Vaccine impact and effectiveness of meningococcal serogroup ACWY conjugate vaccine implementation in the Netherlands: a nationwide surveillance study

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Summary: The MenACWY vaccination programme in the Netherlands was effective in preventing invasive meningococcal W disease in the target population during an epidemic.
ABSTRACT

Background

In response to the recent serogroup W invasive meningococcal disease (IMD-W) epidemic in the Netherlands, meningococcal serogroup C (MenC) conjugate vaccination for 14-month-olds was replaced with a MenACWY conjugate vaccination, and a mass campaign targeting 14-18 year-olds was executed. We investigated the impact of MenACWY vaccination implementation in 2018-2020 on incidence rates and estimated vaccine effectiveness (VE).

Methods

We extracted all IMD cases diagnosed between July 2014 and December 2020 from the national surveillance system. We calculated age group-specific incidence rate ratios by comparing incidence rates before (July 2017-March 2018) and after (July 2019-March 2020) MenACWY vaccination implementation. We estimated VE in vaccine-eligible cases using the screening method.

Results

Overall, IMD-W incidence rate lowered by 61% (95%CI 40-74). It declined by 82% (95%CI 18-96) in vaccine-eligible age group (15-36 month-olds and 14-18 year-olds) and by 57% (95%CI 34-72) in vaccine non-eligible age groups. VE was 92% (95%CI -20-99.5) against IMD-W vaccine-eligible toddlers. No IMD-W cases were reported in vaccine-eligible teenagers after the campaign.

Conclusions

The MenACWY vaccination programme was effective in preventing IMD-W in the target population. The IMD-W incidence reduction in vaccine non-eligible age groups may be caused by indirect effects of the vaccination programme. However, disentangling natural fluctuation from vaccine-effect was not possible. Our findings encourage the use of toddler- and teenager MenACWY vaccination in national immunization programmes especially when implemented together with a teenager mass campaign during an epidemic.

Keywords: invasive meningococcal disease, meningococcal ACWY vaccination, vaccine impact, vaccine effectiveness, herd immunity
INTRODUCTION

*Neisseria meningitidis*, a Gram-negative bacterium with a polysaccharide capsule that confers the specific serogroup, is an important cause of meningitis and septicaemia [1]. Worldwide, invasive meningococcal disease (IMD) is most often caused by serogroup A, B, C, W, X and Y [2]. The meningococcus can be carried asymptomatically in the nasopharynx, but can also act as harmful pathogen when crossing the mucosal barriers. Carriage rates are high in teenagers, which is attributed to factors like social behaviour including kissing and crowding [3, 4]. Although teenagers show low incidence rates in most infectious diseases [5], they are disproportionately affected by IMD, together with young children. On average, 1 in 10 patients dies from IMD in countries with excellent health care [6]. Furthermore, survivors may experience severe sequelae like deafness and limb amputation despite proper medical treatment [7]. Meningococci elude most of the host innate immune response and IMD can develop within hours. Hence, the host cannot rely on memory mechanisms that are important for a cellular response. Thus, circulating antibodies, together with the complement system, are essential for bacterial killing [8]. Vaccination is the best strategy to prevent disease by inducing such protective antibodies. The majority of currently applied meningococcal vaccines induce the production of antibodies that specifically target the meningococcal polysaccharide capsule.

A recent IMD serogroup W (IMD-W) epidemic in the Netherlands led to dozens of disease cases in individuals of all ages with a high mortality rate [9], caused by meningococci belonging to the hyperinvasive clonal complex 11 (cc11) [10]. This cc11 was already known for its ability to cause IMD-W epidemics in other countries such as the United Kingdom [11, 12]. To halt the epidemic, the meningococcal serogroup C conjugated to tetanus toxoid (MenC-TT) vaccine for toddlers was replaced by the MenACWY-TT vaccine in May 2018. In addition, a mass campaign in 2018-2019 targeting 14-18 year-olds (birth cohort 2001-2005) was implemented and the quadrivalent vaccine was introduced for all 14-year-olds in the NIP as from 2020. This strategy aimed to directly protect these teenagers from disease and also limit transmission through this group [9].

