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Review

Effectiveness and duration of protection of primary and booster immunisation against meningococcal serogroup C disease with meningococcal conjugate C and ACWY vaccines: Systematic review

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SUMMARY

Objectives: To estimate vaccine effectiveness (VE) and duration of protection of single primary and booster immunisation with meningococcal C (MenC) and ACWY (MenACWY) conjugate vaccines in preventing MenC invasive meningococcal disease (IMD).
Methods: We performed a systematic review on studies of VE and immunogenicity (rSBA/hSBA titers) of participants aged 12–23 months for primary and 6–18 years for booster immunisation (last search: 18 August 2023). Risk of bias and certainty of evidence were evaluated (PROSPERO: CRD42020178773).
Results: We identified 10 studies. Two studies reported VE of primary immunisation with MenC vaccines ranging between 90% (74.9 – 96.1) and 84.1% (41.5 – 95.7) for periods of 2 and 7 years, respectively. Eight studies reported immunogenicity of primary immunisation with MenC and/or MenACWY vaccines, of which two reported -in addition- on booster immunisation. The percentage of participants with protective rSBA titers was high after primary immunisation but waned over the following 6 years. A single booster at the age of 7 years or older seems to prolong protection for several years.
Conclusions: A single dose of MenC or MenACWY vaccine at 12–23 months of age provides robust protection against MenC IMD. Data on booster immunisation are sparse, but indicate prolonged protection for three years at least.

Introduction

Invasive meningococcal disease (IMD) is caused by the bacterium *Neisseria meningitidis* and is associated with severe clinical symptoms such as meningitis, bacteremia, and Waterhouse-Friderichsen syndrome.[1] *N. meningitidis* is transmitted by droplets. While about 10% to 20% of the general population are asymptomatic carriers in the nasopharynx, invasive disease rarely occurs.[2,3] Most IMD cases are caused by the serogroups A, B, C, W, and Y.[4–6]

Worldwide, the annual IMD incidence has been low in recent years, ranging from 0 to 10.2 cases per 100,000 inhabitants per year in 2010–2019.[7] Case-fatality is around 10%, and 10–20% of survivors experience lifelong, disabling sequelae.[8] Epidemiology varies by age, serogroup, and region. In the European Union and the European Economic Area (EU/EEA) countries, the IMD incidence was 0.1 cases per 100,000 population with highest incidences (3.2 per 100,000) being observed in infants (< 1year), followed by children aged 1–4 years (0.6 per 100,000).[9] Several countries report a second incidence peak at 15–24 years of age, with an incidence of 0.2 per 100,000.[9] In most countries, including those in Europe, serogroup B was predominant in the years 2010–2019.[9] Serogroup C (MenC) emerged in the late 1990s and remains the second most common cause of IMD with the highest mortality rate in persons aged 15 years and under in the EU/EEA countries.[9,10]

Polysaccharide vaccines against MenC have been available since the 1960s. However, these first vaccines did not induce the production of memory cells, resulting in a short duration of protection and poor response to booster doses, particularly during infancy.[11] Currently used MenC conjugate vaccines evoke better immunogenicity, longer duration of protection and improved capability to induce herd immunity.[11–13] The first MenC conjugate vaccines were introduced in the United Kingdom in 1999 and have since been licensed in many countries along with quadrivalent ACWY (MenACWY) conjugate vaccines.[11,14]

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As cases of IMD are rare and therefore clinical endpoints are difficult to evaluate in randomised controlled trials (RCTs) and cohort studies, correlates of protection have been established for meningococcal vaccines. In particular, serum bactericidal antibodies (SBA) are a well-known and internationally accepted correlate of protection (CoP) for MenC vaccines. For the rabbit complement serum bactericidal assay (rSBA) a titer level of ≥8 and for the human complement serum bactericidal assay (hSBA) a titer level of ≥4 are considered as protective thresholds.[15–18]

In 11 European countries, the respective National Immunisation Technical Advisory Groups (NITAGs) recommend a single dose primary immunisation against serogroup C meningococci for children and some of them recommend a booster dose for adolescents.[14,19] However, there is some variation across the countries of the European Union regarding the general recommendation for immunisation. The age for primary immunisation with MenC or MenACWY varies between 2 and 15 months of age depending on the country. This is similar for booster immunisations, with most countries recommending the MenACWY vaccination between the age of 11 to 18 years, with a single exception regarding age range and vaccine (see Appendix 1 for a vaccine recommendation overview in EU countries).

The aim of this systematic review was to estimate the effectiveness as well as the duration of protection of a single primary immunisation and booster immunisation with meningococcal conjugate vaccines C and ACWY in preventing IMD caused by meningococci serogroup C.

Methods

The systematic review is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[20] The protocol was registered with the Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42020178773. As this systematic review is based on published studies, the approval of a data protection officer or an ethics committee was not required.

Eligibility criteria

Studies that fulfilled the following criteria (according to the PICO (population, intervention, comparator, outcome) scheme) were included: (a) population: infants at 12–23 months of age for primary immunisation and children 6–18 years of age for booster vaccination; (b) intervention: single dose of either conjugate MenC or conjugate MenACWY vaccine for primary and/or booster vaccinations. Studies investigating co-administration of MenC/MenACWY vaccines with human papillomavirus vaccines (HPV) and/or tetanus, diphtheria, pertussis, and inactivated poliomyelitis vaccines (TdaP/TdaP-IPV) or other vaccines (e.g., *Haemophilus influenzae* type b (Hib), *S. pneumoniae*) were also included; (c) comparator: no vaccination or placebo, or any vaccination with other than meningococcal vaccine; (d) outcome (1): vaccine effectiveness (VE) for preventing IMD including meningitis and septicaemia caused by serogroup C (2); immunogenicity with protective titer thresholds: hSBA ≥4, or ≥8 and/or rSBA ≥8, ≥32, or ≥128. All studies that had a comparison group were eligible. Studies fulfilling the following criteria were excluded: (a) animal studies, non-human studies; (b) studies investigating outer membrane vesicle vaccines (OMV), the combination of Hib-MenC vaccines and vaccines with a route of administration other than injection; (c) no comparison group or other meningococcal vaccines (e.g., polysaccharide vaccines, MenB vaccines, Hib-Men-vaccines, OMV vaccines) as comparator.

