup> | MenB-FHbp <sup>2</sup> |
| <5          | 44          | 61% (27)              | 32% (14)               | 34% (15)            | 64% (28)               |
| 5-14 years  | 17          | 65% (11)              | 41% (7)                | 24% (4)             | 59% (10)               |
| 15-24 years | 59          | 51% (30)              | 29% (17)               | 31% (18)            | 68% (40)               |
| All ages    | 167         | 53% (88)              | 31% (51)               | 34% (57)            | 66% (110)              |

<sup>1</sup> registered for individuals aged 2 months and older; <sup>2</sup> registered for individuals aged 10 years and older. Note, to determine the maximal strain coverage, i.e., interpreting all isolates classified as 'insufficient' as being covered by the vaccines through cross-protection, the percentage in the 'insufficient' and in the 'covered' category should be added up.

While MenB vaccines are not registered for serogroups other than MenB, the included proteins are (partly) shared with other serogroups. Depending on the circulating strains, MenB vaccines can therefore also partially protect against IMD caused by other serogroups (28, 29). For 2023-2024, also non-B IMD strains were subjected to whole genome sequencing and their strain coverage for 4CMenB and MenB-FHbp was determined, however, numbers per serogroup were small. Five of the eight IMD-W isolates were categorised as being covered by 4CMenB; three were 'insufficient'. Of the five sequenced IMD-Y strains, all were 'insufficient'. Two of the three IMD-C strains were categorised as being covered by 4CMenB; the other one was 'insufficient'. For MenB-FHbp, all 8 IMD-W isolates were classified as 'insufficient', while all 5 IMD-Y isolates were predicted to be covered. Two of the 3 IMD-C isolates were covered and 1 was classified as 'insufficient' for MenB-FHbp. Whether or not these results are representative for the strain coverage of the currently circulating meningococcal serogroup CWY strains is uncertain because of the low numbers and the high number of strains with 'insufficient' results.

### 3.3 Immunogenicity

Assessment of immunogenicity for MenB vaccines is based on the serum bactericidal antibody assay (SBA), with rabbit (rSBA) or human complement (hSBA), as serocorrelate of protection against IMD (30). An hSBA titre of at least 4 is defined as correlate of protection, however, different cut-offs are used depending on the study.

We first describe recent data (published after the 2022 RIVM report (1)) on immunogenicity of the 4CMenB and MenB-FHbp vaccines. Then we describe immunogenicity data of the two MenABCWY vaccines compared with 4CMenB, MenB-FHbp or MenACWY vaccination alone.

#### 3.3.1 MenB vaccines

There is little new data on immunogenicity of MenB vaccines since the 2022 RIVM report (1). We describe a study on premature children, a

study on a different age group, a study with a new assay to assess the breadth of the immune response and a review on co-administration of MenB vaccine with other vaccines. Also, two studies on persistence of antibody levels are described.

A randomized clinical trial from the UK, where 4CmenB is offered in a 2+1 schedule in the NIP, reported on the immunogenicity of this schedule in preterm infants (31). The study included 136 infants born at <35 weeks, who were randomly assigned to 4CmenB in a 2+1 (8 weeks, 16 weeks and 1 year) or 3+1 (8 weeks, 12 weeks, 16 weeks, 1 year) schedule. SBA activity was measured at 5, 12 and 13 months of age, reflecting post-primary, pre-booster and post-booster timepoints, respectively. There were no significant differences in geometric mean titers between the schedules following primary or booster vaccination. However, the proportion of infants with an SBA titer  $\geq 4$  against one of the three analyzed strains (NZ98/254) was lower in the 2+1 than in the 3+1 schedule after the primary series (70% vs. 87%), but this difference was no longer present after administration of the booster dose (88% vs. 95%).

The MenB-FHbp vaccine is only licensed for individuals of 10 years and older (16). However, the immunogenicity of this vaccine was also assessed in a randomized controlled trial among younger children, i.e. those aged 1-9 years (32). Children from four different countries received three doses of MenB-FHbp at 0, 2 and 6 months after study inclusion. The study included 396 toddlers (age 12-23 months) and 400 older children (2-9 years) and immunogenicity was measured using hSBA assays against four test strains. Percentages of participants whose hSBA titers were above the lower limit of quantification (LLOQ; 1:8 for strains A56, B24, B44 and 1:16 for A22) at 1 month after the third dose ranged between 72-100% in toddlers and between 79-100% among older children. Two years after the third dose these proportions ranged between 0-41% for toddlers. For older children, no data were collected at this time point.

The breadth of the immune response of three different schedules (0-2, 0-6, 0-2-6) of 4CMenB was investigated in 3651 healthy 10-25 year-olds in a phase 3 randomized controlled trial using a new method called endogenous complement (enc)-hSBA assay (33). Each serum sample of each participant was tested against 35 randomly selected strains of a panel of 110 MenB test strains, so each sample had up to 35 valid test results. Then the percentage of *tests* without bactericidal activity against the test strains after 4CMenB was compared with control vaccination (test-based approach). And the percentage of *participants* whose postvaccination sera killed  $\geq 70\%$  of the test strains was calculated (responder-based approach). Immunogenicity was also assessed by the traditional hSBA assay against four reference strains (fHbp, NadA, NHBA, PorinA). At one month after the last dose (0-6 schedule), 14% of the *tests* in the 4CMenB group and 79% of the tests in the control group (MenACWY vaccine) showed no bactericidal serum activity, resulting in a relative risk of 0.18 and a '4CMenB breadth of immune response' of 82%. Similar results were found for the 0-2 and 0-2-6 schedule (79% and 83%, respectively). At one month after the last dose, 90% of *participants* in the 4CMenB 0-6 schedule group had sera that killed

$\geq 70\%$  of the MenB test strains. For the 0-2 and 0-2-6 schedules this was 85% and 93%, respectively. The percentage of participants with a 4-fold rise in hSBA from baseline against the MenB reference strains fHbp, NadA, NHBA, PorinA was 82%, 95%, 70% and 57%, respectively, at one month after the 4CMenB 0-6 schedule. For the 0-2 schedule these were 75%, 96%, 59%, 55% and for the 0-2-6 schedule the percentages were 87%, 99%, 67%, 57%.

A review summarized the available literature on the immunogenicity of co-administration of 4CmenB vaccination with other vaccines (34). The review included 16 papers published between 2012 and 2022. The studies mostly concerned children, with one study also containing data on adults. The review contained studies on co-administration with hexavalent DTP, pneumococcal, rotavirus, MMR and MenACWY vaccines. No clinically relevant immunological interferences were reported in any of the reviewed studies.

#### *Persistence of antibody levels*

Persistence of antibody titers up to four years after primary MenB-FHbp vaccination and up to 26 months after a booster MenB-FHbp vaccination was assessed in participants aged 11-18 years (35). Five different primary vaccination schedules were studied with two doses (0-2, 0-4, 0-6 months) or three doses (0-1-6, 0-2-6 months), and then a booster dose 48 months after the last primary series dose. The study included 698 participants in the post-primary stage and 304 participants in the post-booster stage. One month after the primary series, the proportion of participants with hSBA titer  $\geq$  LLOQ (1:8 for strains A56, B24, B44 and 1:16 for A22) ranged between 74-100% across the four MenB test strains, with higher percentages for strain A56. Titers declined during the first 12 months after primary vaccination and then remained relatively stable throughout the rest of the 48 months follow-up period, with proportions  $\geq$  LLOQ ranging between 18-61% depending on strain and vaccination schedule. One month after the booster, between 93-100% of participants had titers  $\geq$  LLOQ. At 12 months after the booster dose, between 59-100% of participants still had titers  $\geq$  LLOQ depending on strain and primary vaccination schedule. At 12 and 26 months follow-up post-booster percentages were higher compared with post-primary series, indicative of induction and persistence of immune memory. Percentages decreased from 12 to 26 months post-booster to 58-83%. The decrease in the percentage with a hSBA titer  $\geq$  LLOQ was slower after booster than after primary vaccination.