Meningococcal vaccines are registered based on a serological correlate of protection that reflects the vaccine-induced immune response [13]. The reason is that rare diseases like IMD do not allow the use of clinical endpoints in pre-licensure studies that investigate vaccine efficacy directly. Consequently, post-licensure observational studies are necessary to evaluate effectiveness and impact of meningococcal vaccination [14]. Previous studies have proved that a mass campaign with a MenC conjugate vaccine targeting children can limit
an epidemic [15]. However, comprehensive data on MenACWY vaccine effectiveness is lacking and it is unknown whether vaccinating only 14-18 year-olds restricts a national outbreak and induces herd immunity.

In this paper, we describe the impact of the MenACWY vaccination programme in the Netherlands between 2018-2020. We determined the impact of vaccination in different age groups by comparing nationwide incidence rates before and after the mass campaign, thereby investigating both direct and indirect protection. We report estimates of the vaccine effectiveness in vaccine-eligible toddlers and teenagers in the Netherlands.

METHODS

IMD surveillance in the Netherlands

The national IMD surveillance system is based on two data sources: the notifications from the Regional Public Health Service (RPHS) and the laboratory data from the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM, Amsterdam UMC, Amsterdam, the Netherlands). Data from these two sources are linked on a national level by the National Institute for Public Health and the Environment. In short, the notification of a case with clinical information from the RPHS, combined with a report of microbiological data including the serogroup from the NRLBM, results in a complete overview of all nationally occurring IMD cases. Linking between the two sources was possible for 87% of all unique records, as described previously [16].

A case was defined as a positive sample from a sterile site either confirmed by culture, by PCR or both. Vaccination status of each case was obtained from the national vaccination registry. Cases were only included in mortality analyses if the outcome status was known. A vaccine failure was defined according to the WHO guidelines as follows: a laboratory-confirmed meningococcal case with onset more than 10 days after the scheduled dose of the vaccine targeting the respective disease-causing serogroup [17]. The national electronic vaccination register monitors the vaccination status for all children up to 18 years. The routine coverage in 14-month-olds was estimated at 93%, based on yearly published vaccine coverage data from this register [18]. The vaccine coverage within the teenager mass campaign was previously estimated at 86% [19].
Periods for impact analyses

Epidemiological years were used to describe IMD cases from 2014-2020, with a year starting at July 1 and ending June 30 the year thereafter. The period of quartile 3 (Q3)-2017 until Q1-2018 was chosen as period before implementation because of corresponding length and seasonal characteristics as the period after implementation (Figure 1). The period also reflects the epidemiology of disease during the epidemic well. By only including the period during the peak of the IMD-W epidemic, the risk of underestimating the impact was limited. The period after implementation was defined as starting Q3-2019 and ended at Q1-2020 to limit interference of the measures taken, starting close to Q2-2020, to control the COVID-19 pandemic. Data from Q2-2020 until Q4-2020 were also analyzed to determine the effect of the COVID-19 containment measures on IMD incidence. A sensitivity analysis repeated the before-after analyses but additionally included Q2-18 and Q3-2018 in the period before implementation, in order to evaluate to what extent the chosen period affected the estimated impact (Figure 1). This sensitivity period included the period when the MenACWY-TT vaccine was already implemented for 14-month-olds but the mass campaign for teenagers had not yet started.

Statistical analysis

The impact of the MenACWY vaccination campaign was analyzed by comparing incidence rates per 100,000 individuals per year in periods before and after implementation (Figure 1), expressed as incidence rate ratio (IRR). We estimated the impact for different serogroups within different age groups and for the whole population. We calculated 95% confidence intervals (CIs) of IRR by use of a Poisson regression model. Age groups were categorized in accordance with the vaccination programme, 15-36 month-olds and 14-18 year-olds being defined as vaccine-eligible age groups while under 15 months of age, 3-13 years and above 19 years were defined as vaccine non-eligible. Since IMD-B is not targeted by the vaccine, this serogroup was included in the impact analysis as means of a negative control.