Search strategy & study selection process

We conducted initial electronic searches in MEDLINE (via PubMed) and EMBASE on 5 April 2020 (see Appendix 2 for description of the search strategy). The search was updated on 18 August 2023 in PubMed. A hand search was conducted in reference lists of retrieved systematic reviews and in clinicaltrials.org[21] by a single reviewer (MG). The Covidence software was used to manage the screening and selection process.[22] Titles and abstracts from the retrieved references were independently screened by pairs of two reviewers (VS, StS, AF, IT, and MG) according to the eligibility criteria. The same procedure was used for the full-text screening (VS, LH, UR, AF, IT, and MG). In case of disagreement between two reviewers a third reviewer (VS or TH) was consulted for the final decision.

Data collection & items

Data extraction was done by a single reviewer and double-checked by a second reviewer (IT, MG). Disagreements in the data extraction were discussed between the two reviewers, and if necessary in consultation with a third reviewer (VS or TH). An Excel data extraction form was used to collect the data. The following variables were extracted: Study details (e.g., authors, title, country of study, funding, conflicts of interest, study design, and study period), meningococcal serotype, vaccine composition, vaccination schedule, comparator, age at vaccination, sex (% female), ethnicity, definition of protective SBA titer, duration of follow-up after vaccination, number of eligible participants, number of participants with disease, VE, number and proportion (%) of participants with protective SBA titers (see protocol for a detailed list of extracted variables). When data were missing in the study documents, study authors were contacted.

Risk of bias

Risk of bias in Non-Randomised Studies of Intervention (NRSI) was assessed by using the ROBINS-I tool.[23] For single-armed studies with pre-intervention vs. post-intervention comparisons (including single arms of RCTs), risk of bias was assessed using the Quality in Prognosis Studies (QUIPS) tool.[24] In such cases, vaccination was considered as a prognostic factor. The certainty of evidence for each outcome was assessed by applying the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[25]

Effect measures and synthesis method

A descriptive synthesis of the findings from each study using tables and text was provided. We planned to calculate risk ratios (RR), odds ratios (OR) and prevalence ratios (PR) (with corresponding 95% confidence intervals). Vaccine efficacy and VE would have been calculated as 1 – RR (or OR or PR) comparing vaccine and control recipients. Where data from more than one study on a given outcome were available, a meta-analysis was planned. I^2 and Chi^2 statistics would have been used to assess between-study heterogeneity. In the absence of heterogeneity, a fixed-effects model would have been used; otherwise, we would have pooled data using a random-effects model. A publication bias assessment by visual inspection of funnel plots and formal testing was planned. Subgroup/sensitivity analyses were planned to detect possible sources of heterogeneity. All descriptions and analyses were performed separately according to study design (RCTs and observational studies).

Results

We identified 21,357 references through database searches and 39 additional references through manual searches up to 18 August

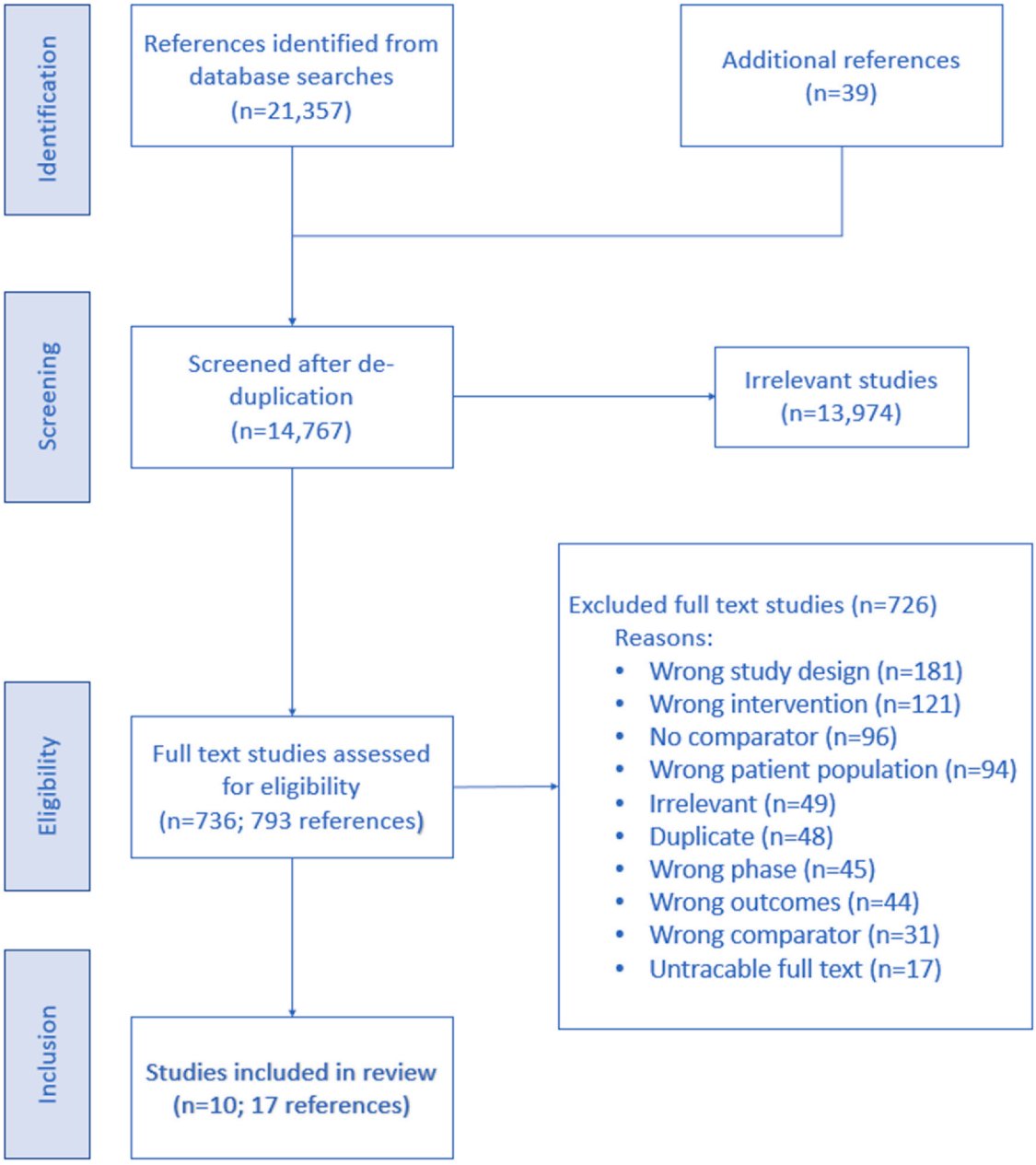

Fig. 1. PRISMA flow chart of studies screened and included.