Persistence of MenB-fHbp was studied in a randomized trial of MenABCWY vaccination (see below), where MenB-fHbp was the control vaccine (36). The persistence stage of the study included 138 10-25 year-olds who had received MenB-fHbp in a 2-dose schedule (6 months apart). The percentages of MenB-fHbp recipients with seroprotective hSBA titers against each of the MenB primary test strains declined considerably during the 12 months following the second primary dose and then remained generally stable through 48 months, ranging from 16.2% to 31.9% across strains at 48 months.

Persistence of 4CMenB was studied in a randomized trial of MenABCWY vaccination (see below), where 4CMenB was the control vaccine (REF). The percentage of participants with hSBA titers  $\geq$  LLOQ (lower limit of

quantification) declined substantially from 1 month to 24 months after 4CMenB against all four antigen-specific MenB test strains (82% to 18% fHbp, 99% to 82% for NadA, 88% to 16% for PorA, 66% to 28% for NHBA) (37).

### 3.3.2 *MenABCWY vaccines*

We first discuss results of trials of the Pfizer MenABCWY vaccine (Penbraya), and then of the GSK MenABCWY vaccine (Penmenvy). Neither of these vaccines are currently registered by the EMA, as Penbraya's registration was withdrawn in January 2025 at the request of the manufacturer due to commercial reasons.

#### *MenABCWY – Penbraya*

The immunogenicity of the MenABCWY vaccine that combines MenB-fHbp and MenACWY-TT has been investigated in a randomized controlled trial including 1610 participants aged 10-25 years (809 MenACWY-naïve and 801 MenACWY-primed) (38). The study assessed hSBA titers after two doses of MenABCWY (6 months apart) compared with MenB-fHbp (2 doses at 0-6 months) and MenACWY-CRM (1 dose). The hSBA response after two doses of MenABCWY was non-inferior (margin of 10% difference in percentage seroprotection) compared with the response after two doses of MenB-fHbp at 1 month after vaccination with 76-95% of participants achieved at least four-fold increases in hSBA titers against MenB strains. The hSBA response to serogroup A, C, W and Y was also non-inferior when comparing one dose of MenABCWY to one dose of MenACWY-TT with four-fold increases in 76-97% of participants.

Another trial included 300 11-14 year olds and assessed antibody responses after two doses of MenABCWY given 12 months apart (39). Receiving two doses of MenABCWY 12 months apart, compared with a 6 months interval, gave a better immune response against MenB strains, with seroprotection (hSBA titers of  $\geq 8$ ) in 98-100% of participants after two doses of MenABCWY.

Persistence of antibody levels up to four years after MenABCWY was studied in a subset of 353 participants of the trial described above, of which 215 received two doses of MenABCWY (36). Antibody titers against MenB strains waned quickly after MenABCWY with only 20-30% of participants with a titer  $\geq 8$  at 12 months after vaccination. After 12 months, seroprotection (hSBA titers of  $\geq 8$ ) levels against MenB strains remained stable and generally above baseline up to four years after vaccination (18-37%). Seroprotection (hSBA titers of  $\geq 8$ ) against serogroup A, C, W and Y remained high up to four years after MenABCWY and was higher than after MenACWY-TT.

#### *MenABCWY - Penmenvy*

Immunogenicity of the other MenABCWY vaccine (Penmenvy) that combines 4CMenB with MenACWY-CRM has been assessed in several phase 1-2 studies and two phase 3 studies (40-42). The two phase 3 studies included 3651 participants aged 10-25 years of whom most were MenACWY-naïve (41) and 1250 MenACWY-primed participants aged 15-25 years (42), respectively, and compared MenABCWY at 0 and 6 months with two or three doses of 4CMenB and one dose of MenACWY-CRM.

In the first study (41), MenABCWY in a 0-6 month schedule was non-inferior to 4CMenB 0-2 month schedule for three antigens (fHbp, NadA and NHBA) with 62-93% of MenABCWY recipients showing a 4-fold increase in hSBA titers compared with baseline at one month post-vaccination. However, no non-inferiority was shown for the antigen PorA (42% with 4-fold increase); non-inferiority was defined as a lower limit of the 95%CI  $> -10\%$  for the difference in proportion between groups. The study also used the enc-hSBA assay as described above. The percentage of serum *samples* with bactericidal serum activity (test-based approach) was 83% after MenABCWY vaccination and 83% after 4CMenB 0-2 dose vaccination and the non-inferiority criterion was met (lower limit  $> -5\%$  for the difference). The percentage of *participants* whose sera killed  $\geq 70\%$  of 35 MenB strains (responder based approach) was 84% of MenABCWY recipients and 85% of 4CMenB recipients (0-2 schedule). Of note, after 4CMenB in a 0-6 schedule the percentage of serum samples with bactericidal serum activity and of participants whose sera killed  $\geq 70\%$  of MenB strains was significantly higher (86% and 90%, respectively) than after MenABCWY vaccination. With regard to serogroups A, C, W and Y, the percentage of participants with a 4-fold increase in hSBA titers was higher at one month after one dose of MenABCWY vaccination (range 67-76%) compared with one dose of MenACWY-CRM vaccination (range 57-72%) for serogroups C, W and Y, showing non-inferiority, but for serogroup A (74 vs. 86%) non-inferiority was not met.

In the second study with MenACWY-primed participants (42), the percentage of participants with a 4-fold increase in hSBA titers after one dose of MenABCWY vaccination (93-94%) was non-inferior to MenACWY-CRM vaccination (94-95%) for all serogroups.

In a phase 2b study investigating different schedules of MenABCWY vaccination, antibody persistence at 24 months after MenABCWY vaccination was assessed in adolescents (10-18 years) (37). The percentage of participants with hSBA titers  $\geq$  LLOQ (lower limit of quantification) declined substantially from 1 month to 24 months post-primary MenABCWY vaccination against all four antigen-specific MenB test strains (for MenABCWY 0-6 schedule: 86% to 26% for fHbp, 97% to 74% for NadA, 63% to 18% for PorA, 66% to 37% for NHBA). Although, they tended to be higher than pre-primary vaccination.

### 3.4 Vaccine effectiveness

#### 3.4.1 Protection against MenB carriage

Previous studies already reported that MenB vaccines do not prevent MenB carriage (17, 18). A longitudinal study published in 2024 on meningococcal carriage in adolescents and young adults in South Australia found a similar result (43). The study used data from repeated cross-sectional studies among school leavers aged 17-25 years of which 2980 had oropharyngeal swabs taken over several years. Based on results from these studies, it is unlikely that MenB vaccines will decrease meningococcal B transmission.