The vaccine effectiveness (VE) was assessed for laboratory-confirmed IMD-W cases in vaccine-eligible children. Vaccine-eligibility in toddlers was defined as born on or after March 1, 2017 and diagnosed at the age of 14 months or older between May 1, 2018 and December 31, 2020. Vaccine-eligible teenagers were born between January 1, 2001 and December 31, 2005 and diagnosed between July 1, 2019 and December 31, 2020.
at an age of 14 years or older. We calculated the VE by comparing the proportion of cases vaccinated to the proportion of the population vaccinated in the studied cohort, which is the vaccine coverage in the respective cohort, using the screening method [20] with the following formula:

\[ VE = 1 - \frac{PCV}{1 - PCV} \times \frac{1 - PPV}{PPV} \]

with PCV = proportion of cases vaccinated in the studied cohort and PPV = proportion of population vaccinated

Data on population size was obtained from Statistics Netherlands to calculate incidence per population time. Population data for 2020 was not yet available at time of analyses (January 2021), therefore population data from 2019 was used to calculate population size for 2020. Statistical analyses were performed using Excel, GraphPad Prism 8 and SPSS Statistics 24.

RESULTS

A total of 884 IMD cases was reported in a 6-year period from 2014-15 until 2019-20 (Figure 2). IMD cases were predominantly caused by serogroup B in 2014-15 (Figure 2) and the years before (data not shown). While only 5 cases of IMD-W were observed in 2014-15, it was the most common serogroup in 2017-18 with 104 cases. IMD-C has rarely been observed since the introduction of MenC vaccination in 2002, with only a few cases occurring throughout the studied years (Figure 2). IMD-Y accounted for 12% (n=109) of all cases in the period 2014-15 to 2019-20, whereas IMD due to other serogroups like IMD-E and IMD-X, and non-groupable IMD accounted for a few cases per year (data not shown). In the studied period, IMD-A was never reported. The largest proportion of fatal IMD-W cases in the study period occurred in 2017-18 (47%; 22 out of 47 cases). Of 22 deceased cases in 2017-18, 13 (59%) were adults aged 45 or older and 6 were individuals aged between 14-24 years. In 2019-20, only 3 fatal IMD-W cases were reported.

While IMD-W cases were rare and only observed in adults in 2014-15, incidence started to increase in 2015-16 with highest incidence in children under 15 months of age, albeit low absolute numbers (Figure 3). In 2016-17, incidence increased particularly in 14-18 year-olds (0.20 to 1.07 per 100 000) followed by a rise in incidence in
almost all age groups in the year thereafter. Children under the age of 36 months were disproportionally affected during the peak years although the absolute number of cases was highest in middle-aged adults and elderly (Figure 3). The number of cases dropped in 2018-19 in all age groups except in the 14-18 year-olds, with 13 cases that year compared to 10 cases the year before. Over the years, the number of cases and incidence rates were continuously low in 3-13 year-olds and 25-44 year-olds.

Already during the mass campaign, the incidence in vaccine-eligible groups rapidly declined (Figure 4). After the mass campaign, the IMD-W incidence rate had declined in all age groups (Table 1). The most pronounced reduction was observed in vaccine-eligible 14-18 year-olds with 8 cases before implementation and zero after implementation. Older age cohorts (adults 45-64 years and 65 years and older) also showed a significant decrease in incidence and the overall IRR for the vaccine non-eligible age groups was 0.43 (0.28-0.66).

