



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

## **Meningococcal disease in the Netherlands**

Background information for the  
Health Council

RIVM Report 2017-0031

M.J.Knol et al.





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and the Environment  
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## Colophon

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M.J. Knol (author), RIVM  
H.E. de Melker (author), RIVM  
G.A.M. Berbers (author), RIVM  
M.B. van Ravenhorst (author), RIVM  
W.L.M. Ruijs (author), RIVM  
J.A. van Vliet (author), RIVM  
J.M. Kemmeren (author), RIVM  
A. Suijkerbuijk (author), RIVM  
E.A. van Lier (author), RIVM  
E.A.M Sanders (author), RIVM  
A. van der Ende (author), Netherlands Reference Laboratory for Bacterial Meningitis, Academic Medical Center, Amsterdam, the Netherlands

### Contact:

M.J. Knol  
Center for Epidemiology and Surveillance of Infectious Diseases  
mirjam.knol@rivm.nl

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P.O. Box 1 | 3720 BA Bilthoven  
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[www.rivm.nl/en](http://www.rivm.nl/en)

## Synopsis

### **Meningococcal disease in the Netherlands**

Background information for the Health Council

Meningococcal disease is a very serious infectious disease caused by a bacterium, the meningococcus. There are different types of meningococcus; people become ill mainly from the B, C, W and Y serogroups. Since 2002, vaccination against serogroup C meningococcal disease has been included in the National Immunisation Programme for children of 14 months. As a result, serogroup C meningococcal disease has virtually disappeared. Vaccines against serogroup B have recently become available. In addition, since 2015, there has been a rapid increase in serogroup W meningococcal disease. Multi-component vaccines are available against A, C, W and Y serogroups.

Based on these developments, among others, the Health Council will advise the Minister for Health, Welfare and Sport on whether and how the current immunisation programme against meningococcal disease should be adapted. To this end, RIVM has collected background information and recent data on meningococcal disease in the Netherlands. It includes the number of people in the Netherlands who become ill each year, the efficacy and safety of the vaccines, and what the public thinks about vaccination against invasive meningococcal disease.

The infection causes a severe medical condition such as meningitis or blood poisoning, which can rapidly develop into shock, frequently causing death. The disease often begins with flu-like symptoms and fever which subsequently worsen very rapidly. The infection is relatively rare in the Netherlands; there are currently 100 to 150 patients a year. Five to ten percent of these patients die despite antibiotics and intensive care. Thirty percent of the patients are left with lifelong impairments such as hearing loss, limb amputation or epilepsy. Meningococcal disease is most common in children under the age of 5, adolescents and the elderly.

Keywords: meningococcus, meningococcal disease, vaccination, disease burden, cost-effectiveness, safety, acceptance, implementation aspects



## Publiekssamenvatting

### **Meningokokkenziekte in Nederland**

Achtergrondinformatie voor de Gezondheidsraad

Meningokokkenziekte is een zeer ernstige infectieziekte die veroorzaakt wordt door een bacterie, de meningokok. Er zijn verschillende typen meningokokken; mensen worden vooral ziek van de serogroepen B, C, W en Y. Vaccinatie tegen meningokokkenziekte serogroep C is in Nederland sinds 2002 opgenomen in het Rijksvaccinatieprogramma voor kinderen van 14 maanden. Hierdoor komt meningokokkenziekte door serogroep C nauwelijks meer voor. Sinds kort zijn vaccins beschikbaar tegen serogroep B. Daarnaast is er sinds 2015 een snelle toename in meningokokkenziekte door serogroep W. Er zijn combinatievaccins beschikbaar tegen serogroep A, C, W en Y.

Vanwege ondermeer deze ontwikkelingen gaat de Gezondheidsraad de minister van VWS adviseren of, en op welke manier, het huidige vaccinatieprogramma tegen meningokokkenziekte aangepast moet worden. Daartoe heeft het RIVM achtergrondinformatie en recente data over meningokokkenziekte in Nederland verzameld. Het gaat onder meer om het aantal mensen in Nederland dat jaarlijks ziek wordt, de effectiviteit en veiligheid van de vaccins, en hoe het publiek denkt over vaccinatie tegen invasieve meningokokkenziekte.

De infectie geeft een ernstig ziektebeeld zoals hersenvliesontsteking of een bloedvergiftiging, die zich snel kan ontwikkelen tot een shock waar veel mensen aan overlijden. De ziekte begint vaak met griepachtige verschijnselen en koorts die vervolgens zeer snel verergeren. De infectie is in Nederland relatief zeldzaam; op dit moment zijn er 100 tot 150 patiënten per jaar. Van deze patiënten overlijdt 5-10 procent ondanks antibiotica en intensieve zorg. 30 procent van de patiënten houdt er levenslang beperkingen aan over zoals gehoorverlies, amputatie van een ledemaat of epilepsie. Meningokokkenziekte komt het meest voor bij kinderen jonger dan 5 jaar, adolescenten en ouderen.

Kernwoorden: meningokok, meningokokkenziekte, vaccinatie, ziektelast, kosteneffectiviteit, veiligheid, acceptatie, invoeringsaspecten



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## 1 Background

Invasive meningococcal disease is a relatively rare (100-150 cases/year in the Netherlands) but severe infectious disease with high mortality. The incidence is highest in children under 5 years of age and adolescents. Disease onset is often aspecific and invasive meningococcal disease may develop within a few hours towards meningitis and/or sepsis and septic shock. Overall, the mortality rate of meningococcal disease is 8%, but meningococcal fulminant septic shock has a high mortality up to 20% or more. Up to 30% of survivors suffer from one or more long term sequelae and 6% suffers from very serious complications like deafness, limb amputation or epilepsy. Since mortality has not changed significantly over the last decades despite improvement of management and therapy, primary prevention by vaccination is considered the best option to eradicate invasive meningococcal disease and its severe sequelae. Meningococcal conjugate vaccines protect vaccinees by inducing serum IgG anti capsular antibodies and offer herd protection for the population as a whole by eradicating carriage and transmission of the vaccine serogroup.

In 2002, in response to the increasing incidence of meningococcal serogroup C (MenC) disease, in a large catch up campaign all 1-18 year olds were vaccinated. This catch-up campaign with high coverage led to reduction in transmission and, therefore, in herd protection for all age groups and the number of cases of MenC disease have remained low ever since. Also, vaccination against MenC disease was introduced in the Dutch National Immunization Program (NIP) at the age of 14 months. From sero-epidemiological studies, however, we know protective antibody levels disappear within a few years after vaccination in infancy, leaving a large part of adolescents unprotected against MenC carriage and disease. Therefore, it is unclear how long herd protection in the population will remain as well as individual protection in case MenC re-emerges.

In addition, since the Autumn of 2015 the number of cases with meningococcal serogroup W (MenW) disease increases rapidly. The incidence increased more than ten-fold from 0.02 per 100,000 per year in the period 2005-2014 to 0.29 per 100,000 in 2016; in the last quarter of 2016 the incidence increased to 0.40 per 100,000. Serogroup W caused 33% of all cases of meningococcal disease in 2016. MenW disease is currently rapidly increasing, implying that more cases are expected in the coming months. Two quadrivalent MenACWY conjugate vaccines are available in Europe.

Serogroup B is still the most prevalent serogroup causing meningococcal disease in the Netherlands, affecting in particular young children and, to a lesser extent, adolescents and young adults. A first vaccine that protects against meningococcal serogroup B (MenB) disease has been licensed in Europe recently. The UK is the first country that introduced MenB vaccine for infants in their national vaccination programme and first results on the effectiveness of this vaccine are encouraging.

In view of the rapid increase in MenW disease and the availability of a MenACWY vaccine, the loss of protective MenC antibodies in adolescents and the recent availability of a MenB vaccine, there is a call for an integrated evaluation of vaccination against meningococcal disease in the Netherlands for optimal prevention against this severe disease.

In this report, we aimed to present the most recent scientific information available on meningococcal disease in general, the burden of disease of meningococcal disease in the Netherlands, the effectiveness, safety, acceptance and cost-effectiveness of available vaccines against meningococcal disease, and aspects of implementation of meningococcal vaccination. Herewith we follow the criteria led down by the Dutch Health Council to assess vaccinations.

## 2 Meningococcal disease

### 2.1 Pathogen

Meningococcal disease is caused by the gram-negative bacterium *Neisseria meningitidis* or meningococcus. The pathogen usually resides in the oropharynx of healthy people without causing disease. If the pathogen invades the bloodstream or the meninges, it can cause severe disease including meningitis and sepsis that may result in septic shock with high mortality. Based on differences in the capsule polysaccharide of the meningococcus, 12 serogroups can be discerned, of which B, C, W, and Y cause most disease in Europe (1). Unencapsulated strains are often found in asymptomatic colonization, but are very rarely involved in disease.

Irrespective of serogroup, meningococci can be classified into clonal complexes (ccs) using multilocus sequence typing (MLST). Meningococci belonging to cc11 are hyperinvasive and may express serogroups C or W and, less frequently, B or Y (2). They are associated with high morbidity and mortality. The MenC increase in the 1990s/2000s in the Netherlands and several other European countries was caused by strains belonging to cc11. Currently, the rapid MenW increase in the UK and the Netherlands is also caused by cc11.

### 2.2 Transmission

Humans are the only reservoir for the meningococcus. Asymptomatic carriage occurs in 10-20%, and is highest in adolescents and young adults and related to life style (3). Transmission occurs from humans to humans through respiratory droplets or saliva or spit. The pathogen can be transmitted by intensive contact, for example by coughing, sneezing, speaking or direct contact like kissing. Smoking, sharing water pipes and drinking glasses are also associated with increased (asymptomatic) meningococcal colonization in the oropharynx. Following infection, most persons become asymptomatic carrier for a short period but they still can transmit the pathogen. After a case of meningococcal disease, risk of secondary disease cases is highest in the first 7 days after contact with the index case; thereafter the risk decreases rapidly.

### 2.3 Symptoms and outcomes

The symptoms of meningococcal disease can vary widely and are usually not specific at disease onset, often presenting like a sudden flu like disease and then rapidly progressing to severe disease. High fever, headache, neck stiffness, nausea and vomiting are frequently occurring symptoms. In infants and young children, symptoms like low temperature, fever, drowsiness, feeding problems, and convulsions can occur. An important diagnostic symptom of meningococcal sepsis is the occurrence of a typical 'pin prick' rash (petechiae) that develops in the course of disease. Due to fast disease progression and often atypical symptoms at presentation, meningococcal disease is often not recognised in time which contributes to the overall high case fatality rate of 5-10% (4). Mortality of septic shock that may develop within hours can be as high as 20-50%. In 6% of survivors of meningococcal disease,

lifelong severe sequelae occur including deafness, limb amputation and brain damage (4). In addition, a Dutch study showed that 32% of children that survived bacterial meningitis (caused by various pathogens including *N. meningitidis*) experienced cognitive and/or behavioural limitations (5). The highly invasive MenW strain that is currently spreading rapidly in the UK and the Netherlands has a high mortality, which is probably partly due to the atypical onset of disease. Throat pain, pneumonia and gastro-intestinal symptoms have been reported as symptoms at presentation and these are not initially recognized as the start of invasive meningococcal disease (see sections 3.2.3 and 3.5.3).

## **2.4 Diagnostics**

The diagnosis of meningococcal disease is confirmed by isolation of *N. meningitidis* from a normally sterile body site (e.g. blood or CSF, or less commonly, synovial, pleural, or pericardial fluid) or from purpuric lesions, or by detection of *N. meningitidis*-specific nucleic acid in a specimen obtained from a normally sterile body site (e.g., blood or CSF) using PCR.

## **2.5 Treatment**

Meningococcal disease can be treated with (intravenous) antibiotics but severe sequelae are not necessarily prevented by this treatment. Antibiotic prophylaxis is given as quickly as possible to household members and close contacts of the patient to prevent invasive meningococcal disease. If the disease is caused by a serogroup for which a vaccine is available, vaccination is also provided to household members and close contacts (6).

## **2.6 Risk factors**

Known risk factors for meningococcal disease are hyposplenia and asplenia, an open connection between the naso- and oropharynx and the meninges, and immune disorders like complement deficiency and antibody deficiency. Also 'crowding', meaning many people in a limited space, is a risk factor (e.g. day care centres, discotheques and summer camps). The impact of crowding has been shown previously for example in the Hajj pilgrimage where, before vaccination recommendations for pilgrims were given, outbreaks have occurred with considerable number of cases (7).