### 3.4.2 *Protection against IMD-B*

In the previous report, vaccine effectiveness (VE) estimates of the 4CMenB vaccine were reported from Canada, Portugal, Italy, the UK and South Australia (1). Three new studies (in Italy, Spain and South Australia) on VE of 4CMenB were published since the last report (Table 5, new data marked with \*), which we describe below. As the MenB-FHbp vaccine is hardly used in NIPs, no VE data for this vaccine are available.

A nationwide age-matched case-control study from Spain estimated the VE for 4CMenB in children under 5 years old in the period October 2015 to October 2019 (44). During this period, 4CMenB was privately available but not included in the NIP. The vaccination rate was relatively high as 24% of the controls received at least one dose of 4CMenB. The study included 306 IMD cases, of which 243 were serogroup B cases, and 1224 controls. The effectiveness against IMD-B was 71% (95%CI 45-85%) for complete vaccination (at least two doses and administered according to recommendation of manufacturer) and 64% (95%CI 41-78%) for at least one dose, independent of strain coverage. Genotyping with gMATS was performed on strains of 138 IMD-B cases. Of these, 44 (32%) had strains expected to be covered by 4CMenB and none of these cases were vaccinated; 62 had strains that were not expected to be covered, of which 8 received at least one vaccine dose, and 32 had strains for which coverage could not be predicted, of which 2 received at least one vaccine dose.

The VE of 4CMenB in Spain was also estimated against any non-serogroup B IMD including 35 cases and 140 controls. The VE was 92% (95%CI 28-99%) for complete vaccination and 82% (95%CI 21-96%) for vaccination with at least one dose. Most non-B cases were caused by serogroup W (n=20), and more specifically by a strain which was shown to be covered by 4CMenB according to MATS.

In Italy, VE was assessed with the screening method using data from three regions and with a age- and sex-matched case-control study using data from six regions; data up to December 2019 were used (45). 4CMenB vaccination was implemented in the NIP of Italy in 2017. The analysis using the screening method included 15 IMD-B cases born after implementation of MenB vaccination and aged 0-3 years (not stated how many were vaccinated). The mean vaccination coverage at age 24 months ranged between 81% and 84% in the three regions. The estimated VE considering all three regions was 95% (95%CI 83-98%). In the case-control study, 26 IMD-B cases with a median age of 6 months were identified in the postvaccine era, of which three had received at least one vaccine dose. They were matched to 52 controls who were referred to the emergency department or were hospitalized for conditions other than meningococcal disease, of which 27 had received at least one dose. This resulted in a VE of 88% (95%CI 55-97%). When only including children who were old enough to receive at least one dose (19 cases and 38 controls), the VE was 92% (95%CI 68-98%). When only including children who were old enough for full vaccination and excluding partial vaccinated children (resulting in 14 cases and 24 controls), the VE was 96% (95%CI 72-99%).

In South Australia, the VE of 4CmenB among adolescents had previously been reported (46). A 2023 study evaluated the VE among children and adolescents up to three years after the introduction of 4CmenB for infants and adolescents (47). The study included data from 2018-2021, and estimated VE independent of time since vaccination, using the screening method and a case-control study with 20 age-matched controls per case. During the three years after implementation of 4CmenB, two children developed IMD-B after one dose and one child developed IMD-B after two doses; there were no IMD-B cases in young children who received three doses of 4CmenB. After two doses, the VE in young children was 93% (95%CI 29-99%) using the screening method and 91% (95%CI 7-99%) in the case-control study (not described how many cases and controls were included in the analyses). Among adolescents, there was one IMD-B case who had received two doses of 4CmenB, resulting in a VE of 84% (95%CI 0-98%) using the screening method and 89% (95%CI 0-99%) in the case-control study (47).

A 2024 report on MenB vaccination by Ständige Impfkommision (STIKO) of the Robert Koch Institute in Germany included a meta-analysis on VE of 4CmenB in children and adolescents (48). Non-adjusted VE estimates and VE obtained through the screening method were excluded. The meta-analysis included four studies in children (from the UK, Spain, Italy and South-Australia), one study in adolescents (from South Australia) and two studies in any age group (from Canada and Portugal); the results of the individual studies are included in Table 5. For children younger than six years, a pooled VE of 81% (95%CI 68-89%) was reported. For adolescents, the reported VE based on one study was 89% (95%CI 0-99%). For any age group, a pooled VE of 79% (95%CI 48-92%) was reported.

#### 3.4.3 *Duration of protection*

There is little data available on the duration of protection of 4CmenB against IMD-B. The case-control study from Spain described before also estimated VE by time since last dose, but only for IMD caused by any serogroup (so not specifically for IMD-B) (44). No significant difference in VE for full vaccination <12 months ago (78%, 95%CI 57-88%) or ≥12 months ago (68%, 95%CI -4-90%) was found.

The UK JCVI reported results from models by UKHSA (49). Based on the JCVI report, limited information is available on the actual model that was used or the exact results. However, the JCVI reported that modelled IMD-B incidence in the absence of vaccination was significantly higher than observed incidence in children up to 6 years of age, indicating sustained impact of vaccination over time. The models estimated high VE in the first year after vaccination with a small decline in VE up to six years after vaccination.

#### 3.4.4 *Protection against gonorrhoea*

Currently, there are no vaccines licensed against *Neisseria gonorrhoeae*, the pathogen that causes the sexually transmitted infection (STI) gonorrhoea. However, OMV-based MenB vaccines, for example 4CmenB has shown some cross-protection against gonorrhoea. This is likely due to the high genetic and antigenic homology between *N. meningitidis* and *N. gonorrhoeae*. The outer membrane components of the OMV MenB

vaccines may trigger an immune response that targets similar structures on *N. gonorrhoeae*, providing some level of protection against gonococcal infections. Non-OMV vaccines lack these components and are unlikely to provide such cross-protection.

Since gonorrhoea is a common STI in the Netherlands and elsewhere, and *N. gonorrhoeae* is prone to the development of antimicrobial resistance, cross-protection from a MenB vaccine could be of benefit to control gonorrhoea. Recently, two systematic reviews and meta-analyses have been published, evaluating VE of meningococcal vaccines in preventing gonorrhoea.

The first systematic review focused specifically on 4CMenB vaccination (50). The authors included eight studies, published between 2013 and September 2024. Four of these studies were from the US, two from Australia, one from Italy and one from France. The two European studies focused on men who have sex with men (MSM), while the others included a broader population of young persons with an age range of 15 to 30 years old. The study from France was the only randomized controlled trial (RCT); the other studies had a case-control or retrospective cohort design.

The French RCT was the only study not reporting a significant efficacy of 4CMenB against gonorrhoea. The seven observational studies reported an effectiveness of one or more doses of 4CMenB of 23% to 47% against gonorrhoea. The pooled VE estimated in the meta-analysis was 32% (95% CI, 26%-39%). Additional tests did not show publication bias or study heterogeneity. Limited studies assessed the duration of protection. One Australian study showed higher protection within 6-36 months after vaccination than >36 months after vaccination. The Italian and one US study did not report specific durations of protection but did have a relatively long follow-up time of 45 months and 37 months, and reported 2-dose VE of 44% and 40%, respectively.