After implementation of the MenACWY vaccination, IMD-Y cases were absent in age groups eligible for vaccination, in contrast to two cases in the period before implementation (Table 1). In vaccine non-eligible age groups, no difference was observed in IMD-Y incidence (IRR 0.92). Although IMD-C cases were already rare and only observed in individuals 45 years of age and older, there were even less cases after implementation of MenACWY vaccination (5 before, 1 after). Overall, the impact on total MenACWY cases was larger in vaccine-eligible age groups than in vaccine non-eligible age groups, IRR = 0.15 (0.03-0.68) and IRR = 0.50 (0.35-0.72), respectively, though all age groups showed a decreasing incidence (data not shown). The incidence of IMD-B did not change in vaccine-eligible age groups and decreased slightly but not significantly in vaccine non-eligible age groups.
A sensitivity analysis was carried out by including two additional quartiles (Q2-2018 and Q3-2018) to the period before implementation and showed that IRRs did not change when the analysed period included this extended period before implementation (Supplementary Table 1). The incidence of IMD-W during COVID-19 containment measures (Q3-Q4 2020) was lower than in Q3-Q4 2019 (Figure 4), a period just after implementation of the vaccination with the same seasonal characteristics but before COVID-19 measures were taken (Figure 1). The incidence of IMD-B also decreased during the time COVID-19 measures were in place, although the decrease in non-eligible age groups was less pronounced than for IMD-W and IMD-Y (Table 2).

The estimated vaccine effectiveness for one dose of MenACWY-TT in 14-month-olds against IMD-W was 92% (95% CI: -20-99.5). Two IMD-W cases occurred in this eligible cohort, both older than 14 months at time of diagnosis and eligible for vaccination based on date of birth (being born after March 2017). One case was vaccinated 16 months prior to becoming ill, and one was unvaccinated. No IMD-W cases were observed in teenagers eligible for vaccination, therefore VE could not be estimated in this cohort. For the other serogroups included in the vaccine (serogroup ACY), it was also not possible to estimate the VE due to the lack of cases in both vaccine-eligible cohorts.
DISCUSSION

In response to a national IMD-W epidemic in the Netherlands, MenACWY vaccination was implemented in the NIP for toddlers from April 2018 onwards and teenagers from October 2018 onwards, together with a mass campaign for 14-18 year-olds between October 2018 and June 2019. In this study, we evaluated IMD cases in the Netherlands from 2014-15 onwards, at the time the IMD-W epidemic emerged and the NIP consequently was adjusted to counter the epidemic. We found an overall 61% decrease in IMD-W incidence, and even higher reduction of cases of 82% in vaccine-eligible toddlers and teenagers, already within the first year after the mass campaign was completed. The VE in toddlers was 92%; only one vaccinated toddler became ill with IMD-W. No cases were observed in teenagers after the mass campaign, thereby precluding an estimate of VE in this cohort. Whereas incidence of the vaccine-preventable serogroup Y did also decrease in the vaccine-eligible cohort, there was hardly any decline in IMD-Y in vaccine non-eligible age groups (IRR 0.92) in the first three quartiles after completion of the mass campaign.

A catch-up programme in the UK between 2015-2017 provided the MenACWY vaccination to all 13-18 year-olds [21]. Despite a low coverage of 36.6% in the first cohort to be vaccinated, 69% fewer IMD-W cases were observed than were predicted to occur without intervention during the first 12 months of the teenager MenACWY vaccination programme [22]. Comparable to our findings in toddlers, the early estimated VE in teenagers in that study was 100% for IMD-W, but with wide confidence intervals (-47-100) due to small numbers. A study from Chile showed a 92% reduction in IMD-W cases in the first four years after the mass campaign in the MenACWY vaccinated cohort that consisted of young children aged 9 months to 4 years [23]. Indirect effects were not yet observed one year after vaccination in Chile; the lack of infants and teenagers in the target group was given by the authors as possible explanation. Several European countries reported an increase in IMD-W during the years 2013-17, however, the Netherlands was among the most strongly affected countries [12], and one of the few that implemented the MenACWY vaccination in response to the epidemic. In less affected countries, implementation was considered but often not recommended by National Immunization Technical Advisory Groups for benefit, risk, and cost reasons.
Most studies that investigated the effectiveness of the monovalent MenC conjugate vaccine reported similar VE results to what we observed for the quadrivalent MenACWY conjugate vaccine. According to a systematic review that studied meningococcal transmission and disease in adolescents, MenC-TT effectiveness was approximately 90% within the first year post-vaccination [24]. The effectiveness of MenC-TT in the routinely vaccinated cohort in England (three doses given to 2-4 month-olds) was 93% within one year of the scheduled vaccination [25]. In Italy, a major reduction of cases was observed after a single dose of MenC-TT was provided at an age of 13-15 months since 2005, with some regions carrying out mass-campaigns with either MenC or MenACWY conjugate vaccinations in the years thereafter [26]. Overall, high vaccine effectiveness of the MenC-TT vaccine was observed in the past across different European countries, with only rarely a vaccine failure.

