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Public health impact and cost-effectiveness of introducing MenACWY vaccination strategies in Germany

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Abstract

Background The invasive meningococcal disease (IMD) routine immunization recommendation in Germany is a meningococcal serogroup C (MenC) conjugate vaccine for toddlers aged 12 months with a catch-up for unimmunized up to 17 years. However, there are no recommendations for routine meningococcal serogroups A, C, W, Y (MenACWY) vaccination or for adolescent vaccinations; this differs from other European countries. This analysis aimed to understand the benefits of implementing adolescent MenACWY vaccination in Germany.

Methods A static population-cohort model evaluating IMD burden and related health outcomes (e.g., cases, cases with long-term sequelae, deaths) was developed to compare any two meningococcal vaccination strategies. We compared hypothetical vaccination strategies that included different approaches to adolescent vaccination in Germany, such as vaccinating at 13-year olds versus 16-year olds and vaccinating with MenC versus MenACWY. Additional strategies considered the benefit that could be provided by switching the current MenC vaccine recommendation in toddlers to MenACWY.

Results All strategies that included MenACWY vaccine were effective in decreasing the number of cases, preventing mortality and offered good value for money. The greatest benefit was observed in individuals vaccinated with MenACWY at 12 months and 16 years of age (2,978 IMD cases averted; 563 IMD deaths prevented). Compared with the current strategy of MenC vaccination at 12 months of age, two-dose strategies that included MenACWY reported incremental cost-effectiveness ratios <€13,205 per quality-adjusted life year. Adolescent strategies of MenC or MenACWY vaccine at 16 years old (with no vaccination at 12 months) dominated current vaccination strategies. Adolescent vaccination at 16 years old versus 13 years old offered slightly better value for money.

Conclusions With recent increases in IMD cases and outbreaks occurring globally following the COVID-19 pandemic, there is a greater urgency to proactively implement a MenACWY vaccine recommendation to protect adolescents in Germany. This recommendation would provide direct protection to a group at increased risk and offer indirect protection to other population groups. Implementation of a school-based immunization program could increase vaccine uptake and overcome hurdles in adolescent vaccination.

Keywords Invasive meningococcal disease, Vaccination, Public health, Public policy, Germany, MenACWY

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Background

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, typically manifests as meningitis, sepsis, or both [1]. While IMD is relatively rare, it is associated with rapid onset, severe outcomes, and high fatality rates (4–20%) [2, 3]. IMD is further characterized by severe long-term sequelae in many survivors [4–6].

IMD has historically been predominantly caused by five serogroups of *Neisseria meningitidis* (A, B, C, W, and Y). From 2010 to 2019, IMD incidence ranged from 0.0 to 10.2, with the highest incidences associated with outbreaks reported in Niger and Burkina Faso. Excluding these outliers, the highest incidence of 2.8 was reached in New Zealand in 2019. The incidence in Saudia Arabia, the United States, and Bulgaria was consistently below 0.2 during this 10-year interval. During the COVID-19 Pandemic, the incidence rates of IMD decreased globally due to mitigation measures [7]. However, the easing of lockdown restrictions and the return to pre-pandemic behaviors led to increases in IMD [8, 9].

The incidence of IMD is age-specific, and the highest incidence is observed among infants and young children [10]. Due to typical social behaviors (e.g., close living, sharing food and drinks, close contact and intimacy, and frequent visit to crowded places), adolescents and young adults are also at an increased risk of disease, which leads to a second incidence peak in this age group in many countries [10, 11]. Additionally, this age group is the primary carrier and transmitter of the meningococcus [12–15], and immunizing this group can interrupt transmission and provide indirect protection to other age groups [16].

Across Europe, meningococcal serogroup B (MenB) is responsible for most IMD cases, followed by meningococcal serogroup C (MenC) [10]. Although meningococcal serogroup W (MenW) and meningococcal serogroup Y (MenY) cases are not as frequently observed, their numbers have been increasing [10].

In Germany, the overall incidence of IMD in 2019 was 0.3/100,000 persons [17]. The incidence was highest in infants < 1 year old and one-year olds (2.8/100,000 and 1.9/100,000, respectively) with a second peak in adolescents and young adults (0.5/100,000 in 15- to 19-year-olds and 0.6/100,000 in 20- to 24-year-olds) [18]. In Germany, the German Standing Committee on Vaccination (Ständige Impfkommission, STIKO) issues recommendations on vaccination [19], as well as federal state-specific committees in Germany, e.g., SIKO (Saxon Vaccination Committee) [20]. In 2006, STIKO recommended routine immunization with a monovalent MenC conjugate vaccine for all children aged 12 months [19] along with a catch-up for unvaccinated people ≤ 17 years of age [19, 21] However, federal state committees may make different recommendations aligning with pioneering immunization practices in other countries, such as SIKO recommending MenACWY vaccination in infants, toddlers, and adolescents as well as MenB vaccination in infants and toddlers [20].

While recent IMD outbreaks observed in other European countries have rarely occurred in Germany, the value of apreventive vaccination program in minimizing the public health and economic impact have been clearly demonstrated in other countries [22]. Many countries reactively introduced IMD vaccination programs following increases in cases and outbreaks, such as mass immunization in the United Kingdom (UK) and the Netherlands following a MenC outbreak in the mid-1990s and early-2000s [23–27]. In both countries, MenC vaccination has now been switched to MenACWY vaccination after MenW outbreaks [23, 24, 28–30]. Accordingly, proactively extending current vaccination recommendations against IMD should be a public health goal considering the increased uncertainty and unpredictability of IMD [31] despite the relatively low number of cases. Incidence rates are also changeable, for example MenY incidence in Germany for infants had an average incidence of 0.13 per 100,000 persons between 2010 and 2019, increased to 0.25 in 2022 and, as of June 2023, was 0.38 [32].