The studies that were included in the second systematic review (51) mostly overlapped, but this review also included three studies that analysed VE of MenB-FHbp and MeNZB against gonorrhoea (MeNZB is a vaccine against a specific strain of MenB, used to control an epidemic in New Zealand; it is not registered for use by EMA or FDA). Meta-analyses showed that the pooled VE of OMV-based MenB vaccines (including 4CMenB and MeNZB) against gonococcal infections in fully immunized individuals was 34% (95% CI, 27%-41%) based on four case-control studies. In two cohort studies of 4CMenB, the pooled adjusted HR was 0.67 (95% CI, 0.44-0.91). MenB-FHbp did not show protection against gonorrhoea.

Just like for the protection against IMD, the protection that 4CMenB provides against gonorrhoea depends on how much the vaccine components match the genetic variants of the circulating strains. We have, however, not determined the theoretical strain coverage of the gonorrhoea isolates in the Netherlands.

Table 5 Description of studies on vaccine effectiveness of 4CMenB against IMD-B.

| Target population          | Country  | Period    | Study design                | Schedule                                   | Strain coverage                               | VE against IMD-B  | VE corrected for covered strains                         | Reference |
|----------------------------|----------|-----------|-----------------------------|--|---|---|--|-----------|
| Infants in NIP             | UK       | 2015-2016 | Screening method            | 2 doses (booster was not yet administered) | 73% pre vaccine introduction                  | 83% (95%CI 24-95).  | 94%  | (52)      |
| Infants in NIP             | UK       | 2015-2018 | Screening method            | 2+1  | 73% pre vaccine introduction                  | 53% (95%CI -34-83) for 2 doses, 59% (95%CI -31-87) for 3 doses.     | 64.4% (2 doses) and 71% (3 doses)                        | (53)      |
| Infants in NIP             | UK       | 2015-2018 | Register-based cohort study | 2+1  | 73% pre vaccine introduction                  | 79% (95%CI 72-85) after 2 doses and 80% (95%CI 71-87) after 3 doses |  | (54)      |
| Children and adolescents   | Portugal | 2014-2019 | Case-control study          | 2-4 doses, depending on age                | Not provided at population level              | 79% (95%CI 45-92)   | -  | (55)      |
| 0-20 years                 | Canada   | 2014-2018 | Register-based cohort study | 2-4 doses, depending on age                | 85% in 2006-2009                              | 79% (95%CI -231-99)   | -  | (56)      |
| 0-5 years Private purchase | Spain    | 2015-2019 | Case-control study          | At least two doses                         | 44/138 (32%) tested cases were gMATS positive | 71% (95%CI 45-85)   | All cases with covered strains (gMATS) were unvaccinated | (44)*     |

| <b>Target population</b>   | <b>Country</b>    | <b>Period</b> | <b>Study design</b>                   | <b>Schedule</b>             | <b>Strain coverage</b>      | <b>VE against IMD-B</b>   | <b>VE corrected for covered strains</b> | <b>Reference</b> |
|----------------------------|-------------------|---------------|---------------------------------------|-----------------------------|-----------------------------|---|---|------------------|
| 0-6 years                  | Italy – 6 regions | 2006-2020     | Screening method & case-control study | 3+1                         | 87% (CI 70-93) in 2015 (57) | Screening method: 95% (95%CI 83-98)<br>Case-control study: 96% (95%CI 72-99)            | -                                       | (45)*            |
| Children                   | South Australia   | 2018-2021     | Screening method & case-control study | 2-4 doses, depending on age | 90% (17)                    | Screening method: 93.2% (95%CI 29.3-99.3)<br>Case-control study: 90.7% (95%CI 6.9-99.1) | -                                       | (47)*            |
| Adolescents (school-based) | South Australia   | 2018-2021     | Screening method & case-control study | 1+1                         | 90% (17)                    | Screening method: 83.5% (95%CI 0-98.2)<br>Case-control study: 89.4% (95%CI 0-99%)       | -                                       | (47)*            |

\* newly added studies as compared with the previous report for the Health Council (1)

### 3.5 Vaccine impact

The impact of vaccination describes 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, in practice, the impact is a combination of the VE and the vaccine coverage. Although impact assessment can be complicated because of natural fluctuation in IMD-B. In the previous RIVM report (1), results on vaccine impact on IMD-B incidence from Canada and the UK were already described, with a 86% (95%CI -2-98%) decrease in Canada four years after 4CMenB introduction, and with a 75% (95%CI 64-81%) decrease in the UK three years after introduction (47). Since the previous report, additional results from South Australia and Italy have been published.

A study from South Australia compared the IMD-B incidence between the post-vaccination period (2018-2021) and the pre-vaccination period (2012-2018) for different age groups (45). In infants aged 4-11 months a reduction of 63% (95%CI 29-81) was observed (average annual number of IMD-B cases: 1 vs. 2.7). In other childhood age groups no significant decrease was seen, but numbers were very low (average annual number of cases of 0-1, both pre- and post-vaccination period). In adolescents aged 15-18 years, a reduction of 79% (95%CI 33-93) was observed (average annual number of IMD-B cases: 1 vs. 4).

A study in three regions of Italy compared the IMD-B incidence in a pre-vaccine period (2006-2014/2017, depending on region) and a post-vaccine period (2014/2017-2019, depending on region) in children aged 0-6 years (53, 56). A total of 103 IMD-B cases were reported in the three regions during the study period. The overall incidence was 1.6 per 100,000 in the pre-vaccine period and 0.79 per 100,000 in the post-vaccine period, resulting in a reduction of 50% (95%CI 14-71%).

A study from England assessed characteristics and outcomes of 371 IMD-B cases younger than 5 years and born after 4CMenB implementation (from May 2015) that were diagnosed until March 2021 (58). The proportion of children with sequelae was not significantly different between unvaccinated and vaccinated cases (15 vs. 16%). Also a composite outcome of death, sequelae or PICU admission was not different between unvaccinated and vaccinated cases (61 vs. 62%). Of 325 IMD-B cases eligible for 4CMenB vaccination, 62 (19%) were unvaccinated, and 105 (32%), 82 (25%) and 76 (23%) were vaccinated with 1, 2, or 3 doses, respectively. Among unvaccinated children, nearly all strains (92%) were predicted to be covered by 4CMenB, compared with 67% of vaccinated children. In children younger than 5 years, average annual number of cases after 4CMenB implementation (Sept 2015 – March 2020: 148) were 55% lower than the pre-vaccine average (Sept 2010 – March 2015: 328), while cases among children aged  $\geq 5$  years remained constant (1158 vs 1112 cases). Together, these data indicate that 4CMenB protects against IMD-B, but when IMD-B occurs in a vaccinee, vaccination does not decrease the severity of the disease.

### 3.6 Reactogenicity / side effects

As presented in the previous report (1) after MenB vaccines local reactions including pain, redness, swelling and fever are commonly reported. The Summary of Product Characteristics (SPC) of 4CMenB describes that in clinical studies in infants vaccinated at 2, 4 and 6 months of age fever was reported by 69-79% of subjects when 4CMenB was co-administered with routine vaccines compared with 44-59% of subjects receiving the routine vaccines alone (15). We here report studies on reactogenicity or side effects of MenB vaccines that have been published since the previous report of 2022. Also, we describe reactogenicity of MenABCWY vaccines.