Since the start of the COVID-19 containment measures in March 2020, partial lockdowns did not just reduce COVID-19 disease but also reduced the incidence of many other infectious diseases [27, 28]. At the time of COVID-19 containment measures, which was more than a year after the MenACWY mass campaign was completed, all-serogroup IMD incidence decreased substantially. As a consequence of those measures, we could only include a constrained period in our before-after analysis, with both periods consisting of three quartiles. The analysis showed a decrease in IMD-W incidence in vaccine non-eligible age groups, suggesting a herd effect. However, stabilization of the incidence already appeared at the start of the mass campaign. In addition, we did not find any early impact in vaccine non-eligible groups for other vaccine-targeted serogroups like IMD-Y, but the number of cases was low. Remarkably, in vaccine non-eligible age groups, the decrease in IMD-W and IMD-Y incidence (IRR 0.19 (0.07-0.55) and 0.17 (0.02-1.38) respectively) during the period with COVID-19 measures was larger than for IMD-B (IRR 0.67 (0.37-1.21), which is not covered by the vaccine. This could be supportive for an additional effect of group immunity by MenACWY vaccination. However, the epidemiology of IMD-B is different from IMD-W and IMD-Y, for example in terms of age-related susceptibility, and the decrease in IMD-B in vaccine eligible groups was similar to IMD-W and IMD-Y in vaccine non-eligible age groups during the measures with IRR 0.19 (0.07-0.55). Thus, the significance of these findings remains uncertain.
One of the drawbacks of observational research is that it may be confounded by natural trends in the incidence of disease over time. Meningococci are known for seasonal variation [29], and incidence varies not only within a year, but also throughout the years. For example, IMD-B incidence has been steadily declining since the 00’s in the Netherlands without demonstrable reason, while in contrast IMD-W suddenly increased rapidly in 2015-16. This highlights the importance of comparing periods with same seasonality if available, and a critical appraisal of the periods chosen for the before-after analysis. Our sensitivity analysis showed that the period chosen for analysis, albeit consisting of only three quartiles, was robust for the impact analyses. However, we cannot rule out natural changes in epidemiology adding to a vaccine-induced effect as possible explanation for the observed decrease. Carriage studies should verify if the vaccination campaign truly led to the proposed herd effect through reduced transmission, although behavioral factors like intimacy with others and smoking may also affect carriage rates [4]. Evidence for reduced meningococcal carriage after a quadrivalent vaccine is present but limited [30], and sometimes controversial. A cross-sectional carriage study in the UK in university students observed a substantial rise in meningococcal serogroup W carriage despite a coverage of 71% with the MenACWY-TT vaccine [31]. It should however be taken into account that this study investigated a close-contact, thus high-risk setting. Also, a recent modelling study using the same carriage data showed that vaccination led to a carriage plateau and the authors predicted that a higher coverage rate would have produced further reduction in carriage levels [32].

