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Vaccine Impact and Effectiveness of Meningococcal Serogroup ACWY Conjugate Vaccine Implementation in the Netherlands: A Nationwide Surveillance Study

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

Methods. We extracted 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, the IMD-W incidence rate declined by 61% (95% confidence interval [CI], 40 to 74). It declined by 82% (95% CI, 18 to 96) in the vaccine-eligible age group (individuals aged 15–36 months and 14–18 years) and by 57% (95% CI, 34 to 72) in vaccine-noneligible age groups. VE was 92% (95% CI, –20 to 99.5) in vaccine-eligible toddlers (aged 15–36 months). No IMD-W cases were reported in vaccine-eligible teenagers after the campaign.

Conclusions. The MenACWY vaccination program was effective in preventing IMD-W in the target population. The IMD-W incidence reduction in vaccine-noneligible age groups may be caused by indirect effects of the vaccination program. However, disentangling natural fluctuation from vaccine effect was not possible. Our findings encourage the use of toddler and teenager MenACWY vaccination in national immunization programs.

Keywords. invasive meningococcal disease; meningococcal ACWY vaccination; vaccine impact; vaccine effectiveness; herd immunity.

Neisseria meningitidis, a gram-negative bacterium with a polysaccharide capsule that confers the specific serogroup, is an important cause of meningitis and septicemia [1]. Worldwide, invasive meningococcal disease (IMD) is most often caused by serogroups A, B, C, W, X, and Y [2]. The meningococcus can be carried asymptomatically in the nasopharynx but can also act as a harmful pathogen when it crosses the mucosal barriers. Carriage rates are high in teenagers, which is attributed to factors such as social behavior, including kissing and crowding [3, 4]. Although teenagers show low incidence rates in most infectious diseases [5], they are disproportionally affected by IMD, together with young children. On average, 1 in 10 patients dies from IMD in countries with excellent healthcare [6]. Furthermore, survivors may experience severe sequelae such as 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]; it was 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 including the United Kingdom [11, 12]. To halt

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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 that targeted individuals aged 14–18 years (birth cohort 2001–2005) was implemented, and the quadrivalent vaccine was introduced for all individuals aged 14 years in the national immunization program (NIP) in 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 such as IMD do not allow the use of clinical end points in prelicensure studies that investigate vaccine efficacy directly. Consequently, post-licensure observational studies are necessary to evaluate effectiveness and the impact of meningococcal vaccination [14]. Previous studies have proven that a mass campaign with a MenC conjugate vaccine that targets minors can limit an epidemic [15]. However, comprehensive data on MenACWY vaccine effectiveness (VE) are lacking, and it is unknown whether vaccinating only individuals aged 14–18 years restricts a national outbreak and induces herd immunity.

Here, we describe the impact of the MenACWY vaccination program in the Netherlands between 2018 and 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 VE in vaccine-eligible toddlers (aged 15–36 months) and teenagers (aged 14–18 years) in the Netherlands.

METHODS

IMD Surveillance in the Netherlands

The national IMD surveillance system is based on 2 data sources: notifications from the Regional Public Health Service (RPHS) and laboratory data from the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM, Amsterdam University Medical Center Amsterdam, the Netherlands). Data from these 2 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 2 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 confirmed by culture, by polymerase chain reaction, 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 World Health Organization 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 minors up to age 18 years. The routine coverage in children aged 14 months 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 to 2020, with a year starting July 1 and ending June 30 the year thereafter. The period of quartile 3 (Q3)–2017 until Q1–2018 was chosen as the 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 ending Q1–2020 to limit interference of the measures taken, starting close to Q2–2020, to control the coronavirus disease 2019 (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 Q2–2018 and Q3–2018 in the period before implementation in order to determine 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 children aged 14 months, but the mass campaign for teenagers had not yet started.

Statistical Analyses

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 using a Poisson regression model. Age groups were categorized in accordance with the vaccination program; individuals aged 15–36 months and 14–18 years were defined as the vaccine-eligible age groups, and individuals aged <15 months, 3–13 years, and >19 years were defined as the vaccine-noneligible age groups. Since IMD-B is not targeted by the vaccine, this serogroup was included in the impact analysis as means of a negative control.