2023. After duplicates were removed, 14,767 references were screened by title and abstract, resulting in 13,974 irrelevant references. We included 736 studies (793 references) into full-text screening. Of these, 726 studies were excluded due to the following reasons: wrong study design (181), wrong intervention (121), no comparator (96), wrong patient population (94), irrelevant,[49] duplicate,[48] wrong phase,[45] wrong outcomes,[44] wrong comparator,[31] and untraceable full text.[17] Finally, 10 studies (17 references) [26–42] were included in this systematic review (see flowchart in Fig. 1 and for lists of included and excluded studies, see appendix 3).

Characteristics of included studies

Of the 10 studies included, two reported VE against clinical endpoints, both after primary immunisation with one dose of MenC conjugate vaccines.[26,27] The remaining eight studies reported CoP outcomes (rSBA and/or hSBA titer) for MenC and/or MenACWY conjugate vaccines after primary or booster immunisation.[28–42] The studies were predominantly conducted in high-income countries (e.g., United Kingdom, Canada, Australia, Austria, Germany, Greece, Finland) and assessed the effect of primary immunisation at 12–23 months.[26–37,40–42] Five studies had arms with co-administration, where the MenC or MenACWY vaccine was administered in combination with other vaccines (e.g., measles, mumps, rubella vaccine, 13-valent pneumococcal conjugate vaccine, 10-valent pneumococcal conjugate vaccine, Hib conjugate vaccine).[30–34,37,40,41] Two studies examined the effect of booster immunisation with MenC-TT (tetanus toxoid) conjugate[38,39] or MenACWY-TT conjugate vaccine[35] at about 10 years (9.9 (standard deviation (SD) 0.3)), and 7 years of age, respectively. Six of the 10 included studies were RCTs assessing MenC and/or MenACWY vaccines.[26–37,40–42] The remaining studies were NRSI of MenC vaccines with a retrospective design.[26–29,38,39] VE studies used the screening method (based on Farrington *et al.* 1995)[26] or retrospective cohort method (based on Orenstein *et al.* 1988)[27] to calculate VE. For CoP (immunogenicity) studies, the number of included participants ranged from 100 to 739 for primary

Table 1
Study characteristics.

Study	Country	Conflict of interest	Funding	Study design	Primary or booster vaccination	Study period	N of eligible participants/ cases	Age at vaccination	Sex - % female	Meningococcal vaccine	Co-administered vaccine	Reported outcomes (reported cutoffs)
Studies with clinical endpoints												
Andrews et al., 2003[26]	United Kingdom	NR	NR	Screening method (based on national surveillance data)	Primary	01/ 2000- 12/ 2001	NA[a] /48 (7 vaccinated)	Range: 12–23 months	NR	MenC-CRM$_{197}$	NR	VE
De Wals et al., 2011[27]	Canada	NR	Industry sponsored	Cohort method (based on national registry data)	Primary	01/ 1990- 12/ 2008	NA/4 (2 vaccinated)	Range: 12–23 months	NR	MenC-CRM$_{197}$	NR	VE
Studies with CoP // immunogenicity endpoints												
Bettinger et al., 2016[28,29]	Canada	More than 33% of authors or first- or last author declare relevant financial COIs	Non-industrial (governmental) sponsored	Cohort study	Primary	07/ 2009- 05/ 2011	155/NA	Mean (SD): 1.04 years (0.03)	46.6%	MenC-TT	None	rSBA titers (≥8, ≥128)
Cutland et al., 2023[30,31]	Australia, Canada, Czech Republic, Panama, South Africa and Turkey	More than 33% of authors or first- or last author declare relevant financial COIs	Industry sponsored	RCT[b]	Primary	10/ 2013- 12/ 2019	605/NA	Mean (SD): Cutland_2023_1: 12.8 months (0.9); Cutland_2023_2: 12.8 months (0.9); Cutland_2023_3: 12.7 months (0.9)	Cutland_2023_1: 46.3%; Cutland_2023_2: 48.8%; Cutland_2023_3: 48.8%	MenACWY-TT	Cutland_2023_2: PCV13	rSBA titers (≥8, ≥128); hSBA titers (≥4, ≥8)
Knuf et al., 2011[32]	Austria, Germany, Greece	More than 33% of authors or first- or last author declare relevant financial COIs	Industry sponsored	RCT[b]	Primary	08/ 2007- 10/ 2008	793/NA	Mean (SD): Knuf_2011_1: 14.6 months (3.01); Knuf_2011_2: 15 months (3.33); Knuf_2011_3: 14.9 months (3.17); Knuf_2011_4: 14.6 months (2.99)	Knuf_2011_1: 49.1%; Knuf_2011_2: 48.2%; Knuf_2011_3: 53.1%; Knuf_2011_4: 48%	Knuf_2011_1: MenACWY-TT; Knuf_2011_2: MenACWY-TT; Knuf_2011_3: MenACWY-TT; Knuf_2011_4: MenC-CRM$_{197}$	Knuf_2011_1: DTaP-IPV-HepB-Hib (Hexa)	rSBA titer (≥8, ≥128)
Nolan et al., 2019[33–35]	Australia	More than 33% of authors or first- or last author declare relevant financial COIs	Industry sponsored	RCT[b]	Primary, booster	2006- 2016	Primary: 100/NA Booster: 37/NA	Mean (SD): Primary: 12.5 months (0.8); Booster: 7 years (NR)	Primary: 63%; Booster: 37.8%	Primary: MenC-CRM$_{197}$ Booster: MenACWY-TT	Primary: Hib-TT, MMR	rSBA titer (≥8, ≥128)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Conflict of interest	Funding	Study design	Primary or booster vaccination	Study period	N of eligible participants/ cases	Age at vaccination	Sex - % female	Meningococcal vaccine	Co-administered vaccine	Reported outcomes (reported cutoffs)
Richmond et al., 2001[36]	United Kingdom	NR	Non-industrial (governmental) sponsored	RCT[b]	Primary	10/ 1997 – 07/ 1998	226/NA	Mean (range): 13.6 months[12–18]	43.4%	Richmond_2001_1: MCC-CRM_{197} (Chiron); Richmond_2001_2: MCC-CRM_{197} (Wyeth); Richmond_2001_3: MCC-TT	MMR	rSBA titers (≥8, ≥32)
Ruiz-Palacios et al., 2013[37]	Mexico, Taiwan	More than 33% of authors or first-or last author declare relevant financial COIs	Industry sponsored	RCT[b]	Primary	10/ 2008-11/ 2009	357/NA	Mean (SD): Ruiz-Palacios_2013_1: 17.2 months (1.97); Ruiz-Palacios_2013_2: 17.2 months (1.88); Ruiz-Palacios_2013_3: 17.4 months (1.86)	Ruiz-Palacios_2013_1: 45.6%; Ruiz-Palacios_2013_2: 61.5%; Ruiz-Palacios_2013_3: 52.2%	MenACWY-TT	Ruiz-Palacios_2013_1: PHiD-CV	rSBA titer (≥8, ≥128)
van Ravenhorst et al., 2016[38,39]	The Netherlands	Less than 33% of authors and neither first or last author declare relevant financial COIs	Non-industrial (governmental) sponsored	Cohort study	Booster	10/ 2011	66/NA	Mean (SD): 9.9 years (0.3)[c]	58%	MenC-TT	None	rSBA titer (≥8, ≥128)
Vesikari et al., 2015[40–42]	Finland	More than 33% of authors or first or last author declare relevant financial COIs	Industry sponsored	RCT[b]	Primary	06/ 2007-NR	270/NA	Range: Vesikari_2015_1: 12–18 months; Vesikari_2015_2: 12–21 months	Vesikari_2015_1: 48.6%; Vesikari_2015_2: 45.8%	Vesikari_2015_1: MenACWY-TT; Vesikari_2015_2: MenC-CRM_{197}	MMR	rSBA titer (≥8, ≥128)[d]; hSBA titer (≥4, ≥8)

