Introduction

Invasive meningococcal disease (IMD) is a major public health challenge [1], caused by the human gram-negative bacteria, *Neisseria meningitidis*, which attacks the bloodstream and membrane lining of the brain and spinal cord. [2] IMD has been strongly associated with high mortality and life-long disabilities in survivors, with fatality rates as high as 50% if untreated, and up to 15% if treatment is initiated, with death occuring within 24 to 48 hours following disease onset.[3] Approximately 30% of survivors suffer at least one or more disability, including amputations, limb length discrepancies, skin scarring, hearing loss, cognitive difficulties, visual disturbances, and psychological distress. [4,5]

While *Neisseria meningitidis* has 13 established serogroups, over 90% of infections are caused by A, B, C, X, Y and W-135 serogroups [6], however, Meningococcal serogroup B (MenB) has become the leading cause of IMD in several countries since the introduction of effective conjugate vaccines against serogroups A, C, W, and Y. Globally, MenB causes almost 500,000 cases of IMD yearly [7], with approximately 70% of reported IMD cases in Europe in 2012 attributed to MenB [8], and over 80% of cases in the UK, New Zealand and Australia [9–11]. There has also been a rise in the incidence of MenB in the US, accounting for over 30% of IMD cases. [11]

In January 2013, the first multicomponent MenB vaccine (4CMenB, Bexsero®) was licensed in Europe by the European Medicine Agency [7,12], and has since been introduced in other countries, including Australia, Chile, Canada, Uruguay, and Brazil [13]. The US Food and Drug Administration (FDA) licensed another MenB vaccine (MenB-FHbp, Trumenba ®) in October 2014, primarily for adolescents and young adults aged 10-25 years. [14] Meanwhile, the UK became the first country to introduce a publicly funded national MenB immunization program in September 2015. [15] However, this decision was inconsistent with cost-

effectiveness findings which suggest that routine vaccination does not offer good value for money. [16]

MenB vaccines have proven to be effective, yet the cost-effectiveness of such vaccines remains unclear, particularly in the context of introducing a routine national MenB immunization program.[17,18] Existing cost-effectiveness reviews of meningococcal vaccines do not include MenB vaccines, while a 2018 study that included these vaccines had a limited literature search and focused on studies conducted in Europe. [19] Therefore, the objective of this review is to synthesize the available evidence to investigate the cost-effectiveness of MenB vaccination from a global perspective.

2.0. **Methodology**

The conduct of this review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for conducting systematic reviews [20], and the Centre for Review and Dissemination's (CRD's) guidelines for systematic reviews of economic evaluations. [21] The review protocol was registered in the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42019139748). [22]

2.1. Inclusion criteria

1. **Population**

Studies conducted in humans, aged zero to 100 years plus, in any country, and in any setting (primary healthcare, secondary healthcare, community, school, etc).

2. **Intervention**

Any form of MenB vaccination, with any form of delivery/strategy (e.g. routine national immunization programs, vaccination of high-risk individuals or vaccination during outbreaks).

3. **Comparators**

All possible comparators were considered, including current standard care **(**e.g. acute hospitalization) and alternative vaccination strategies.

4. **Outcomes**

Any clinically or economically relevant measure of health, such as Quality-Adjusted Life-Years (QALYs), Disability-Adjusted Life Years (DALYs), life-years gained, cases averted, disabilities averted, deaths averted, etc.

5. **Study designs**

Any recognized economic evaluation comparing both costs and health outcomes of MenB vaccination, (e.g. cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequence analysis, etc). [23] Evaluations could be conducted alongside randomized controlled clinical trials or using decision-analytic modelling.

2.2. Exclusion criteria

Vaccine type:. MenB vaccines are currently only available as a single strain vaccine so any studies that evaluated polyvalent or combination vaccines against MenB were excluded.

Target disease: Studies that assessed the effect of MenB vaccines against diseases other than IMD were excluded (e.g. *Neisseria gonorrhoea).*

Evaluation type: Partial economic evaluations, such as studies which only investigated costs or the economic burden of meningococcal disease, were excluded.

Language: Studies not published in English.

2.3. Systematic literature search

The following databases were searched based on the recommended databases for systematic reviews of economic evaluations [24,25]: MEDLINE, EMBASE, Web of Science, Econlit, Tufts Cost Effective Analysis (CEA) registry, National Health Service Economic Evaluation Database (NHS EED) and Health Technology Assessment (HTA).

The search strategy was developed by the primary reviewer, with the assistance of an information specialist. The search terms were formulated in relation to the intervention and study design. Therefore, terms such as ‘vaccine’, ‘meningococcus’, and ‘economic evaluation’ were searched, including their synonyms, abbreviations and acronyms, and, where applicable,

medical subject heading (MeSH) terms. No search term or filter was applied to the study population, comparators or outcomes to ensure a robust and comprehensive search.

We adapted peer-reviewed search strategies for identifying economic evaluations. For MEDLINE, we used the approach developed by Wilczynski et al. [26], for high rates of optimization of sensitivity and precision [27]. For EMBASE, the validated CRD search strategy was used., while we developed our own search strategy for Web of Science database. For the databases Econlit, NHS EED, Tufts CEA registry, and HTA, we searched using only free-text words. Each database was approached slightly differently due to their unique search configuration (see appendix 1). A manual search through the reference list of selected studies was also conducted.

2.4. Selection of studies

After removing duplicates, the retrieved studies were screened by title and abstact by two reviewers. Then, full texts of studies identified as potentially relevant were retrieved, and the inclusion/exclusion criteria applied by three reviewers independently. Any disagreements between the reviewers was discussed and resolved through a consensus. A list of studies that were excluded during the full-paper screening is provided in Appendix 2.