## 3 Epidemiology of meningococcal disease

### 3.1 Surveillance of meningococcal disease in the Netherlands

Meningococcal disease has been a notifiable disease since 1905. Notification to the Municipal Health Center should take place if the patient suffered from at least one of the five following symptoms fever, neck stiffness, petechiae, septic shock or septic arthritis in combination with laboratory confirmation.

Laboratory surveillance of meningococcal disease is performed by the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) at the AMC in collaboration with the RIVM. The NRLBM receives blood or CSF isolates positive for *Neisseria meningitidis* of all microbiological laboratories in the Netherlands on a voluntary basis since 1959. The NRLBM determines the serogroup of the isolate. Additionally, the finetype is determined based on sequencing of the PorA and FetA protein. Whole genome sequencing is done in specific research projects. Also PCR-positive material is sent to the NRLBM and a serogroup can often be determined by using RT-PCR with serogroup specific probes.

Data of the notification system and the laboratory surveillance have been actively linked since 2003 to get a comprehensive surveillance system.

### 3.2 Incidence in the Netherlands

Historical time trends of meningococcal disease show natural fluctuations in meningococcal disease with, for example, an incidence of 0.5 per 100,000 in the beginning of the 1960s and an incidence of 4.0 per 100,000 in the 1990s (1). Figure 1 shows the incidence of meningococcal disease by serogroup from 1992 to 2016 in the Netherlands. Since 2002, the incidence declined over the years to 0.5-1.0 per 100,000 per year (around 100 cases per year) due to eradication of MenC disease after the mass vaccination campaign in 2002 and a gradual decline of MenB disease. MenW incidence has been very low but increased in 2016, while MenY disease and meningococcal disease including MenA caused by other serogroups is very rare. We will discuss the incidence by serogroup in more detail below.

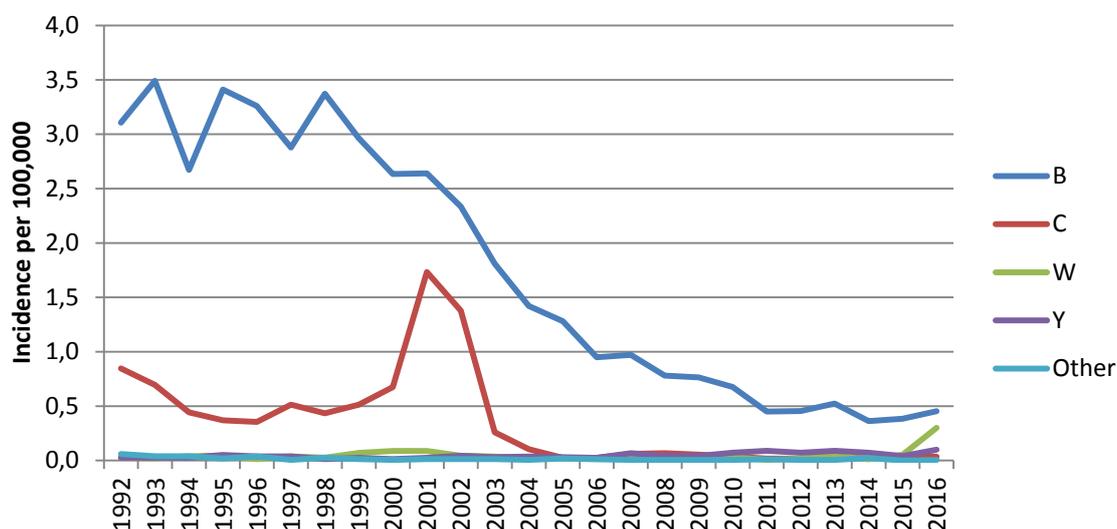


Figure 1 Incidence of meningococcal disease by serogroup during 1992-2016

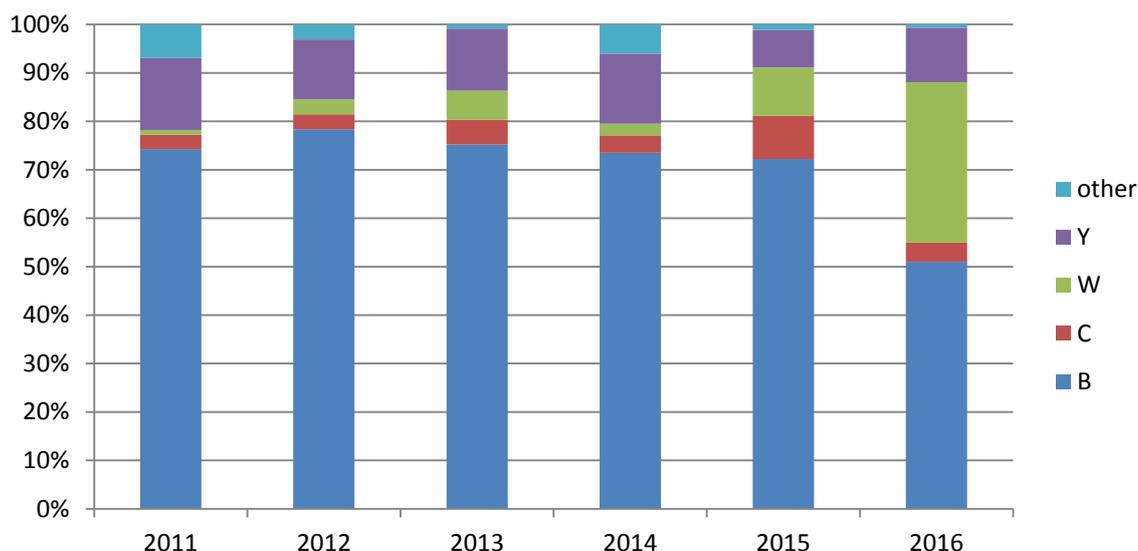


Figure 2 Serogroup distribution of meningococcal disease during 2011-2016

### 3.2.1

#### *Meningococcal disease serogroup B*

Serogroup B is the most common cause of meningococcal disease in the Netherlands contributing to 70-80% of all meningococcal cases from 2011 to 2015 (Figure 2). In 2016, only 50% of all cases were caused by serogroup B because of the high increase in MenW disease. The incidence of MenB disease has decreased greatly during the last two decades from an incidence of 3.4 per 100,000 in 1998 (528 cases) to 0.45 per 100,000 in 2011. Since 2011, the incidence of MenB disease has been quite stable with an incidence of 0.38 and 0.45 per 100,000 in 2015 and 2016 (65 and 77 cases). The reason for the large decline in MenB disease is unknown. Life style changes including the smoking ban from public places may have contributed to this decline (8). Although the decline in MenB disease coincides with the decline in MenC disease after 2002, the decline in MenB disease is not a consequence of introduction of MenC vaccination; vaccine induced antibodies against

MenC are not protective against MenB. The incidence of MenB disease is highest in children under 5 years of age; during the last 6 years the incidence in this age group was on average 3.4 per 100,000 per year. In 2015 and 2016, 19 and 26 MenB patients, respectively, were under 5 years of age (Figure 3). In 2016, serogroup B was still the dominant disease-causing serogroup in most age groups, with the highest incidence in children under 5 years of age (3.0 per 100,000) and a smaller peak in adolescents (0.77 per 100,000) (Figure 4). MenB disease is expected to rise again in the future when a new, more invasive, clone would expand.

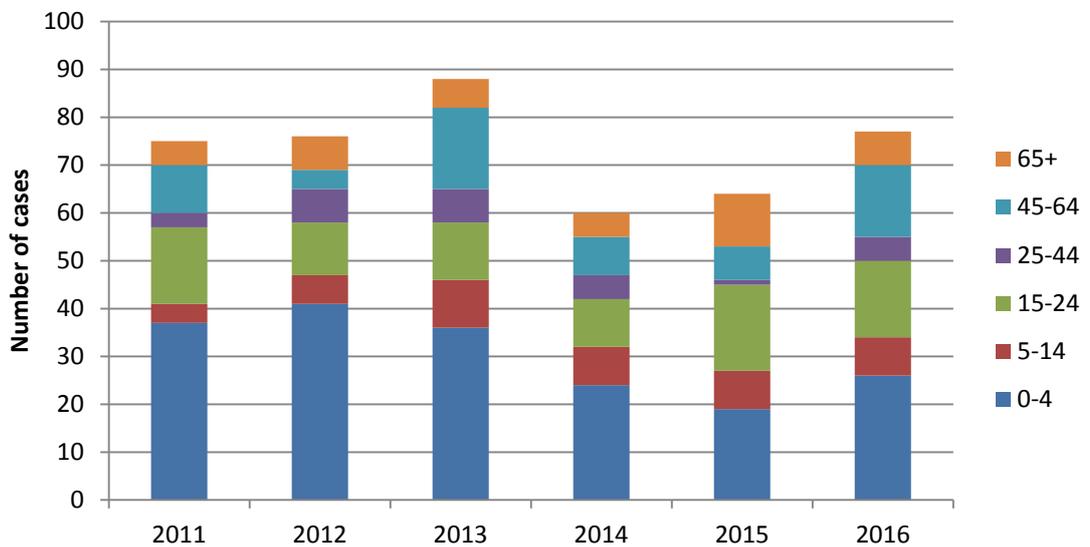


Figure 3 Number of cases with meningococcal serogroup B disease by age group during 2011-2016

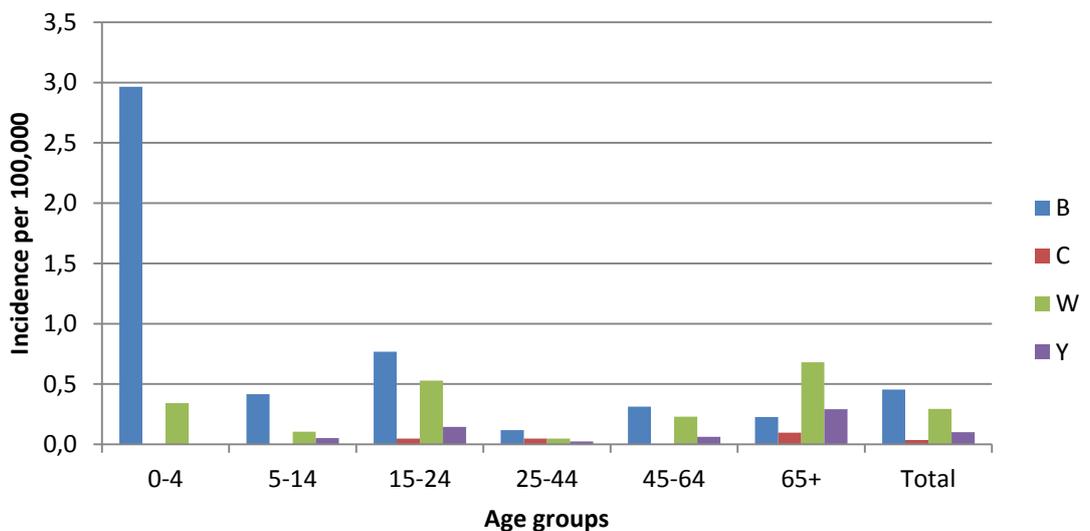


Figure 4 Incidence of meningococcal disease by serogroup and age group in 2016.

### 3.2.2 Meningococcal disease serogroup C

In 2001, a steep increase in MenC disease was observed in the Netherlands (incidence of 1.7 per 100,000; 277 patients; Figure 1) and there were several small clusters (9). At that time, the MenC incidence was highest among children under 5 years of age and adolescents. In response to the increase in MenC disease, a large vaccination campaign was set up in 2002 (June-December) in order to vaccinate all children between 14 months and 18 years of age with a conjugated monovalent MenC vaccine (NeisVac-C). In addition, MenC vaccination at the age of 14 months was introduced in the Dutch NIP in September 2002. The vaccination coverage of the catch up campaign was 94% (10) and the vaccination coverage of the MenC vaccination at 14 months has been around 95-96% since its introduction (11). After 2002, a steep decline in the number of MenC cases was seen in the vaccinated age groups as well as in all unvaccinated age groups through herd protection (12, 13).

During the last 6 years, three to eight MenC cases per year were observed (Figure 5), and during this period five cases younger than 5 years of age were notified. These children were all younger than 14 months of age and not yet vaccinated. Since the introduction of MenC vaccination in 2002, there have been four MenC cases who were vaccinated and were considered to be vaccine failures. These patients were diagnosed in 2009, 2010, 2011 and 2015 and they were 26, 19, 20 and 22 years old; none of the patients died and two patients had an immune disorder.