Study Arms: Cutland_2018_1: one dose of MenACWY-TT at month 0; Cutland_2018_2: one dose MenACWY-TT and PCV13 at month 0; Cutland_2018_3: one dose PCV13 at month 0 and one dose MenACWY-TT at month 2; Knuf_2011_1: one dose ACWY-TT and DTaP-HBV-IPV/Hib (InfaNRixTM hexa, GSK Biologicals) on the same day (visit 1); Knuf_2011_2: one dose of ACWY-TT at visit 1 and DTaP-HBV-IPV/Hib one month later at visit 2; Knuf_2011_3: one dose of DTaP-HBV-IPV/Hib at visit 1 and one dose ACWY-TT at visit 2; Knuf_2011_4: one dose of licensed monovalent MenC conjugate vaccine (Meningitec); Ruiz-Palacios_2013_1: one dose MenACWY-TT and PHiD-CV coadministered at the same vaccination visit; Ruiz-Palacios_2013_2: one dose MenACWY-TT at first visit and 1 month later PHiD-CV; Ruiz-Palacios_2013_3: one dose PHiD-CV at first visit followed by one dose MenACWY-TT 1 month later; Richmond_2001_1: one dose of MCC-CRM (Chiron) and MMR vaccine; Richmond_2001_2: one dose of MCC-CRM (Wyeth) and MMR vaccine; Richmond_2001_3: one dose of MCC-TT and MMR vaccine; Vesikari_2015_1: included those subjects vaccinated with MenACWY-TT (either coadministered with MMRV or alone); Vesikari_2015_2: vaccinated with one dose MenC-CRM197 (before or after a dose of MMRV).

Abbreviations: DTaP-IPV-HepB-Hib: diptheria, tetanus, pertusis, polio, hepatitis B, Haemophilus influenzae b vaccine;); Hib-TT: Haemophilus b conjugate vaccine (tetanus toxoid conjugate); hSBA: human complement serum bactericidal antibody assay; MenACWY-CRM197: tetravalent meningococcal conjugate vaccine (cross-reacting material 197 (CRM197)); MenACWY-TT: tetravalent meningococcal conjugate vaccine (tetanus toxoid conjugate); MenC: Neisseria meningitidis serogroup C; MenC-CRM197: Meningococcal serogroup C conjugate vaccine (cross-reacting material 197 (CRM197)); MenC-TT: Meningococcal serogroup C conjugate vaccine (tetanus toxoid conjugate); MMR: Measles, mumps, rubella vaccine; NA: not applicable, NR: not reported; PCV13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: 10-valent pneumococcal conjugate vaccine; RCT: randomised controlled trial; rSBA: rabbit complement serum bactericidal antibody assay; SD: standard deviation; VE: vaccine effectiveness.

[a] Not applicable for screening method.

[b] Single study arms used for pre-post comparison.

[c] Age at primary vaccination with MenC-TT vaccine: Mean (SD): 1.2 years (0.1).

[d] Preliminary data for rSBA titer not provided. Therefore, data was not included in the analysis.

Table 2
Study outcomes – vaccine effectiveness following primary immunisation against IMD caused by meningococcal serogroup C.

Study	Meningococcal vaccine	Primary/Booster immunisation	Observation period	VE (95% CI)	
				Overall	*VE according to time interval after vaccination*
Andrews et al., 2003[26]	MenC-CRM$_{197}$	Primary	2 years	90.1% (74.9–96.1)	NA
De Wals et al., 2011[27]	MenC-CRM$_{197}$	Primary	7 years	84.1% (41.5–95.7)	Within 2 years 91.7% (60.1–98.3) Over 2 years to 7 years 66.7% (−38–92)

Abbreviations: CI: confidence interval; MenC-CRM$_{197}$: Meningococcal serogroup C conjugate vaccine (cross-reacting material 197 (CRM197)); NA: not applicable; VE: vaccine effectiveness.

immunisation. Booster studies included 37 and 66 eligible participants, respectively. Gender distribution was well balanced in most studies, except of one booster study[35] that included a substantially larger number of male than female participants (for details, see Table 1).

Risk of bias

We had major concerns about bias in all studies reporting VE outcomes due to possible confounding bias. Furthermore, we had at least some concerns about bias in all studies reporting CoP (immunogenicity) outcomes (see Appendix 2 for detailed results of risk of bias assessment per study and outcome).