Given the recent increase in serogroup Y cases in Germany and the increase in serogroups Y and W cases in neighbouring countries, such as France, the aim of this analysis was to estimate the impact of switching from a MenC to a MenACWY vaccine in the recommendation at 12 months of age and introducing an adolescent MenACWY vaccine dose in Germany to increase population protection against IMD and to mitigate a potential further increase in vaccine-preventable serogroups, such as those observed in France.

Reaching adolescents with vaccines is challenging in Germany, leading to low uptake rates compared to some other countries. In the United States, where adolescent MenACWY vaccination is recommended at age 11 and 16, approximately 90% of 17 year olds have received at least one dose [33]. Furthermore, in 16 to 17 year old females and males in the UK, one-dose coverage of human papilloma virus (HPV) vaccine in 2021–2022 was 86.5% and 81.5%, respectively, and two-dose coverage was 76.8% and 70.9%, respectively [34]. This is versus only 47.2% among 15-year old females in 2019 in Germany [35]; Germany's HPV vaccine uptake rates are currently comparable to those in France which has no school based program, with one dose coverage among 15-year olds at 45.8% and complete coverage of 16 years old at 41.5% in the 2006 birth cohort [36]. Implementation of a school-based IMD adolescent vaccination program, similar to those implemented in the UK or the Netherlands, or similar to HPV school-based vaccination pilots implemented in one German school district could further

increase these vaccine uptake rates [37, 38]. For example, the HPV school pilot in the German federal state of Hesse reported a greater average vaccine uptake of 71.2% compared with the federal state average of 59.1%, when considering uptake of two HPV doses within one year [38]. Although HPV vaccination rates may be lower than other adolescent vaccinations due to the stigmatization of an adolescent vaccine targeting a sexually transmitted infection, evidence suggests that in Germany, many other factors (e.g., school vaccination programmes, vaccine misinformation on social media, and vaccine reimbursement) have a more important impact on vaccination uptake and would be expected to influence IMD vaccination uptake [39–46]. Therefore, the analysis additionally explores the impact of increases in vaccination uptake on direct and indirect protection achieved by implementing school-based vaccination programs.

Methods

Multi-cohort population model

The structure of the present model to evaluate the burden of IMD and its associated costs and outcomes was informed by a review of previous infectious disease cost-effectiveness modeling literature and models investigating IMD vaccination [47–68]. Based on this review of previously published models, a static model was selected; this is more conservative than a dynamic modeling approach [69]. A static multi-cohort population model was constructed in Microsoft Excel® to compare the cost effectiveness of various meningococcal vaccination strategies while considering the clinical course of IMD in the overall German population.

For each age group, after applying the base-case incidence, the number of IMD cases in the population caused by serogroups A, C, W, and Y in the absence of an intervention or comparator vaccination strategy is calculated. The model calculates the cost and effectiveness outcomes based on the number of IMD cases, applying the vaccine effectiveness on the number of cases in the absence of intervention. In the model, certain input parameters are stratified by age, IMD serogroup, and/or disease manifestation. A diagram of the model structure is provided in Additional File 1, Figure A1.

The model considers the health and cost outcomes due to acute disease and long-term complications following IMD. The model includes a payer perspective to capture the direct costs and effects of IMD and a societal perspective to capture the direct and indirect outcomes of IMD. The key outcomes evaluated by the model are the number of cases, number of deaths, incremental quality-adjusted life years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs). The QALY losses of patients and their caregivers and the reason for the QALY loss (i.e., loss due to acute disease, long-term loss without sequelae, long-term loss with sequelae, and loss due to death) were considered to capture a broader range of patient and caregiver outcomes. The average age of caregivers in the model is assumed to be 40 years old and it is assumed that each IMD case has two caregivers [70].

The model adopts a 30-year vaccine program duration. New population cohorts enter the model for a duration of 30 years and are followed until death, which is assumed to occur at no older than 100 years of age. Therefore, discounting was applied because the model accumulates costs and health outcomes over 100 years. Discount rates of 3% were applied to the cost and health outcomes based on STIKO cost-effectiveness modelling guidelines, with sensitivity analyses conducted with a 1% discount rate for health outcomes, respectively [71]. To determine the values of the model parameters, a literature search was conducted to obtain the latest available data of the disease burden of IMD, vaccination programs, health resource utilization, associated costs, and utilities. When possible, German-specific input values were used in the model, and if German-specific data were unavailable, robust input values derived from other regions that could be generalizable to Germany were used.

Vaccination strategies

The standard of care in Germany for meningococcal protection is a routinely recommended vaccination against MenC with one dose at 12 months of age. All vaccination strategies included in this analysis are outlined in Additional File 1, Table A1. They reflect the most feasible strategies that could be implemented in Germany based on guidance from other regional recommending bodies, such as SIKO [20]. The introduction of MenB vaccinations was not in the scope of this analysis and can be found in Scholz et al. [72].

Toddler (i.e., 12 month old) MenC vaccine uptake rates were assumed to be 76.83% (average uptake of the birth cohorts 2008 [71.7%] [73], 2009 [81.0%] [74], and 2016 [77.8%] [73]) across all 12-month doses. Adolescent vaccine uptake rates were assumed to be 65%, which is higher than the current vaccine uptake rates observed in HPV adolescent vaccination. However, the base-case analysis assumes that increased uptake rates can be achieved by introducing school based vaccination to overcome challenges with adolescent vaccination [75].

Epidemiological data

Epidemiological data were used to determine the number of IMD cases in Germany. The numbers of German inhabitants in 10 age groups (< 1 year, 1 year, 2–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–29 years, 30–59 years, and 60 + years) were included in the model. The population size in each age group is shown in

Additional File 1, Table A2 based on data from the German Federal Statistical Office.