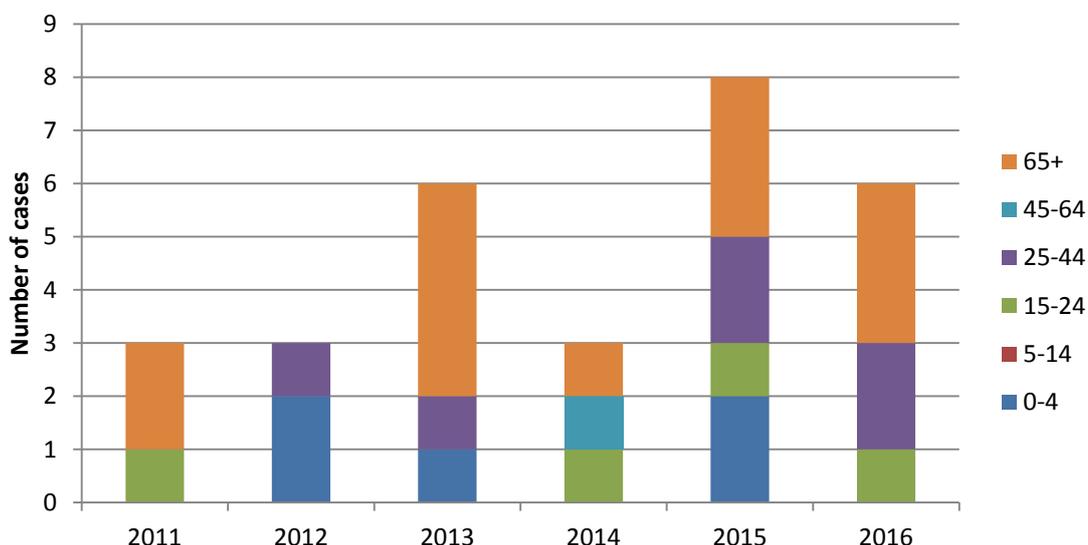


Figure 5 Number of cases with meningococcal serogroup C disease by age group during 2011-2016

### 3.2.3 Meningococcal disease serogroup W

The incidence of MenW was very low in the last decades (Figure 1). The years 1999 to 2001 showed a small increase in MenW incidence, due to an outbreak associated with the Hajj pilgrimage to Saudi Arabia (7, 14). On average four MenW cases per year were seen during the period 2003 to 2014 (average incidence: 0.02 per 100,000 per year). In 2015, the number of MenW cases increased to 9 (incidence: 0.05 per 100,000), a

doubling of cases compared with the period 2003 to 2014. In 2016, the number of MenW cases increased more than 10-fold to 50 cases, resulting in an incidence of 0.29 per 100,000. The proportion of serogroup W increased from 2.4% (48/2076 cases) in 2003-2014 to 10% (9/90) in 2015, and to 33% (50/151 cases) in 2016 (Figure 2). In 2016, the incidence of MenW disease was highest in persons of 65 years or older (0.68 per 100,000), followed by the 15-24 year olds (0.53 per 100,000) and <5 year olds (0.34 per 100,000) (Figure 4).

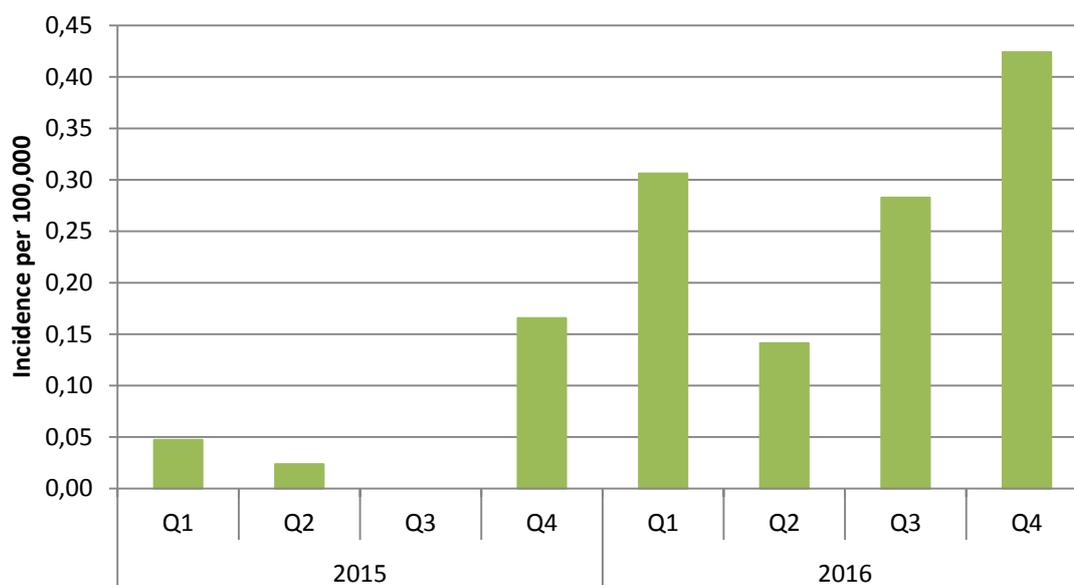


Figure 6 Incidence of meningococcal serogroup W disease by quarter in 2015 and 2016

The increase of MenW disease started in the fourth quarter (Q4) of 2015 (Figure 6). Of note, meningococcal disease has a seasonal trend with the highest incidence in the winter period (Q1). From July 2015 up to December 2016, 56 MenW cases were reported (Figure 7). Of these, four were under 5 years of age (7%), two were between 5 and 14 years (4%), 11 were between 15 and 24 years (20%), three were between 25 and 44 years (5%), 13 were between 45 and 64 years (23%) and 23 were 65 years or older (41%) (Figure 8). Six patients died (case fatality rate of 11%); their ages were 18, 20, 52, 61, 67 and 75 years. Most of the patients presented with sepsis (41%, n=21), 10 with meningitis (20%), and three with sepsis and meningitis (6%). The other patients had atypical presentations (n=17, 33%) including pneumonia (n=9), septic arthritis (n=2) and mild meningococemia (n=6). The three patients who died all had sepsis. There was no geographical clustering and there were no epidemiologically related cases. The majority of the strains were of finetype W:P1.5,2:F1-1 (48/52; 92%) and belonged to clonal complex 11 (37/41; 90%). Though the number of MenW cases is still relatively low with the highest incidence in older adults, the steep rise in MenW disease caused by this hyperinvasive strain is similar to the rapid increase in MenW disease in the UK caused by the same hyperinvasive strain (see for further details section 3.5.3). Also the age distribution, the distribution of clinical presentations and the case fatality rate are similar.

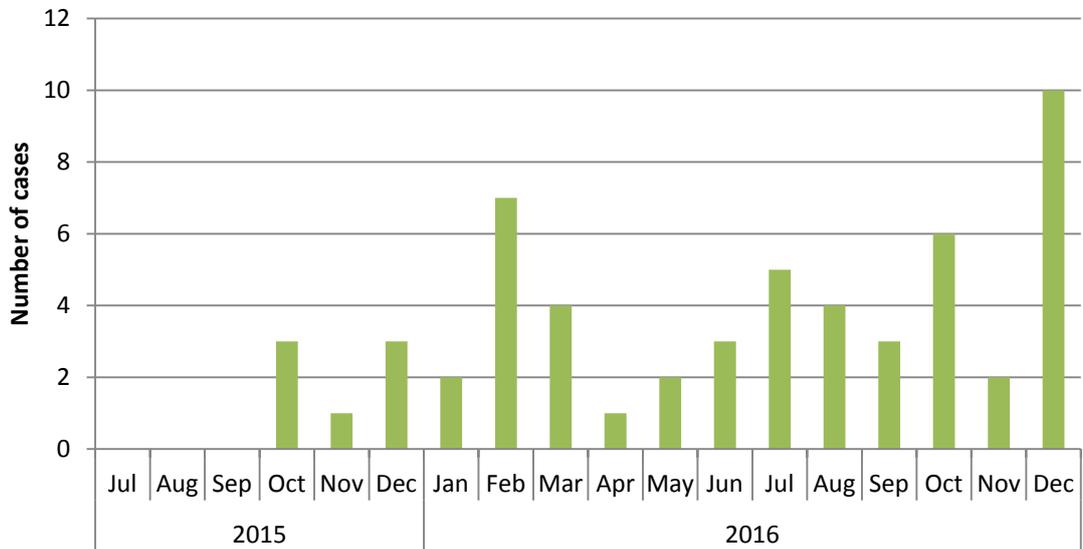


Figure 7 Number of cases of meningococcal serogroup W disease from July 2015 up to December 2016 (n=56)

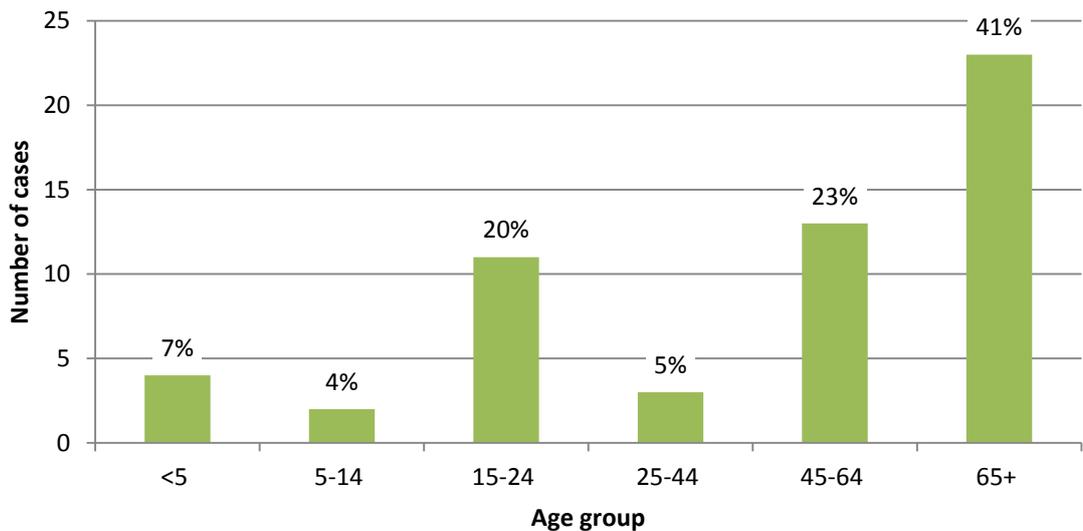


Figure 8 Number of cases of meningococcal serogroup W disease by age group from July 2015 up to December 2016 (n=56)

### 3.2.4 Meningococcal disease serogroup Y

The incidence of MenY is very low (<0.10 per 100,000 per year), although MenY increased slightly during the last years. There were on average 13 MenY cases per year during the last 6 years; in 2016 there were 17 cases of MenY (Figure 9). The number of MenY cases is highest in persons aged 65 years or older accounting for an incidence of 0.29 per 100,000 in 2016 (Figure 4).

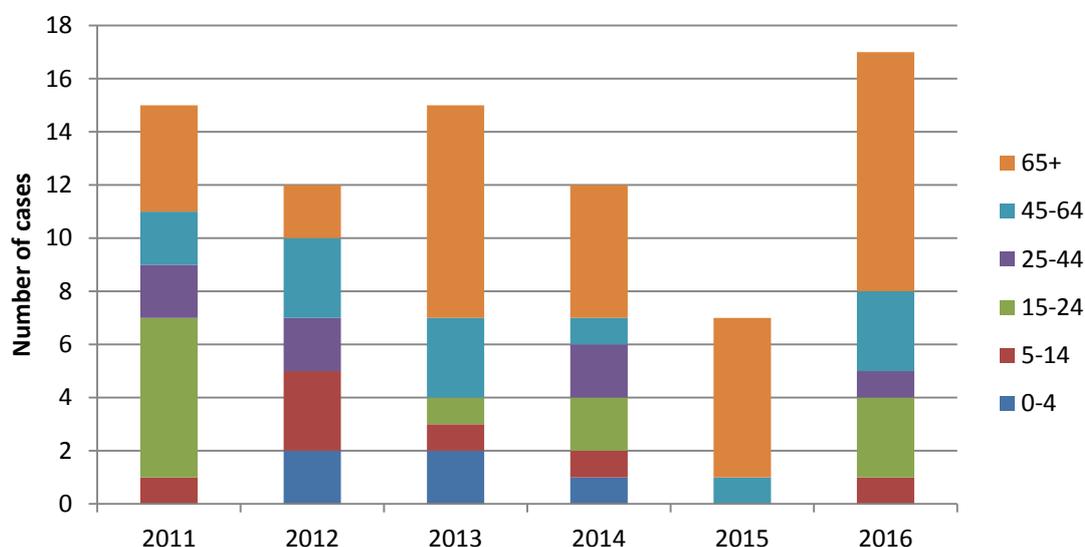


Figure 9 Number of cases with meningococcal serogroup Y disease by age group during 2011-2016

### 3.2.5 Meningococcal disease serogroup A

From 1992 to 2016 there have been only 15 cases of MenA disease in the Netherlands. Since 2004, there have been no cases of MenA disease.

