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REVIEW

Real-world impact and effectiveness of MenACWY-TT

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ABSTRACT

In response to escalating cases of serogroup W (MenW) invasive meningococcal disease (IMD), multiple countries introduced quadrivalent conjugate MenACWY vaccines into their national immunization programs (NIPs). Here, we summarize the real-world impact and vaccine effectiveness (VE) data of MenACWY-TT from Chile, England, the Netherlands, and Australia. Incidence rate reductions (IRRs) and VE from baseline to post-NIP period were extracted from publications or calculated. After the administration of a single dose of MenACWY-TT, substantial IRRs of MenCWY were observed across the countries in vaccine-eligible age groups (83%-85%) and via indirect protection in non-vaccine-eligible age groups (45%-53%). The impact of MenACWY-TT was primarily driven by MenW IRRs, as seen in vaccine-eligible age groups (65%-92%) and non-vaccine-eligible age groups (41%-57%). VE against MenW was reported in vaccine-eligible toddlers (92%) in the Netherlands and in vaccine-eligible adolescents/young adults (94%) in England. These real-world data support the implementation and continued use of MenACWY-TT in NIPs.

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Introduction

Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* is associated with high morbidity and mortality worldwide. IMD occurs in all age groups, although incidence rates are highest in young children, adolescents and young adults.[1] Based on the structural differences of the polysaccharide capsule, *N. meningitidis* can be categorized into 12 distinct serogroups, of which 5 (A, B, C, W, and Y) have historically predominated as the main cause of disease.[2] IMD is mostly sporadic with seasonal variations and occasional epidemics or small outbreaks in specific settings, which occur at unpredictable intervals. The ever-changing IMD epidemiology together with sudden switches in serogroup and/or clonal complex predominance contribute to the unpredictable nature of IMD.

Meningococcal vaccines containing single or multiple capsular polysaccharides were developed in the 1970s and their effectiveness and safety have been established in older children and adults.[3] Polysaccharide-protein conjugate vaccines were subsequently developed and predominantly superseded plain polysaccharide vaccines. These conjugate vaccines have been used in diverse vaccination strategies against IMD caused by serogroups A, C, W, and Y globally.[4] In addition to direct protection, meningococcal conjugate vaccines reduce the acquisition of nasopharyngeal carriage, and thus these vaccines disrupt transmission, providing indirect protection to unvaccinated individuals.[5–8]

Due to the relatively low incidence rate of IMD, large-scale clinical trials with efficacy endpoints are not feasible. Consequently, efficacy of meningococcal vaccines is inferred from the induction of serum bactericidal antibody (SBA) – a surrogate of protection – measured using human (hSBA) or rabbit complement (rSBA).[9] Post-licensure vaccine effectiveness is therefore important to understand the public health benefit of meningococcal vaccine implementation into national immunization programs (NIPs). The introduction of a MenC conjugate vaccine (MCCV) into the United Kingdom (UK) NIP in 1999 proved highly effective in controlling MenC disease and subsequently other countries included MCCV in their immunization schedules.[10,11] A further example is the significant reduction in MenA disease in the Meningitis Belt region (Sub-Saharan Africa region with highest burden of the disease: Benin, Burkina Faso, Chad, Côte d'Ivoire, Ghana, Mali, Niger, Nigeria, and Togo) following large-scale implementation of a monovalent MenA conjugate vaccine beginning in 2010.[12,13]

In recent years, a serogroup shift from MenC to MenW[14] and MenY[15] has prompted many countries to update NIP recommendations from monovalent to quadrivalent conjugate MenACWY vaccines.[16] MenACWY-TT (Nimenrix®, Pfizer Inc, Sandwich, UK) is a quadrivalent formulation conjugated with tetanus toxoid that has been licensed since 2012.[17] Post-licensure real-world effectiveness data from surveillance systems have recently become available confirming the clinical benefit of quadrivalent MenACWY conjugate vaccines.[7–20] In this review, we focus on the immunization programs exclusively or primarily utilizing MenACWY-TT, and summarize

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the current data on the impact and real-world effectiveness reported from Chile, England, the Netherlands, and Australia.