2.5. Data extraction and quality assessment

Data extraction was conducted by the lead reviewer, and included general study characteristics, key elements of economic evalutions, study results and conclusions (see Appendix 4). For model-based studies, these items were extended to include model structure and key assumptions.

Study quality was assessed using the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) checklist, as recommended by the International Society for

Pharmacoeconomics and Outcomes Research (ISPOR). [28,29] The lead reviewer conducted the quality assessment.

2.6. Data synthesis and analysis

Pooling of ICER estimates using meta-analysis or any method of quantitative synthesis was not conducted as it is not recommended in systematic review of economic evaluations due to various possible sources of heterogeneity [21]; therefore, a narrative synthesis was conducted.

3. Results

3.1. Literature search

The literature search produced a total of 2,667 publications. After removing duplicates, this was reduced to 1,935 studies. Title and abstract screening eliminated 1876 studies, leaving a total of 59 papers for full-text screening. No additional papers were identified by manual hand search through the reference list of these studies. A total of 13 papers met the eligibility criteria after full-text screening (see *Figure 1*)

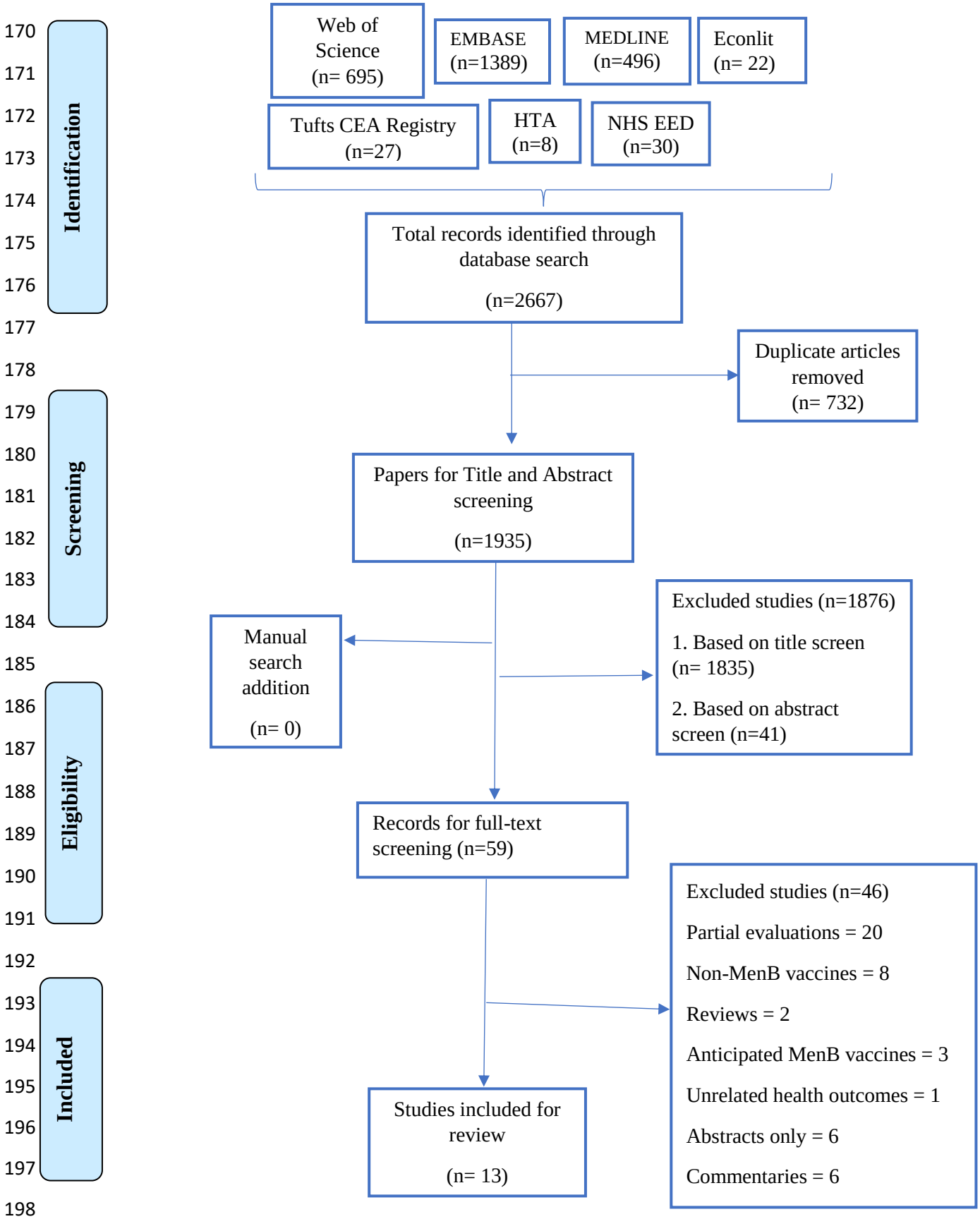

Figure 1. **Prisma flow diagram showing search results.**

3.2. Overview of included studies

The characteristics of the included studies are summarized in Table 1. All thirteen studies were published between 2013 and 2019. Studies were conducted in England [30–32], Italy [17,18], Germany [33], France [34], the Netherlands [35], Belgium [36], Israel [37], Canada [38], USA [39] and Chile. [40] All studies were conducted in high-income countries based on the current classifications for the World Bank's 2020 fiscal year. [41]

Twelve studies assessed the cost-effectiveness of routine universal MenB vaccination [17,18,38,39,30–37], while Izquierdo et al. evaluated the cost-effectiveness of MenB vaccination in the context of a hypothetical epidemic MenB outbreak. [40] Only one study assessed the cost-effectiveness of introducing MenB vaccines under different policies (free routine vaccination, partly reimbursed and private markets). [36]