In conclusion, we found that the implementation of a MenACWY conjugate vaccine for 14-18 year-olds through a mass campaign, alongside its introduction in the NIP for toddlers and teenagers, led to a reduction in IMD-W cases in vaccine-eligible age groups. A decline in IMD-W incidence was also observed in vaccine non-eligible groups, but it remains uncertain to what extent the reduction can be attributed to indirect effects of the vaccination campaign because it is difficult to disentangle natural fluctuation from vaccine-effect. This study provides information for countries facing an IMD-W epidemic and highlights the importance of continuous surveillance to improve vaccination policies and quickly intervene during an outbreak. It underlines the high effectiveness of the MenACWY vaccination and encourages its use as toddler- and teenager vaccination in national immunization programmes.
NOTES

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Author contributions

M.O. and M.J.K. conceived and designed the study. M.J.K, A.v.d.E. and N.M.v.S. were involved in data collection. M.O. and M.J.K. performed the analyses and interpreted and verified the data. M.O. and M.J.K. made the figures and drafted the manuscript. All authors interpreted the data, critically reviewed the manuscript, and approved the final version.

Potential conflicts of interest

N.M.v.S declares grants and fee for service, directly paid to institution, from GSK and MSD, and grants from Pfizer outside the submitted work; reports patent on vaccine development against Streptococcus pyogenes, (WO 2013/020090 A3; royalties paid to/licensed to University of California San Diego (inventors: Nina van Sorge/Victor Nizet)) not related or part of the work submitted here. A.v.d.E declares a grant from Pfizer outside the submitted work (investigator Initiated project: Program WI242174 Meningococcal factors causing the atypical presentation in meningococcal serogroup W clonal complex 11 invasive disease). All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.
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Table 1. Incidence rate (IR) and incidence rate ratio (IRR) for meningococcal serogroup W per age
group, and for serogroup B, C and Y per vaccine-eligible or vaccine non-eligible age group, in the period
before and after implementation of meningococcal A, C, W and Y conjugated to tetanus toxoid
(MenACWY-TT) vaccination. Q = Quartile; CI = confidence interval; NA = not applicable; vaccine-eligible = 15-36 month-olds and 14-18 year-olds; vaccine non-eligible = under 15 months, 3-13 years, 19 years and older.

| Age group | N | IR Q3-2017 to Q1-2018 (before) | N | IR Q3-2019 to Q1-2020 (after) | IRR | 95% CI |
|-----------|---|--------------------------------|---|-------------------------------|-----|--------|
| Serogroup W | | | | | | |
| <15 months | 4 | 2.49 | 1 | 0.63 | 0.25 | 0.03–2.27 |
| 15-36 months | 3 | 1.31 | 2 | 0.88 | 0.67 | 0.11–4.02 |
| 3-13 years | 0 | 0.0 | 1 | 0.07 | NA | NA |
| 14-18 years | 8 | 1.03 | 0 | 0.0 | NA | NA |
| 19-24 years | 5 | 0.52 | 2 | 0.21 | 0.39 | 0.08–2.03 |
| 25-44 years | 7 | 0.22 | 3 | 0.09 | 0.42 | 0.11–1.64 |
| 45-64 years | 24 | 0.66 | 8 | 0.22 | 0.33 | 0.15–0.74 |
| 65+ years | 27 | 1.13 | 14 | 0.56 | 0.50 | 0.26–0.95 |
| All | 78 | 0.61 | 31 | 0.24 | 0.39 | 0.26–0.60 |
| Vaccine-eligible | 11 | 1.09 | 2 | 0.20 | 0.18 | 0.04–0.82 |
| Vaccine non-eligible | 67 | 0.57 | 29 | 0.24 | 0.43 | 0.28–0.66 |
| Serogroup C | | | | | | |
| Vaccine-eligible | 0 | 0.0 | 0 | 0.0 | NA | NA |
| Vaccine non-eligible | 5 | 0.04 | 1 | 0.01 | 0.20 | 0.02–1.69 |
| Serogroup Y | | | | | | |
| Vaccine-eligible | 2 | 0.20 | 0 | 0.0 | NA | NA |
| Vaccine non-eligible | 15 | 0.13 | 14 | 0.12 | 0.92 | 0.45–1.91 |
| Serogroup B | | | | | | |
| Vaccine-eligible | 18 | 1.79 | 19 | 1.90 | 1.06 | 0.56–2.02 |
| Vaccine non-eligible | 46 | 0.39 | 30 | 0.25 | 0.65 | 0.41–1.02 |
Table 2. Incidence rate (IR) and incidence rate ratio (IRR) for meningococcal serogroup W, Y and B per vaccine cohort (vaccine-eligible, vaccine non-eligible and overall), comparing period before and during COVID-19 containment measures. Q = Quartile; CI = confidence interval; NA = not applicable; vaccine-eligible = 15-36 month-olds and 14-18 year-olds; vaccine non-eligible = under 15 months, 3-13 years, 19 years and older.