Methods

Impact of MenACWY-TT

We identified impact data for MenACWY-TT following its introduction into NIPs from published manuscripts for the Netherlands and England.[7,20]

For Australia and Chile, because there were no comprehensive impact data reported for MenACWY-TT at the time of analysis, we extracted the number of serogroup C, W, and Y IMD cases from respective national surveillance systems for incidence rate calculations (Table 1). Serogroup specific and MenCWY incidence rates per 100,000 population were calculated with numerators based on the IMD case numbers reported to their respective surveillance systems. IMD is a notifiable disease with mandatory reporting in both countries. Age-specific population data from Australian Bureau of Statistics[27] and United Nations Development Progamme, Chile[28] were used as denominators. The impact of MenACWY-TT was expressed as IRRs. The IRRs and their confidence intervals were calculated according to the Newcombe-Wilson method using Microsoft Excel, with the formula:

IRR = 1 – Relative Risk (RR), where RR = (incidence rate in the post-NIP introduction period using the most recent reporting year)/(incidence rate in the baseline period, which was the reporting year of, or immediately prior to NIP introduction).

For all countries, the IRRs were presented for vaccine-eligible age groups (age group[s] directly or closely corresponding to those offered MenACWY vaccination), non-vaccine-eligible age groups (age group[s] not offered MenACWY vaccination), and the entire population (all age groups) (Table 1).

Serogroup A IMD cases were not considered due to there being few or no cases in these countries during the time periods investigated.

Effectiveness of MenACWY-TT

We extracted MenACWY-TT vaccine effectiveness (VE) data from published manuscripts for the Netherlands and England. For the Netherlands, VE data were reported following the implementation of MenACWY-TT along with supporting IMD case data by Ohm and colleagues.[7] Similarly, VE data following implementation of the MenACWY adolescent program in England which predominantly used MenACWY-TT was reported by Campbell and colleagues.[20] No VE data for MenACWY-TT in Australia or Chile had been published at the time of analysis.

Results

The immunization programs in Chile, England, the Netherlands, and Australia which have introduced MenACWY-TT into their NIP are summarized in Table 1. The vaccine-eligible age groups, timing, and implementation of MenACWY-TT varied across all four countries. In Chile, only toddlers at 12 months of age were immunized in the NIP which superseded a prior MenACWY campaign in children from 9 months to 4 years of age. In England, adolescents 13–14 years of age were routinely immunized in the NIP along with a corresponding catch-up campaign for older adolescents and young adults. The Netherlands and Australia immunized both toddlers and adolescents with corresponding catch-up campaigns in older adolescents. In general, vaccine uptake was high across all countries in the vaccine-eligible NIP cohorts (Table 1).

Impact and effectiveness of MenACWY-TT

Serogroup specific and MenCWY IRRs are described in Figures 1 and 2 and Supplementary Table S1. Reported VE from the Netherlands and England are detailed in Table 2.

Impact and effectiveness of a single dose of MenACWY-TT in toddlers

In Chile, the incidence of MenW in children 1–4 years of age had declined from 1.31/100,000 population ($n = 13$ cases) to 0.10/100,000 population in 2019 ($n = 1$ case). The IRR following the program with a single MenACWY-TT dose against MenW disease was 92% (95% CI 42%-99%) (Figure 1 and Supplementary Table S1). In the Netherlands, the single dose, 14-months of age, toddler program was reported to have a high VE against MenW disease of 92% (95% CI −20%-99.5%) (Table 2).[7] Ohm and colleagues were not able to calculate VE against MenCY disease due to zero MenCY cases in the toddlers immunized with MenACWY-TT.[7]

Impact and effectiveness of a single dose MenACWY-TT in adolescents/young adults

In England, a single dose of MenACWY vaccine at 13–14 years of age resulted in a VE against MenCWY disease of 94% (95% CI 80%-99%) with similar VE against MenW and MenY disease independently (Table 2).[20] This high VE corresponded to IRRs in the 14–18 years of age vaccine-eligible cohort of between 65% (95% CI 24%-83%) and 89% (95% CI −1%-99%) for MenC, MenW, and MenY disease (Figure 1 and Supplementary Table S1). Although VE was reported for the Dutch toddler program, Ohm and colleagues were unable to do the same for either the routine adolescent or catch-up programs due to zero MenACWY cases in those who had received MenACWY-TT.[7]

Impact of a single dose of MenACWY-TT in both toddlers and adolescents/young adults

In toddler and adolescent/young adult vaccine-eligible cohorts, the IRR following the program of a single MenACWY-TT dose against MenCWY disease was 83% (95% CI 61%-93%) in Australia and 85% (95% CI 32%-97%) in the Netherlands. In these cohorts, the predominant serogroup was MenW. The incidence of MenW decreased from 1.09/100,000 population ($n = 11$ cases) to 0.20/100,000 population ($n = 2$ cases) in

Table 1. Data elements collected for the reporting of MenACWY incidence rate reduction and vaccine effectiveness in the Netherlands, and England and the data analysis of incidence rate reduction in Australia, and Chile.