## 3.3 Mortality and morbidity

Around 90% of the cases reported to the NRLBM can be linked to the notifications of the Municipal Health Services. Of these cases, clinical data on mortality (from 2004), clinical presentation (from 2015) and underlying diseases (from 2016) are available. The number of cases that died due to meningococcal disease decreased during the last years, because of the decrease in MenB incidence (Figure 10). The case fatality rate of meningococcal disease was 6% (111/1771) during 2004 to 2016. The case fatality rate for MenB was 5% (70/1430), for MenC 16% (13/83), for MenW 11% (10/94) and for MenY 14% (15/111). The case fatality rate was highest in cases of 65 years or older (15%; 31/208), attributing to the relatively high case fatality rate among MenC and MenY patients. Note that most meningococcal disease deaths in 2016 were due to serogroup W (n=6), resulting in a case fatality rate of 12% for MenW disease in 2016. This relatively high case fatality rate is similar to the case fatality rate during the current MenW outbreak in the UK (12%; see section 3.5.3).

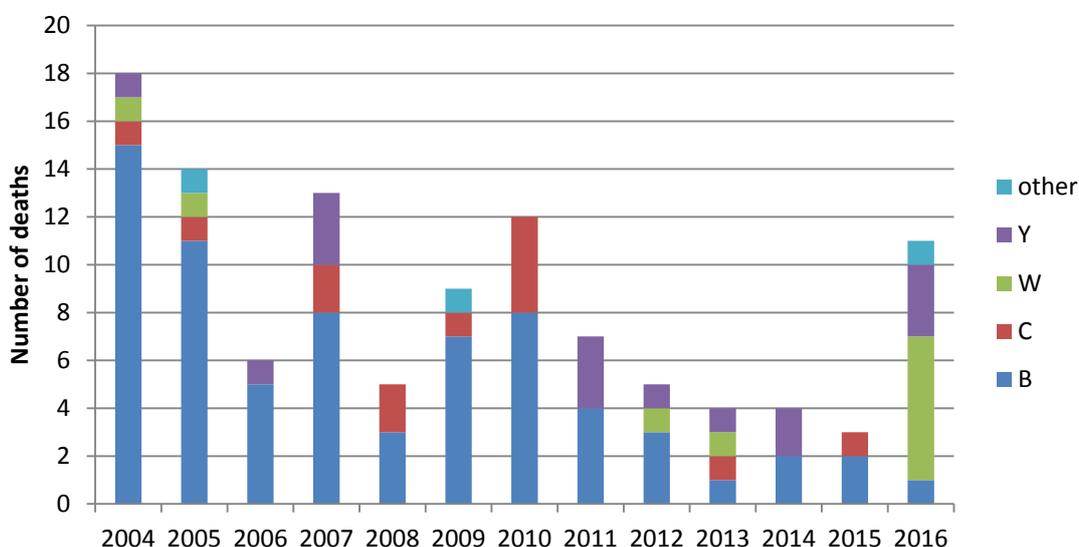


Figure 10 Number of deaths due to meningococcal disease by serogroup during 2004-2016 based on notification data

Stoof and others collected clinical data of patients with meningococcal disease diagnosed between June 1999 and June 2011 in one of the nine sentinel microbiological laboratories of the NRLBM (4). These nine sentinel laboratories are spread across the Netherlands and cover around 25% of the Dutch population. Clinical data were collected of 879 patients and included duration of hospital admission, ICU admission, mortality and sequelae. The median duration of hospitalization was 10 days (IQR: 8-13) and was highest among patients aged 65 years or older (15 days, IQR: 7-23). 38% of the patients was admitted to the ICU with a median duration of 3 days (IQR: 2-5). The case fatality rate in this study was 7.9%. Of all patients, 29% had sequelae, while 6% had at least one severe sequelae including amputation, deafness requiring cochlear implant, renal insufficiency, epilepsy and peripheral paralysis/paresis. In this study, there was no significant association between serogroup and case fatality rate or presence of sequelae after adjustment for age, clinical presentation and comorbidity. This study included mostly patients with MenB disease (77%) and MenC disease (19%).

### 3.4 Burden of disease

The burden of disease can be expressed in DALYs (disability adjusted life years), and is a combination of the number of patients and the mortality and morbidity of the disease. In 2015, the disease burden of meningococcal disease in the Netherlands was estimated to be 521 DALYs of which 38 YLDs (years lived with disability) and 483 YLL (years life lost) (15). For comparison, the estimated disease burden of invasive *Haemophilus influenzae* disease (644 DALYs) in 2015 was comparable to the burden of meningococcal disease, while the estimated disease burden of invasive pneumococcal disease in 2015 was 15 times higher (9292 DALYs). In 2016, the estimated disease burden of meningococcal disease was much higher than in 2015 amounting to 818 DALYs of which 59 YLD and 759 YLL. This increase was mainly due to the increase in

MenW disease in 2016. The estimated disease burden was highest for MenB disease (525 DALYs) followed by MenW disease (212 DALYs).

The number of DALYs per 100 infections reflects the severity of the disease and this was 558 for meningococcal disease. The number of DALYs per 100 infections was lower for invasive *Haemophilus influenzae* disease (301) and invasive pneumococcal disease (313), which denotes the severity of meningococcal disease.

### 3.5 Incidence in other countries

#### 3.5.1 *MenB disease*

Over the last 10 years, the incidence of MenB disease also decreased in other European countries. The MenB incidence in the EU/EEA decreased from 0.73 per 100,000 in 2007 to 0.31 per 100,000 in 2014 [ECDC – Surveillance Atlas of Infectious diseases, accessed Jan 2017]. A large decrease in MenB disease was seen in England with 1614 cases in 2000/2001 to 418 cases in 2014/2015 (16). This decline is likely due to natural secular trends and MenB incidence is expected to increase again in the future, due to, for example, the introduction of a new MenB strain into the population (16).

#### 3.5.2 *MenC disease*

Also in other countries MenC vaccination, introduced as a response to increased incidence, has proven to be very effective in reducing MenC incidence in vaccinated as well as unvaccinated age groups (17). The MenC incidence in 2014 in the EU/EEA countries, including countries with and without MenC vaccination, was very low with an incidence of 0.08 per 100,000 [ECDC – Surveillance Atlas of Infectious diseases, accessed Jan 2017].

However, during the last years there have been several clusters of MenC disease among men having sex with men (MSM). In 2013, there were clusters among MSM in Berlin and Paris (18, 19). In 2016, there was an outbreak of MenC among MSM in California (20). As far as we know, no MenC clusters among MSM have occurred in the Netherlands as of yet (21).

Additionally, MenC disease increased in 2015 and 2016 in Tuscany, Italy (22). From January 2015 to end February 2016, 43 cases were reported, of whom 10 died, compared with two cases in 2014 and three in 2013. The age group 20-29 years was most affected (n=15; IR: 3.9/100,000), followed by the age group 9-19 years (n=10; IR: 2.6/100,000). Five of 42 patients had been vaccinated with a meningococcal C conjugate vaccine. Thirty-five of the 40 strains analysed belonged to C:P1.5-1,10-8:F3-6:ST-11(cc11), which is the same type associated with several outbreaks among MSM in past years in various countries. A large MenC vaccination campaign has started in the Tuscany region in response to the outbreak. Of note, MenC vaccination was introduced in the Tuscany immunization schedule for infants in 2005 with a catch-up until six years of age, and a catch-up program for 11-14 year olds was implemented in 2007. At national level, MenC vaccination was introduced in the Italian National Immunisation Plan in 2012.

### 3.5.3

#### *MenW disease*

##### *United Kingdom*

Since 2009, the incidence of MenW disease has increased in the UK from 19 cases in 2008-2009 to 176 in 2014-2015 (incidence: 0.32/100,000), which was 24% of all meningococcal disease cases (23, 24). This percentage was 15% in 2013/2014, 7% in 2012-2013 and 1.7% in 2008-2009. First, the increase in MenW disease was mainly seen among elderly, but later on the incidence increased in all age groups, especially adolescents (15-19 years of age) and infants (<1 year of age). Clinical follow-up of MenW cases diagnosed from 2010-2011 to 2012-2013 in the UK showed that the majority of cases were previously healthy (81%) and that the case fatality rate was 12% (24). Patients were diagnosed with sepsis in 49% of the cases, meningitis in 12%, sepsis and meningitis in 16%, and 25% had an atypical presentation including pneumonia (12%), septic arthritis (7%) and epiglottitis/supraglottitis (4%).

A case review of 15 teenagers diagnosed with MenW disease between July 2015 and January 2016 in the UK revealed that seven teenagers presented predominantly with an acute history of gastrointestinal symptoms, and five of these seven cases died (25). This clinical presentation with predominantly gastrointestinal symptoms is rare and seems to be associated with the current outbreak strain in the UK. Gastrointestinal clinical presentation was also observed during the MenW outbreak in Chile in 14 of 58 MenW patients, and 8 of these 14 patients died (26). In the Netherlands, we have had one signal of a 68-year old patient presenting predominantly with gastro-enteritis who was diagnosed in December 2016 with meningococcal sepsis due to serogroup W. The patient was adequately treated and recovered.

The MenW isolates in England in 2014-2015 were predominantly PorB serotype 2a, a surrogate marker for clonal complex 11, and strongly related to finetype P1.5,2:F1-1 which is the finetype causing the majority of MenW cases in the Netherlands. Clonal complex 11 is also responsible for the current MenW outbreaks in South America (2, 27).

Because of the continuing rapid increase in MenW disease, the UK replaced the adolescent MenC conjugate vaccine for 13-14 year olds with the MenACWY conjugate vaccine in the Autumn of 2015 (16, 23) (see for further details section 5.2). In addition, catch up campaigns have been set up to give the MenACWY vaccine to all 13-18 year olds and new university admissions during 2015 to 2017.

The incidence of MenW disease in 2016 in the Netherlands (0.29 per 100,000) is rather similar to the MenW incidence in the UK in 2014-2015 (0.32 per 100,000). In addition, the case fatality rate (11% in NL, 12% in UK) and the percentage of patients with sepsis (41% in NL, 49% in UK) and an atypical presentation (33% in NL, 22% in UK) are rather similar. Also, the age distribution with most cases among elderly and a high incidence in adolescents is similar in the Netherlands and the UK. In the UK, the incidence was also high among young children (especially <1 years) but this occurred later during the outbreak. Therefore, in the Netherlands, we may expect to see an increase in young children in the coming months to years.

*Other European countries*

Also Spain reported an increase in MenW disease; the number of cases in the first half of 2016 was 2 times higher than in previous years (28). The majority of isolates was of finetype P1.5,2.

From personal communication with Public Health Institutes of other European countries, we know that several European countries other than the UK and Spain also observed an increase of MenW cases although the number of cases was small. Also in these countries the increase seems to be caused by the W:P1.5,2:F1-1:cc11 strain.

**3.5.4** *MenY disease*

The incidence of MenY disease in the EU/EEA countries is very low at the moment, although it increased from 0.02 per 100,000 in 2000 to 0.06 per 100,000 in 2011; from 2011 to 2014 the incidence stabilized [ECDC – Surveillance Atlas of Infectious diseases, accessed Jan 2017]. In several European countries including Switzerland, Norway, Finland and Sweden, the proportion of MenY was more than 20% of all meningococcal disease cases in 2011 (29).