The VE was assessed for laboratory-confirmed IMD-W cases in vaccine-eligible toddlers and teenagers. Vaccine eligibility

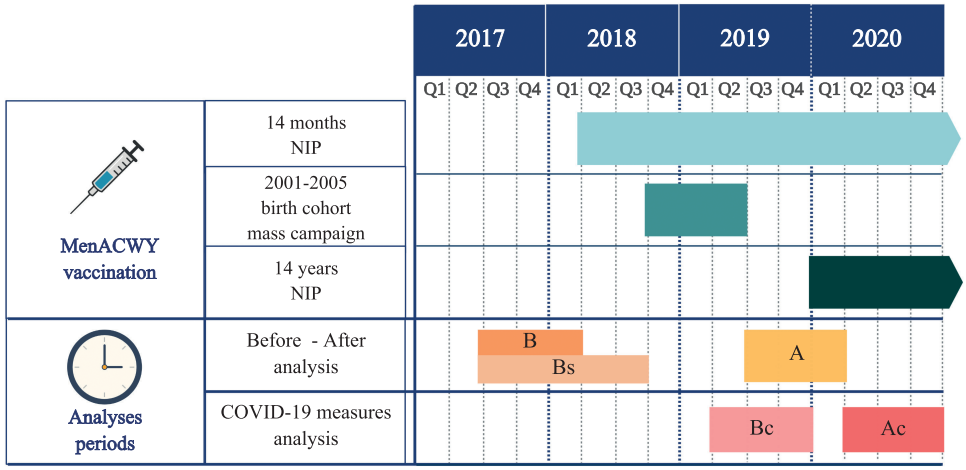

Figure 1. Timeline of implementation and analyzed periods. Abbreviations: A, post-implementation period; Ac, period with COVID-19 containment measures; B, pre-implementation period, base case analyses; Bc, period before COVID-19 containment measures; Bs, pre-implementation period within the sensitivity analysis; COVID-19, coronavirus disease 2019; MenACWY, meningococcal serogroup A, C, W and Y; NIP, national immunization program; Q, quartile. Created with BioRender.com.

in toddlers was defined as born on or after 1 March 2017 and diagnosed at age ≥14 months between 1 May 2018 and 31 December 2020. Vaccine-eligible teenagers were born between 1 January 2001 and 31 December 2005 and diagnosed between 1 July 2019 and 31 December 2020 at age ≥14 years. 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:

$$VE = 1 - \frac{PCV}{1 - PCV} * \frac{1 - PPV}{PPV}$$

where *PCV* is the proportion of cases vaccinated in the studied cohort and *PPV* is the proportion of the population vaccinated.

Data on population size were obtained from Statistics Netherlands to calculate incidence per population time. Population data for 2020 were not yet available at the time of analyses (January 2021); therefore, population data from 2019 were 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 were reported in the 6-year period from 2014–2015 until 2019–2020 (Figure 2). IMD cases were predominantly caused by serogroup B in 2014–2015 (Figure 2) and the years before (data not shown). While only 5 cases of IMD-W were observed in 2014–2015, it was the most common