Country	Evaluation time periods		Age groups considered as vaccine-eligible for analysis	MenACWY vaccine program	Data sources and references	Vaccine coverage
	Baseline	Post-NIP introduction				
The Netherlands	July-2017 to March-2018	July-2019 to March-2020	15–36 months and 14–18 years of age	May 2018: MenACWY-TT introduced into NIP at 14 months of age, replacing MCCV. October 2018 to June 2019: MenACWY-TT mass campaign for those 14–18 years old. January 2020: MenACWY-TT introduced into NIP at 14 years of age.	Ohm et al.[7] The vaccine effectiveness and impact estimates were directly identified in Ohm et al.[7] Incidence of IMD cases was calculated based on the reported numbers of IMD cases to the national surveillance system. The vaccine effectiveness was estimated with the screening method in the study.	Vaccination schedule and uptake: 14 months of age, 93% in 2019; 14–18 years of age, 86% in 2019[7]
England	Academic year 2015/16*	Academic year 2018/19*	14–18 years of age (routine cohorts)	August 2015: MenACWY introduced into NIP at 13–14 years of age, replacing MCCV which had been used since September 2013. August 2015 to December 2017: MenACWY** catch-up campaign for those aged 14–18 years old. August 2015: MenACWY** introduced for first time university entrants <25 years of age not previously vaccinated with a MenACWY vaccine. This was later extended so that any individual <25 years of age could receive MenACWY** vaccination. Vaccination schedule and uptake: all students in school years 9 or 10 (at around 14 years of age) and any individual <25 years of age not previously vaccinated with a MenACWY vaccine; the school-based program achieved uptake of 71–86% by August 2019. Reference:[20,21]	The vaccine effectiveness and impact estimates were directly identified in Campbell et al.[20] Meningococcal septicemia is a. Incidence of IMD cases was calculated based on the number of IMD cases reported to the meningococcal disease surveillance in England. Vaccine effectiveness was estimated with the indirect screening method in the study.	An 83% vaccine uptake of MenACWY** was achieved over the first four years of the program. The school-based program achieved uptake of 71–86% by August 2019[20,21]
Australia	2017	2019	1–4 years and 15–19 years of age	July 2018: MenACWY-TT implemented into NIP at 12 months of age replacing MCCV, which had been used in NIP since 2003. This also replaced some state MenACWY*** programs which had been introduced from 2017. April 2019: MenACWY-TT implemented into NIP at 14–16 years of age replacing a number of state MenACWY*** programs which had been introduced from 2017. April 2019 onwards: MenACWY-TT catch up campaign for those 15–19 years of age[22–24]	The incidence of IMD was estimated by using the reported number of IMD cases extracted from the National Meningococcal Surveillance Program annual report, 2017 and 2019[22,25] and the Australian Bureau of Statistics.	Vaccination schedule and uptake: 12 months of age, 95.0% in 2020; 15–19 years of age, 74.3% in adolescents by 17 years of age in 2020[22–24]
Chile	2012	2019	1–4 years of age	January 2014: MenACWY-TT introduced into NIP at 12 months of age. This replaced a prior MenACWY# program undertaken between October 2012 and December 2013 where vaccine was offered to those between 9 months and 4 years of age.:[19,26]	The age specific incidence of IMD was estimated by using the reported number of IMD cases extracted from Villena et al.[19,26]	Vaccination uptake at 12 months of age was 94.3% between 2013 and 2019.[19,26]

*Academic years run from September to August the following year.
**Both MenACWY-TT and MenACWY-CRM were initially used in the program but from December 2016 MenACWY-TT was exclusively supplied.
***State programs incorporated the use of multiple MenACWY vaccines. Vaccines available at this time included MenACWY-DT, MenACWY-CRM and MenACWY-TT.
#MenACWY-DT and MenACWY-CRM were used.