Vaccine effectiveness of primary immunisation

Two studies reported VE of primary immunisation against IMD caused by MenC with one dose of MenC conjugate vaccine. They had observation periods of 2 years[26] and 7 years,[27] and reported overall VE estimates of 90% and 84.1%, respectively (Table 2). De Wals *et al.* reported separate VE estimates for the observation periods of 2 years and 2–7 years.[27]

Immunogenicity of primary immunisation

Seven studies investigated the immunogenicity of MenC or MenACWY after primary immunisation, six reported on rSBA titers (Table 3) and two reported on hSBA titers (Table 4), of which two studies had a long-term observation of 5 and 6 years post-vaccination. Immunogenicity was reported using the proportion of patients with rSBA titers ≥8 or ≥128 as a CoP for the pre-vaccination time point (day 0) and post-vaccination follow-up (Table 3). All studies reported pre-vaccination and 30-day post-vaccination proportions of protected participants for rSBA ≥8 and ≥128. Pre-vaccination rSBA ≥8 ranged from 0%[30] to 27.6%,[28,29] and rSBA ≥128 ranged from 0%[30] to 8.8%[32] of study participants. At 30 days post-vaccination, proportion of participants with rSBA ≥8 ranged from 91%[36] to 100%,[32] and rSBA ≥128 proportion ranged from 66.9%[28,29] to 100%.[37] Ruiz-Palacios *et al.* reported titer estimates at 60 days post-vaccination, with rSBA ≥8 in 98% and rSBA ≥128 in 97.5% of study participants.[33] Richmond *et al.* reported 210 days post-vaccination titer estimates, with rSBA ≥8 ranging from 57% to 86% and rSBA ≥32 ranging from 41% to 83% of participants.[36] Cutland *et al.* reported titer estimates at 1, 3, and 5 years post-vaccination. Titer estimates 1-year post-vaccination ranged for rSBA ≥8 between 42.7% and 50.3%, and rSBA ≥128 between 15.8% and 21%, and for 5 years post-vaccination for rSBA ≥8 between 19.4% and 23.9% and ≥128 between 6.1% and 12%.[30,31] Bettinger *et al.* reported titer estimates at 3 years post-vaccination, with rSBA ≥8 in 92.4% and rSBA ≥128 in 0.8% of participants.[28,29] Nolan *et al.* reported titer estimates at 1, 2, 3, and 6 years post-vaccination. Titer estimates 1-year post-vaccination were rSBA ≥8 76.4% and rSBA ≥128 41.6%, and rSBA ≥8 14.7% and ≥128 5.9% 6 years post-vaccination, respectively.[33–35] Up to 5 years after primary vaccination, the percentage of patients with rSBA antibody titers ≥8 remained above pre-vaccination levels (Fig. 2). Titers reported by Cutland *et al.*, Nolan *et al.*, and Richmond *et al.* showed a decrease in proportion of protected participants according to rSBA titers over time.[30,31,33–36] Richmond *et al.* reported varying decrease in protection depending on the meningococcal vaccine.[36]

Data on proportion of patients with hSBA titers above thresholds ≥4 or ≥8 were reported by two studies from the pre-vaccination time point up to 4 and 5 years post-vaccination (Table 4).[30,31,40–42] Proportion of pre-vaccination hSBA ≥4 ranged from 0.5%[40–42] to 4.2%.[40–42] At 30 days post-vaccination, proportion of participants with hSBA ≥4 ranged from 82.6%[40–42] to 98%.[30] Cutland *et al.* further reported estimates up to 5 years post-vaccination. Post-vaccination hSBA ≥4 was observed in 81.7% of participants one year after immunisation, and in 60.7% five years after primary immunisation.[30,31] Vesikari *et al.* reported estimates up to 4 years post-vaccination. In this study, post-vaccination hSBA ≥4 ranged from 57.9% and 88% 2 years after, and between 46.9% and 73.7% 4 years after primary immunisation.[40–42] The hSBA ≥8 titers were nearly identical to hSBA ≥4 titers at all reported time points in both studies.

Immunogenicity of booster immunisation

We identified 2 studies that reported on the immunogenicity of MenC or MenACWY booster immunisation. Pre-booster protection was indicated by the proportion of patients with rSBA titers ≥8 or ≥128 approximately 6 years[33–35] and 9 years,[38,39] up to 8[33–35] and 12[38,39] years after primary immunisation (Table 5). Nolan *et al.* estimated a pre-booster proportion of 14.7% for rSBA ≥8. Titer estimates for rSBA ≥8 at 1 month, and 2 years post-booster immunisation ranged from 100% to 93.9%, respectively.[33–35] Van Ravenhorst *et al.* estimated a pre-booster proportion of 19% for rSBA ≥8. Titer estimates for rSBA ≥8 from 1 month to 3 years post-booster immunisation remained constant at 100%.[33–35]

Certainty of evidence

The certainty of evidence for primary immunisation is “very low” due to critical risk of bias and imprecision (lower bound of confidence interval under 50%). For booster immunisation the certainty of evidence is “very low” due to risk of bias and indirectness (use of CoP).

Discussion

The aim of this systematic review was to evaluate the effectiveness and duration of protection of primary and booster immunisation with meningococcal conjugate C and ACWY vaccines against invasive meningococcal serogroup C disease. Studies which evaluated primary immunisation with one dose at 12 to 23 months of age and eventually followed by booster immunisation at 6 to 17 years of age were eligible.

Table 3
Study outcomes – immunogenicity of primary immunisation against meningococcal serogroup C: proportion of participants with rSBA titers above the indicated cutoff.