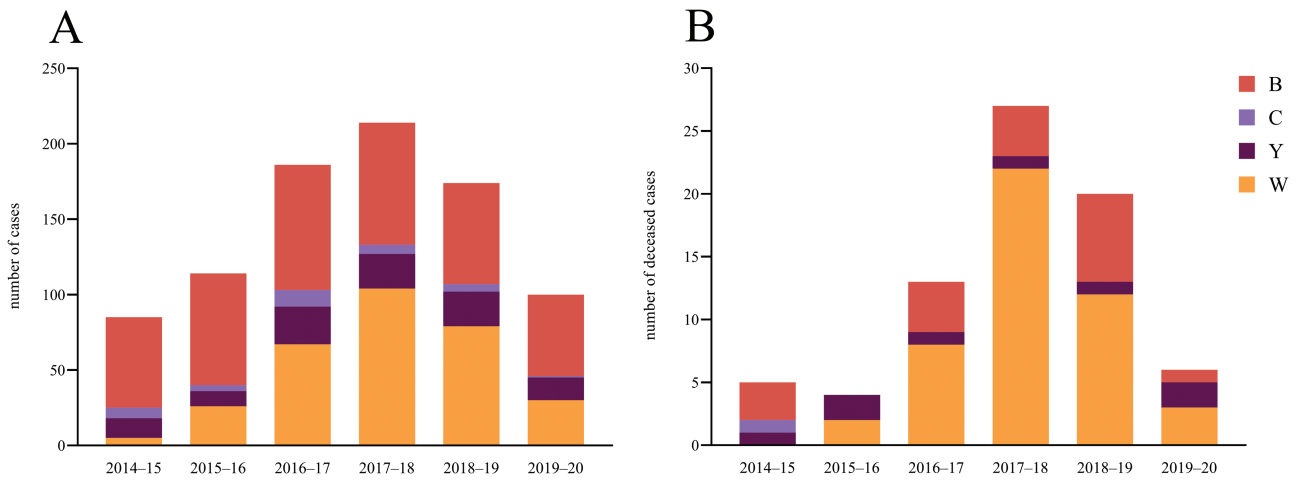

Figure 2. Number of invasive meningococcal serogroup B, C, Y, and W disease cases *(A)* and deceased cases* *(B)* in the period 2014–2015 to 2019–2020. *Only cases with known outcome status are shown (outcome status missing for 12 invasive meningococcal disease [IMD]-B cases, 0 IMD-C cases, 8 IMD-Y cases, and 7 IMD-W cases in this 6-year period).

serogroup in 2017–2018 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 2014–2015 to 2019–2020, whereas IMD due to other serogroups, such as IMD-E and IMD-X, and nongroupable 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 2017–2018 (47%; 22 of 47 cases). Of 22 deceased cases in 2017–2018, 13 (59%) were adults aged ≥45 years and 6 were individuals aged between 14 and 24 years. In 2019–2020, only 3 fatal IMD-W cases were reported.

While IMD-W cases were rare and only observed in adults in 2014–2015, incidence started to increase in 2015–2016, with the highest incidence in infants aged <5 months, albeit low absolute numbers (Figure 3). In 2016–2017, incidence increased, particularly in individuals aged 14–18 years (0.20 to 1.07 per 100 000), followed by a rise in incidence in almost all age groups in the year thereafter. Children aged <36 months were disproportionally affected during the peak years, although the absolute number of cases was highest in middle-aged adults and the elderly (Figure 3). The number of cases dropped in 2018–2019 in all age groups except in individuals aged 14–18 years, with 13 cases that year compared with 10 cases the year before. Over the years, the number of cases and incidence rates were continuously low in individuals aged 3–13 years and 25–44 years.

During the mass campaign, the incidence in vaccine-eligible groups rapidly declined (Figure 4). After the mass campaign, the IMD-W incidence rate declined in all age groups (Table 1). The most pronounced reduction was observed in vaccine-eligible individuals aged 14–18 years, with 8 cases before implementation and zero after implementation. Older age cohorts (adults