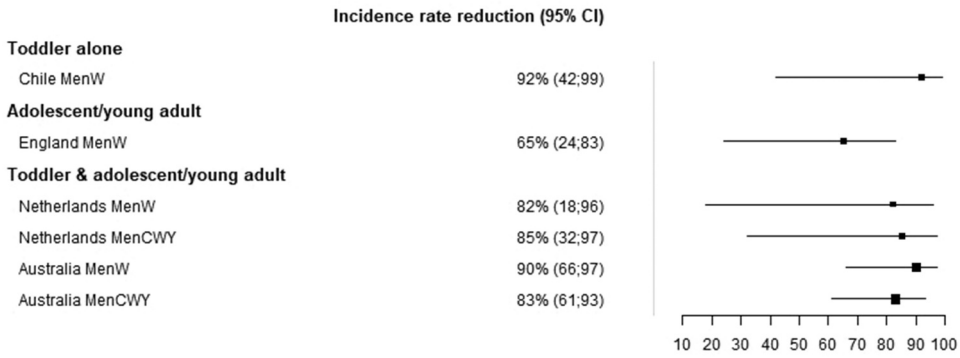

Figure 1. Incidence rate reductions (95% CI) against MenW and MenCWY disease following the introduction of MenACWY vaccination programs among vaccine-eligible age groups.

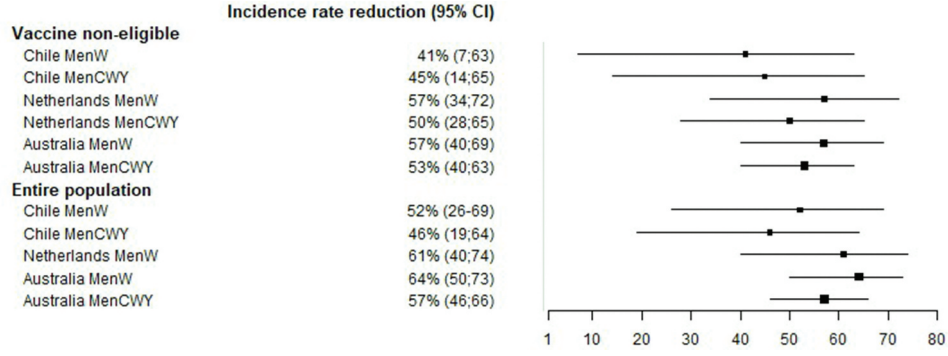

Figure 2. Incidence rate reductions (95% CI) against MenW and MenCWY disease following the introduction of MenACWY vaccination programs among non-vaccine-eligible age groups and the entire population.

Table 2. Reported vaccine effectiveness (95% confidence interval) of MenACWY from the Netherlands and England.

	The Netherlands (toddlers)[7]	England (adolescents and young adults)[20]
MenW	92% (−20%; 99.5%)*	94% (76 ; 99)**
MenY	NA	82% (16 ; 98)**
MenCWY	NA	94% (80 ; 99)**

*Children born on or after March 1, 2017 and diagnosed at the age of 14 months and older between May 1, 2018 and December 31, 2020.
**Vaccine-eligible cohorts as detailed in Table 1.

Australia and from 0.95/100,000 population ($n = 29$ cases) to 0.10/100,000 population ($n = 3$ cases) in the Netherlands. The IIRs against MenW disease in the Netherlands and Australia were 82% (95% CI 18%-96%) and 90% (95% CI 66%-97%), respectively (Figure 1 and Supplementary Table S1).

Indirect and total impact of MenACWY-TT vaccination programs

In addition to the direct protection of immunized individuals, indirect protection was induced by MenACWY-TT as indicated by the IIRs in non-vaccine-eligible cohorts. These ranged from 45% (95% CI 14%-65%) in Chile, to 50% (95% CI 28%-65%) in the Netherlands, to 53% (95% CI 40%-63%) in Australia (Figure 2 and Supplementary Table S1). Considering all age groups, which included both vaccine-eligible and non-eligible cohorts, MenCWY IRR was 46% (95% CI 19%-64%) in Chile (a decrease in incidence from 0.36 to 0.17/100,000 population, from 65 cases to 31 cases) and 57% (95% CI 46%-66%) in Australia (a decrease in incidence from 0.93 to 0.40/100,000 population, from 230 cases to 101 cases) (Figure 2 and Supplementary Table S1). MenCWY IRR data for all age groups were not reported for the Netherlands or England. Similar MenW IRRs were seen in the Netherlands, Australia, and Chile when comparing non-vaccine-eligible cohorts and all age groups (Figure 2 and Supplementary Table S1). MenW IRR data were not reported for non-vaccine-eligible cohorts or all age groups for England.

During the evaluation period (i.e., from the baseline to post-NIP period), MenC incidence remained low (≤0.06/100,000 population) in both vaccine-eligible and non-eligible cohorts in Chile, the Netherlands, and Australia for which MenC case numbers were available (Supplementary Table S1).