A study from Italy reported adverse events following immunisation (AEFI) of 4CMenB vaccination between 2019 and 2023 (59). Parents of 4CMenB vaccinated children under one year filled in a post-vaccination diary for one week after vaccination. Results were then categorized according to WHO guidelines. Of 4773 completed diaries, 78% contained at least one AEFI report, with the most common being systemic reactions such as malaise, fatigue, fever, and redness or swelling. Twenty-three cases reported serious AEFI's, three of which led to hospitalization. A statistically significant protective effect of antipyretics (paracetamol) against high fever was reported (OR 0.75, 95%CI 0.66-0.86).

Data on AEFI of MenB-fHbp vaccination among children older than 10 years was also reported in Italy (60). In a retrospective observational study, data on reported AEFI were collected from 2018-2021. In this period, 42 AEFI were reported, with a reporting rate of 97.5 per 100.000 vaccinations of which 12 were classified as severe. These AEFI included hyperpyrexia, fainting, urticaria, convulsions and vomiting. No deaths or impairment were notified.

A randomized controlled trial assessing the immunogenicity of the Pfizer MenABCWY vaccine also reported data on adverse events (38). Participants aged 10-25 years were given either a MenABCWY vaccine or a MenACWY and a MenB vaccine. Local reactions and systemic events were reported by a similar proportion of participants across groups. Injection site pain was the most commonly reported local reaction (82.2-90.3%) and fatigue and headache were the most commonly reported systemic events (41.6-56.5%). Fever was reported in 6.6% after the first dose and in 3.0% after the second dose. Reports of adverse events were similar between groups with 19.9-25.7% reporting an adverse event within 30 days of receiving any dose. The amount of serious adverse events was also similar between groups (1.3-2.2%) and none of the serious adverse events were considered related to the administered vaccine.

Safety data generated by 12 clinical studies conducted by GSK on their MenABCWY vaccine was analysed in a pooled integrated safety analysis and presented by the manufacturer (40). A total of 7048 participants, ranging between 9-42 years, received at least 1 dose of MenABCWY in these studies. The percentage of participants with solicited local and systemic adverse events within 7 days was similar after MenABCWY and

4CMenB vaccination but higher than after MenACWY-CRM vaccination. The amount of vaccine related unsolicited adverse events among the MenABCWY group was comparable to the group receiving only 4CMenB (7% vs. 6%), both of which were higher than the group receiving only MenACWY-CRM (3%). Serious vaccine related adverse events were reported in 0.1% of participants in both MenABCWY and 4CMenB groups, and 0% in the MenACWY-CRM group, although the MenACWY group was much smaller than the other groups.



## 4 Cost-effectiveness of meningococcal B vaccines

### 4.1 Methods

We conducted a health economic evaluation to assess the cost-effectiveness of different vaccines (4CMenB, MenB-fHBp, MenABCWY) to protect against IMD-B from a Dutch societal perspective. To do so we built a single-cohort Markov model with monthly model cycles and a lifetime horizon. We evaluated the vaccines based on clinical outcomes, i.e., the number of IMD-B cases and related deaths avoided and the incremental cost-effectiveness ratio (ICER), i.e., quality adjusted life years (QALY) gained per costs (€). As the abovementioned vaccines do not prevent serogroup B carriage and thus do not provide herd immunity, only direct effects on clinical outcomes were considered.

Health effects and costs were discounted at a rate of 1.5% and 3% per year, respectively. The model incorporated costs and effects for vaccination, IMD-B, complications, sequelae and deaths of IMD-B, productivity losses, costs for special education as a result of IMD-B sequelae, and costs that fall onto the patient and their families. Based on previous studies which included an evaluation of the impact of sequelae of IMD-B (61-63), we included the following sequelae in our assessment: unilateral hearing loss, bilateral hearing loss, severe neurological impairments, mental retardation/low IQ, speech problems, motor deficits, limb amputation, epilepsy/seizures, skin scarring, renal disease, blindness, ADHD, anxiety and separation anxiety.

The analysis was performed for infants, with 4CMenB compared to no vaccination and for adolescents, with 4CMenB, MenB-fHBp and MenABCWY compared with no vaccination. Note that, for MenABCWY, the MenABCWY vaccine replaced the MenACWY dose of the NIP at 14 years, while as second dose, MenB-fHBp was used. We implemented different vaccine schedules according to the age groups: for infants, the vaccination schedule consisted of vaccine doses at 2, 4 and 15 months of age. The vaccination schedule for adolescent consisted of two vaccine doses given with a 6-month interval at 15 years of age. The applied cost per vaccine dose was €85.65 (64), €80.65 (65) and €91.09 (66) for 4CMenB, MenB-fHBp and MenABCWY respectively. Furthermore, each new vaccine administration was applied with a cost of €14.68 (61). The age-specific vaccination coverages were informed by the national coverages for MenACWY, PCV10 and HPV vaccination (26). For infants the applied vaccination coverage was 0.95 for the first and second dose and 0.9 for the third dose. For adolescents the coverage was 0.9 for the first dose and 0.8 for the second dose.

As of the 5th of February 2025, the marketing authorization of Penbraya (a MenABCWY vaccine containing MenB-fHBp and MenACWY-TT) by the EMA was withdrawn on request of its marketing-authorization holder Pfizer because of commercial reasons (67). Because the active ingredient of the B component in Penbraya is the same as that in MenB-fHBp, the VE of the MenABCWY vaccine was assumed to be equal to that of MenB-fHBp. Because the marketing authorization of Penbraya was only withdrawn late in the modelling process of this cost-effectiveness analysis, many assumptions of the model are still based on the MenABCWY vaccine being Penbraya. The MenABCWY vaccine of GSK

(Penmenvy) which includes the 4CMenB component, is approved by the US FDA but not (yet) by EMA (20). Note that the ICER for Penmenvy would be slightly higher than the ICER presented in the current analysis for MenABCWY (based on Penbraya). This is the result of a slightly lower strain coverage for 4CMenB compared to MenB-fHBp.

#### 4.1.1 *Transition probabilities*

We modelled age-specific IMD-B incidence and case-fatality rates. The data on incidence and case-fatality rates was based on Dutch surveillance data of the RIVM and NRLBM (see chapter 2). The incidence data in the model was collected between May 2022 and October 2024. Data on the case-fatality rate was collected between 2019 to 2024. The VE of the different vaccines was informed by a systematic review and meta-analysis conducted for the German NITAG (ständige Impfkommision; STIKO) (68). The systematic review identified four articles (44, 45, 47, 54) that report on the VE of 4CMenB for infants and one article that reports on the VE of 4CMenB for adolescents (47). Because the VE of MenB-fHBp and MenABCWY is unknown, we extrapolated the VE for these vaccines from the VE of 4CMenB (see below). The VE of MenABCWY against serogroups A, C, W, and Y was assumed to be equal to that of the currently used MenACWY in the NIP. Consequently, the incremental impact of MenABCWY on these serogroups was presumed to be zero, and no additional effect on serogroups A, C, W, and Y was modelled. We modelled VE from one month after each administration.

The STIKO review/meta-analysis did not consider the strain coverage of the different vaccines. For infants, the STIKO meta-analysis reported a VE of 81% (95%CI 68-89) after completing the primary series (2 doses) and the same value after completing the full series. We did not adjust the VE of 4CMenB for infants for the Dutch strain coverage estimates, given the considerable uncertainty in the strain coverage estimates (see chapter 3.2). After the first dose, we applied a VE of 35% based on values reported by Argante (54) and Wang (47).