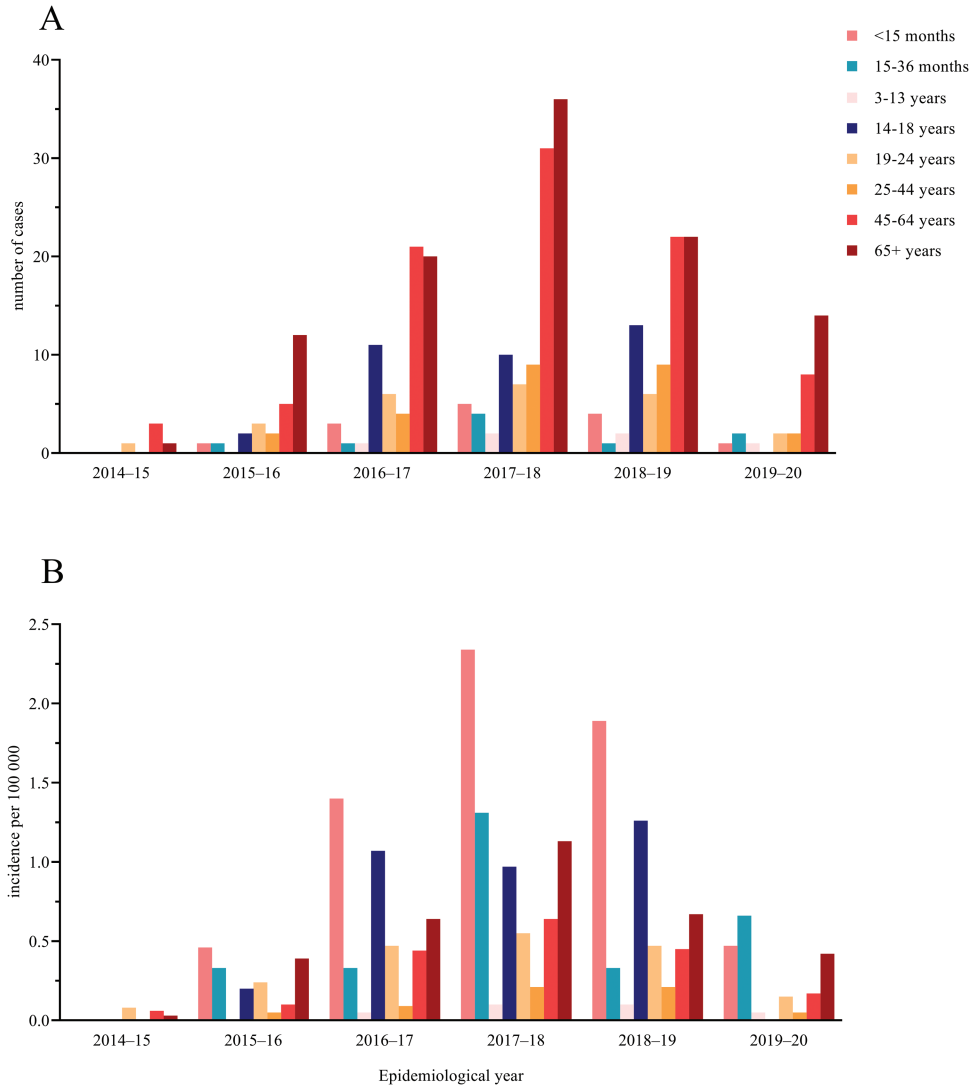

Figure 3. Number of cases *(A)* and incidence *(B)* of invasive meningococcal disease W per age group.

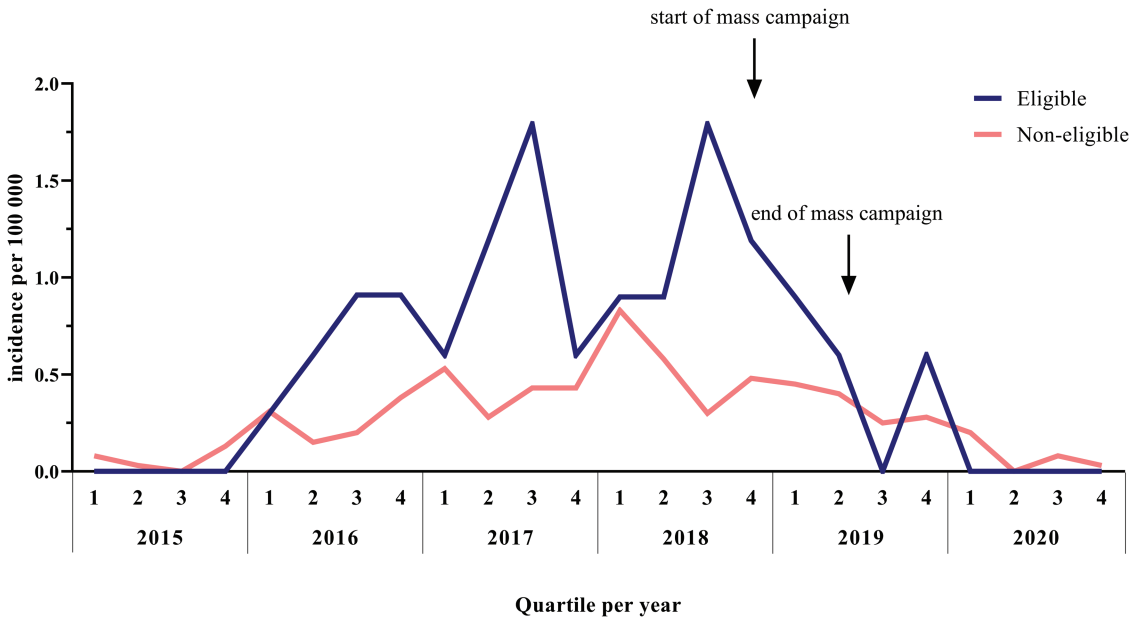

Figure 4. Invasive meningococcal disease W incidence per quartile during the calendar years 2015–2020 in vaccine-eligible (aged 15–36 months and 14–18 years) and vaccine-noneligible (aged <15 months, 3–13 years, and ≥19 years) groups.

aged 45–64 years and ≥65 years) also showed a significant decrease in incidence; the overall IRR for the vaccine-noneligible 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; this is in contrast to 2 cases in the period before implementation (Table 1). In vaccine-noneligible 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 aged ≥45 years, there were even fewer 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-noneligible 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