Study	Meningococcal vaccine	Outcome rSBA cutoff	Study arms	Time points % of participants with rSBA above cutoff (95% CI)								
				pre-vaccination	30 days	60 days	210 days	1 year	2 years	3 years	5 years	6 years
Bettinger et al., 2016[28,29]	MenC-TT	≥8 / ≥128	Bettinger_2016	27.6% (21–5.4) / 0% (0–2.6)	100% (97.4–100) / 66.9% (58.9–74)	ND	ND	ND	ND	92.4% (86.2–96) / 0.8% (0.1–4.6)	ND	ND
Cutland et al., 2023[30,31]	MenACWY-TT	≥8 / ≥128	Cutland_2023_1	2.9% (0.9–6.5) / 1.1% (0.1–4.1)	95% (90.7–97.7) / 85.5% (79.4–90.3)	ND	ND	49.1% (41.3–56.9) / 21% (15.1–27.9)	ND	35.4% (27.7–43.7) / 9.5% (5.3–15.5)	20.5% (13.9–28.3) / 6.1% (2.7–11.6)	ND
	MenACWY-TT	≥8 / ≥128	Cutland_2023_2	1.2% (0.1–4.2) / 0.6% (0–3.2)	96% (92–98.4) / 88.1% (82.3–92.5)	ND	ND	42.7% (35.2–50.5) / 15.8% (10.7–22.1)	ND	28.5% (21.4–36.4) / 14.6% (9.4–21.2)	23.9% (17.2–31.8) / 12% (7.1–18.5)	ND
	MenACWY-TT	≥8 / ≥128	Cutland_2023_3	0% (0–2.1) / 0% (0–2.1)	95.3% (90.9–97.9) / 85.8% (79.6–90.7)	ND	ND	50.3% (42.5–58.1) / 20.1% (14.4–27)	ND	31.8% (24–40.5) / 10.6% (5.9–17.2)	19.4% (13–27.3) / 7.8% (3.8–13.8)	ND
Knuf et al., 2011[32]	MenACWY-TT	≥8 / ≥128	Knuf_2011_1	21.5% (13.7–31.2) / 5.4% (1.8–12.1)	100% (98.1–100) / 99% (96.3–99.9)	ND	ND	ND	ND	ND	ND	ND
	MenACWY-TT	≥8 / ≥128	Knuf_2011_2	27.5% (18.6–37.8) / 8.8% (3.9–16.6)	97.3% (93.7–99.1) / 94% (89.5–97)	ND	ND	ND	ND	ND	ND	ND
	MenACWY-TT	≥8 / ≥128	Knuf_2011_3	14.1% (7.7–23) / 5.4% (1.8–12.2)	100% (97.9–100) / 88.2% (82.5–92.5)	ND	ND	ND	ND	ND	ND	ND
	MenC-CRM$_{197}$	≥8 / ≥128	Knuf_2011_4	20.4% (10.6–33.5) / 5.6% (1.2–15.4)	98.2% (93.8–99.8) / 89.5% (82.3 - 94.4)	ND	ND	ND	ND	ND	ND	ND
Nolan et al., 2019[33–35]	MenC-CRM$_{197}$	≥8 / ≥128	Nolan_2019	8.4% (3.5–16.6) / 3.6% (0.8–10.2)	100% (96.3–100) / 90.8% (83.3–95.7)	ND	ND	76.4% (66.2–84.8) / 41.6% (31.2–52.5)	60.5% (49.3–70.8) / NA	53.2% (41.5–64.7) / NA	ND	14.7% (5–31.1) / 5.9% (0.7–19.7)
Richmond et al., 2001[36]	MenC-CRM$_{197}$	≥8 / ≥32	Richmond_2001_1	1% (NR) / 1% (NR)	92% (NR) / 82% (NR)	ND	57% (NR) / 41% (NR)	ND	ND	ND	ND	ND
	MenC-CRM$_{197}$	≥8 / ≥32	Richmond_2001_2	3% (NR) / 3% (NR)	91% (NR) / 83% (NR)	ND	75% (NR) / 66% (NR)	ND	ND	ND	ND	ND
	MenC-TT	≥8 / ≥32	Richmond_2001_3	4% (NR) / 1% (NR)	100% (NR) / 97% (NR)	ND	86% (NR) / 83% (NR)	ND	ND	ND	ND	ND
Ruiz-Palacios et al., 2013[37]	MenACWY-TT	≥8 / ≥32	Ruiz-Palacios_2013_1	10.5% (6.3–16) / 5.2% (2.4–9.7)	99.4% (96.8–100) / 98.9% (95.9–99.9)	ND	ND	ND	ND	ND	ND	ND

(*continued on next page*)

Table 3 (*continued*)

Study	Meningococcal vaccine	Outcome rSBA cutoff	Study arms	Time points % of participants with rSBA above cutoff (95% CI)								
				pre-vaccination	30 days	60 days	210 days	1 year	2 years	3 years	5 years	6 years
	MenACWY-TT	≥8 / ≥128	Ruiz-Palacios_2013_2	11.8% (5.6–21.3) / 7.9% (3–16.4)	100% (94.5–100) / 100% (95.4–100)	ND	ND	ND	ND	ND	ND	ND
	MenACWY-TT	≥8 / ≥128	Ruiz-Palacios_2013_3	11.1% (5.2–20) / 7.4% (2.8–15.4)	98.8% (93.3–100) / 98.8% (93.2–100)	98.8% (93.2–100) / 97.5% (91.4–99.7)	ND	ND	ND	ND	ND	ND

Study Arms: Cutland_2023_1: one dose of MenACWY-TT at month 0; Cutland_2023_2: one dose MenACWY-TT and PCV13 at month 0; Cutland_2023_3: one dose PCV13 at month 0 and one dose MenACWY-TT at month 2; Knuf_2011_1: one dose ACWY-TT and DTaP-HBV-IPV/Hib (InfaNRixTM hexa, GSK Biologicals) on the same day (visit 1); Knuf_2011_2: one dose of ACWY-TT at visit 1 and DTaP-HBV-IPV/Hib one month later at visit 2; Knuf_2011_3: one dose of DTaP-HBV-IPV/Hib at visit 1 and one dose ACWY-TT at visit 2; Knuf_2011_4: one dose of licensed monovalent MenC conjugate vaccine (Meningitec); Ruiz-Palacios_2013_1: one dose MenACWY-TT and PHiD-CV co-administered at the same vaccination visit; Ruiz-Palacios_2013_2: one dose MenACWY-TT at first visit and 1 month later PHiD-CV; Ruiz-Palacios_2013_3: one dose PHiD-CV at first visit followed by one dose MenACWY-TT 1 month later; Richmond_2001_1: one dose of MCC-CRM (Chiron) and MMR vaccine; Richmond_2001_2: one dose of MCC-CRM (Wyeth) and MMR vaccine; Richmond_2001_3: one dose of MCC-TT and MMR vaccine.
Abbreviations: DTaP-IPV-HepB-Hib: diptheria, tetanus, pertusis, polio, hepatitis B, Haemophilus influenzae b vaccine; MenACWY-CRM$_{197}$: tetravalent meningococcal conjugate vaccine (cross-reacting material 197 (CRM197)); MenC-CRM$_{197}$: Meningococcal serogroup C conjugate vaccine (cross-reacting material 197 (CRM197)); MenC-TT: Meningococcal serogroup C conjugate vaccine (tetanus toxoid conjugate); ND: no data; NR: not reported; rSBA: rabbit complement serum bactericidal antibody assay.

Table 4
Study outcomes – immunogenicity of primary immunisation against meningococcal serogroup C: proportion of participants with hSBA titers above the indicated cutoff.