IMD incidence data vary across serogroups and age groups; thus, the incidence data of each serogroup were obtained from the SurvStat@RKI 2.0 [32] and used to inform the base-case analysis (Table 1). Incidence estimates represent an average of the 10-year period between 2010 and 2019 to provide a stable baseline in the period after MenC vaccination was implemented and prior to the impact of COVID-19 lockdown measures being observed. Hypothetical high incidence scenarios were also explored for MenC, MenW, and MenY serogroups (see Additional File 1, Table A3). High MenC incidence was based on the average MenC incidence observed in the period prior to introduction of MenC vaccination (2002 to 2005); high MenW incidence was estimated as the average of 2016–2018, the years with highest MenW incidence in Germany; and high MenY incidence was estimated based on a hypothetical scenario where peak incidence across each age group observed in Germany between 2010 and 2019 was modeled for each age group; however, given changes in IMD epidemiology post-COVID these scenarios may still underestimate high IMD incidence and the beneficial impact of vaccinations [32]. Given the low number of cases occurring due to serogroup A and that no high incidence scenarios have been seen in the Western world for a significant period, a high MenA incidence scenario was not considered.

Vaccine effectiveness

Vaccine effectiveness (VE), as calculated over time, is dependent on estimates of vaccine efficacy [30], waning [76, 77], and herd effect [78], which are provided in Additional File 1, Table A4 and A5. Effectiveness of MenC or MenACWY vaccine in toddlers was assumed to be 92% [30] for the first dose and second dose for each serogroup with 22.12% annual waning [77]. The VE of MenC and MenACWY vaccine in adolescents was assumed to be 94% [23] with subsequent annual waning of 5.85% for each serogroup [76].

The model also incorporates a static approximation of the herd effect of the MenC and MenACWY vaccines resulting from adolescent vaccination. The model assumes that when applied, the herd effect reduces the number of IMD cases by 50% in the unvaccinated population groups as well as in vaccinated non-responders; however this may be a conservative estimate as those who have an initial response that subsequently wanes would not be protected by herd immunity [78]. Sensitivity analyses were also conducted assuming a lower herd effect of 30%.

Table 1 IMD incidence by Serogroup (per 100,000)

Age	A	C	W	Y
< 1 year	0.015	0.639	0.133	0.134
1 year	0.000	0.389	0.081	0.000
2–4 years	0.009	0.057	0.027	0.013
5–9 years	0.000	0.023	0.003	0.009
10–14 years	0.003	0.040	0.009	0.023
15–19 years	0.000	0.172	0.050	0.122
20–24 years	0.002	0.120	0.045	0.038
25–29 years	0.000	0.072	0.014	0.008
30–59 years	0.001	0.038	0.009	0.012
60 + years	0.003	0.048	0.024	0.053
Source:	SurvStat@ RKI 2.0 data [32], query date: August 2023			
Note:	Incidence values are averages of 10-year incidence, between 2010 and 2019			

Abbreviation: RKI = Robert Koch-Institut

Clinical inputs

The most frequent manifestations of the acute infection are meningitis and septicemia. The model includes meningitis, septicemia, and meningitis + septicemia. The population distribution of IMD cases by manifestation in the model is informed by estimates from the Robert Koch Institute (RKI) based on 2019 data (Additional File 1, Table A6) [18]. The model also includes age-specific case fatality rates, which range from 5 to 28% (Additional File 1, Table A7), and probability of long-term sequelae (Additional File 1, Table A8). The long-term sequelae following the acute phase of IMD include amputation, anxiety, arthritis, cognitive impairment, depression, hearing loss, migraine, motor deficits, neurological disability, renal failure, seizure, skin scarring, speech problems, and visual impairments.

Cost inputs

The model assumes direct cost associated with vaccination, such as vaccine acquisition cost and vaccine administration cost, as well as direct medical costs for treatment of the acute phase of the disease and for the treatment of long-term sequelae. The model includes indirect cost for IMD during the acute phase for patients and their caretakers. Additionally, the model considers patients' and caretakers' productivity losses due to long-term sequelae as well as due to patients' death. All cost values were obtained from publicly availably sources, such as previously published articles and databases, as specified and presented in Additional File 1, Tables A9 to A13. All costs were inflated to 2023 Euros [79].

Disutility inputs

IMD can decrease the quality of life of patients and their caregivers. During the acute phase of IMD, the utilities of patients is assumed to decrease by 0.4 for meningitis and by 0.51 for septicemia with or without meningitis (Additional File 1, Table A14) [61]. Furthermore, IMD can reduce the quality of life of patients and caregivers after

Table 2 Public Health Impact of Various IMD vaccination strategies on IMD cases

No	Vaccination Strategy	Total Cases by Serogroup				Total Cases	Total Cases Averted compared to base case
		A	C	W	Y		
1	MenC at 12 months of age (current schedule and base case)	96.1	2642.3	936.5	1660.0	5334.9	---
2	MenACWY at 12 months of age	92.9	2642.3	911.1	1648.4	5294.7	40.2
3	MenC at 12 months & 13 years of age	96.1	1171.7	936.5	1660.0	3864.3	1470.6
4	MenC at 12 months & 16 years of age	96.1	1158.4	936.5	1660.0	3850.9	1483.9
5	MenC at 12 months & MenACWY at 13 years of age	46.1	1171.7	423.3	753.1	2394.3	2940.6
6	MenC at 12 months & MenACWY at 16 years of age	46.3	1158.4	418.9	751.7	2375.4	2959.5
7	MenACWY at 12 months & 13 years of age	44.6	1171.7	411.5	749.3	2377.1	2957.7
8	MenACWY at 12 months & 16 years of age	44.7	1158.4	406.9	747.2	2357.2	2977.6
9	MenC at 16 years of age	96.1	1205.0	936.5	1660.0	3897.6	1437.3
10	MenACWY at 16 years of age	46.3	1205.0	418.9	751.7	2422.0	2912.9

Abbreviations: IMD = invasive meningococcal disease; MenACWY = meningococcal serogroup A, C, W, Y; MenC = meningococcal serogroup C