Discussion

Although the incidence of IMD is historically low in many regions of the world, as the epidemiology of IMD is changing constantly with sudden switches in serogroup and/or clonal complex predominance contributing to the unpredictable nature of the disease, continued surveillance is paramount to monitor evolving epidemiology and to support implementation of new vaccination strategies. Historical surveillance data show that five serogroups (A, B, C, W and Y) cause the vast

majority of cases,[2] suggesting that these serogroups will remain the dominant cause of IMD. During the last decade, many countries have decided to introduce quadrivalent MenACWY vaccines into their NIPs, in response to increasing MenW and MenY cases.[29] In countries where a switch from MCCV to MenACWY-TT was performed, MenC incidence remains low and substantial reductions of MenW and MenY cases have been observed[7,22] supporting the argument that it is beneficial to replace MCCV with MenACWY-TT to provide broader serogroup coverage.

Several counties have included quadrivalent conjugate MenACWY vaccines in their immunization programs; these include Austria, Belgium, Czech Republic, Greece, Ireland, Italy, Malta, the Netherlands, and Spain in Europe.[30] However, there are limited or no MenACWY vaccine impact/effectiveness data available for most of these countries due to very recent introductions such as Czech Republic, Malta, Spain and Italy in late 2019 - early 2020.[30] The vaccine effectiveness and impact analyses and data were available in four countries after these countries successfully implemented the vaccine program before 2019. MenACWY-TT was introduced and exclusively used in the NIPs in Chile in 2014; the Netherlands and Australia replaced the MCCV program with MenACWY-TT in 2017 and 2018, respectively.[7,19,22] The MenACWY program in England initially used in 2015 both MenACWY-TT and MenACWY-CRM_{197}, but then in 2016 switched to the exclusive use of MenACWY-TT.[31,32] In Chile and Australia, immunization campaigns using other MenACWY vaccines were implemented prior to the introduction of MenACWY-TT to their NIPs. The use of other MenACWY vaccines either prior to the MenACWY-TT NIPs or initially in the NIP along with MenACWY-TT in Chile, England, and Australia makes it difficult to fully attribute the public health impact to MenACWY-TT alone. Nonetheless, as summarized in this review, available data from Chile, the Netherlands, and Australia showed a substantial reduction in MenCWY incidence in vaccine-eligible (83%-85%) and non-vaccine-eligible age groups (45%-53%) after the administration of a single dose of MenACWY-TT, demonstrating both direct and indirect protection.[5,6] Since all four countries were responding to an increase in MenW cases, reductions of MenCWY cases were primarily due to reductions in MenW and supplemented by reductions in MenC and MenY cases. Impact of MenACWY vaccines on MenCWY disease incidence have been previously reported, albeit at lower levels than reported here, from a study evaluating primary and booster doses of MenACWY-DT and/or MenACWY-CRM_{197} in the US adolescent program: MenCWY incidence decreased by 28% in adolescents aged 11–15 years in the post-primary dose period and by 36% in those aged 16–22 years in the post-booster dose period.[18]

The substantial IRRs in vaccine-eligible age groups observed following a single dose of MenACWY in toddlers, adolescents or the two combined are driven by the high VE, as reported in the Netherlands and England.[7,20] The continued maintenance of high VE in individuals is expected to be dependent upon the persistence of circulating protective antibodies.[33] Antibody persistence for MenACWY-TT has been extensively evaluated across all age groups,[34–39] including persistence data out to 5–10 years following a single dose in toddlers, children, adolescents, and adults. The reported data suggest that MenACWY-TT provides long-term protection against IMD across multiple age groups and support its use in vaccination programs where a single toddler dose is followed by a booster dose in adolescence. Further analysis of VE and IRRs over time will help to inform on the duration of the impact imparted by vaccination programs incorporating MenACWY-TT.