All studies included infant vaccination, except the US study which targeted college-entry students aged 18 years. [39] Six studies investigated the cost-effectiveness of infant or childhood strategies only [17,18,32,35,37,38], with Christensen et al. exclusively exploring different catch-up strategies in English children aged 1, 2, and 3-4 years. [32] Four studies assessed infant, adolescent, and combined strategies [31,33,34,36] and one study targeted the susceptible population (2 months to 25 years) in a hypothetical outbreak. [40]

Overview of methods used in included studies

All studies compared MenB vaccination with current standard care (i.e. no vaccination). This involved treatment of MenB cases which required hospitalization, as well as management of resulting complications (e.g. amputations, hearing loss). Only one study included MenB vaccination based on an individual decision [39], using an assumption that a single confirmed

MenB case led to mass vaccination of students, faculty, and staff. [39] Seven studies compared different vaccination strategies. [30–37]

All studies except one were cost-utility analyses [17,18,39,30–35,37,38], the exception being a cost-consequence analysis. [40] Five studies were conducted under the societal perspective, either in base case [17,35,37,39] or scenario analysis [33]. One study reported using a 'restricted societal' perspective, including only direct medical costs. [34] Three UK studies were from a NHS and personal and social care perspective [30–32], while three studies were conducted from the healthcare payer perspective alone. [18,36,38] Two others assessed both healthcare payer and societal perspectives. [17,33] One US study included both the health sector (costs incurred by both individuals and private insurance) and societal perspectives. [39] Izquierdo et al. did not explicitly state any perspective, but it appears to use a societal perspective based on the inclusion of indirect costs. [40] The time horizons reported ranged from four to 100 years (i.e. lifetime).

All studies used decision analytical modelling. Three studies [30,33,36] employed both the Markov model and a transmission dynamic model (the former model assumed MenB vaccine offered direct disease protection only, while the latter incorporated herd effects). Three studies made use of Markov models alone [18,35,38], two studies utilized transmission dynamic models alone [31,32] while two other studies employed decision trees. [17,39] Two studies were not explicit about the models used [37,40], and it was impossible to make inference based on the information provided.

Five studies did not model the effect of herd immunity, either in the base case or sensitivity analysis. [17,18,35,39,40] Four studies modelled the effect of herd immunity by assuming a 30% reduction in carriage rate [31–33,36], while one study assumed a higher proportion of 60%. [30]

Seven studies did not include indirect costs of MenB disease. [18,30–32,34,36,38] Two UK studies included the cost of litigation to the NHS. [31,32] Of the five studies that included indirect costs in the base-case analysis [17,35,37,39,40], only three studies captured the cost associated with premature deaths [17,39,40], although Gasparini et al. only included this cost in scenario analysis. [17] Nine studies also included the cost of public health response to a case. [17,30–33,35,36,38,39]

Eleven studies reported QALYs gained as the primary outcome measure. [17,18,39,30–36,38] Only one study reported outcomes in DALYs averted [37], while one study did not report either QALYs or DALYs due to the nature of the study design (CCA); hence, outcomes were reported only in natural units (cases, sequelae, and deaths averted). [40] Other secondary outcome measures included cases averted [17,18,40,30,31,33–38], deaths averted [17,30,31,36,37,40], morbidities averted [40] and life-years gained. [31,36]

Table 1. **Study Characteristics**

Author, year	Country	Intervention	Target Population	Discounting	Comparators	Study Design	Time horizon	Perspective	Included costs	Outcome Measures	Sensitivity analysis
Infant/Childhood Strategies											
Christensen et al, 2017 [32]	England	Catch-up vaccination	Young children (1-4 years)	3.5% for costs and benefits	Standard care (i.e. no vaccination)	CUA	100 years	NHS & Personal and Social service	vaccination, acute hospital care and initial follow-up, adverse reaction, long-term support for survivors, litigation.	QALY gained	scenario analysis varying vaccine strain coverage and efficacy
Gasparini et al, 2016 [17]	Italy	Routine vaccination	Infants	3% for both costs and utilities	No vaccination	CUA	Lifetime (82 years)	Societal and National Health Service (scenario analysis)	Costs associated with vaccination, cost of acute illness and long-term sequelae and social cost of death.	QALY gained, cases and deaths averted	One-way and multivariate sensitivity analyses.
Ginsberg et al, 2015 [37]	Israel	Nationwide MenB vaccination	Children	3% for both cost and DALYs	No vaccination	CUA	100 years	Societal	vaccine price; treatment cost; transport; work losses; side effects; cost of acute cases and sequelae	DALY averted; cases averted, and deaths averted	One-way, two-way, and three-way sensitivity analyses

Table 1 (continued)

Author, year	Country	Intervention	Target Population	Discounting	Comparators	Study Design	Time horizon	Perspective	Included costs	Outcome Measures	Sensitivity analysis
Pouwels et al, 2013 [35]	Netherlands	Routine infant vaccination (with various vaccine strategies)	Infants	4% and 1.5% for cost and health effects respectively.	No vaccination	CUA	99 years	Societal	Direct cost (treatment of acute illness and long-term disabilities); indirect cost (productivity losses)	QALY gained; life-years gained	One-way sensitivity and probabilistic sensitivity analysis.
Tirani et al, 2015 [18]	Italy	Routine infant MenB immunization	Infants	3% for both costs and utilities	No vaccination	CUA	100 years	Public health payer	Cost of acute disease and sequalae, vaccination cost.	QALY gained	Univariate, bivariate and probabilistic sensitivity analysis (PSA)
Tu et al, 2014 [38]	Canada (Ontario)	Routine MenB vaccination	Infants	5% for both costs and benefits	No vaccination	CUA	lifetime	Healthcare payer	vaccination cost (including adverse effects), treatment of invasive MenB disease, public health cost of contact management.	QALY gained	Scenario analysis, one-way and two-way sensitivity analysis

Table 1 (continued)