Table 3 Public Health Impact of Various IMD vaccination strategies on IMD deaths (base-case results)

No	Vaccination Strategy	Total Deaths by Serogroup				Total Deaths	Total Deaths Averted compared to base case
		A	C	W	Y		
1	MenC at 12 months of age (current schedule and base case)	21.7	491.7	189.6	362.8	1065.9	---
2	MenACWY at 12 months of age	21.5	491.7	187.4	362.0	1062.6	3.3
3	MenC at 12 months & 13 years of age	21.7	231.8	189.6	362.8	806.0	259.9
4	MenC at 12 months & 16 years of age	21.7	229.5	189.6	362.8	803.7	262.2
5	MenC at 12 months & MenACWY at 13 years of age	10.6	231.8	90.8	175.1	508.3	557.5
6	MenC at 12 months & MenACWY at 16 years of age	10.6	229.5	90.1	174.6	504.8	561.1
7	MenACWY at 12 months & 13 years of age	10.5	231.8	89.7	174.9	506.9	559.0
8	MenACWY at 12 months & 16 years of age	10.5	229.5	89.1	174.2	503.3	562.6
9	MenC at 16 years of age	21.7	233.7	189.6	362.8	807.9	258.0
10	MenACWY at 16 years of age	10.6	233.7	90.1	174.6	509.0	556.9

Abbreviations: IMD = invasive meningococcal disease; MenACWY = meningococcal serogroup A, C, W, Y; MenC = meningococcal serogroup C

the acute phase depending on various factors, such as death or long-term sequelae due to IMD. Therefore, the model considers the utility decrements of patients after the acute phase, and the utility decrements incorporated into the model are shown in Additional File 1, Table A15.

Analysis approach

The base-case analysis was conducted from a German societal perspective using the settings and inputs described previously. All hypothetical vaccine strategies were compared to the current vaccination schedule in Germany, i.e., one dose of MenC vaccine at 12-months of age. Additional deterministic sensitivity analyses and scenario analyses were conducted to explore the validity and robustness of the results and the key drivers of the clinical impact and cost-effectiveness of various IMD vaccination strategies.

Results

Public health impact

The modeling of the various hypothetical vaccination strategies compared with the current standard in Germany (i.e., MenC vaccination at 12 months of age) demonstrates that each of the strategies provides incremental benefit with respect to preventing cases and preventing deaths over the model time horizon (Tables 2 and 3). All strategies that include an adolescent MenACWY vaccine are extremely effective, with the greatest benefit compared to the base case observed when individuals are vaccinated with MenACWY at 12 months and 16 years of age (2,978 IMD cases averted; 563 IMD deaths prevented, Table 1).

Of the strategies explored, those including toddler-alone vaccinations resulted in the fewest numbers of additional cases prevented. However, even these strategies were more effective in preventing IMD cases than the incumbent strategy of vaccination at 12 months with MenC only. Switching from the currently recommended

MenC vaccination to MenACWY vaccine would prevent three additional IMD deaths and 40 MenA, MenW and MenY cases.

High incidence scenarios

Different high incidence scenarios of MenC, MenW, and MenY were explored to understand the public health impact of the different vaccination strategies in hypothetical situations in which the incidence rates may peak. Three vaccination strategies were selected for exploratory purposes: MenC at 12 months and 13 years of age; MenC at 12 months and MenACWY at 13 years of age; and MenACWY at 12 months and 13 years of age. Of these three strategies and when compared with MenC vaccination at 12 months of age alone, the vaccination strategy offering the greatest protection was MenACWY at 12 months and 13 years of age (greatest number of cases and deaths averted in the various high incidence scenarios); assuming simultaneous high incidences for CWY, a total of 6306 IMD cases would be averted (51.5 MenA cases, 3094.1 MenC cases, 828.1 MenW and 2332.5 MenY cases) and 993 IMD-related deaths prevented (11.2 MenA deaths, 352.2 MenC deaths, 156.7 MenW, 473.6 MenY) (Table 4).

Economic impact

Total costs of MenC at 12 months of age was €1,200.72 million, and QALY loss was 21,735. The cost-effectiveness of each IMD vaccination strategy was also estimated (see Table 5). All strategies involving the administration of an adolescent MenACWY (No 5 to No 8 and No 10) vaccine offered a great value for money compared with the current strategy of a MenC vaccination at 12 months of age alone. Two dose strategies (No 5 to No 8) reported ICERs less than € 13,205 per QALY. Single-dose strategies of MenC or MenACWY at 16 years dominated the current vaccination strategy. Vaccination strategies that included an adolescent vaccine were more cost-effective than vaccination strategies that included only toddler vaccinations regardless of whether it was a MenC or MenACWY vaccine. Two-dose vaccination strategies including adolescent vaccination at 13 years of age were marginally more cost-effective than those at 16 years of age.

To better understand the costs contributing to the cost-effectiveness estimates, the breakdown of discounted costs was considered for each of the vaccine strategies. Vaccine costs (acquisition and administration), death-related costs, and broader caregiver costs represented the greatest relative proportions of the total costs (Table 6).

Scenario analyses

The parameters considered most important in the German context and the parameters with the greatest uncertainty were evaluated in deterministic sensitivity analyses comparing MenACWY vaccination at 12 months and 13 years of age versus only MenC vaccination at 12 months of age. Since vaccination strategies containing an adolescent MenACWY vaccine already reported favorable ICERs, similar trends were observed when variables further decreased costs or improved the cost-effectiveness ratio. When applying the alternate STIKO discounting rate of 1% for health outcomes; when adding in sequelae costs for migraine; and when removing recurring annual costs for long-term sequelae, the vaccination strategy of MenACWY at 12 months of age and MenACWY at 13 years of age continued to offer significant value for money.