Study	Meningococcal vaccine	Outcome hSBA cutoff	Study arms	Time points% of participants with hSBA above cutoff (95% CI)						
				pre-vaccination	30 days	1 year	2 years	3 years	4 years	5 years
Cutland et al., 2023[30,31]	MenACWY-TT	≥4 / ≥8	Cutland_2023_1	3.7% (0.8–10.3) / 3.7% (0.8–10.3)	98.7% (93.1–100) / 98.7% (93.1–100)	81.7% (70–89.9) / 80.3% (69.1–88.8)	ND	65.6% (52.3–77.3) / 65.6% (52.3–77.3)	ND	60.7% (47.3–72.9) / 60.7% (47.3–72.9)
Vesikari et al., 2015[40–42]	MenACWY-TT	≥4 / ≥8	Vesikari_2015_1	0.5% (0–2.9) / 0.5% (0–2.9)	98.3% (95.2–99.7) / 98.3% (95–99.7)	ND	88% (82.2–92.4) / 86.9% (81–91.5)	80.6% (75.2–85.3) / 78.3% (73–83.2)	73.7% (67.2–79.5) / 73.2% (67–79.1)	ND
	MenC-CRM$_{197}$	≥4 / ≥8	Vesikari_2015_2	4.2% (0.1–21.1) / 4.2% (0.1–21.1)	82.6% (61.2–95) / 82.6% (61–95)	ND	57.9% (33.5–79.7) / 52.6% (29–75.6)	41.9% (24.5–60.9) / 41.9% (25–60.9)	46.9% (29.1–65.3) / 46.9% (29–65.3)	ND

Study Arms: Cutland_2023_1: one dose of MenACWY-TT at month 0; Vesikari_2015_1: included those subjects vaccinated with MenACWY-TT (either co-administered with MMRV or alone); Vesikari_2015_2: vaccinated with one dose MenC-CRM197 (before or after a dose of MMRV).
Abbreviations: hSBA: human complement serum bactericidal antibody assay; MenACWY-TT: tetravalent meningococcal conjugate vaccine (tetanus toxoid conjugate); MenC-CRM$_{197}$: Meningococcal serogroup C conjugate vaccine (cross-reacting material 197 (CRM197)); MenC-TT: Meningococcal serogroup C conjugate vaccine (tetanus toxoid conjugate); ND: no data.

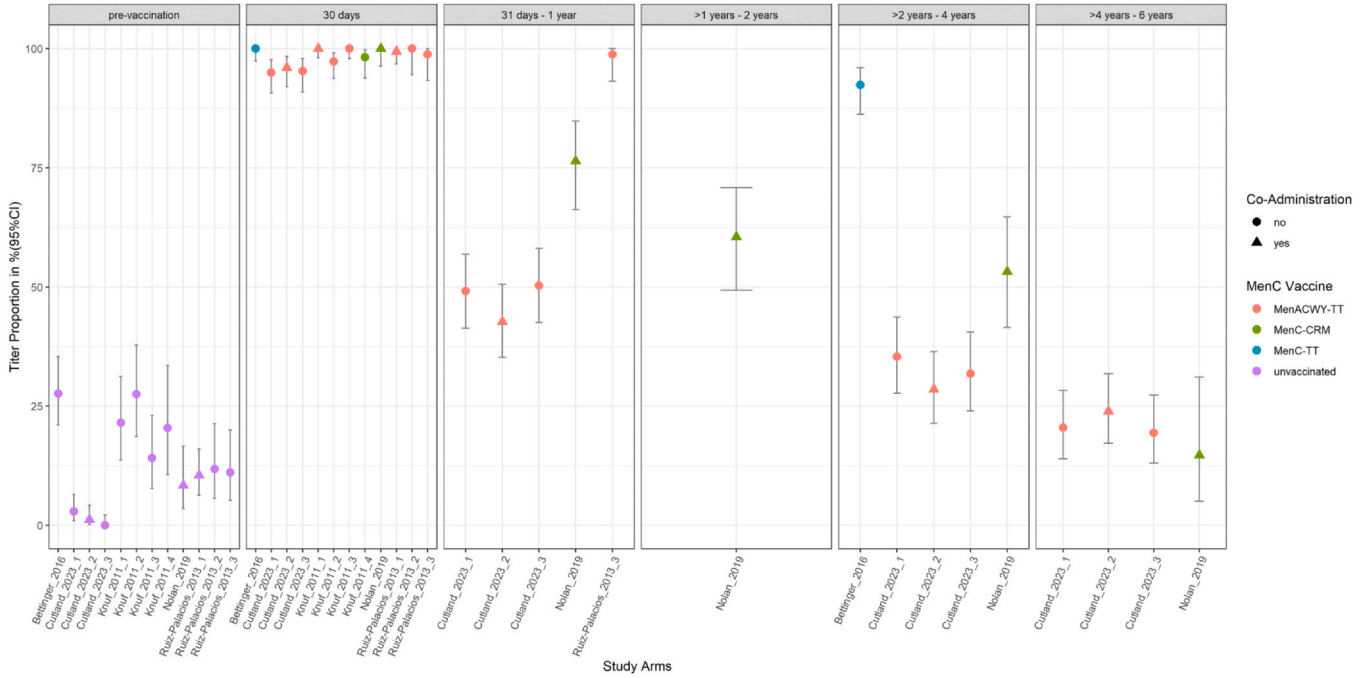

Fig. 2. Percentage of subjects with rSBA titers ≥8 against meningococcal serogroup C over time (immunogenicity for pre- and post-primary immunisation). Bars around the point estimate show 95% confidence intervals; Primary vaccination at 12–23 months of age; time categories refer to interval after the primary dose.

We found evidence for high protection against IMD caused by meningococci serogroup C after primary immunisation with a single dose of meningococcal vaccine. The VE estimates obtained indicate protection in the first years after immunisation. However, De Wals *et al.* observed a decline in VE over the 7-year observation period.[27] The robustness of the immunological reaction is also mirrored by the overall increase in rSBA and hSBA titers in the first months following a single dose vaccination. There were no apparent differences in CoP outcomes between the vaccines applied in the included studies. However, the percentage of participants with protective SBA titer levels decreased in the subsequent years, as shown by Nolan *et al.*[33–35] and Richmond *et al.*[36] for rSBA titers, and Vesikari *et al.*[40–42] for hSBA titers, indicating a possible waning of the vaccine-induced protection. Also, in the booster vaccination studies, less than 20% of participants had protective pre-booster immunisation rSBA titers. After booster immunisation, rSBA titers increased and remained stable up to 3 years post booster dose; no results were found for longer time intervals.[33–35,38,39] No data were available on clinical measures of VE of booster vaccination.