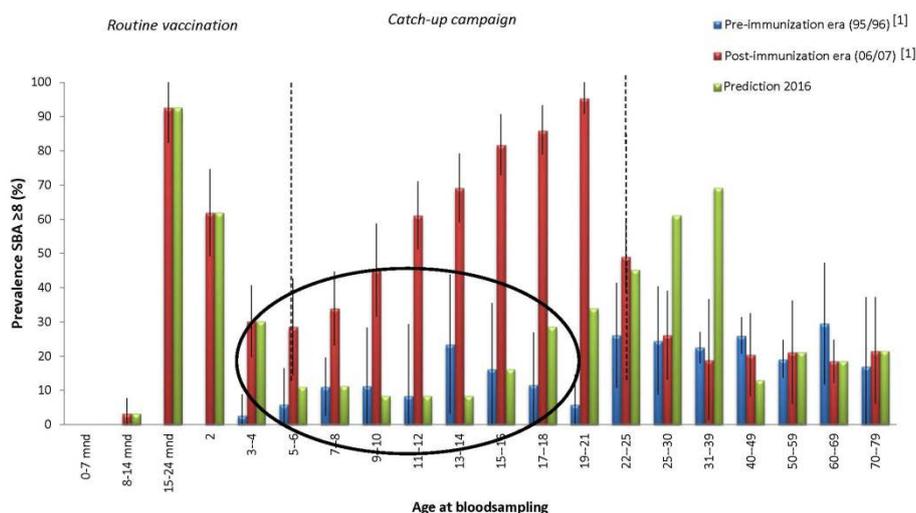
**3.5.5** *MenA disease*

In Europe, there are virtually no cases of MenA disease [ECDC – Surveillance Atlas of Infectious diseases, accessed Jan 2017]. However, in the African meningitis belt, which is considered to have the highest annual incidence of meningococcal disease in the world, serogroup A has been the most important cause of disease (30). However, since the introduction of a MenA vaccine specifically developed for this region (MenAfriVac) through mass campaigns, the incidence of MenA disease has now dramatically decreased (31). Between 1 January and 12 May 2013, there were 9249 suspected meningitis cases with a case fatality ratio of 9.3% (857 deaths) across 18 countries – the lowest number of cases recorded during the epidemic season in the last 10 years, with the majority of cases occurring during 2009 (31).

**3.6 Seroepidemiology**

The RIVM conducted cross-sectional sero-epidemiologic studies in 1995/1996 and 2006/2007, in which antibody levels were measured against the NIP diseases in a random sample of the Dutch population (Pienter1 and Pienter2 study) (32, 33). In these studies, circulating antibody levels against MenC appeared to decrease quickly after the MenC vaccination at 14 months of age (34) (Figure 11). It was also shown that children who were vaccinated at a higher age during the catch-up campaign in 2002 had higher antibody levels 5 years after the vaccination than children who were vaccinated at lower age. Currently, data are collected in the third sero-epidemiological study (Pienter3). Figure 11 presents the anticipated antibody titers against MenC in 2016/2017 (Pienter3 study). It is estimated that the percentage of adolescents that currently will have protective antibody levels against MenC is very low. High circulating antibody levels are important for protection against meningococcal disease because of the acute severity of the disease. Without sufficient circulating antibodies levels individuals are not protected against invasive meningococcal disease; i.e. a memory response is not fast enough to lead to timely presence of

sufficient antibody levels (17). Adolescents are, together with children under the age of five, at highest risk of MenC disease. The incidence of MenC, however, is currently very low in the Netherlands, so apparently herd protection is still present. It is difficult to predict how long this herd protection will last.



[1] de Voer et al. *PLoS ONE* (2010)

Figure 11 Prevalence of protective antibody levels ( $SBA \geq 8$ ) by age group during the pre-immunization era (1995/1996) and post-immunization era (2006/2007), and estimated prevalence in 2016/2017

### 3.7 Carriage

Meningococcal carriage is relatively low in young children (4.5%) and increases during childhood up to a peak of 24% in 19 year olds (3). Subsequently, carriage decreases to about 8% in 50 year olds. A large carriage study was conducted in the Netherlands during 2013 and 2014 (the so-called Carmen study)(35). Oropharyngeal swabs and questionnaires were collected from 1715 Dutch adolescents and young adults aged 13-23 years. A meningococcal isolate was identified in 270 subjects (16%) by culture. The most prevalent serogroups identified by whole-genome sequencing were MenB (4%), MenX (2%) and MenY (2%). Carriage of MenW and MenC was very low. Carriage was age-dependent with a sharp increase before the age of 15 years and related to life style including smoking.

A carriage study in the UK carried out during 2011 and 2012 among 10-25 year olds showed MenB carriage of 6.5% and MenY carriage of 5.5% (36). Carriage of MenC and MenW was very low (<2.0%).

The studies in the Netherlands and the UK were both conducted before the increase of MenW disease. Currently, it is unknown what the carriage rate of MenW is. Of note, even during a MenC outbreak in Putten, the Netherlands, in 1998, MenC carriage in 2-20 year olds was low (1.7%), although it was higher than in Venlo (0.5%) where no MenC cases were reported (37). Also in the UK, MenC carriage was very low (0.45%) before introduction of MenC vaccination while MenC incidence was high (38). However, MenC carriage rates decreased significantly to

0.15% after introduction of MenC vaccination. This shows that carriage rates do not necessarily have to be high in case of an outbreak with hyperinvasive strains that may only colonize the oropharynx for a very short time.

The UK currently performs a meningococcal carriage study, the UKMenCar4 study, which will provide new carriage rates of MenW during the current MenW outbreak.

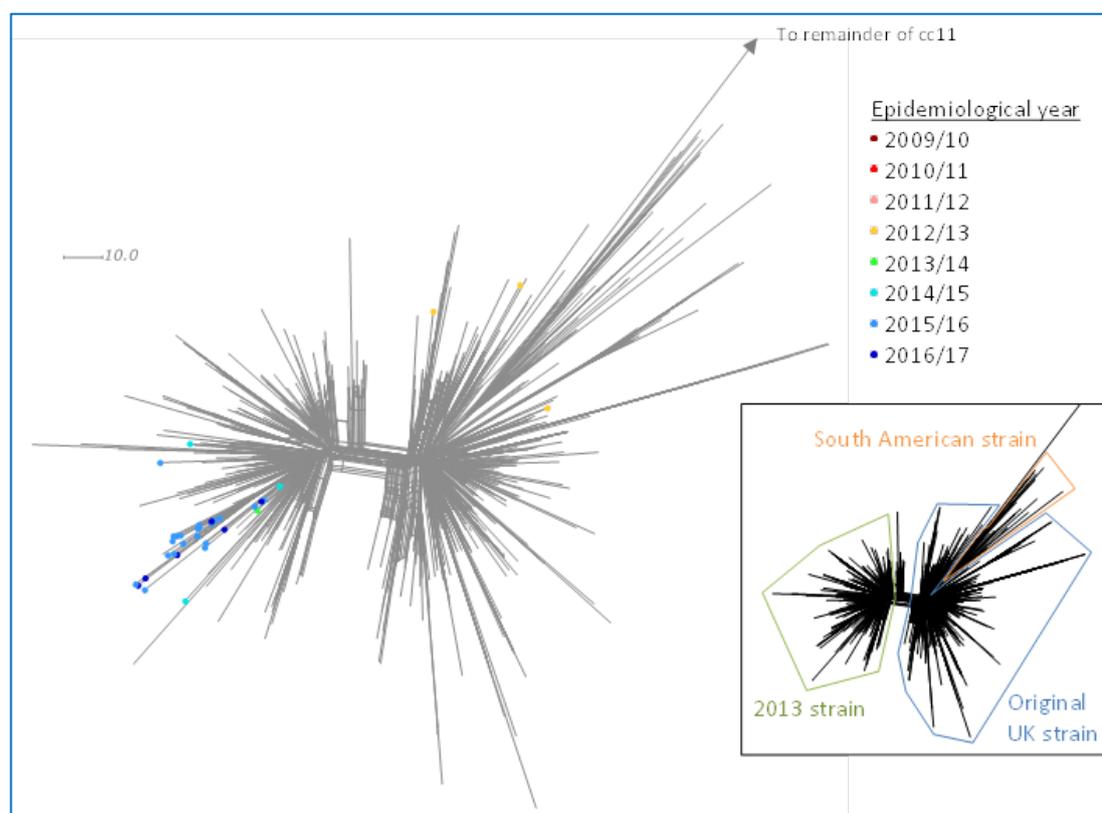


Figure 12 Neighbour-net phylogenetic network based on a comparison of 1546 core genome loci of MenW:cc11 South American strain sublineage isolates by epidemiological year in the Netherlands, 2009-2010 to 2016-2017\*. The insert indicates the position of individual strains within the South American strain sublineage. \*Up until 27/09/2016 in the Netherlands.

### 3.8 Genomic analyses of MenW

The increase in MenW in the UK was initially due to the rapid expansion of a single strain belonging to the sequence type (ST-) 11, which is part of the ST-11 clonal complex (cc11) (24). Genomic analyses of geotemporally diverse meningococcal cc11 strains of various serogroups showed that the vast majority of W:cc11 isolates belonged to cc11 lineage 11.1 following what is believed to be a single capsular switching event occurring prior to 1970 (2, 39). There are two main divergent sublineages of lineage 11.1, the Hajj strain sublineage and the South American strain sublineage (2). The Hajj strain sublineage includes the Hajj strain that caused a global Hajj-associated outbreak in the early 2000s. The South American strain sublineage includes the South American strain that emerged in 2003 in Southern Brazil, spreading to Argentina and Chile. In 2009, this strain was first found in the UK.

Recent genomic analyses showed that in 2013 this original UK strain diversified into a new strain, now called the '2013-strain' (40). The incidence of this 2013-strain increases more rapidly than the incidence of the original UK strain.

In the Netherlands, the South American strain sublineage emerged in 2012-2013 causing three cases of MenW disease, but it disappeared in the years afterwards (Figures 12 and 13). In contrast, the 2013-strain, first found in the Netherlands in 2013-2014 got established and is causing the current, rapidly evolving outbreak of MenW disease. Within this outbreak, we observed a distinct genetic cluster responsible for 20 cases in 2015-2016 and July-September 2016 (Figure 12).

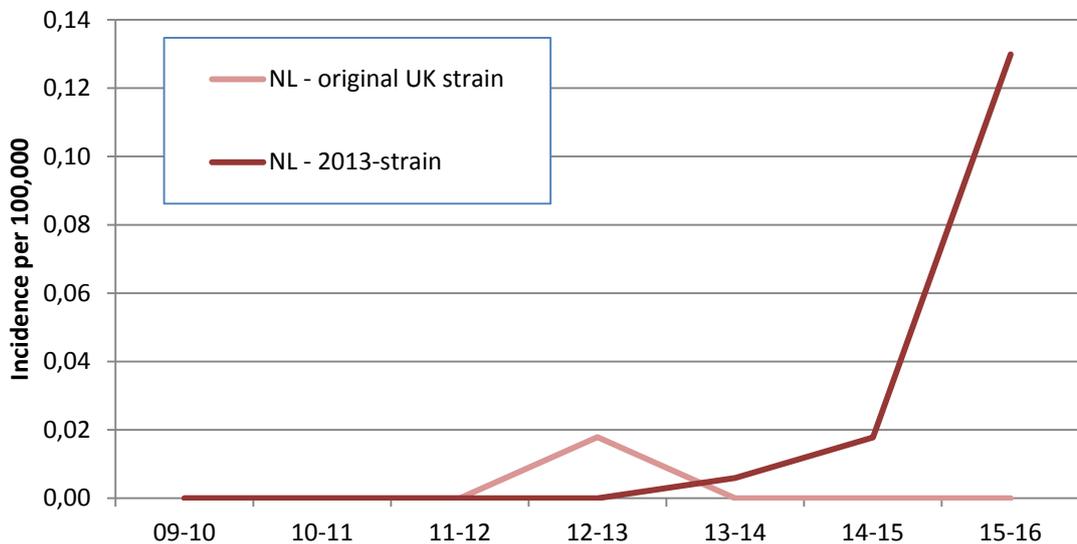


Figure 13 Incidence of invasive meningococcal serogroup W disease caused by the W:cc11 original UK strain and 2013-strain by epidemiological year in the Netherlands, 2009-2010 to 2015-2016.

## 4 Vaccines against meningococcal disease

### 4.1 MenC vaccines

There are three monovalent serogroup C conjugate vaccines: Menjugate (MCC-CRM197), Meningitec (MMC-CRM197) and NeisVac-C (MCC-TT) (for a description of the vaccines see (41)). NeisVac-C is used in the Dutch NIP. All MenC conjugate vaccines are licensed for children older than 2 months, adolescents and adults. The vaccines have been licensed based on immunogenicity using the validated correlate of protection of an rSBA (rabbit complement Serum Bactericidal Antibody) titer of 8 (42, 43). A cut off of 128 is used for long-term protection. Clinical efficacy studies have not been performed, because of the low incidence of meningococcal disease.

#### 4.1.1 Immunogenicity

In a study in which all three MenC conjugate vaccines were compared, NeisVac-C gave the highest antibody levels 12 months after a booster dose in infants (44). A study performed at the RIVM showed a very good immune response after a MenC booster vaccination in 10-, 12- and 15-year olds even up to 1 year (45). A follow-up study showed that antibody levels were still high 3 years after the booster vaccination (46). Long-term protection (>50 years) of a booster dose is especially expected in 12- and 15-year olds.