Table 1. Incidence Rate and Incidence Rate Ratio for Meningococcal Serogroup W per Age Group and for Serogroups B, C, and Y per Vaccine-Eligible or Vaccine-Noneligible Age Group, in the Period Before and After Implementation of Meningococcal A, C, W, and Y Conjugated to Tetanus Toxoid Vaccination

Serogroup	Age Group	N	IR Q3–2017 to Q1–2018 (Before)	N	IR Q3–2019 to Q1–2020 (After)	IRR	95% Confidence Interval
W	<15 months	4	2.49	1	0.63	0.25	.03 to 2.27
	15–36 months	3	1.31	2	0.88	0.67	.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	.08 to 2.03
	25–44 years	7	0.22	3	0.09	0.42	.11 to 1.64
	45–64 years	24	0.66	8	0.22	0.33	.15 to .74
	65 + years	27	1.13	14	0.56	0.50	.26 to .95
	All	78	0.61	31	0.24	0.39	.26 to .60
	Vaccine-eligible	11	1.09	2	0.20	0.18	.04 to .82
	Vaccine-noneligible	67	0.57	29	0.24	0.43	.28 to .66
C	Vaccine-eligible	0	0.0	0	0.0	NA	NA
	Vaccine-noneligible	5	0.04	1	0.01	0.20	.02 to 1.69
Y	Vaccine-eligible	2	0.20	0	0.0	NA	NA
	Vaccine-noneligible	15	0.13	14	0.12	0.92	.45 to 1.91
B	Vaccine-eligible	18	1.79	19	1.90	1.06	.56 to 2.02
	Vaccine-noneligible	46	0.39	30	0.25	0.65	.41 to 1.02

Vaccine-eligible, aged 15–36 months and 14–18 years; vaccine-noneligible, aged under <15 months, 3–13 years, and ≥19 years.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; NA, not applicable; Q, quartile.

groups and decreased slightly but not significantly in vaccine-noneligible age groups.

A sensitivity analysis was carried out by including 2 additional quartiles (Q2–2018 and Q3–2018) in the period before implementation and showed that IRRs did not change when the analyzed period included this extended period before implementation (Supplementary Table 1). The incidence of IMD-W during COVID-19 containment (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 noneligible age groups was less pronounced than for IMD-W and IMD-Y (Table 2).

The estimated VE for 1 dose of MenACWY-TT in children aged 14 months against IMD-W was 92% (95% CI, –20 to 99.5). Two IMD-W cases occurred in this eligible cohort, both aged >14 months at the 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 1 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 for the vaccine (serogroup ACY), it was also not possible to estimate 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 onward and for teenagers from October 2018 onward, together with a mass campaign for individuals aged 14–18 years between October 2018 and June 2019. In this study, we evaluated IMD cases in the Netherlands from 2014–2015 onward, 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 an even higher reduction of cases of 82% in vaccine-eligible toddlers and teenagers, within the first year after the mass campaign was completed. The VE in toddlers was 92%; only 1 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 decrease in the vaccine-eligible cohort, there was very little decline in IMD-Y in vaccine-noneligible age groups (IRR, 0.92) in the first 3 quartiles after completion of the mass campaign.

A catch-up program in the United Kingdom between 2015 and 2017 provided the MenACWY vaccination to all individuals aged 13–18 years [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 program [21]. Comparable to our findings in toddlers, the early estimated VE in teenagers in that study was 100% for IMD-W but with wide CIs (95% CI, –47 to 100) due to small numbers. A study from Chile showed a 92% reduction in IMD-W cases in the first 4 years after a mass campaign in the MenACWY vaccinated cohort that consisted of infants and children aged 9 months to 4 years [22]. Indirect effects were not yet observed 1 year after vaccination in Chile; the lack of infants younger than 9 month of age and teenagers in the target group was given by the authors as a possible explanation. Several European countries reported an increase in IMD-W during the years 2013–2017; 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

Table 2. Incidence Rate and Incidence Rate Ratio for Meningococcal Serogroups W, Y, and B per Vaccine Cohort (Vaccine-Eligible, Vaccine Noneligible, and overall) Comparing Period Before and During Coronavirus Disease 2019 Containment Measures