Factors that were identified as having the greatest relevance in Germany on the effectiveness of the adolescent MenACWY vaccination strategies included the vaccine uptake rates and the estimated herd effect. Therefore, scenario analyses were conducted exploring low and high adolescent vaccine uptake scenarios (50% and 80%, respectively) compared with the base-case assumption of 65% adolescent vaccine uptake as well as a lower estimate of herd effect (30% compared with the base-case assumption of 50% herd effect) (See Tables 7 and 8). High adolescent uptake rate of 80% resulted in almost 2-fold ICER increase (€ 21,012 per QALY). However, when adolescent vaccine uptake was assumed to be 50%, the ICER dropped almost 5-fold, to € 2,695 per QALY. With 50% adolescent vaccine uptake and lower herd effect (30%), the ICER almost doubled (€ 20,788 per QALY) while still offering significant value for money.

Discussion

Public health and policy implications

Reducing the meningococcal disease burden is paramount not only in Germany but also worldwide [80]. Given the high number of bacterial meningitis cases globally, the World Health Organization (WHO) *Global Road Map to Defeat Meningitis* sets overall goals targeting a 70% reduction in deaths and a 50% reduction in cases [80]. Prevention of IMD cases and deaths is therefore an important component of the overall strategy for achieving the holistic meningitis roadmap goals. Every country is expected to make progress in supporting the introduction of IMD vaccination programs and achieving high vaccine uptake to be better able to provide additional protection than currently achieved. Some European countries (e.g., France, Netherlands, and the UK) have already established MenACWY vaccination programmes for toddlers and/or adolescents, allowing for greater IMD population protection than the 12 month old MenC vaccination programme that is currently the recommended care in Germany [23–25, 81–84].

Table 4 Public Health Impact of Various IMD vaccination strategies vs. the current strategy on IMD cases averted and IMD-Related deaths averted

Comparator Strategies	Base	High MenC incidence	High MenW incidence	High MenY incidence	High MenC-WY incidence
Cases Averted					
MenC at 12 months & MenC at 13 years of age	1470.6 (ACWY)	3094.1 (ACWY)	1470.6 (ACWY)	1470.6 (ACWY)	3094.1 (ACWY)
	A: 0	A: 0	A: 0	A: 0	A: 0
	C: 1470.6	C: 3094.1	C: 1470.6	C: 1470.6	C: 3094.1
	W: 0	W: 0	W: 0	W: 0	W: 0
	Y: 0	Y: 0	Y: 0	Y: 0	Y: 0
MenC at 12 months and MenACWY at 13 years of age	2940.6 (ACWY)	4564.1 (ACWY)	3236.1 (ACWY)	4347.2 (ACWY)	6266.2 (ACWY)
	A: 50	A: 50	A: 50	A: 50	A: 50
	C: 1470.6	C: 3094.1	C: 1470.6	C: 1470.6	C: 3094.1
	W: 513.2	W: 513.2	W: 808.7	W: 513.2	W: 808.7
	Y: 906.8	Y: 906.8	Y: 906.8	Y: 2313.4	Y: 2313.4
MenACWY at 12 months & MenACWY at 13 years of age	2957.7 (ACWY)	4581.2 (ACWY)	3260.9 (ACWY)	4379.6 (ACWY)	6306.3 (ACWY)
	A: 51.5	A: 51.5	A: 51.5	A: 51.5	A: 51.5
	C: 1470.6	C: 3094.1	C: 1470.6	C: 1470.6	C: 3094.1
	W: 525	W: 525	W: 828.1	W: 525	W: 828.1
	Y: 910.7	Y: 910.7	Y: 910.7	Y: 2332.5	Y: 2332.5
Cases with Long-term Sequelae Averted					
MenC at 12 months & MenC at 13 years of age	487.3 (ACWY)	1103.6 (ACWY)	487.3 (ACWY)	487.3 (ACWY)	1103.6 (ACWY)
MenC at 12 months and MenACWY at 13 years of age	959.2 (ACWY)	1575.5 (ACWY)	1055.5 (ACWY)	1410.9 (ACWY)	2123.5 (ACWY)
MenACWY at 12 months & MenACWY at 13 years of age	965.5 (ACWY)	1581.8 (ACWY)	1064.6 (ACWY)	1422.8 (ACWY)	2138.3 (ACWY)
Deaths Averted					
MenC at 12 months & MenC at 13 years of age	259.9 (ACWY)	352.2 (ACWY)	259.9 (ACWY)	259.9 (ACWY)	352.2 (ACWY)
	A: 0	A: 0	A: 0	A: 0	A: 0
	C: 259.9	C: 352.2	C: 259.9	C: 259.9	C: 352.2
	W: 0	W: 0	W: 0	W: 0	W: 0
	Y: 0	Y: 0	Y: 0	Y: 0	Y: 0
MenC at 12 months and MenACWY at 13 years of age	557.5 (ACWY)	649.8 (ACWY)	613.7 (ACWY)	841.9 (ACWY)	990.4 (ACWY)
	A: 11.1	A: 11.1	A: 11.1	A: 11.1	A: 11.1
	C: 259.9	C: 352.2	C: 259.9	C: 259.9	C: 352.2
	W: 98.9	W: 98.9	W: 155	W: 98.9	W: 155
	Y: 187.7	Y: 187.7	Y: 187.7	Y: 472.1	Y: 472.1
MenACWY at 12 months & MenACWY at 13 years of age	559 (ACWY)	651.3 (ACWY)	615.8 (ACWY)	844.6 (ACWY)	993.7 (ACWY)
	A: 11.2	A: 11.2	A: 11.2	A: 11.2	A: 11.2
	C: 259.9	C: 352.2	C: 259.9	C: 259.9	C: 352.2
	W: 99.9	W: 99.9	W: 156.7	W: 99.9	W: 156.7
	Y: 188	Y: 188	Y: 188	Y: 473.6	Y: 473.6