#### 4.1.2 Vaccine effectiveness

The MenC conjugate vaccines have been shown to be very effective in NIPs (41). The UK reported a vaccine effectiveness of 92% in infants, 89% in toddlers (47) and 97% in adolescents (48). In the Netherlands, the MenC incidence decreased with 99% in the vaccinated age groups (49). Currently, the number of MenC cases in the Netherlands is very low (<10 cases per year), and there have been only 4 patients with vaccine failure since the introduction of vaccination (15). However, antibody levels decrease quickly after the MenC vaccination at 14 months, and therefore in the Netherlands many older children and adolescents are at risk because their antibody levels have decreased below the protective threshold (see also section 3.6).

#### 4.1.3 Safety

The MenC conjugate vaccines are very safe. No serious side effects are known. Mild side effects including redness, swelling, pain and fever can occur and can last for 1 to 3 days (50-54).

### 4.2 MenACWY vaccines

There are two quadrivalent conjugate vaccines licensed in Europe which protect against serogroup A, C, W and Y: Menveo (MenACWY-CRM197) and Nimenrix (MenACWY-TT). Nimenrix is licensed for individuals of 6 weeks and older and Menveo is licensed for individuals of 2 years and older. Both vaccines are available in the Netherlands.

#### 4.2.1 *Immunogenicity*

Both the MenACWY-CRM vaccine and the MenACWY-TT vaccine give a good immune response in infants and young children (55, 56), and in adolescents (57).

In a randomized controlled study performed by the RIVM, the quadrivalent MenACWY-TT vaccine (Nimenrix) was compared with the monovalent MenC-TT vaccine (NeisVac-C) in healthy children aged 10-, 12- and 15-years, who had been primed once with NeisVac-C [Van Ravenhorst et al, submitted manuscript]. MenC antibody levels one year after the booster were higher in the MenC-TT vaccine group compared to the MenACWY-TT vaccine group. Nevertheless, 99% of all participants maintained MenC rSBA titers  $\geq 128$  up to one year after the vaccination. One year after receipt of the MenACWY vaccine, 94% of the participants maintained rSBA titers  $\geq 128$  against MenA, MenW and MenY.

A study from the UK compared antibody responses between the MenACWY-CRM vaccine and the MenACWY-TT vaccine in teenagers primed with different MenC conjugate vaccines at preschool age (58). Postboosting, both MenACWY vaccines induced protective SBA titers to all four serogroups in almost all participants ( $\geq 98\%$  at 1 month and  $\geq 90\%$  by 9 months postboost). The highest MenC SBA titers were seen in those MCC-TT-primed and MenACWY-TT-boosted.

#### 4.2.2 *Vaccine effectiveness*

MacNeil and others provide an early estimate of the effectiveness of the MenACWY-D vaccine (registered in US but not Europe) within 3 to 4 years among adolescents in the US (59). They used a simulation approach and estimated an effectiveness of 80 to 85% based on 14 vaccine failure cases. A recent study from the same group in the US showed overall vaccine effectiveness 0 to 8 years after MenACWY-D vaccination of 69% (60). Vaccine effectiveness waned over time with 79% effectiveness at  $< 1$  year after vaccination, 69% at 1-3 years after vaccination and 61% at 3-8 years after vaccination. There are no data yet about the effectiveness of the other two MenACWY vaccines, which are registered in Europe, because they have been introduced just recently in NIPs of a few countries.

#### 4.2.3 *Safety*

Several studies were performed to explore the safety profile of MenACWY-CRM (61-63), MenACWY-TT (64, 65) and MenACWY-D (66, 67). In these studies, all vaccines were well tolerated with no attributable serious adverse events, when given as a single dose, 2 dose series or booster dose. Furthermore, the co-administration of MenACWY-TT with routine childhood vaccines had a clinically acceptable safety profile (68).

Despite differences in composition, the MenACWY-CRM and MenACWY-TT vaccines had a comparable reactogenicity profile (58, 69). Also, up to 5 years after administration of MenACWY-TT or MenACWY-PS, no vaccine-related serious adverse events were reported (70, 71).

However, recently Tseng et al observed a temporal association between occurrence of Bell's palsy and receipt of MenACWY-CRM concomitantly given with other vaccines in a cohort aged 11 to 21 years (72). The association needs further investigation as it could be due to chance, concomitant vaccination, or underlying medical history predisposing to Bell's palsy.

### 4.3 MenB vaccines

There is one MenB vaccine licensed in Europe called Bexsero. The vaccine is registered for use in individuals of 2 months or older. Bexsero is a multicomponent protein vaccine and it includes three proteins (fHbp, NadA and NHBA) and the outer membrane vesicles (OMV) from the New Zealand outbreak strain, which incorporates the immunodominant Porin A (porA) P1.4 protein (73). While the vaccine is registered to prevent MenB disease, it may also protect to some extent against meningococcal disease caused by other serogroups (16). Specifically, one of the components of Bexsero (neisserial adhesion A, NadA) is found on the surface of the emergent MenW:cc11, and therefore this vaccine may also provide protection against the currently circulating MenW strains. Although Bexsero is licensed in the Netherlands, it is at present (January 2017) not available. There is a shortage in the supply of the vaccine doses and all available doses are distributed in the UK, as Bexsero is included in their NIP. As the production process of the vaccine takes two years, it takes a while before scaling up the production leads to larger supplies. Bexsero will at least not be available in the Netherlands in the coming year.

Another MenB vaccine called Trumenba (Pfizer) is licensed in the US for individuals aged 10 through 25 years. The European Medicines Agency (EMA) is currently evaluating the Marketing Authorization Application for Trumenba. It is expected to be registered in Europe and the Netherlands in June-July 2017.

In the remainder of this chapter, we focus on Bexsero as this vaccine is registered in Europe and because it is the only vaccine registered for infants.

#### 4.3.1 *Vaccine coverage*

To determine how many MenB patients can be prevented by the vaccine, Meningococcal Antigen Typing System (MATS) is used. This technique can predict which proportion of the circulating MenB strains is covered by the MenB vaccine. A study from 2007 and 2008 in five European countries showed that the MenB vaccine covers 73-87% of the circulating MenB strains (74). Frosi et al predicted 88% coverage against a diverse panel of MenB strains from patients in England and Wales (75). However, in a recent university outbreak in the USA, only 66% of the participants who received two doses of the MenB vaccine were seropositive for the outbreak strain, which was predicted by MATS to express two vaccine antigens (76). The latter study therefore suggests lower strain coverage of the MenB vaccine.

#### 4.3.2 *Immunogenicity*

Vesikari and others studied the hSBA response against the four vaccine components in infants vaccinated with the MenB vaccine at 2, 4, 6 and 12 months of age (77). At 12 months, before the booster dose, the percentage of infants with an hSBA titer  $\geq 5$  was 80%, 100%, 20% and 65% against fHbp, NadA, OMV PorA and NHBA, respectively. At 13 months, one month after the booster, these percentages were 100%, 100%, 90% and 95%, respectively, for the four vaccine antigens, showing good protection. Antibodies waned over 12 months, particularly for OMV PorA for which only 15% of infants had hSBA titer  $\geq 5$  one year after the booster dose. Another study assessing immune responses in

infants who received the MenB vaccine at 2, 3, 4 and 12 months of age showed similar percentages of infants with hSBA titers  $\geq 5$  pre-booster and one month after the booster (78). Although the level of protection after three primary doses and a booster dose of MenB vaccine are adequate, SBA titers after the MenB vaccine are much lower than for meningococcal polysaccharide conjugate vaccines including the monovalent MenC vaccines or quadrivalent MenACWY vaccines.

#### 4.3.3 *Vaccine effectiveness*

The UK introduced MenB vaccination into their NIP in September 2015 in a reduced dose schedule at 2, 4 and 12 months of age. First results of the effectiveness and impact of the program have been recently published (79). Vaccination coverage was high with 95% for one dose and 89% for two doses by 6 months of age. Using the screening method, the estimated vaccine effectiveness of two doses was 83%. Vaccine effectiveness of one dose was 22%. Compared with the prevaccine period, the incidence rate decreased with 50%; in the vaccine eligible age group, 37 MenB cases were reported since the program started, while on average 74 cases were reported in the same period during the previous 4 years. When adjusting for the decreasing trend of MenB disease before implementation of vaccination, the incidence rate reduction was 36-42%.

It is uncertain whether MenB vaccination provides herd protection. A randomized controlled trial among students aged 18-24 years in England showed that MenB vaccination significantly reduced overall meningococcal carriage with 18.2%, from 3 months after the second dose (80). A non-significant reduction of 15.6% was observed for serogroup B carriage. It is unknown whether this reduction is enough to provide herd protection, although for pathogens with a low estimated basic reproduction number, including *N. meningitidis* ( $R_0$  about 1.36), even a modest individual carriage effect might translate into a significant level of herd protection (80).

#### 4.3.4 *Safety*

The MenB vaccine is reported to have an acceptable safety profile, although local reactions including pain, redness, swelling and fever were commonly reported (77, 81, 82). Especially if the MenB vaccine was concomitantly administered with other vaccines, local reactions including fever were common (83). Therefore, the UK advises to give prophylactic paracetamol to infants when receiving the MenB vaccine and routine vaccines concomitantly. Previous research showed that prophylactic paracetamol decreased the immune response against several antigens including tetanus, pneumococcal serotypes and hepatitis B (84, 85). In a recent clinical trial, however, immune responses after the MenB vaccine and concomitantly administered DTaP-HBV-IPV/Hib vaccine were not decreased by the use of prophylactic paracetamol (78). One severe adverse event was reported after administration of the MenB vaccine concomitantly with two routine vaccinations in a 5-month-old infant (86). This child developed prolonged upper extremity dysfunction, which resolved after treatment within two months.

## 5 Target population for vaccination

In this chapter, we describe the possible target groups for MenC, MenACWY and MenB vaccination. To determine the best target group both individual protection as well as herd protection needs to be taken into account.

### 5.1 MenC vaccination

#### *Current situation*

MenC vaccination is included in the NIP at 14 months of age. MenC incidence is currently very low probably due to herd protection from the catch-up campaign in 1-18 year olds in 2002. As also described in sections 3.6 and 4.1, antibody levels decline quickly after the MenC vaccination at 14 months of age, leading to low protective levels against MenC in adolescents.

#### *Aim of vaccination*

In the current situation with low incidence but also low immunity in the population, the aim of MenC vaccination would be to maintain herd protection. As overall meningococcal carriage is highest among adolescents, vaccinating this age group would likely maintain herd protection against MenC disease. When herd protection is sustained, e.g. through adolescent vaccination, a MenC vaccination at 14 months of age will most likely not contribute to herd immunity while direct protection is not needed.

#### *Other countries*

In the UK, a MenC booster for adolescents was introduced in 2013 to prevent an increase in MenC incidence (87). This was a pre-emptive precautionary approach to maintain indirect protection, based on serological data and modelling predictions (17). Several other European countries also introduced a MenC booster vaccination for adolescents, including Austria, Greece, Ireland and Spain [ECDC vaccine scheduler, accessed Jan 2017]. MenC vaccination in infancy was maintained in these countries.

### 5.2 MenACWY vaccination

#### *Current situation*

MenACWY vaccination is not included in the NIP. It is recommended for individuals who have an increased risk of infection with one of the four serogroups, for example pilgrims of the Hajj or individuals with asplenia or complement deficiency. The MenW incidence in the Netherlands is currently increasing rapidly (from 0.02/100,000 in 2003-2014 to 0.29/100,000 in 2016; 0.42/100,000 in the last quarter of 2016), and was, in 2016, highest in adolescents and young adults (15-24 year age group: 0.53 per 100,000) and in persons aged 65 years or older (0.65 per 100,000) (Figure 4). The MenW incidence in children <5 years is currently still low (0.34 per 100,000), but this is likely to change in the near future. In the UK, a rise in MenW disease in infants was observed only after the increase in MenW disease among elderly followed by adolescents. In the Netherlands, the same pattern is expected, leaving

children younger than 5 years of age and in particular under 1 year of age highly vulnerable.

#### *Aim of vaccination*

In the current situation with a rapidly increasing incidence of MenW, the aim of vaccination would be to directly protect the age groups with the highest incidence and to establish herd protection to indirectly protect other age groups. Targeting adolescents and young adults and also elderly would give direct protection to the age groups with at present the highest incidence. Also infants could be targeted as the MenW incidence is expected to rise in this age group in the near future. Additionally, as meningococcal carriage is highest among adolescents, vaccinating adolescents and young adults could provide herd protection by reducing carriage acquisition and transmission, thereby protecting other age groups against MenW disease. However, this will take some time, e.g. after the MenC vaccination campaign in 2002 it took one to two years before MenC disease decreased in all age groups.