Author, year	Country	Intervention	Target Population	Discounting	Comparators	Study Design	Time horizon	Perspective	Included costs	Outcome Measures	Sensitivity analysis
Adolescent strategies											
Leeds et al, 2019 [39]	USA	Universal vaccination at college entry	College-aged young adults	3% for costs and benefits	No universal vaccination, with an outbreak response	CUA	4 years (health sector); lifetime (societal)	Health sector and societal	Direct medical cost (vaccination cost, acute hospitalization, and long-term disability) and indirect cost (productivity losses due to sequalae and death)	QALY gained	Univariate and multivariate probabilistic sensitivity analysis.
Combined strategies											
Christensen et al, 2013 [30]	England	Introducing new MenB vaccine (with various vaccine strategies)	Infants and adolescents	3.5% for costs and benefits	No vaccination	CUA	100 years	NHS & Personal and Social service	Vaccination cost, including adverse effects, cost of acute and long-term treatment.	QALY gained, cases averted, and deaths averted	Scenario and probabilistic sensitivity analyses (PSA)

Table 1 (continued)

Author, year	Country	Intervention	Target Population	Discounting	Comparators	Study Design	Time horizon	Perspective	Included costs	Outcome Measures	Sensitivity analysis
Christensen et al, 2014 [31]	England	Introducing new MenB vaccine (with various vaccine strategies)	Infants and adolescents	3.5% for costs and benefits.	Standard care (i.e. no vaccination)	CUA	100 years	NHS & Personal and Social service	Vaccination cost, cost of treatment and care, litigation cost, treating adverse reactions.	QALY gained, case averted and death averted, life year gained.	Scenario analysis
Christensen et al, 2016 [33]	Germany	Universal vaccination against MenB (with various vaccine strategies)	Infants and adolescents	3% for costs and benefits	No universal vaccination	CUA	100 years	Payer and societal (scenario analysis)	Vaccination, acute healthcare cost, productivity losses, cost of aftercare, annual support cost; adverse reaction.	QALY gained, cases averted and deaths averted	Scenario and probabilistic sensitivity analysis (PSA)
Hanquet et al, 2014 [36]	Belgium	Routine vaccination against MenB (with different policies and strategies)	Infants and adolescents	3% and 1.5% for cost and benefits respectively	No vaccination and including adolescent vaccination to infant strategies	CUA	100 years	Health care payer	Direct medical cost only (vaccination program, acute hospitalization, follow up care, public health case management)	QALY gained, life-years gained, cases and deaths averted.	Univariate and multivariate analysis

Table 1 (continued)

Author, year	Country	Intervention	Target Population	Discounting	Comparators	Study Design	Time horizon	Perspective	Included costs	Outcome Measures	Sensitivity analysis
Izquierdo et al, 2015 [40]	Chile	Vaccination during an epidemic outbreak	Susceptible population (2 months to 25 years)	6% for costs only	No vaccination	CCA	Not stated	Not stated (appears to be societal perspective)	Cost of mass vaccination campaign, cost of acute illness and sequalae, including the cost of death.	Cases averted, deaths averted, and sequalae averted	Not explicitly stated (appears to be one-way sensitivity)
Lecocq et al, 2016 [34]	France	Routine vaccination against MenB (with various vaccine strategies)	Infants, toddlers, and adolescents	4% for the first 30 years for both cost and outcomes, then a progressive decline to 2% afterwards.	No vaccination	CUA	100 years	Restricted societal perspective	Direct costs only (vaccination, cost of acute disease, long-term sequalae)	QALY gained	One-way sensitivity and probabilistic sensitivity analysis

3.3. Narrative synthesis of findings

3.3.1. Infant Strategies

The findings suggest that none of the infant strategies were considered cost-effective in base-case analyses. Assuming herd immunity had little impact on the ICER estimates; infact strategies were still not cost-effective. [30–34,36,37,40] In a scenario analysis, Gasparini et al., however, found that routine infant vaccination (2,4,6,12 months and a booster dose at 11 years) could be cost-effective (ICER of €26,599 per QALY gained) in Italy if the possible underestimation of disease incidence was taken into consideration. [17] In contrast, another Italian study reported a much higher estimate of over €350,000 per QALY at the current reported incidence rate. [18] Both Italian studies did not model the effects of herd protection. In Canada, infant vaccination was predicted to prevent only 0.5 deaths and 4.6 cases of invasive MenB disease, resulting in an ICER of C$4.76 million per QALY gained, well above the Canadian national threshold of C$50,000 per QALY gained. [38] Even under favourable assumptions of herd effects and an implausible vaccine price of C$0, the ICER (C$ 128,736 per QALY gained) was still above the threshold.

UK studies found that routine infant vaccination offered the best value for money (assuming no herd protection) compared to adolescent and combined strategies. [30,31] Similar findings were reported in France [34], Germany [33] and Belgium [37], where strategies targeting infants had the lowest ICERs, under the assumption that MenB vaccines provided direct protection only. However, a high ICER (over €2,000,000 per QALY gained) was reported in Germany, due to low MenB incidence of 0.15 per 100,000 persons. [33] When herd effects were included, infant vaccination was considered the most effective short-term strategy in terms of reduction in MenB cases. [31,33,36] Regarding catch-up strategies, Christensen et al. found that extending vaccination to one-year-olds had the lowest ICER compared to strategies that included two to four-year-olds. [32] Sensitivity and scenario analyses revealed that routine

immunization may be cost-effective at a higher incidence of 0.69 per 100,000 persons, particularly if the possible underreporting of MenB cases is considered. [17]