In Chile, the Netherlands, and Australia, reductions of MenCWY cases or MenW cases were observed in non-vaccine-eligible age groups, indicating an indirect effect of the vaccination programs (in England, IRRs for non-vaccine-eligible age groups were not reported). For indirect protection of unvaccinated individuals to occur, it has been established that implementation of adolescent/young adult vaccination is required, and three countries – England, the Netherlands, and Australia – vaccinated this age group. As adolescents and young adults have the highest meningococcal carriage rate, immunization of this age group with a conjugate vaccine affords the benefits of reducing carriage acquisition, and subsequently interrupting the transmission to the unvaccinated.[40] Further, this population often exhibits social behaviors such as attendance at nightclubs, intimate kissing, smoking, and living in close proximity (e.g. student dormitories), which are linked to increased meningococcal transmission and IMD cases.[41] Thus, vaccination programs targeting the adolescents represent a strategic approach in achieving direct protection in vaccinated individuals as well as indirect protection across other age groups. Previous evaluations have shown that monovalent and MenACWY vaccines reduced meningococcal acquisition and carriage in vaccine recipients,[5,8,42–44] although one UK university study suggested that the impact varies on the circulating meningococcal clone.[45] The exact mechanism of carriage interruption remains to be fully elucidated, although it is widely accepted that a high vaccine uptake in a population with a high carriage rate (e.g., adolescents) is required to successfully interrupt transmission.[40] Differences in the indirect effects observed in our analysis between the countries may be explained by differences in circulating IMD disease causing strains, time periods analyzed, catch-up programs, speed of NIP implementation/catch-up completion, uniformity of vaccine uptake within a country and vaccine uptake in NIP, catch-up, and age cohorts analyzed.

It is worth noting that Chile was the only country that did not have an adolescent MenACWY NIP. The indirect protection was observed after about 7 years of vaccination in Chile, instead of 2 years in the other countries where adolescents were incorporated in the vaccination strategy. There were marked IRRs of MenCWY (45%) and MenW (41%) in non-vaccine-eligible age groups. MenCWY cases in non-vaccine-eligible age groups reduced from 52 to 30 cases between 2012 and 2019, which was primarily due to a reduction in MenW cases from 47 to 29 (MenW cases initially increased from 2012 to 2014, and then gradually decreased from 2014 to 2019). It is not clear why the incidence of MenW decreased in non-vaccine-eligible age groups in the absence of an adolescent

vaccination program. However, as *N. meningitidis* epidemiology is known for its cyclical nature,[46] it is possible that the reduction of MenW incidence was associated with a natural decline.[19] Such secular trend of MenW disease has been reported in Argentina, where MenW incidence started to decline prior to the vaccine implementation.[47] Further, given the social and family dynamics in Chile, including frequent children-elderly contact,[48] it is also possible that the toddler vaccination program may have contributed to the observed indirect effects.

Our review is not without limitations. First, among the four countries included in our analysis, the Netherlands was the only country that used MenACWY-TT exclusively and where there was no prior use of MenACWY vaccines. Chile and Australia exclusively used MenACWY-TT in the NIP but there had been some prior use of other MenACWY vaccines. In England the NIP initially also incorporated MenACWY-CRM_{197} for a limited time. These caveats must therefore be considered when assessing the impact of MenACWY-TT in these three countries. Nonetheless, data from Chile, England, and Australia are consistent with those observed in the Netherlands, which collectively confirm the public health impact of MenACWY-TT. The fact that all countries have an active and well-established IMD surveillance system, providing high-quality monitoring of disease trends and achieved similarly high rates of MenACWY vaccine uptake in the age groups targeted supports this conclusion.

The review may be confounded by the natural changes in IMD epidemiology due to factors other than vaccination. As discussed above, unpredictable cyclical nature of MenW disease causing natural changes in IMD incidence cannot be ruled out in the observed incidence reductions.[19] Although we were not able to separate the effects of vaccination programs from temporal trends in IMD incidences, VE calculations against MenW among toddlers in the Netherlands and adolescents in England did show that there is a vaccine-driven impact on IMD. These MenACWY NIPs also differed in the baseline IMD incidence rates, timing of the implementation (starting year 2012–2017), and the target age groups (toddlers alone vs. adolescents/young adults alone vs. toddlers and adolescents/young adults), all of which may have contributed to the differences in the observed vaccine effects.

Conclusion

Recent real-world data have confirmed the public health impact and effectiveness of a single dose of MenACWY-TT in toddlers, adolescents and young adults in multiple countries, through both direct protection of vaccinated individuals and the indirect protection of unvaccinated individuals. The move from MCCV or no meningococcal vaccine use to the broader protection afforded by MenACWY-TT highlights that a proactive approach toward IMD disease prevention is beneficial. The development of a pentavalent MenABCWY vaccine, which combines the serogroup B protein-based vaccine with the ACWY conjugate vaccine into a single vaccine, will likely enhance prevention of IMD due to the broader protection against all five serogroups with a simplified vaccination schedule.

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