Our findings are consistent with those of other systematic reviews that have evaluated meningococcal vaccines. A meta-analysis comparing immunisation with MenACWY-TT vaccines with other licensed meningococcal vaccines in different age groups reported a robust immune response after vaccination.[43] Tin Tin Htar *et al.* reported similar results considering only monovalent vaccines against MenC. VE was highest in the first year after vaccination and decreased over time.[44] A review on immunogenicity of meningococcal vaccines also found an increase in titers 1 month after the primary immunisation that declined during the subsequent follow-up period.[45]

Although there are some similarities and overlaps with the above-mentioned reviews, our systematic review distinguishes itself with several aspects and strengths resulting in a distinct study pool. Foremost, we evaluated a different study question of the available literature and included additional studies in our systematic review. Rather than examining comparisons between different meningococcal vaccines (e.g., different monovalent conjugates, monovalent vs. quadrivalent, or different quadrivalent conjugates), we assessed immune response based not only on clinical VE but also on immunogenicity data.[43,44,46–48] Furthermore, instead of concentrating on a single vaccine, we included monovalent MenC vaccines as well as polyvalent MenACWY vaccines administered by a particular vaccination schedule. By focusing on a single vaccine primary immunisation at the age of 12 to 23 months and a possible single booster vaccine at the age of 6 to 17 years, we improved homogeneity and comparability between included studies and extracted outcomes. Additionally, at the time of reporting, we have a timely study search (update 18 August 2023) and literature overview. Finally, we did not put any limit on study designs and included studies estimating VEs with screening method or cohort method.[38] Not including these study methods might have led to exclusion of valid findings from countries where these methods were used to evaluated immunisation campaigns.

However, our systematic review has also some limitations. A major limitation is that we were not able to perform a meta-analysis as planned. The retrieved studies did not provide enough data in terms of clinical VE and had different estimation methods to conduct a sensible meta-analysis. Only two studies examined the VE of primary immunisation using the screening method and cohort method, respectively.[26,27] The retrieved VE outcomes had major concerns regarding their risk of bias due to confounding.

The majority of included studies were RCTs or cohort studies that provided immunogenicity estimates rather than VE against clinical outcomes. Being widely accepted, immunogenicity, reported as rSBA/hSBA titers, serves as a CoP and is a proxy measure instead of a real-world evidence against IMD. An rSBA titer of ≥8 is considered as a strong short-term correlate of VE but appears to underestimate protection over time.[15] Thus, it is unclear whether the decreasing percentage of participants with rSBA titers of ≥8 over time, as shown by Nolan *et al.*[33–35] and Richmond *et al.*,[36] correlates with a decrease in clinical protection against IMD. However, other long-term observations, such as those by Vesikari *et al.*,[40–42] who examined the immunogenicity of primary immunisation over 4 years using hSBA titers of ≥4, and those by De Wals *et al.*,[27] who determined the VE of primary immunisation over 7 years, also show a lower percentage of children with protective titers and a decline in VE over time,

Table 5
Study outcomes – immunogenicity of booster immunisation against meningococcal serogroup C: proportion of participants with rSBA titers above the indicated cutoff.

Study	Meningococcal vaccine	Outcome rSBA cutoff	Study Arms	Age at booster immunisation	Time points % of participants with rSBA above cutoff (95% CI)				
					Pre-booster	1 month	1 year	2 years	3 years
Nolan et al., 2019[33–35]	MenC-CRM$_{197}$	≥8 / ≥128	Nolan_2019	7 years	14.7% (5 - 31.1) / 5.9% (0.7 - 19.7)	100% (90 - 100) / 97.1% (85.1 - 99.9)	ND	93.9% (79.8 - 99.3) / 78.8% (61.1 - 91)	ND
van Ravenhorst et al., 2016[38,39]	MenC-TT	≥8 / ≥128	vanRavenhorst_2016	9.9 years	19% (12–28)/ 7% (3% - 14)	100% (95 - 100) / 100% (95 - 100)	100% (95 - 100) / 100% (95 - 100)	ND	100% (95 - 100) / 97% (93 - 100)

Abbreviations: rSBA: rabbit complement serum bactericidal antibody assay; MenC-CRM$_{197}$: Meningococcal serogroup C conjugate vaccine (cross-reacting material 197 (CRM197)); MenC-TT: Meningococcal serogroup C conjugate vaccine (tetanus toxoid conjugate); ND: no data.

respectively. Thus, the protection provided by primary immunisation does actually appear to decline over time, but it cannot be excluded that the waning effect is overestimated by the obtained rSBA titer estimates. Furthermore, immunogenicity studies provided evidence from pre-intervention vs. post-intervention cohorts, which had high internal validity, but might pose a challenge to transfer the results to the general population. Additionally, it should be considered that even if standardised rSBA assay methods have high interlaboratory comparability,[49] it cannot be excluded that differences in laboratory methods and instruments limit the comparability of immunogenicity studies.

Another limitation is that we only identified two studies on booster vaccination, including only about 100 participants in total. Only one of these studies represented long-term follow-up data based on the primary immunisation.[33–35] The study performed by Van Ravenhorst *et al.*[38,39] provides no information on the immune response of the included children to primary immunisation. Both studies had relatively short follow-up periods of 2 and 3 years following booster vaccination. Although the proportion of participants with protective rSBA titers remained at a high level over these observation periods, no sufficient conclusion can be made regarding the long-term duration of protection or on best timing of booster immunisation. The review process itself has some limitation. The focus remained on the VE measures. We focused on studies with primary immunisation at the age of 12 to 23 months (as recommended in 11 European countries), and 6 to 18 years for the booster immunisation, as epidemiology shows a rise in of serogroup C IMD in teenagers and young adults. Furthermore, we did not include experimental or Hib-MenC vaccines, as they are not authorised in Germany.

This review supports the current practice of primary immunisation, as it provides sufficient protection against serogroup C IMD. We observed waning after primary immunisation, indicated by decreasing rSBA and hSBA titers and based on VE data from a single study. However, with sparse clinical VE data over a longer period of time, we do not know if immunogenicity data translate into a reduction or loss of clinical VE. Long-term studies of booster vaccination in teenagers and young adults on protection and duration of protection could help to provide evidence for potential recommendations.

In conclusion, a single vaccine as primary immunisation at age 12 to 23 months induces a sufficient protection against serogroup C IMD. CoP data suggest that this immunity wanes over a period of 6 years. A single booster at the age of 6 years or older induces a sufficient protection in the subsequent years, but the data are too sparse for conclusions regarding the duration of protection. An appropriate age for a potential booster immunisation has to be set depending on the regional IMD epidemiology.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106228.

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