3.3.2. Adolescent strategies

When including herd protection, all five studies that assessed the impact of targeting adolescents alone suggested that routine adolescent vaccination was the most cost-effective strategy compared to infant and combined strategies, although still not cost-effective at commonly used national thresholds.[30,31,33,34,36] In the US, universal MenB vaccination of young adults (18 years old) at college entry did not offer value for money compared to standard care, with ICER estimates of $13.8 million and $13.9 million per QALY gained for the societal and health sector perspectives respectively.[39] Three studies modelled the impact of adolescent strategies without herd effects [31,34,36], and found that vaccinating adolescents alone had the least epidemiological impact in terms of the number of cases and deaths averted, and accordingly, the highest ICER estimates. [31,34,36]

3.3.3. Combined strategies

The impact of combined infant and adolescent immunization was considered in France [34], Germany [33], England [31], and Belgium. [36] Targeting both infants and adolescent was the most effective long-term strategy compared to targeting infants or adolescents alone (including herd immunity) [31,33,34,36], preventing over 50% of MenB cases in France [34] and England [31] and almost 70% of cases in Belgium. [36] This strategy also offered more value for money than targeting infants alone. Izquierdo et al. reported that mass vaccination of the susceptible population (2months to 25 years old) in event of a MenB epidemic outbreak in Chile would be cost-effective at a vaccine price of $18 per dose or less. [40]

316 *Table 2*. **Summary of major findings**

Author, year	Analytical approach	Key assumptions (Base case)	Results (Base case)	Threshold value	Results (sensitivity/scenario analysis)	Stated Conclusion
Infant/Childhood strategies						
Christensen et al, 2017 [32]	Transmission dynamic model	95% vaccine effectiveness; 30% protection against carriage acquisition; 88% strain coverage, vaccination price of £75 per dose; herd protection after 2nd dose	-Catch-up in 1 year old: £143, 200/QALY -Catchup in 1-2 year olds: £199,800/QALY -Catch up in 1-4 year olds: £264,800/QALY	£20,000 per QALY	(Assuming 66% vaccine coverage and no heard immunity) Catch-up in 1 year old: £262, 700/QALY Catchup in 1-2 year olds: £401,800/QALY Catch up in 1-4 year olds: £613,700/QALY	Based on current JCVI criteria, only catch-up in 1 year old children could be cost-effective at a low vaccine price.
Gasparini et al, 2016 [17]	Decision tree	90% vaccine coverage, 87% strain coverage, 95% disease protection; protection began after 2nd dose and wanes over time, 10 years of protection, vaccination price of £50 per dose, no herd effects.	Two base-case ICERs reported At official incidence: €109,762/QALY At estimated incidence: €26,599/QALY	€50,000 per QALY	Including cost of death at official incidence: €109, 191/QALY (human capital approach) NHS perspective: €120,999/QALY (official incidence); €37827/QALY (estimated incidence)	Routine vaccination could be cost-effective if the possible underestimation of disease incidence is considered.
Ginsberg et al, 2015 [37]	Basic model	90% vaccine efficacy (second offered 47% efficacy); 66% strain coverage; vaccine price of $60/dose; no herd immunity.	ICER: $234,394/QALY	$108,501 per DALY averted	Assuming herd effect was still not cost effective ($ 234,000-284,000/ QALY)	Cost-effective at a vaccine price below $19.44/dose

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317 *Table 2* (continued)

Author, year	Analytical approach	Key assumptions (Base case)	Results (Base case)	Threshold value	Results (sensitivity/scenario analysis)	Stated Conclusion
Pouwels et al, 2013 [35]	Markov model	75% efficacy one month after 2nd dose, €40 per dose. Duration of protection (1.5 and 3 years following 3rd and 4th doses), no herd effects.	2,3,4,11months: €243,778/QALY 12+14 months: €221,139/QALY	€20,000 to 50,000 per QALY	At a higher incidence of 3.46 per 100,000 person-years. 2,3,4,11months: €85,931/QALY 12+14 months: €70,898/QALY	Routine infant MenB vaccination (2, 3, 4 +11 months) is unlikely to be cost-effective.
Tirani et al, 2016 [18]	Markov model	75% vaccine efficacy, 3 years protection, 80% vaccine coverage, 100% strain coverage, €67 per vaccine dose, no herd immunity.	ICER: €376, 042 per QALY gained	€40, 000 per QALY	Cost effective at six times higher incidence rate and 1.5% discount rate (< €40,000/QALY)	Immunization is unlikely to be cost-effective at current incidence and vaccine price.
Tu et al, 2014 [38]	Markov model	97% coverage, 90% effectiveness, 66% strain coverage, 10-year protection, vaccine cost of C$75 per dose, no herd effects.	ICER: C$4.76 million per QALY	C$ 50,000 per QALY	Cost effective at 4.5 times higher incidence and vaccine price of C$6.24 per dose (< C$ 50,000/QALY)	Intervention exceeds commonly used cost-effectiveness thresholds and thus unlikely to be considered economically attractive.

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320 *Table 2* (continued)

Author, year	Analytical approach	Key assumptions (Base case)	Results (Base case)	Threshold value	Results (sensitivity/scenario analysis)	Stated Conclusion
Adolescent Strategies						
Leeds et al, 2019 [39]	Decision tree	Equal risk of MenB infection; entered college at 18 years of age and left after 4 years; 50% vaccine efficacy, no herd immunity.	Health sector perspective: $13.9 million/QALY Societal perspective: $13.8 million/QALY	$150,000 per QALY	Cost effective at incidence of 4.6 cases per 100,000 persons or vaccine less than $65. (<$150,000/QALY)	Universal vaccination at college entry is not cost-effective.
Combined Strategies						
Christensen et al, 2013 [30]	1. Markov Cohort model	75% vaccine efficacy, 100% strain coverage, vaccine cost of £40, protection begins after 2nd dose; modelled only infant strategies. No herd effect	Lowest ICER: 2,3,4, 12 months (£162,800/QALY)	£30,000 per QALY	Routine vaccination (2,3,4, 12 months) cost effective at vaccine price of £9/dose (£29,900/QALY)	Immunization programs could be cost effective if the vaccine is competitively priced
	2.Transmission dynamic model	75% vaccine efficacy, 100% strain coverage, vaccine cost of £40/dose, protection begins after 2nd dose; modelled adolescent strategies; herd effect	Lowest ICER: Routine adolescent strategy plus catch-up in 13-17 year olds (£39,200/QALY)		Routine infant vaccination: at vaccine coverage of 75%, high ICER (£131,800/QALY)	