For adolescents, the STIKO meta-analysis only includes one article from South Australia (47) in which the estimated VE against IMD-B was 89% (95% CI: -0.6-99.0%), with no information on strain coverage provided. The reported VE was, however, higher than the estimated maximal strain coverage for the Netherlands for 4CMenB for adolescents (82%; see chapter 3.2), and is therefore unrealistic in this context. For the effective VE for adolescents, we therefore corrected the VE for strain coverage. The authors of the South Australian article refer elsewhere (69) to a 90% strain coverage for the studied population. Using this strain coverage, we calculated the VE for covered strains in adolescents by dividing the reported VE with the strain coverage ( $0.89 / 0.90$ ). To calculate the effective VE for the Netherlands used in the base case, we multiplied the VE for covered strains with the estimated *maximum* strain coverage for the specific vaccine in the Netherlands, i.e., 82% for 4CMenB and 97% for MenB-fHBp and MenABCWY. Note that this is an optimistic calculation as the maximum strain coverage for each vaccine is substantially higher than the (minimum) strain coverage as determined using the BAST method (see chapter 3.2; strain coverage in adolescents for 4CmenB: 31%; for MenB-fHBp: 68%).

Little data is available about the decrease of the VE over time.

Immunogenicity data suggests that the antibody response wanes quickly

during the first year after vaccination and stays relatively stable thereafter (see section 2.3). We assumed the duration of protection after the primary series in infants or the first dose in adolescents to be 2 years. If infants received a booster or adolescents received their second dose, the duration of protection was assumed to be 5 years after completing the primary series (or 1 dose in adolescents). VE was assumed to linearly decrease from the beginning of protection until VE reaches 0% when the duration of protection was completed. Pouwels (61) and Christensen (70) have taken similar approaches to model the decrease of VE over time in their cost-effectiveness models.

#### 4.1.2 *Uncertainty assessment*

To investigate the sensitivity of model results to the variation in individual parameters and assumptions, we conducted standard probabilistic analyses (i.e., varying a set of parameters within their distribution at the same time), deterministic sensitivity analyses (i.e., varying a set of parameters within their distribution individually) and scenario analyses (i.e., varying key assumptions and methodological choices).

The VE values as well as the duration of protection are highly uncertain because of scarcity of data, arguably due to the low IMD-B incidence and limited test databases for strain coverage. Consequently, we had to combine evidence from different sources and from different contexts for key parameters. We therefore emphasize exploring the uncertainty relating to VE inputs and the duration of protection.

#### 4.1.3 *Validation*

The model has been internally validated using the TECH-VER (71) technical validation checklist. The costs have been validated by implementing the costs by Zeevat (63) in the model. This changed the ICER by less than 1% in each case suggesting that we implemented a similar cost per case as the one calculated by Zeevat. More detailed information on the methods and on the results of the cost effectiveness analyses will be published elsewhere.

## 4.2 **Results**

### 4.2.1 *Public health gains*

According to our modelled results, if no MenB vaccination is implemented in the NIP, 87 individuals of the infants in one birth cohort (n=166,073) or 62 individuals of the adolescents of a 15-year old cohort (n=197,782) would develop IMD-B during their lifetime, and 4-5 or 2-3 of those would die from the infection (Table 6). It is estimated that vaccinating infants has more impact on prevention of IMD-B and its related burden of disease than vaccinating adolescents. Over a lifetime horizon, inclusion of 4CMenB in the NIP for infants would reduce the number of IMD-B cases by 11 and the number of IMD-B related deaths by 1. An inclusion of any MenB vaccine in the NIP for adolescents would reduce the number of cases by ~7-9 and would not reduce the number of IMD-B related deaths.

Table 6 Clinical outcomes at population level.

| Population (n)                          | Schedule                   | Total Costs (in million) | Total LYs | Total QALYs | Total IMD-B Cases (lifetime) | Total IMD-B related Deaths (lifetime) |
|---|----------------------------|--------------------------|-----------|-------------|------------------------------|---------------------------------------|
| <b>Infants – Age 0 (n=166,073)</b>      | No vaccine                 | € 4.61                   | 7,780,314 | 7,290,378   | 86.63                        | 4.87                                  |
|   | 4CMenB (2+1)               | € 58.32                  | 7,780,353 | 7,290,468   | 75.52                        | 4.01                                  |
| <b>Adolescents – Age 15 (n=197,782)</b> | No vaccine                 | € 2.16                   | 8,315,450 | 7,982,520   | 62.27                        | 2.63                                  |
|   | 4CMenB (1+1)               | € 40.67                  | 8,315,460 | 7,982,564   | 55.0                         | 2.38                                  |
|   | MenB-fHBp (1+1)            | € 39.01                  | 8,315,462 | 7,982,573   | 53.61                        | 2.29                                  |
|   | MenABCWY + MenB-fHBp (1+1) | € 38.98                  | 8,315,462 | 7,982,572   | 53.67                        | 2.31                                  |

LYs: life years; QALYs: Quality-adjusted life-years (sum of life years multiplied with the quality of life)

#### 4.2.2 Cost-effectiveness results

Table 7 shows the health economic results. The results can be interpreted as the average costs and public health effects per individual. Note that the costs mentioned if no vaccine is implemented in the NIP are the average costs per individual due to IMD-B during a lifetime.

In line with the public health results, our model estimates that vaccinating infants is more cost-effective than vaccinating adolescents. When comparing the different vaccination schedules to no vaccination in the base case scenarios, analyses indicate that the ICER of the different scenarios ranges between approximately 500,000 €/QALY and 900,000 €/QALY gained (Table 7). These ICERs far exceed the commonly used threshold values (20,000 €/QALY to 80,000 €/QALY) in the Netherlands (72), rendering vaccination not cost effective.

Table 7 Cost-effectiveness outcomes per individual in the Netherlands.

| Population                  | Schedule             | Costs    | QALY     | Incremental Costs | Incremental QALYs | ICER      |
|-----------------------------|----------------------|----------|----------|-------------------|-------------------|-----------|
| <b>Infants (Age 0)</b>      | No vaccine           | € 27.79  | 43.89864 | //                | //                | //        |
|                             | 4CMenB (2+1)         | € 351.18 | 43.89918 | € 323.39          | 0.00054           | € 592,279 |
| <b>Adolescents (Age 15)</b> | No vaccine           | € 10.98  | 40.36020 | //                | //                | //        |
|                             | 4CMenB (1+1)         | € 205.66 | 40.36041 | € 194.67          | 0.00022           | € 885,701 |
|                             | MenB-fHBp (1+1)      | € 196.98 | 40.36046 | € 186.31          | 0.00026           | € 716,312 |
|                             | MenABCWY + MenB-fHBp | € 197.08 | 40.36046 | € 186.09          | 0.00026           | € 720,740 |

LYs: life years; QALYs: Quality-adjusted life-years (sum of life-years multiplied with the quality of life); ICER: incremental cost-effectiveness ratio (incremental costs divided by incremental QALYs)

### 4.2.3 *Uncertainty assessment*

The sensitivity analyses indicate that the impact of uncertainty due to parameters and assumptions is substantial for each of the modelled schedules. The most impactful sources of uncertainty are inputs and assumptions around the VE and sequelae prevalences. Figure 5 shows the ICER of 4CMenB compared to no vaccine when varying the VE between 20% (0.2) and 100% (1.0). 4CMenB was chosen here as it was the most cost-effective vaccine included in this study. The figure illustrates that even if the VE would be 100% the ICER was 480,643 €/QALY gained, well above common thresholds.