Abbreviations: MenACWY = meningococcal serogroup A, C, W, Y; MenC = meningococcal serogroup C

Our analysis demonstrates that the introduction of MenACWY vaccination would have a positive public health impact by preventing IMD cases and IMD-related deaths in Germany in the vaccinated cohort as well as in other population groups when adolescents are immunized. Compared with the current vaccination recommendation of MenC at 12 months of age alone, this would offer significant value for money in most scenarios from a societal perspective. Given the proven effectiveness as well as a potential herd effect offered by MenACWY vaccination of adolescents, the clinical effectiveness demonstrated by our results are unsurprising. While meningococcal vaccines may not always be considered cost-effective (e.g. MenB vaccinations), these analyses demonstrate that providing MenACWY adolescent vaccination can be considered good value for money. In the absence of adolescent vaccination, switching the currently recommended MenC vaccine program to MenACWY vaccine in toddlers would maintain the same level of MenC protection as demonstrated by clinical studies concluding comparable MenC immunogenicity of MenACWY-TT and monovalent MenC vaccines [85].

Table 5 Cost-effectiveness of IMD vaccination strategies compared with current vaccination strategy (MenC vaccine at 12 months of age)

No	Comparator Strategies	ICER	Incremental Costs € (millions)	Incremental QALY Gain
1	**MenC at 12 months of age (current schedule and base case strategy against which other vaccination strategies are compared)**	---	---	---
2	MenACWY at 12 months of age	€ 6,560	€ 1.59 M	241.65
3	MenC at 12 months & 13 years of age	€ 51,850	€ 321.81 M	6,206.58
4	MenC at 12 months & 16 years of age	€ 53,880	€ 337.38 M	6,261.64
5	MenC at 12 months & MenACWY at 13 years of age	€ 11,766	€ 140.86 M	11,972.22
6	MenC at 12 months & MenACWY at 16 years of age	€ 12,946	€ 155.99 M	12,049.91
7	MenACWY at 12 months & 13 years of age	€ 12,053	€ 145.69 M	12,087.32
8	MenACWY at 12 months & 16 years of age	€ 13,205	€ 160.71 M	12,170.17
9	MenC at 16 years of age	Dominant	-€ 149.85 M	5,964.81
10	MenACWY at 16 years of age	Dominant	-€ 331.24 M	11,753.07

Abbreviations: ICER = incremental cost-effectiveness ratio; MenACWY = meningococcal serogroup A, C, W, Y; MenC = meningococcal serogroup C; QALY = quality-adjusted life year

This switch to a multivalent vaccine for toddlers would also provide additional direct protection within a vulnerable population group against the estimated forty MenA, MenW, and MenY cases over the modelled period and would potentially provide additional protection if MenW or MenY cases increased as has been recently observed in other European countries [31]. Despite these benefits, a toddler alone vaccination program only provides direct protection across a limited age group and is not expected to provide herd protection across the German population. This explains why the Netherlands subsequently introduced MenACWY vaccine into adolescents shortly after switching their toddler program from MenC to MenACWY [30] and why MenACWY adolescent programs are increasingly employed throughout Europe.

The benefits of adolescent vaccination and achieving direct protection in this age group coupled with herd protection across the entire German population is highlighted by our results where up to 2,978 additional IMD cases could be prevented with adolescent vaccination over the modelled period compared to the incumbent toddler MenC program. The broader protection afforded by MenACWY vaccines is emphasized by results demonstrating that their addition at 13 or 16 years of age to the current MenC toddler program prevents approximately twice the number of IMD cases and deaths as compared to introducing MenC vaccine at these adolescent ages. Similarly, replacing the current toddler MenC dose with adolescent alone MenACWY vaccination would prevent approximately twice the number of IMD cases and deaths than an adolescent alone MenC vaccine program. The greatest impact, however, is when toddler and adolescent MenACWY vaccination are combined with up to an additional 2978 IMD cases and 563 deaths averted over the modelled period. Recommending the same vaccine for both age groups would simplify vaccination schedules and facilitate vaccine provision while providing the broadest protection. This would be very similar to the approach adopted in the Netherlands, where MenACWY is offered at 14 months and 14 years of age [30]. In other European countries, adolescent MenACWY vaccination programs are firmly established, providing protection

Table 6 Breakdown of discounted costs for IMD vaccination strategies

No	Comparator Strategies	Vaccine Acquisition	Vaccine Admin.	Acute IMD	Death	Sequelae	Broader Patient	Broader Caregiver
1	**MenC at 12 months of age (current schedule)**	€ 404 M	€ 91 M	€ 15 M	€ 413 M	€ 36 M	€ 89 M	€ 153 M
2	MenACWY at 12 months of age	€ 411 M	€ 91 M	€ 15 M	€ 411 M	€ 35 M	€ 88 M	€ 151 M
3	MenC at 12 months & 13 years of age	€ 823 M	€ 186 M	€ 11 M	€ 310 M	€ 25 M	€ 61 M	€ 108 M
4	MenC at 12 months & 16 years of age	€ 837 M	€ 189 M	€ 11 M	€ 309 M	€ 25 M	€ 60 M	€ 108 M
5	MenC at 12 months & MenACWY at 13 years of age	€ 831 M	€ 186 M	€ 7 M	€ 198 M	€ 15 M	€ 38 M	€ 67 M
6	MenC at 12 months & MenACWY at 16 years of age	€ 845 M	€ 189 M	€ 7 M	€ 197 M	€ 15 M	€ 37 M	€ 67 M
7	MenACWY at 12 months & 13 years of age	€ 839 M	€ 186 M	€ 7 M	€ 197 M	€ 15 M	€ 37 M	€ 67 M
8	MenACWY at 12 months & 16 years of age	€ 853 M	€ 189 M	€ 7 M	€ 196 M	€ 15 M	€ 37 M	€ 66 M
9	MenC at 16 years of age	€ 433 M	€ 98 M	€ 11 M	€ 311 M	€ 25 M	€ 62 M	€ 110 M
10	MenACWY at 16 years of age	€ 442 M	€ 98 M	€ 7 M	€ 199 M	€ 16 M	€ 39 M	€ 69 M