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Table 2 (continued)

Author, year	Analytical approach	Key assumptions (Base case)	Results (Base case)	Threshold value	Results (sensitivity/scenario analysis)	Stated Conclusion
Christensen et al, 2014 [31]	Transmission dynamic model	95% disease protection; protection begins after 2nd dose; 30% protection against carriage acquisition; 88% strain coverage, vaccination price of £75 per dose, herd protection	Lowest ICER: Adolescent with catch up in 14-17 years (£60,300/QALY) Most effective: 2,3,4, 12 months and 13 years (£131,600/QALY)	£20,000 per QALY	Assuming no herd effects & 66% vaccine coverage. Lowest ICER: 2,4, 12months (£183,330/QALY) Highest ICER: 13 year olds (£627,900/QALY)	Routine infant vaccination is the most effective short-term strategy and could be cost-effective at a low vaccine price.
Christensen et al, 2016 [33]	1. Cohort Markov model	65% vaccine uptake, 82 % strain coverage; vaccine price of €96.96 modelled only infant strategies, no herd effect, no herd effects.	Lowest ICER: Infant- 2,3,4 12 months (€2,015,300/QALY) Highest ICER: Infant- 6,8,12 months plus catch-up in 1-17years old (€3,309,900/QALY)	€50,000 per QALY	Increased incidence: €1,339,600 per QALY (lowest ICER) Societal perspective with QoL loss for carers: €1,978,00/QALY	Universal MenB vaccination would only prevent a small absolute number of cases, at a high overall cost.
	2.Transmission dynamic model	65% vaccine uptake, 82 % strain coverage; vaccine price of €96.96 modelled only infant strategies, no herd effect, herd effects	Lowest ICER: Adolescents with catch-up (€520,100/QALY) Highest ICER: Infant; 2,4,6,12 months (€1,429,400/QALY)		Increased incidence: €1,016,000 per QALY (lowest ICER) Societal perspective with QoL loss for carers: €1,367,200/QALY	

324*Table 2* (continued)

Author, year	Analytical approach	Key assumptions (Base case)	Results (Base case)	Threshold value	Results (sensitivity/scenario analysis)	Stated Conclusion
Hanquet et al, 2014 [36]	Markov Cohort model	95% vaccine efficacy in infants and 100% efficacy in adolescents; 55% uptake; 27 months protection after the booster; only infant strategies, no herd effect.	Routine free infant (3,5,6,12 months): €422,700/QALY Partly reimbursed: €663,600/QALY Private market: €677,800/QALY	Benchmark ICERs of €10,000 and €33,000 per QALY	Best case scenario: €98,300/QALY Worst case scenario: €2,688,900/QALY	Regardless of herd immunity, infant vaccination strategies, have minimal impact and are not cost-effective.
	Transmission dynamic model	With (and without) herd; protection starts after second dose; modelled adolescent strategies, 30% efficacy against carriage.	**No herd effect**: Lowest ICER: Infant (€303,000/QALY) Highest ICER: Adolescent (€314,600/QALY) **Herd effect:** Lowest ICER: Adolescent (24,400/QALY) Highest ICER: Infant (€260,700/QALY)		Best case scenario: €17,400 per QALY Worst case scenario: €2,638,700/QALY	
Izquierdo et al, 2015 [40]	None stated	80% effectiveness in infants and 92% in adolescents; vaccine coverage ranging from 92-95%	215 cases prevented 60.9 sequelae averted 15.7 deaths prevented cost savings: $41,995,724	Not applicable	Cost effective at vaccine cost of $18/dsose	Intervention would be cost-effective at a vaccine cost per dose of $18 or less

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Table 2 (continued)

Author, year	Analytical approach	Key assumptions (Base case)	Results (Base case)	Threshold value	Results (sensitivity/scenario analysis)	Stated Conclusion
Lecocq et al, 2016 [34]	Multi-generational Markov model	With (alternative base case) and without herd immunity; 85% strain coverage; no transmission by infected; vaccine cost per €40 per dose.	**Herd effect** Lowest ICER: Adolescent (135, 902 per QALY) Highest ICER: Delayed infant (€246,648/QALY) **No herd effects** Lowest ICER: Infant (€380,973 per QALY) Highest ICER: Adolescents (€618,847/QALY)	€90, 000 per QALY	**Herd effect** Best case: € 79,810/QALY Worst case: € 402,280/QALY **No herd effects** Best case: €224,570/QALY Worst case: €988,047/QALY	Routine MenB vaccination is not cost-effective.