#### *Other countries*

Because of the continuing rapid increase in MenW disease, the UK replaced the adolescent MenC conjugate vaccine for 13-14 year olds with the MenACWY conjugate vaccine in September 2015 (16, 23). In addition, catch up campaigns have been set up to give the MenACWY vaccine to all 13-18 year olds and new university admissions during 2015 to 2017. The rationale for this decision was that the number of cases continued to increase in an accelerating manner, and that it was very plausible that the trend in incidence would continue in a similar way as was seen with the MenC:cc11 outbreak in the 1990's (88). Moreover, the confirmation of the relatedness of the strain, circulating in the UK, to the South American strain (see section 3.8), which was associated with particularly high case fatality rates, contributed to the decision. In addition, although the MenW outbreak first caused cases in older adults, later on cases were seen in all age groups and deaths occurred in infants, toddlers and adolescents.

Two other European countries, Austria and Greece, have also included MenACWY vaccination for adolescents in their NIP [ECDC vaccine scheduler, accessed Jan 2017].

### **5.3 MenB vaccination**

#### *Current situation*

MenB vaccination is not included in the NIP. The MenB incidence has decreased dramatically from 2000 to 2010 and has been quite stable during the last five years (incidence of 0.5 per 100,000). The MenB incidence is highest among children under 5 years of age (3.0 per 100,000 in 2016), and especially in children under 1 year of age (8.2 per 100,000 in 2016), followed by 15-24 year olds (0.77 per 100,000 in 2016) (Figure 4).

#### *Aim of vaccination*

In the current situation with the highest incidence among infants, young children and adolescents, the aim of vaccination would be to directly protect children up to the age of 5 years, in particular those under one year of age, and adolescents. It is uncertain whether MenB vaccination

will give herd protection as only a modest and non-significant decrease in MenB carriage has been shown after MenB vaccination (80).

*Other countries*

The UK is the only European country that introduced MenB vaccination in their NIP at 2, 4 and 12 months of age. It is expected that MenB vaccination will also provide (some) protection against meningococcal disease caused by other serogroups, and also specifically MenW:cc11, in this age group because of cross protection.



## 6 Cost-effectiveness

### 6.1 MenC vaccination

In 2001, the cost-effectiveness of routine MenC vaccination at 14 months and of a catch up campaign for all persons aged 14 months to 18 years was estimated (89). The cost-effectiveness ratio for routine vaccination at 14 months was €1900 per QALY gained and for the catch up programme it was €15,000 per QALY gained; both from a societal perspective.

The cost-effectiveness of a MenC booster vaccination in adolescents cannot be calculated because there are currently virtually no MenC cases in adolescents and very few cases in other age groups. The UK removed an infant dose of MenC (MenC was given at 2, 4 and 13 months) to adolescents and therefore implementation of an adolescent MenC booster vaccination was cost-neutral. In the Netherlands, we give one MenC dose at 14 months so we would have to remove the single dose from childhood to adolescence to be cost-neutral.

### 6.2 MenACWY vaccination

Cost-effectiveness analysis of MenACWY vaccination for adolescents has not been performed in the Netherlands with the current number of MenW (and MenY) cases. In 2013, Hepkema et al. evaluated the cost-effectiveness of meningococcal vaccination at 14 months and an additional vaccination at the age of 12 years, both with a MenACWY vaccine (90). Vaccination with MenACWY at 14 months was found to be cost-saving, because a MenACWY vaccine dose was assumed to be cheaper than a MenC vaccine dose (43 vs 55 euros). Using meningococcal incidence data from 2007-2011, a booster dose with MenACWY resulted in an ICER (incremental cost-effectiveness ratio) of €635,334 per QALY gained, and was therefore not cost-effective. A threshold analysis was performed to determine the overall incidence of serogroups A, C, W and Y meningococcal disease which is required for vaccination to have an ICER of €50,000 per QALY gained. When assuming herd protection against serogroup A, W and Y disease, the overall incidence of serogroups A, C, W and Y meningococcal disease should be 0.4-0.6 per 100,000 to reach an ICER of €50,000 per QALY gained when comparing MenACWY vaccination at 14 months and at adolescence to MenC vaccination at 14 months. In 2016, the overall incidence of serogroups A, C, W and Y meningococcal disease was 0.44 per 100,000 with an increasing trend.

In the UK, the MenC booster was replaced by the MenACWY vaccine in adolescents for a similar price. Moreover, because introduction of MenACWY vaccination was seen as an outbreak control measure in the UK, assessment of cost-effectiveness was not needed in the UK, in contrast to UK's policy for routine vaccination where cost-effectiveness is needed.

### 6.3 MenB vaccination

Pouwels et al. assessed in 2013 the cost-effectiveness ratio of vaccinating infants in the Netherlands with the MenB vaccine (91). They

found that routine infant vaccination in a four-dose schedule could prevent 39 cases of MenB disease in a single birth cohort, corresponding to a total gain of 133 QALYs. However, this strategy was not cost-effective at vaccine costs of €40 per dose (€243,778 per QALY gained). Only if the MenB disease incidence increases or the vaccine price drops substantially below €40, routine infant vaccination has the potential to be cost-effective.

In the UK, it was found that an infant MenB vaccination program could be cost-effective (threshold of £20,000-£30,000) in a four-dose schedule only if the vaccine price was very low (92-94). To make the program more cost-effective, it was decided that a 3-dose schedule instead of a 4-dose schedule could be used. Furthermore, an infant dose of MenC vaccination was removed. The UK managed to procure the MenB vaccine at a cost-effective price as MenB vaccination was implemented in the UK in 2015.

Several other European countries recently evaluated the cost-effectiveness of a MenB vaccine for use in individuals of 2 months of age and older. Gasparini et al. assessed the cost-effectiveness of vaccinating Italian infants less than 1 year of age with 4 doses (at 2, 4, 6 and 12 months of age) as opposed to non-vaccination (95). Using a static cohort simulation model the ICER per QALY gained was €109,762 in the base case and €26,599 if underestimated cases were taken into account. However, Tirani et al. found universal vaccination would not be cost-effective, based on epidemiological data from the most populated Italian regions (Lombardia and Piemonte) (96).

A previously developed model for England was adapted to the German setting to predict the potential health impact and cost-effectiveness of universal vaccination against MenB disease (97). Vaccination strategies included infant and adolescent vaccination, alone or in combination. 65% vaccine uptake and 82% strain coverage were assumed. Under base case assumptions with a vaccine list price of €96.96 the ICER was >€500,000 per QALY gained for all considered strategies. Given the current very low incidence of MenB disease in Germany, universal vaccination would prevent only a small absolute number of cases, at high overall costs.

Lecocq et al. assessed the cost-effectiveness of five MenB vaccination strategies in France: infants at 3, 5, 6 and 13 months, toddlers at 13, 15 and 27 months and adolescents at 15 years provided two doses one month apart (98). A booster dose at 15 years old and a catch-up for 15 years old subjects during the first 15 years of the programme were added to the infant and toddler strategies. Under the assumption of herd immunity, the adolescent vaccination would provide the lowest costs per QALY gained (€135,902) preventing 24% of cases. Given the current meningococcal epidemiology in France and the available data on the efficacy of the vaccine, routine vaccination against serogroup B meningococcal disease was not considered cost-effective.

The cost-effectiveness of offering catch up vaccination with the MenB vaccine in addition to the recently introduced infant programme was assessed in England in 2016 (99). Vaccination of 1 year old children could be cost-effective with a vaccine price of ≤£8 per dose. Extending

vaccination to 2 year olds could only be cost-effective (incremental on infant and 1 year old catch-up) with a vaccine price of  $\leq$ £3 per dose  
Extending catch-up further to 3-4 year olds was not cost-effective.



## 7 Acceptance of vaccination

### 7.1 MenC vaccination

The vaccination coverage during the MenC catch up campaign in 2002 was high with an overall uptake of 94% (10). The coverage was 94-95% in the 1-4, 5-9 and 1-14 years age groups, and somewhat lower in the 15-18 years age group (89%). The vaccination coverage of the routine MenC vaccination at 14 months has been 95-96% since the start of the program (11). In the UK, coverage of the MenC adolescent booster was around 70-85% [personal communication with H. Campbell, Public Health England, 12 January 2017]. It may also be relevant to look at the vaccination coverage of HPV vaccination as this vaccine is also given to adolescents (only girls at 12 years). In the Netherlands, the current HPV vaccination coverage is 61% (11).

### 7.2 MenACWY vaccination

There is no reason to believe that acceptance or coverage of MenACWY vaccination will be different from MenC vaccination, as the vaccines are very similar and have a similar safety profile.

In the UK, coverage for the first cohorts to be routinely offered MenACWY vaccine in schools from September 2015 and evaluated up to the end August 2016 was 84.1% (Year 9) and 77.2% (Year 10) (100). Coverage for the catch-up cohort offered MenACWY vaccine through the school based programme (those born 1 September 1999 to 31 August 2000 (Year 11 in 2015/16)) and evaluated up to the end of August 2016 was 71.8%. In the first two school leaver groups, who were largely invited for vaccination by GPs, the MenACWY vaccine coverage has been quite low (around 30% and 38%) (101).

### 7.3 MenB vaccination

Three questionnaire studies have been performed by the RIVM about the acceptance of new vaccinations among parents with child(ren) <4 years old. In these questionnaires, also the intention to vaccinate against MenB disease was included. The reported positive intention to vaccinate against MenB disease was 83% in 2012 [Van Lier et al, manuscript in preparation], 72% in 2013 and 71% in 2015 when the vaccine would be given within the NIP (Figure 14). The percentage of participants with a positive intention to vaccinate against MenB disease was about 10% lower in case parents would have to pay for the vaccine. In all three studies, the reported positive intention was highest for MenB disease, when compared with Hepatitis A (2015: 69%), RSV infection (2015: 57%), rotavirus infection (2015: 54%), varicella (2015: 51%) and influenza (2015: 34%). MenB disease was also ranked highest by medical doctors and nurses of child welfare centres on a question of whether or not vaccination within the NIP is necessary (mean score of 4.63 on a 7-point Likert scale), when compared with RSV infection (mean score 4.50), rotavirus infection (mean score 4.13), varicella (mean score 3.09), and influenza (mean score 2.78) [Harmsen et al, manuscript submitted].

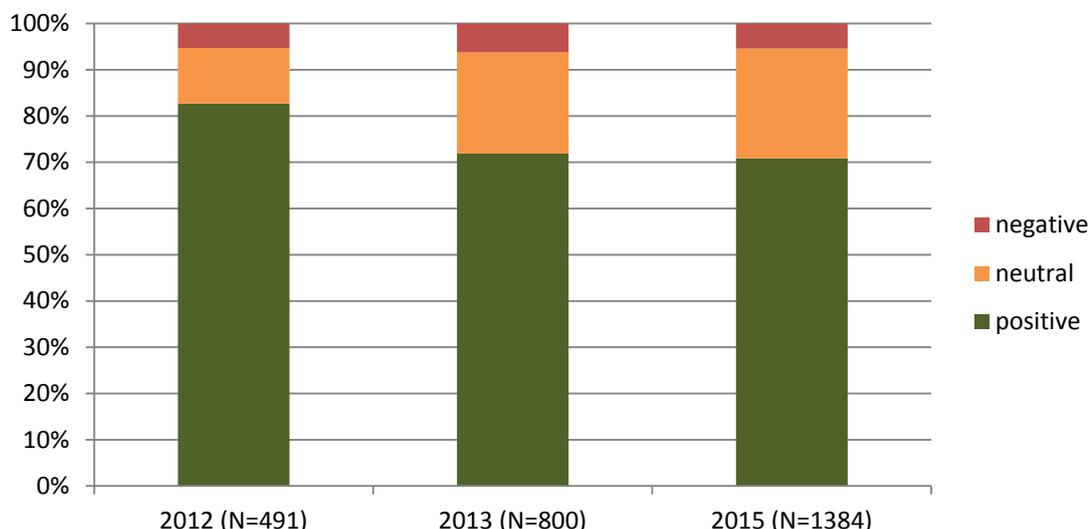


Figure 14 Intention to vaccinate against MenB disease within NIP by study.  
 \*In 2012 intention was measured on a 5-point scale (positive=score 4-5, neutral=score 3, negative=score 1-2); in 2013 and 2015 intention was measured on a 7-point scale (positive=score 5-7, neutral=4, negative=1-3).