| Serogroup | Cohort                  | N   | IR Q3-19 to Q4-19 (before COVID) | N   | IR Q3-20 to Q4-20 (during COVID) | IRR   | 95% CI       |
|-----------|-------------------------|-----|---------------------------------|-----|---------------------------------|-------|-------------|
|           | Vaccine-eligible        | 2   | 0.30                            | 0   | 0.0                             | NA    | NA          |
|           | Vaccine non-eligible    | 21  | 0.26                            | 4   | 0.05                            | 0.19  | 0.07–0.55   |
|           | Overall                 | 23  | 0.27                            | 4   | 0.05                            | 0.17  | 0.06–0.50   |
|           | Vaccine-eligible        | 0   | 0.0                             | 0   | 0.0                             | NA    | NA          |
|           | Vaccine non-eligible    | 6   | 0.08                            | 1   | 0.01                            | 0.17  | 0.02–1.38   |
|           | Overall                 | 6   | 0.07                            | 1   | 0.01                            | 0.17  | 0.02–1.38   |
|           | Vaccine-eligible        | 13  | 1.95                            | 3   | 0.45                            | 0.19  | 0.07–0.55   |
|           | Vaccine non-eligible    | 18  | 0.23                            | 14  | 0.18                            | 0.67  | 0.37–1.21   |
|           | Overall                 | 31  | 0.36                            | 17  | 0.20                            | 0.55  | 0.30–0.99   |
FIGURE LEGENDS

Figure 1. *Timeline of implementation and analyzed periods.* Q = quartile, NIP = national immunization programme, A = post-implementation period, B = pre-implementation period, base case analyses, Bs = pre-implementation period within the sensitivity analysis, Bc = period before COVID-19 containment measures, Ac = period with COVID-19 containment measures. *Created with BioRender.com.

Figure 2. *Number of invasive meningococcal serogroup B, C, Y and W disease cases (A) and deceased cases* (B) in the period 2014-15 to 2019-20. *only cases with known outcome status are shown (outcome status missing for 12 IMD-B cases, 0 IMD-C cases, 8 IMD-Y cases and 7 IMD-W cases in this 6-year period)

Figure 3. *Number of cases (A) and incidence (B) of IMD-W per age group*

Figure 4. *IMD-W incidence per quartile during the calendar years 2015-2020 in vaccine eligible (15-36 month-olds and 14-18 year-olds) and non-eligible (< 15 months, 3-13 years and 19 years and older) groups.*
| MenACWY vaccination | 14 months NIP | 2001-2005 birth cohort mass campaign | 14 years NIP | Before - After analysis | COVID-19 measures analysis |
|---------------------|---------------|--------------------------------------|--------------|------------------------|--------------------------|
| Analyses periods    | 2017          | 2018                                 | 2019         | 2020                   |                          |
|                     | Q1 Q2 Q3 Q4   | Q1 Q2 Q3 Q4                          | Q1 Q2 Q3 Q4  | Q1 Q2 Q3 Q4            |                          |

- Before analysis
  - B
  - Bs

- After analysis
  - A
  - Bc
  - Ac