Figure 5 Incremental Cost-effectiveness Ratio (ICER) by vaccine effectiveness, for 4CMenB used in infants.

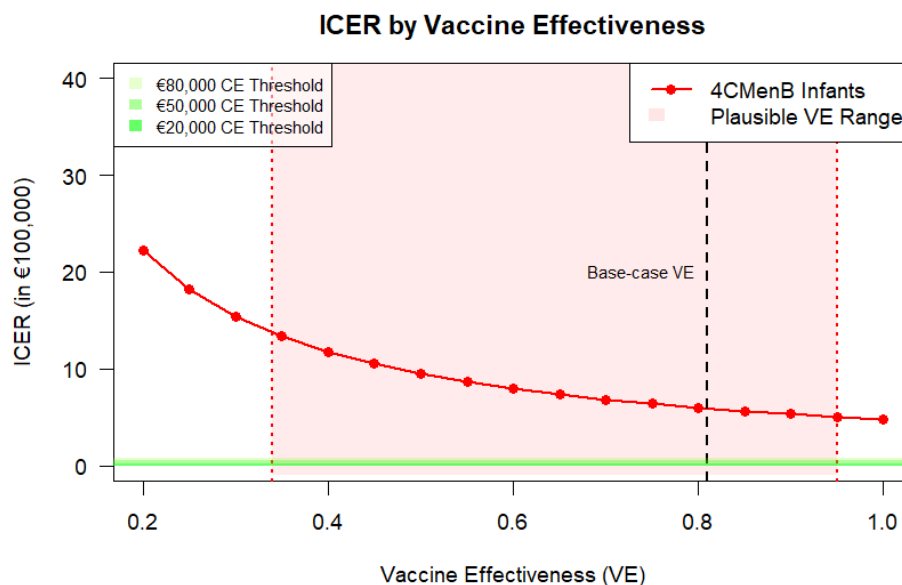
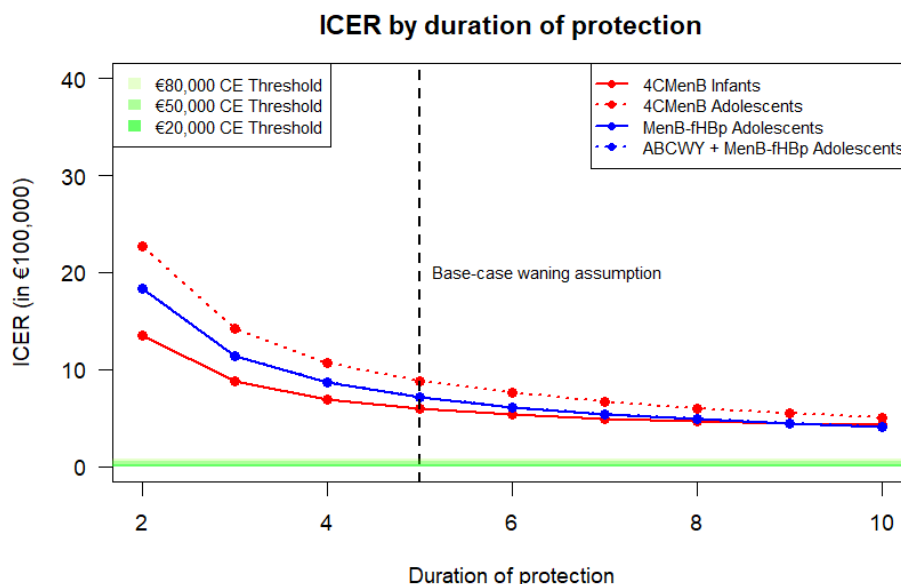


Figure 6 shows the results of the sensitivity analysis when varying the maximum duration of protection from 2 to 10 years. Similar to Figure 5, the sensitivity analysis shows that even in the most optimistic case of a duration of protection of 10 years, the ICERs of all vaccine remain well above common cost-effectiveness thresholds.

Figure 6 Incremental Cost-effectiveness Ratio (ICER) by duration of protection for the different vaccines.



Note that “MenB-fHBp” and “MenABCWY + MenB-fHBp” results are so close that the lines overlap completely

The previous RIVM report on IMD (1) highlighted the prevalence of sequelae as one of the main uncertainties around the cost-effectiveness of IMD-B vaccines because sequelae may remain for the rest of a patient’s lifetime. We explored the uncertainty surrounding the prevalence of sequelae as this affected the results substantially. In our base-case analysis the prevalence of sequelae was informed by multiple data sources from outside of the Netherlands (63, 73, 74). These sources suggest that that the cumulative probability of experiencing a sequela was 51%, including a 10% probability of experiencing severe sequelae. A quite recent Dutch study by Middeldorp (8) reports a substantial reduction of patients experiencing sequelae one year after discharge. We therefore conducted a scenario analysis which implements this reduction. Because Middeldorp does not report sequelae prevalence by sequelae but by severity, this scenario analysis required us to reclassify our base-case sequelae prevalence into sequelae by severity and adjust the rates. This combination of evidence introduces substantial uncertainty and is therefore not considered as base-case analysis. Implementing this scenario analysis, however, increased the ICER to €833,447 for 4CmenB for infants and to €1,407,473, €1,135,178 and €1,135,792 for 4CMenB, MenB-fHBp, and MenACBWY for adolescents respectively.

None of the sensitivity or scenario analyses moved the ICER of any of the schedules into a cost-effective range (to be published by Otten T *etal*). The probabilistic sensitivity analyses showed that even with the highest commonly considered threshold of €80,000 (72) all explored vaccination strategies had a 0% probability of being cost-effective. However, this may change when multiple assumptions are changed at the same time. Beck (62) combines different additional disease burden categories (i.e., adding caregiver quality of life, increasing experienced

disease severity, adjustment of discount rates) to demonstrate that IMD-B could be cost-effective in a UK context given a deviation from the reference case (62). Similarly to the UK context, the inclusion of such additional disease burden categories such as caregiver quality of life is encouraged only for scenario analyses by the Dutch Guideline for health economic evaluations in healthcare (72).

Overall, we therefore conclude that implementation of a MenB vaccine in the NIP is not currently cost-effective. This conclusion is in line with the conclusions of several other cost-effectiveness models including one from the Netherlands (61) and other countries (62, 70, 75). In terms of specific results, our results show a less favorable ICER than the only peer-reviewed health economic evaluation of IMD-B vaccines in the Dutch context (ICER for Infant population in Pouwel's model: 243,778 €/QALY; our model: 595,279 €/QALY) (61). This is likely because the incidence that we used is lower than the incidence reported by Pouwels (61).