3.4. Quality assessment of included studies

Discounts rates were mainly based on national recommendations [18,30,33–36,38,39], although lacked justification in two studies.[32,37] Due to limited vaccine data, certain model inputs were assumed. A common assumption was the duration of protection provided. [17,18,31,33,37,38]

All costs were adjusted to a reference price year and presented in the currency of the country being studied, except in Israel [37] and Chile [40], where the local currencies were converted to US dollars and exchange rates clearly stated. The primary outcome measure was in QALY gained. [17,18,39,30–36,38] However, one study reported DALY averted to capture a decrease in MenB related deaths and morbidities resulting from vaccination.[37] Although ICER estimates were highlighted, only three studies included both the estimated costs and outcomes for the comparator (i.e. no vaccination scenario), upon which the incremental analyses were done. [34,38,39]

Table 3. **Summary of quality assessment using the CHEERS checklist**

Section/item	Item No	Ginsberg [37]	Christensen [30]	Christensen [31]	Christensen [32]	Christensen [33]	Lecocq [34]	Pouwels [35]	Hanquet [36]	Gasparini [17]	Tirani [18]	Tu [38]	Leeds [39]	Izuierdo [40]
Title	1	Y	P	Y	Y	Y	Y	Y	Y	Y	P	Y	Y	Y
Abstract	2	P	P	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	P
Background and objectives	3a	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	3b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Target population and subgroups	4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Setting and location	5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Study perspective	6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Comparators	7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon	8	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	P	Y	N
Discount rate	9	P	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of health outcomes	10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Measurement of effectiveness	11a	Y	N	Y	Y	N	Y	N	NA	Y	Y	Y	Y	Y
	11b	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA	NA	NA
Measurement and valuation of preference-based outcomes	12	Y	NA	Y	N	N	Y	Y	Y	NA	NA	Y	Y	NA
Estimating resources and costs	13a	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	13b	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Currency, price date, and conversion	14	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Choice of model	15	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Assumptions	16	P	Y	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	N
Analytical methods	17	P	P	P	P	P	P	P	P	P	P	P	P	P
Study parameters	18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

N= Not reported; Y= Reported; P= Partially reported; NA=Not applicable

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355 *Table 3* (continued)

Section/item	Item No	Ginsberg [37]	Christensen [30]	Christensen [31]	Christensen [32]	Christensen [33]	Lecocq [34]	Pouwels [35]	Hanquet [36]	Gasparini [17]	Tirani [18]	Tu [38]	Leeds [39]	Izuierdo [40]
Incremental costs and outcomes	19	P	P	P	P	P	Y	P	P	P	P	Y	Y	NA
Characterizing uncertainty	20a	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	20b	P	Y	P	P	Y	Y	Y	Y	Y	Y	P	Y	P
Characterizing heterogeneity	21	NA	Y	Y	Y	Y	Y	NA	Y	NA	NA	NA	NA	NA
Study findings, limitations, generalizability, and current knowledge	22	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Source of funding	23	Y	Y	Y	Y	Y	N	Y	P	Y	N	Y	Y	N
Conflicts of interest	24	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y

356 N= Not reported; Y= Reported; P= Partially reported; NA=Not applicab

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4.0. Discussion

4.1. Summary of main findings

There is a paucity of cost-effectiveness data on MenB vaccines, with only thirteen studies identified. The findings suggest that although routine MenB vaccination could significantly reduce cases of invasive MenB disease, this intervention was not considered cost-effective at national decision-making thresholds. Findings did not differ significantly with geography, vaccination strategy, or age group targeted.

The inclusion of herd effects led to a greater epidemiological impact with respect to number of MenB cases and deaths averted, including more favourable ICER estimates. However, the impact was less significant in infant strategies. Routine infant immunization was considered the most effective short-term strategy, while combined infant and adolescent vaccination provided maximal long-term health benefits. [31,33,34,36] Vaccinating adolescents alone resulted in the lowest ICER estimates, followed by combined strategies, while infant strategies had the highest ICERs. Infant strategies commencing earlier on in life had greater benefits than delayed schedules, with or without herd effects. [33] Assuming no herd protection, routine infant vaccination offered the best value for money, while targeting adolescents alone resulted in the greatest ICER estimates and prevented the least number of MenB cases. [31,36]

Interpretation of findings

While MenB is mostly predominant in industrialized nations, it has an overall low incidence [10], and therefore unsurprising that none of the vaccination strategies were considered cost-effective.

However, it is worth considering the impact of herd effects on economic evaluations, which led to reduced ICERs and more cases averted. While herd effects were not modelled in some studies, there is growing evidence to support that MenB vaccines offer some degree of indirect

protection by disrupting meningococcal carriage acquisition and transmission. [42] Given that the prevalence of asymptomatic meningococcal carriage is much lower in young children compared to adolescents, this may explain why the effect of herd protection was minimal in infant vaccination strategies, but greater in strategies targeting adolescents. [30,31] The positive findings observed in adolescent strategies may be attributable to the reduced cost associated with curtailed dosing schedules in this age group. However, vaccinating adolescents alone takes several years to achieve a substantial reduction in MenB disease burden [31], and therefore tends to neglect short to medium-term health losses in young children. Therefore, it would appear counterintuitive to target adolescents at the expense of infants, who account for the greatest disease burden.

Vaccine price was predictive of cost-effectiveness findings. Being newly introduced into the market, MenB vaccines currently come at a considerable cost. Although routine infant vaccination was predicted to be cost-effective at a low vaccine price [30,31], this assumption only appears to be valid in the context of a considerable level of disease incidence. However, as Gasparini et al. argued, there is a likelihood of an underreporting of MenB cases which potentially underestimates the cost-effectiveness of MenB vaccination [17]. A possible explanation is the widespread use of bacterial culture for meningococcal surveillance which has significantly lower sensitivity compared to molecular methods such as polymerase chain reactions [43]. While this observation was reported in Italy, it is unclear whether the underlying mechanism of underreporting is generalizable to other countries.

Additionally, the cost-effectiveness of MenB vaccination is limited by the fact that immunogenicity wanes quickly, providing only transient protection, and booster doses may be required later in life. [44,45]

4.2. Strengths and limitations of the review methods

4.2.1. Strengths

To the authors' knowledge, this is the first comprehensive systematic review of the cost-effectiveness of MenB vaccination conducted at the global level. Although a similar review was conducted in 2018 [19], this was limited to countries in Europe and included only nine studies. The search strategy also appeared insufficient, searching only two databases. However, the findings were similar.