Abbreviations: ICER = incremental cost-effectiveness ratio; MenACWY = meningococcal serogroup A, C, W, Y; MenC = meningococcal serogroup C; QALY = quality-adjusted life year

Table 7 Public Health Impact Scenarios of MenACWY at 12 months and 13 years

Scenario	Total Cases by Serogroup				Total Cases	Total Cases Averted vs. Current Strategy (MenC at 12 months of age)
	A	C	W	Y		
Base Case (65% adolescent vaccine uptake + 50% herd effect)	44.6	1171.7	411.5	749.3	2377.1	2957.7
High Adolescent Vaccine Uptake (80%)	44.1	1136.5	401.2	731.6	2313.4	3021.5
Low Adolescent Vaccine Uptake (50%)	45.0	1207.0	421.9	767.1	2440.9	2893.9
Low Herd Effect (30%) and Low Adolescent Vaccine Uptake (50%)	63.0	1689.8	590.7	1073.9	3417.3	1917.6
Scenario	**Total Deaths by IMD Serogroups**				**Total Deaths**	**Total Deaths Averted**
	A	C	W	Y		
Base Case (65% adolescent vaccine uptake + 50% herd effect)	10.5	231.8	89.7	174.9	506.9	559.0
High Adolescent Vaccine Uptake (80%)	10.4	228.5	88.8	173.4	501.2	564.7
Low Adolescent Vaccine Uptake (50%)	10.5	235.1	90.7	176.3	512.6	553.3
Low Herd Effect (30%) and Low Adolescent Vaccine Uptake (50%)	14.8	329.1	126.9	246.8	717.6	348.2

Abbreviation: IMD = invasive meningococcal disease

Table 8 Economic impact of scenarios of MenACWY at 12 months and 13 years

Scenario	Incremental Results vs. Current Strategy		
	ICER/QALY	Incr. Costs	Incr. QALY Gain
Base Case (65% adolescent vaccine uptake + 50% herd effect)	€ 12,053	€ 145.69 M	12,087.32
High Adolescent Vaccine Uptake (80%)	€ 21,012	€ 259.55 M	12,352.84
Low Adolescent Vaccine Uptake (50%)	€ 2,695	€ 31.86 M	11,821.89
Low Herd Effect (30%) and Low Adolescent Vaccine Uptake (50%)	€ 20,788	€ 163.32 M	7,856.60

Abbreviations: ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

to other age groups and more vulnerable populations through a herd effect. However, this added protection has been enabled by high vaccine uptake in adolescent populations. Although lower vaccine uptake levels are assumed to be associated with reduced herd protection, to date, no definitive evidence confirms this assumption. Additionally, the model assumes that the herd effect is immediate and reduces IMD incidence in all age groups, which is an unlikely scenario given the absence of a quickly completed high-uptake catch-up program across multiple age cohorts of adolescents/young adults. For example, herd protection following the introduction of the MenACWY vaccine was quickly observed in the Netherlands after a swift high-uptake catch-up campaign in 14- to 18-year-olds, whereas in the UK, it took longer to establish after immunization of the same age group but over multiple years [23, 30]. Malta recently introduced MenACWY vaccine into adolescents but also concurrently to infants and toddlers [37] because of the knowledge that herd protection would not be instantaneous or provide complete protection. Nevertheless, even when using a more conservative assumption of 30% herd effect in our model, a meaningful clinical impact was still observed. The public health impact of an adolescent IMD vaccination strategy in Germany could be even further increased if vaccination rates similar to those in our analysis of a high vaccine uptake among adolescents of 80% are reached; other countries, such as the UK, have been successful in achieving high vaccine uptake levels through school-based vaccination programs, which is a successful approach to achieving greater disease control [78].

The results indicate that vaccination of German adolescents aged 16 years rather than 13 years would prevent a greater number of IMD cases and deaths. However, in addition to the public health impact and economic considerations, the practical implementation issues should also be considered. For example, an adolescent vaccination recommendation at 13 years of age allows a longer follow-up timeframe during which adolescents could visit a physician's office to be immunized, whilst a 16 years of age recommendation only allows two further years during which individuals could obtain vaccination with reimbursement in Germany. A 13 years of age recommendation would also have the added benefit of corresponding with a German optional wellness visit and health-check for adolescents and could provide an opportunity for increased vaccine uptake [86]. School-based programs are important for decreasing hurdles to adolescent vaccination in a population that may not frequently attend doctor visits. The success of a pilot program in German schools for HPV vaccination supports the feasibility of implementing such initiatives in the future [38]. In summary, considering potential implementation success with high uptake rates, recommendation for vaccination at 13 years rather than 16 years would potentially be more beneficial in preventing additional cases even though theoretically vaccination at 16

years would prevent more cases with the same uptake rate, which might not be achieved in practice.

The epidemiology of IMD remains extremely unpredictable, especially since social interactions have increased as COVID-19 lockdown-related restrictions have eased, facilitating meningococcal transmission among a potentially more vulnerable population [87, 88]. Unlike other countries, Germany did not experience the increase in MenW cases before the COVID-19 pandemic but it is interesting that increases in MenY cases have been observed in Germany following the pandemic [32]. The broader protection of a MenACWY vaccine compared to the monovalent MenC vaccine is even more pronounced where high incidence scenarios of serogroups C, W, and Y are considered simultaneously: up to an additional 6306 IMD cases and 993 IMD-related deaths would be prevented by a combined toddler and adolescent MenACWY program vs. monovalent MenC vaccination in toddlers. Furthermore, it must be considered that vaccination is a prophylactic measure and implementation of MenACWY programs would likely prevent such high incidence situations occurring. This would remove the need to react retrospectively to introduce broader MenACWY protection in response to any future rises in MenW, MenC or MenY cases as other European countries have had to do.