Serogroup	Cohort	N	IR Q3–2019 to Q4–2019 (Before COVID)	N	IR Q3–2020 to Q4–2020 (During COVID)	IRR	95% Confidence Interval
W	Vaccine-eligible	2	0.30	0	0.0	NA	NA
	Vaccine-noneligible	21	0.26	4	0.05	0.19	.07 to .55
	Overall	23	0.27	4	0.05	0.17	.06 to .50
Y	Vaccine-eligible	0	0.0	0	0.0	NA	NA
	Vaccine-noneligible	6	0.08	1	0.01	0.17	.02 to 1.38
	Overall	6	0.07	1	0.01	0.17	.02 to 1.38
B	Vaccine-eligible	13	1.95	3	0.45	0.19	.07 to .55
	Vaccine-noneligible	18	0.23	14	0.18	0.67	.37 to 1.21
	Overall	31	0.36	17	0.20	0.55	.30 to .99

Vaccine-eligible, aged 15–36 months and 14–18 years; vaccine-noneligible, aged under <15 months, 3–13 years, and ≥19 years.

Abbreviations: IR, incidence rate; IRR, incidence rate ratio; NA, not applicable; Q, quartile.

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 VE results that were similar 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 [23]. The effectiveness of MenC-TT in the routinely vaccinated cohort in England (3 doses given to infants aged 2–4 months) was 93% within 1 year of the scheduled vaccination [24]. In Italy since 2005, a major reduction of cases has been observed after a single dose of MenC-TT was provided at age 13–15 months, with some regions carrying out mass campaigns with either MenC or MenACWY conjugate vaccinations in the years thereafter [25]. Overall, high VE of the MenC-TT vaccine has been observed in the past across different European countries, with vaccine failure being rare.

Since the start of COVID-19 containment measures in March 2020, partial lockdowns did not only reduce COVID-19 disease, they also reduced the incidence of many other infectious diseases [26, 27]. At the time of COVID-19 containment measures, which was more than 1 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 3 quartiles. The analysis showed a decrease in IMD-W incidence in vaccine-noneligible age groups, suggesting a herd effect. However, stabilization of the incidence had already appeared at the start of the mass campaign. In addition, we did not find any early impact in vaccine-noneligible groups for other vaccine-targeted serogroups such as IMD-Y, but the number of cases was low. Remarkably, in vaccine-noneligible age groups, the decrease in IMD-W and IMD-Y incidence (IRR, 0.19; 0.07–0.55 and IRR, 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 that of 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-noneligible groups during the measures with IRR, 0.19 (0.07–0.55). Thus, the significance of these findings remains uncertain.

One drawback 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 [28], and incidence varies not only within a year but also throughout the years. For example, IMD-B incidence has been steadily declining since early 2000 in the Netherlands without demonstrable reason; in contrast, IMD-W suddenly increased rapidly in 2015–2016. This highlights the importance of comparing periods with the 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, although it consisted of only 3 quartiles, was robust for the impact analyses. However, as possible explanation for the observed decrease, we cannot rule out that natural changes in epidemiology may have added to a vaccine-induced effect. Carriage studies should verify if the vaccination campaign truly led to the proposed herd effect through reduced transmission, although behavioral factors such as intimacy with others and smoking may also affect carriage rates [4]. Evidence for reduced meningococcal carriage after a quadrivalent vaccine is present but limited [29] and sometimes controversial. A cross-sectional carriage study in the United Kingdom in university students showed a substantial rise in meningococcal serogroup W carriage despite a coverage of 71% with the MenACWY-TT vaccine [30]. It should, however, be taken into account that this study investigated a close-contact and thus high-risk setting. Also, a recent modeling 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 [31].

In conclusion, we found that the implementation of a MenACWY conjugate vaccine for individuals aged 14–18 years through a mass campaign, in addition to 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-noneligible 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 enable quick intervention during an outbreak. It underlines the high effectiveness of MenACWY vaccination and encourages its use for toddler and teenager vaccination in national immunization programs.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. O. and M. J. K. conceived of 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. created the figures and drafted the manuscript. All authors interpreted the data, critically reviewed the manuscript, and approved the final version.

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Potential conflicts of interest. N. M. v. S. declares grants and fee for service, directly paid to their institution, from GSK and MSD and grants from Pfizer outside the submitted work; a patent on vaccine development against *Streptococcus pyogenes* (WO 2013/020090 A3; royalties paid to/licensed to the University of California–San Diego; inventors, N. M. v. S./Victor Nizet) not related or part of the work submitted here. A. v. d. E. declares a grant from Pfizer outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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