In addition to intention to vaccinate, in 2012 parents were also asked about perceived severity of MenB disease, worries about side effects of MenB vaccination and the likeliness that their child would get MenB disease. The vast majority of respondents found MenB disease severe enough to vaccinate against (82%), and 66% of respondents thought that most parents would vaccinate their child against MenB disease (Figure 15). About one-third (36%) of respondents was worried about side effects of MenB vaccination and 7% of the respondents thought it was very likely that their child would get MenB disease.

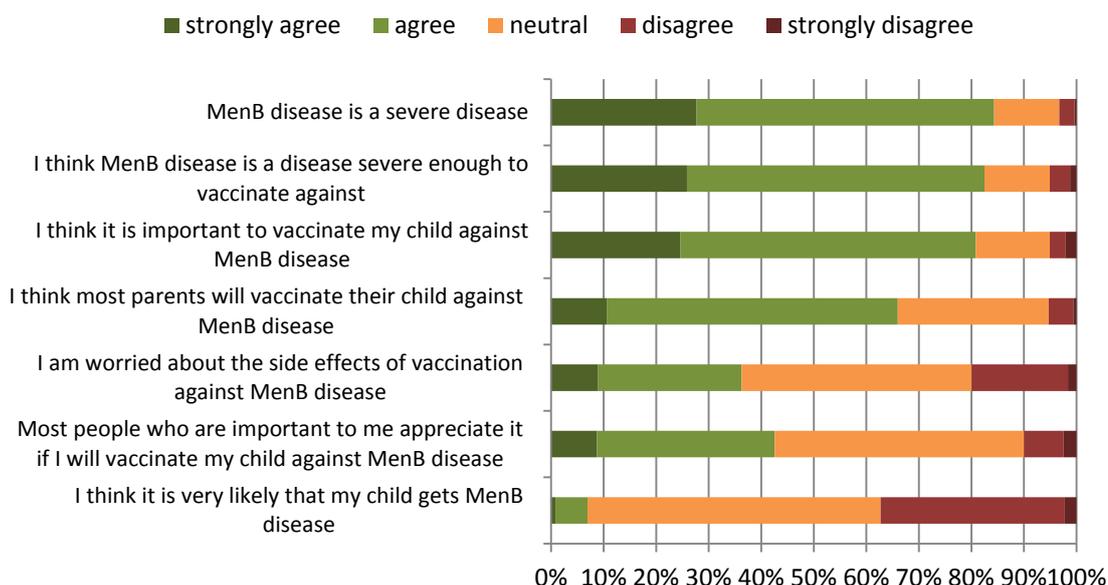


Figure 15 Agreement with statements on vaccination against MenB disease (study 2012, N=491)

Concomitant vaccination with the MenB vaccine and the DTaP-IPV-Hib-HepB vaccine increases the risk of mild side effects including fever (see also section 4.3). Therefore, an advice on prophylactic paracetamol could be considered. The risk of side effects as well as the advice to use paracetamol might negatively influence acceptance of MenB vaccination. This aspect was not explicitly addressed in the questionnaire studies described above.



## 8 Aspects of implementation

In chapter 5, the possible target groups for MenC, MenACWY and MenB vaccination were described based on the need for individual protection and herd protection against the different serogroups. In the current chapter, we use the information on the target groups to provide possible scenarios for meningococcal vaccination in the NIP. For MenW disease, we also take into account the rapidly increasing incidence at the moment, which may require additional outbreak strategies on top of the routine vaccination program.

### 8.1 MenC/MenACWY vaccination

#### 8.1.1 Possible scenarios

Based on the target groups for MenC/MenACWY as described in Chapter 5, there are three age groups to consider: adolescents (herd protection MenC/MenW, individual protection MenW), elderly (individual protection MenW) and infants (individual protection MenW). Additionally, we need to take into account the fact that children are vaccinated with a MenC vaccine at 14 months of age in the current NIP. A further consideration in describing possible scenarios is that herd protection is achieved only after multiple years when vaccinating a single birth cohort of adolescents or after 1-2 years when vaccinating multiple birth cohorts of adolescents at once through a catch up campaign, like the MenC catch-up campaign in 2002 in The Netherlands. The latter is especially useful in an outbreak situation.

Table 1 describes several possible scenarios, which are described in more detail below. Scenario 0 is the current situation with a MenC vaccination at 14 months of age. Scenarios 1 and 2 describe vaccination schedules for the routine NIP, whereas scenarios 3, 4 and 5 describe vaccination schedules that could be applied in an outbreak situation.

*Table 1 Possible scenarios for implementation of MenC and MenACWY vaccination in the routine program (above the dashed line) and in an outbreak situation (below the dashed line)*

Scenario	Description	Infants	14 months	Adolescents	Catch up	Elderly
0	Current	-	MenC	-	-	-
1	Herd C	-	MenC	MenC	-	-
2	Herd ACWY	-	MenACWY	MenACWY	-	-
3	Fast herd ACWY	-	MenACWY	MenACWY	MenACWY	-
4	Fast herd ACWY + infants	MenACWY	MenACWY	MenACWY	MenACWY	-
5	Fast herd ACWY + infants + elderly	MenACWY	MenACWY	MenACWY	MenACWY	MenACWY

#### 8.1.2 Scenario 1 – Herd protection MenC

In scenario 1, an adolescent MenC vaccination is added to the program with the aim to secure herd protection against MenC disease and provide

prolonged individual protection. Obviously, this scenario will not give protection against MenW and MenY disease. When herd protection against MenC is established with this vaccination schedule, it could be considered to leave out the MenC vaccination at 14 months since MenC will not circulate anymore.

### 8.1.3 *Scenario 2 – Herd protection MenACWY*

In scenario 2, a single adolescent MenACWY vaccination is added to the program, e.g. at 12 years of age. This scenario would secure herd protection against MenC and establish herd protection against MenW disease within several years. In addition, in this scenario the MenC vaccination at 14 months is replaced by MenACWY vaccination to protect young children against MenW disease. When herd protection against MenC and MenW is established with this vaccination schedule, it could be considered to leave out the MenACWY vaccination at 14 months as MenC and MenW will not circulate anymore.

#### *Age of adolescent MenC/MenACWY vaccination*

Studies performed at the RIVM showed that high antibody levels remain for many years after a MenC booster at ages 12 and 15 years and that immune responses against MenACWY vaccination are higher in 12- and 15-year olds compared with 10-year olds (46)[Van Ravenhorst et al, manuscript submitted]. Of children who were vaccinated with a MenC vaccine at 12 and 15 years of age during the catch up campaign in 2002, 85% and 95% had SBA titers  $\geq 8$  at 4 to 5 years after vaccination, respectively (34). These data show that also a single MenC vaccination at adolescence will provide protection for several years. Currently, HPV vaccination is offered to girls at 12 years of age. In 2017, the Health Council will prepare an advice considering HPV vaccination of boys. Combining the MenC/MenACWY booster with the HPV vaccination at 12 years of age might be possible; a study that investigated concomitant use of the 9-valent HPV vaccine (Gardasil) and a quadrivalent MenACWY vaccine (Menactra) found no interference between the two vaccines (102). It is unclear how combining these vaccines might influence the coverage of HPV (current coverage 61%). It is anticipated that the coverage of MenC/MenACWY will be 70-90% based on data from the catch up campaign for MenC in 2002 in the Netherlands and the present vaccination coverage of MenC/MenACWY in adolescents in the UK.

### 8.1.4 *Scenario 3 – Fast herd protection MenACWY*

Scenario 3 includes an additional catch up campaign for adolescents vaccinating multiple birth cohorts at once. This scenario would provide immediate individual protection in this age group with high MenW incidence, and herd protection could also be quickly established (within two years) against MenC and MenW disease for adolescents and other age groups.

#### *Age range for catch up program*

During the current MenW increase, MenW cases have occurred among adolescents from 15 years of age up to 22 years of age. A Dutch carriage study among 13-23 year olds performed in 2013 and 2014 showed that carriage increased with age; this increase already started before the age of 15 years (35). Therefore, the catch up program should preferably start before 15 years of age, e.g. 12 years. Meningococcal

carriage is high in secondary school students because of their life style, so the catch up program should at least include adolescents up to 18 years of age. Also college and university students have relatively high meningococcal carriage and disease rates because of their life style, and therefore a broader age range of 12 years up to 22-25 years might provide optimal herd protection and prevention of disease. A broader age range will probably yield more and faster herd protection. In the UK, all 13-18 year olds, and all unvaccinated university entrants up to 25 years of age are offered MenACWY vaccination.

#### 8.1.5 *Scenario 4 - Additional individual protection MenW infants*

The incidence of MenW disease is rapidly increasing at the moment and the incidence among young children, and especially infants, is expected to increase in the near future. Even with a catch up campaign for adolescents (and young adults) it would take one to two years to establish herd protection against MenW (Scenario 3). A single MenACWY vaccination at 14 months might offer only protection for a few years, and vaccination at 14 months is too late to protect infants. Therefore, the adolescent catch up program could be combined with MenACWY vaccination in infants (Scenario 4). Two infant vaccinations with a booster around 12-15 months would then be the optimal schedule. At present in the Netherlands, it is customary to give not more than two injections at one visit. Taking this into account, two priming doses of a MenACWY vaccine could be given at 3 and 5 months of age, with a booster dose at 14 months. An additional visit to the well-baby clinic is then needed at 5 months. Infant MenACWY vaccination could be a temporary outbreak control measure until herd protection against MenW is established.

Note that although carriage rates in young children are presumed to be low, young children are generally important transmitters of colonizing strains, and therefore herd protection may also be expected when vaccinating young children.

In the UK, infants are potentially protected against MenW disease by the current MenB programme, as the vaccine possible also offers some cross protection against other meningococcal strains, in particular cc11 strains (16).

#### 8.1.6 *Scenario 5 - Additional individual protection MenW elderly*

Currently, the incidence of MenW disease is highest among elderly. Therefore, MenACWY vaccination could be also offered to elderly (Scenario 5). However, as the age of elderly patients with MenW disease varies widely (in 2016: median of 75 years, range between 67 and 89 years), it is not straightforward which age cohort should be targeted. In addition, immune responses in older adults between 50-65 years of age after a single MenACWY vaccination are good but not as high as the responses in adolescents for MenAWY and the duration of protection is probably shorter [unpublished data from RIVM study]. As carriage is likely to be low in elderly and transmission may be low due to life style factors, vaccinating elderly will probably not result in herd protection. Alternatively, MenACWY vaccination could be offered to elderly on an individual basis. Similar to the infant MenACWY vaccination, MenACWY vaccination in elderly could be a temporary outbreak control measure until herd protection against MenW is established.

## 8.2 MenB vaccination

To provide protective antibody levels in infancy against MenB, two or three primary vaccinations are needed in the first year of life combined with a booster vaccination between 12 and 15 months of age, and possibly a booster for adolescents. In the UK, MenB vaccination is given in a reduced dose schedule at 2, 4 and 12 months of age.

As described above, at present in the Netherlands, not more than two injections at one visit are given. A study among 1154 Dutch parents with children between 0-12 years showed that most parents would experience three vaccine injections per visit as too much (mean score 5.3; 69% with score >4; based on a 7-point Likert scale) (103). In addition, parents indicated to prefer an extra visit instead of more than two vaccine injections at the same time (mean score 5.6; 77% with score >4). Taking a maximum of two injections at one visit into account, the MenB vaccine could be given at 3, 5 and 12 months. Concomitant vaccination with the MenB vaccine and the DTaP-IPV-Hib-HepB vaccine does not negatively influence the immune response but increases the risk of mild side effects including fever (see also section 4.3).

Taking into account the maximum of two injections, the MenACWY vaccine and MenB vaccine cannot be given simultaneously at 3 and 5 months. However, infant MenACWY vaccination may only be needed for a short period until herd protection against MenW is achieved, and the MenB vaccine is at least not available in the Netherlands in the coming year. In addition, it is expected that MenB vaccination provides some protection against disease caused by other meningococcal serogroups (16), and also specifically to MenW:cc11 strains. Therefore, if MenB vaccination would be implemented, MenACWY vaccination in infants as described in section 8.1.7 as an outbreak control measure may not be necessary. So in the advice on the vaccination program against MenC and MenW disease, it is relevant to take into account the MenB vaccination strategy.

Although MenB vaccination is currently not included in the Dutch NIP, parents can decide to vaccinate their children against MenB on their own costs (if it were available). To this purpose, information on MenB vaccination for professionals (factsheet) and the public (Q&A) is available on the RIVM website (developed as part of the project "Vaccinatie op maat").

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**RIVM**

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