This review was carefully conducted following the PRISMA statement as well as CRD guidelines for reporting systematic reviews of economic evaluation. The review process was based on a comprehensive search strategy and robust quality assessment. The search strategy was developed and adapted using validated, peer-viewed filters that provided optimization of sensitivity and precision..

4.2.2. Limitations

Data extraction and quality assessment of studies were done by a single which might have introduced biases. The review was limited to studies published in English. Hence, there is a possibility that certain relevant papers were excluded, arguably limiting the strength of the evidence provided. The review also excluded studies that evaluated combination MenB vaccines since they do not reflect current real-world practice. Although such vaccines do not currently exist, these studies may provide insights to their cost-effectiveness if they are successfully developed in the future. While there were no regional restrictions, all studies came from ten countries, representing two out of the six WHO regions. Therefore, findings of this review may not be generalizable beyond the countries that were studied in the included papers. Additionally, the largest burden of meningococcal disease is concentrated in sub-Saharan Africa, specifically in a region popularly known as the meningitis belt, which cuts across 26

countries. [3] While MenB is not yet prevalent in the area, there is evidence to support that the distribution pattern of meningitis is shifting, away from meningococcal serogroup A (MenA), towards other serogroups such as C, W and X. [46] This transition is largely attributable to the introduction of mass vaccination campaigns against MenA which started in 2010. [47] Consequently, as more countries continue to roll out effective quadrivalent vaccines against these non-A serogroups, it is likely that, in the future, there may be a significant rise in the prevalence of MenB in unconventional regions. As such, the findings presented in this review may not be applicable in that context, as MenB vaccination may become more cost-effective.

4.3. **Strengths and limitations of the included studies**

4.3.1. **Strengths**

All studies that included adolescent strategies and incorporated herd immunity made use of transmission dynamic models [30,31,33,36], in line with current recommended practice. [48] All studies made use of decision analytical modelling which allowed for extrapolation of time horizon and easy head-to-head comparisons of different vaccination strategies. Studies also assumed a lifetime horizon which captured the long-term cost and benefits of MenB vaccination.

4.3.2. **Limitations**

While the societal perspective is generally recommended, a considerable number of studies were conducted from the healthcare payer perspective alone [18,36,38], which considered only the medical costs of managing MenB cases incurred by the government. As a result, this perspective failed to capture the substantial indirect costs associated with MenB disease, such as productivity losses due to lost work time as a result of hospitalization, reduced productivity in event of a long-term disability as well as productivity losses associated with death.

Consequently, the exclusion of these indirect costs potentially underestimates the cost-effectiveness of MenB vaccination. Similarly, four studies did not include the cost of an outbreak response. [18,34,37,40] Considering the potentially huge cost of public health response to even a single case outbreak, excluding this may lead to bias in favour of no MenB vaccination by neglecting the possible cost savings associated with reduced frequency of disease outbreaks. However, the extent to which inclusion of these costs influenced final findings remains unclear given that ICER estimates remained high in studies that considered them.

Furthermore, included studies were model-based and relied on certain untested assumptions. Models were not standardized, with varying inputs and assumptions across studies. For instance, while some inputs were backed with relevant literature, others (e.g. duration of vaccine protection) were based solely on expert opinions. [31,33,35,38]

4.4. Comparison with similar reviews

Previous reviews of other vaccines against meningococcal serogroups A, C, W, and Y were found to be cost-effecitve [49,50], probably due to the high incidence of these diseases at the time. [51] Nevertheless, these findings indicate that MenB vaccines may be cost-effective at a higher incidence.

Unsurprisingly, findings were consistent with a review of the cost-effectiveness of MenB vaccines in Europe which concluded that routine immunization was a relevant short-term strategy, adding that adolescent vaccination may be more cost-effective in the long run, if herd effects were considered. [19]

4.5. Policy implications

Our findings suggest that routine MenB immunization is not cost-effective. However, the UK introduced routine, national, publicly funded MenB vaccination in infants, despite country-specific evidence that MenB vaccination was not considered cost-effective. This decision came after academics, clinicians and other stakeholders expressed their disapproval [52], following the interim statement by the Joint Committee on Vaccination and Immunization (JCVI) that routine MenB vaccination should not be introduced based on unfavourable cost-effectiveness findings. [16] Therefore, the degree to which cost-effectiveness data influence policy decisions may vary across countries.

Introducing routine immunization has a potentially large budgetary impact. In an attempt to reduce this, policymakers may decide to target only high-risk populations rather than routine universal vaccination. However, a study in this review that compared funding policies (publicly funded, reimbursement and private market) suggested that publicly funded MenB immunization was the most cost-effective policy strategy. [36] This is partly explained by the anticipated high vaccine uptake and potential for governments to purchase vaccines at a competitive price. [36]

Further research is needed to fully establish the true values of vaccine characteristics, including duration of protection, strain coverage, effectiveness against non-B serogroups, and the degree of indirect protection provided. This would reduce methodological variations and improve the confidence of cost-effectiveness findings in the future.

Conclusion

Routine MenB vaccination appears not to be a cost-effective intervention, largely due to the prevailing low MenB incidence and high vaccine cost. The overall findings did not differ with

geography, vaccination, and targeted age group. However, countries seeking to introduce MenB vaccination into their national immunization program should not rely solely on cost-effectiveness data, but consider other policy and programmatic issues.

Authors' Contribution

IBN originated the research topic, developed the search strategy, screened and selected included papers, carried out a quality assessment of selected studies, and wrote the manuscript. TL reviewed the search strategy, screened and selected included papers, and edited the manuscript. MJ reviewed the search strategy, screened and selected included papers, and edited the manuscript. All authors unanimously agreed and approved the final manuscript. All authors attest that they meet the ICMJE recommendation for authorship

Declaration of interests

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

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