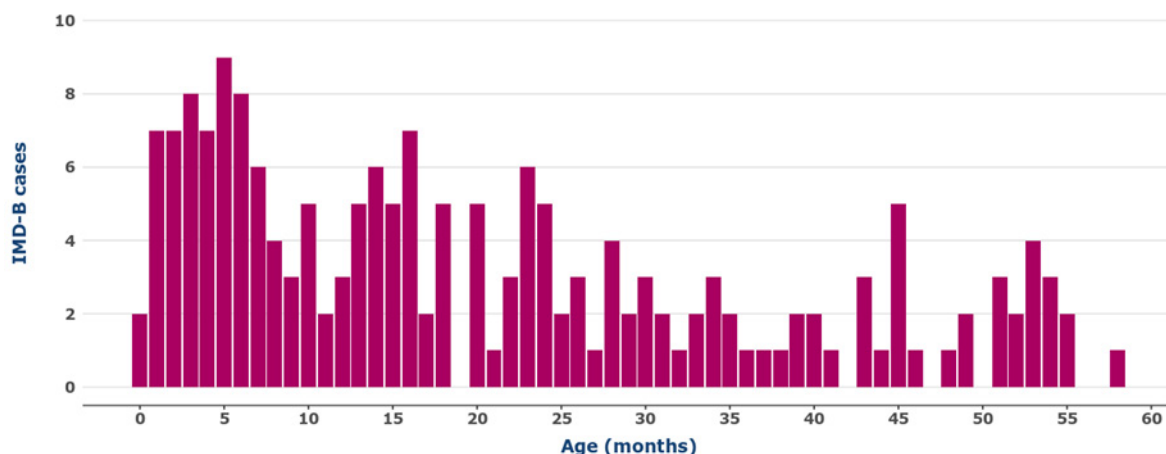


## 5 Aspects of implementation

### 5.1 Infant vaccination

4CMenB is currently the only MenB vaccine that can be used in infants. 4CMenB can be given as a 3+1 schedule starting at 2 months of age or as a 2+1 schedule starting at 3 months of age (76). Based on the number of cases by month of age (Figure 7), it is desirable to vaccinate children as early as possible. Because of the risk of (high) fever (see chapter Reactogenicity / side effects), prophylactic paracetamol could be recommended at the day of MenB vaccination.

Figure 7 Number of IMD-B cases aged younger than 5 years by age in months for the period 2017-2024, the Netherlands.



Generally, not more than two injections at one youth healthcare (JGZ) appointment are given in the Netherlands. In the current schedule (77) MenB vaccination could in that case be given at 2, 4 (and 6) months of age and the booster could be given at 13 or 15 months, as at 14 months of age already two injections are scheduled (MMR and MenACWY).

In 2018, MenACWY vaccination has been implemented at 14 years of age together with a catch-up campaign in 14-18 year olds (78). This adolescent vaccination programme may give herd protection, as MenACWY vaccination has been shown to protect against carriage in some studies, though not in all (13, 79). Currently, MenACWY vaccination is given at 14 months of age. Omitting this MenACWY dose at 14 months of age could be considered if the following conditions are met: 1) MenACWY vaccination provides sufficient herd protection to younger children, 2) the MenACWY vaccine coverage among teenagers remains high enough, and 3) the strain coverage of 4CMenB against serogroups C, W and Y is good. Regarding herd protection, the number of IMD-CWY cases has been largely reduced in the Netherlands since MenACWY introduction, but there were still a few IMD-CWY cases in 2023 and 2024 (3 IMD-W <5 years, 2 IMD-CW 15-24 years, 19 IMD-CWY 25+ years; all unvaccinated). These data indicate that there is still some circulation of serogroup (C)WY. Regarding MenACWY vaccine coverage among teenagers, this decreased from 84% for birth cohort

2006 to 66% for birth cohort 2008, although the latter number will be an underestimation because of introduction of the informed consent procedure for the national vaccination register (26). These data indicate that coverage is decreasing over time. Regarding strain coverage, this is currently highly uncertain because of the low numbers and the high number of strains with 'insufficient' results (see also Genomic analyses – strain coverage). If MenACWY vaccination at 14 months would be omitted and 4CMenB would be introduced, the 4CMenB booster dose could be given at 14 months together with MMR vaccination.

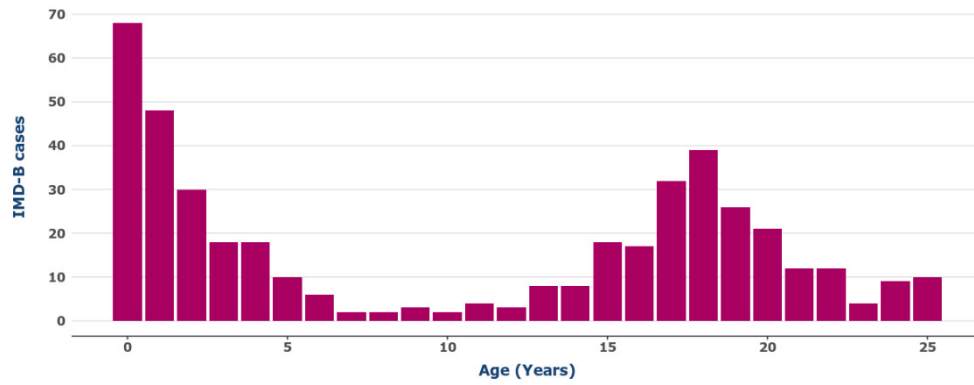
## 5.2 Adolescent vaccination

Both 4CMenB and MenB-fHbp can be used in adolescents, as well as MenABCWY (if registered by EMA). For 4CMenB, from the age of 11 years, two vaccinations are needed, with at least one month in between (15, 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 (16).

In the last years, IMD-B cases started to increase at 13-14 years of age with a peak at 17-18 years of age (Figure 8). Therefore, the preferred age of vaccination would be 13-15 years and, ideally, protection would last at least until 20 years of age. However, duration of protection of MenB vaccination is very uncertain. Immunogenicity data shows a considerable decrease in antibody levels already at one year after vaccination, whereafter it stabilizes for at least 4 years (35, 36). There is no data on (duration of) VE against IMD-B in adolescents.

In the current schedule (77), DTP and MenACWY are offered at 14 years, so if MenB vaccination would be implemented, two additional visits are needed. Alternatively a MenABCWY vaccine could replace the MenACWY vaccine at 14 years; only one additional visit is then needed for the second dose of the MenB component. This second dose could again be a MenABCWY vaccine or just a MenB vaccine. While clinical registration trials assessing immunogenicity and safety used two doses of MenABCWY and not a combination of MenABCWY and MenB-fHbp or 4CMenB, the antibody responses against serogroup B are expected to be similar (see also immunogenicity chapter where MenABCWY is compared with MenB-fHbp or 4CMenB). The interval between two MenABCWY vaccines could be 6 months or 12 months, where 12 months showed higher antibody responses (39).

Figure 8 Number of IMD-B cases aged younger than 25 years by age in years for the period 2017-2024, the Netherlands.





## Acknowledgements

This report includes contributions from:

- Anneke Steens, RIVM (editor)
- Hester de Melker, RIVM (editor)
- Thomas Otten, RIVM (cost-effectiveness analysis)
- Linda Visser, RIVM (strain-coverage data)
- Maartje Visser, RIVM (gonococcal information)
- Rob Mariman, Nynke Rots, Jacco Wallinga, Pieter de Boer, all from RIVM, and Nina van Sorge, from NRLBM (review of the content)

### **Conflicts of interest**

Nina van Sorge has received research funds from Argenx, directly paid to Amsterdam UMC. She has also received consultancy fees, directly paid to Amsterdam UMC, from MSD, GSK and Pfizer on pneumococcal, meningococcal and *Haemophilus* epidemiology.

Other authors and contributors report no conflicts of interest.



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and the Environment, RIVM**

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May 2025

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