Economic insights

In addition to evaluating the public health impact of various IMD vaccination strategies, this study provides insights that can be used to support informed policy discussions regarding the economic impact of adolescent vaccination recommendation in Germany. In most scenarios, adolescent MenACWY vaccinations provided significant value for money. Introducing MenACWY vaccination during adolescence at 13 or 16 years of age is the key driver to reducing the significant burden of IMD in Germany further than the burden decrease that can be achieved with toddler vaccination alone.

The model considers multiple perspectives, payer considerations, conventionally accepted societal elements (i.e., patient and caregiver productivity losses), and broader value elements (i.e., parental or caregiver QALY losses associated with an IMD-related death of a child), which is consistent with more recent and more innovative cost-effectiveness modelling approaches [89].

Several limitations of this study should be considered when interpreting the results. The conservative approaches included in our analyses will likely lead to the underestimation of the full value of meningococcal vaccination programs. Since models must necessarily simplify real-world conditions and rely on the availability of high-quality data to populate the model, it can be difficult to construct models that accurately represent infectious diseases [51, 68]. For illustration, our static multi-cohort population model incorporated simplifying, but conservative assumptions, to estimate the herd effect [69]. Additionally, the base case IMD incidence was the average incidence from 2010 to 2019, a time period where a MenC toddler vaccination program had been in place. Therefore, the MenC cases prevented by the current schedule are not estimated as part of the incremental benefits in our model, and only the additional protective potential of new vaccination strategies are calculated.

Due to the relative rarity of IMD, German-specific inputs with the granularity level allowed in the model (e.g., breakdown of case fatality rates by serogroup or utility decrements by manifestation) were not always available. The model further incorporated approaches to calculating outputs with more innovative broader value, such as sequelae-specific caregiver productivity losses due to IMD, but these approaches were not fully aligned with or robustly reported in the literature [49, 72]. Furthermore, given the unpredictable nature of IMD, projecting the impact of such changes over a long-time horizon involves substantial uncertainty.

The epidemiology of IMD typically varies by country; it has often been observed that IMD patterns in Germany do not follow the trends observed in other neighboring European countries, rendering it even more challenging to anticipate disease burden in Germany. While IMD has reputedly unpredictable epidemiology, the COVID-19 pandemic introduced additional uncertainty [90, 91]. Experience from past pandemics suggests that epidemiologically and clinically important interactions exist between influenza and secondary bacterial respiratory pathogens. Additionally, previous evidence of influenza and influenza-like illnesses show an association between increased carriage and systemic infection of *N. meningitidis* [92]. Given the lower vaccination rates due to COVID-19-related lockdowns and social distancing measures, which may have decreased the carriage rates, how the incidence rates of the IMD serogroups will rebound and evolve in the future remains unclear [93, 94], For example, although modeling studies predicted a long-term reduction in IMD incidence due to the impact of COVID-19 lockdown measures, resurgences in childhood pneumococcal disease have been noted [95, 96]. Data concerning pneumococcal transmission from Israel and Belgium further suggest that COVID-19-related reductions in carriage are not long lasting [88, 97]. As the evidence base of the IMD disease burden continues to develop during the post-COVID-19 pandemic period, the accuracy of IMD vaccination modeling approaches can be improved. The initial assumptions that IMD incidence will remain low for many years as a consequence of the COVID-19 pandemic are already being disproven with the emergence of new evidence suggesting that

meningococcal carriage was not necessarily impacted by social distancing [93], and an increase in adolescent/adult MenB cases was observed in the UK faster than expected. For example, in England, following the relaxation of COVID-19 lockdown measures (September to November 2021), the numbers of IMD cases due to MenB in adolescents and young adults exceeded the pre-pandemic levels [87].

Conclusions

The results of these analyses can be used to inform public health policy decisions and contribute to broader global evidence based IMD vaccination recommendations. Our study provides evidence suggesting that the introduction of MenACWY vaccination, especially for adolescents, can substantially reduce IMD cases and deaths and would offer significant value for money. These results indicate the advantage of providing German toddlers and adolescents with direct protection and other populations with herd protection against IMD caused by serogroups A, C, W and Y instead of C alone.

Although many countries have waited to implement MenACWY vaccination programs or recommendations until after MenW and MenY outbreaks occurred [98], the evidence provided offers an opportunity for Germany to proactively implement MenACWY vaccination programs.

Abbreviations

IMD	Invasive meningococcal disease
HPV	Human papilloma virus
ICER	Incremental cost-effectiveness ratio
LY	Life year
MenACWY	Meningococcal serogroups A, C, W, Y
MenB	Meningococcal serogroup B
MenC	Meningococcal serogroup C
MenW	Meningococcal serogroup W
MenY	Meningococcal serogroup Y
QALY	Quality-adjusted life years
SIKO	Saxon Vaccination Committee
STIKO	Standing Committee on Vaccinations
UK	United Kingdom
US	United States
VE	Vaccine effectiveness
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1: Additional File 1

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Conceptualization, K.S., S.J and J.F.; methodology, K.S., S.M.S. and E.T.; programming, E.T.; formal analysis, E.T.; interpretation, K.S., SJ, and S.M.S. and J.F.; writing—original draft preparation, K.S., S.M.S. SJ, and J.F.; writing—review and editing, KS, SJ, SMS, JF and E.T. All authors have read and agreed to the published version of the manuscript. All authors contributed to reviewing and editing the manuscript.

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Data availability

Data in this study are presented within the article and available in supplementary materials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have consented to the publication of this work.

Competing interests

KS, SJ and JF are employees of Pfizer and may hold stocks or stock options. SMS and ET are employees of Evidera, an organization that provides consultancy services to multiple pharmaceutical companies.

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