



Published in final edited form as:

J Infect Dis. 2025 February 04; 231(1): 61–70. doi:10.1093/infdis/jiae383.

Effectiveness of menb-4C vaccine against gonorrhea: a systematic review and meta-analysis

Winston E. Abara¹, Robert D. Kirkcaldy², Kyle T. Bernstein², Eboni Galloway¹, Emily R. Learner¹

¹Division of STD Prevention, U.S Centers for Disease control and Prevention, Atlanta, Georgia 30333 United States of America

²Center for Scientific Education and Leadership, U.S. Centers for Disease Control and Prevention, Atlanta, Georgia, 30333, United States of America

Abstract

Introduction: There is no licensed vaccine against gonorrhea but *Neisseria meningitidis* serogroup B outer membrane vesicle-based vaccines, like MenB-4C, may offer cross-protection against gonorrhea. This systematic review and meta-analysis synthesized the published literature on MenB-4C vaccine effectiveness against gonorrhea.

Methods: We conducted a literature search of electronic databases (PubMed, Medline, Embase, Global Health, Scopus, Google Scholar, CINAHL, and Cochrane Library) to identify peer-reviewed papers, published in English, from 1/1/2013–7/12/2024 that reported MenB-4C vaccine effectiveness estimates against gonorrhea and gonorrhea/chlamydia co-infection, and the duration of MenB-4C vaccine-induced protection. We estimated pooled MenB-4C vaccine effectiveness (≥ 1 dose) against gonorrhea using the DerSimonian-Laird random effects model.

Results: Eight papers met our eligibility criteria. Receipt of ≥ 1 dose of MenB-4C vaccine was 23%–47% effective against gonorrhea. Two doses of MenB-4C vaccine were 33–40% effective against gonorrhea and one dose of MenB-4C vaccine was 26% effective. MenB-4C vaccine effectiveness against gonorrhea/chlamydia co-infection was mixed with two studies reporting effectiveness estimates of 32% and 44%, and two other studies showing no protective effect. MenB-4C vaccine effectiveness against gonorrhea was comparable in people living with HIV (44%) and people not living with HIV (23%–47%). Pooled MenB-4C vaccine effectiveness (≥ 1 dose) against gonorrhea was 32.4%. One study concluded that MenB-4C vaccine effectiveness against gonorrhea may wane approximately 36 months post-vaccination.

Corresponding author: Winston E. Abara, Division of STD Prevention, U.S. Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, Georgia 30333, United States of America, wabara@cdc.gov.

Author contributions: Winston E. Abara, Robert D. Kirkcaldy, and Kyle T. Bernstein developed the research question and study concept, wrote the manuscript and reviewed drafts of the manuscript. Winston E. Abara and Eboni Galloway extracted data from eligible studies. Winston E. Abara analyzed the data. Eboni Galloway and Emily Learner reviewed drafts of the manuscript.

Disclaimer: The findings of this manuscript are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Conflict of Interest Disclosures: None reported.
The authors do not have any conflict of interest.

Conclusion: MenB-4C vaccine is moderately effective against gonorrhea in various populations. Prospective clinical trials that assess the efficacy of MenB-4C against gonorrhea, gonorrhea/chlamydia co-infection, and duration of protection are warranted to strengthen this evidence.

Keywords

MenB-4C; gonorrhea; STI vaccine; vaccine effectiveness; gonorrhea/chlamydia co-infection; HIV; chlamydia; meta-analysis; pooled vaccine effectiveness; OMV MenB vaccines

INTRODUCTION

Gonorrhea is a common sexually transmitted infection (STI) caused by the bacterium *Neisseria gonorrhoeae*. The World Health Organization estimates that approximately 82 million gonococcal infections occurred among adults aged 15–49 years in 2020 and most infections occurred among young people, gay, bisexual, and other men who have sex with men (MSM), transgender women, racial/ethnic minorities, indigenous populations, and sex workers [1]. In the United States, gonorrhea is the second most common notifiable STI [2]. More than 648,000 cases of gonorrhea were reported in the United States in 2022.

Effective antimicrobial treatment is essential for gonorrhea prevention and control [3], but *N. gonorrhoeae* has developed resistance to every class of antimicrobial drug recommended for gonorrhea treatment [4]. Ceftriaxone is currently recommended by the U.S. Centers for Disease Control and Prevention (CDC) for the treatment of uncomplicated gonorrhea [3]. However, gonococcal susceptibility to ceftriaxone is declining [5]. The increasing gonorrhea burden and the spread of gonococcal strains with declining susceptibility to ceftriaxone raises concerns about the emergence of untreatable gonorrhea [5, 6]. With dwindling antimicrobial treatment options and the growing threat of antimicrobial resistant gonorrhea, the development of safe and effective vaccines against gonorrhea is urgent [7].

There is no licensed vaccine against *N. gonorrhoeae*. Clinical trials of two gonorrhea vaccine candidates, a partially lysed whole cell vaccine candidate and a purified pilin vaccine candidate, were not effective against gonorrhea [8, 9]. However, outer membrane vesicle (OMV)-based serogroup B meningococcal (MenB) vaccines like MenB-4C may be cross-protective against gonorrhea [7]. A growing body of studies have assessed the effectiveness of MenB-4C vaccine against gonorrhea [10–17]. We conducted a systematic review to aggregate and synthesize the findings of published studies that evaluated the effectiveness of MenB-4C vaccine against gonorrhea and used meta-analytic methods to estimate pooled vaccine effectiveness of MenB-4C vaccine against gonorrhea.

METHODS

Search strategy, study selection, and study quality assessment

We conducted a systematic literature search to identify peer-reviewed manuscripts that evaluated the effectiveness of MenB-4C vaccine against gonorrhea. A CDC librarian conducted a search of multiple electronic databases (PubMed, Medline, Embase, Global Health, Scopus, Google Scholar, CINAHL, and Cochrane Library) using the following search terms: (“MenB-4C” OR “4CMenB” OR “meningococcal vaccine” OR “outer

membrane vesicle vaccine” OR “OMV vaccine” OR “Bexsero[®]”), AND (“gonorrhea” OR “gonorrhoea” OR “Neisseria gonorrhoeae” OR “N. gonorrhoeae”) AND (“vaccine effectiveness” OR “effectiveness”) AND (“sexually transmitted diseases” OR “sexually transmitted Infections” OR “STD” OR “STI”).

We limited eligible manuscripts to those that 1) were published from January 1, 2013 (year MenB-4C was first licensed and approved anywhere in the world) to July 12, 2024, 2) reported estimates of MenB-4C vaccine effectiveness against gonorrhea, 3) were published in English, and 4) published in a peer-reviewed journal. We also reviewed the reference list of eligible articles to identify other eligible manuscripts that our literature search may have missed. We excluded data that were reported in abstracts, posters, conference proceedings, dissertations, books, modeling studies, meta-analyses, or from preclinical trials. All included studies were assessed for methodological quality and risk of bias using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, Quality Assessment Tool of Case-Control Studies, and the Quality Assessment of Controlled Intervention Studies by the National Heart, Lung, and Blood Institute [18].

Data extraction and analysis

Two reviewers (W.E.A and E.G) independently reviewed eligible studies. Disagreements were resolved by discussion. We coded data from each eligible study by study site/ jurisdiction, sample size, study design, study period, data source, inclusion criteria, unit of statistical analysis (infection-level or person-level), MenB-4C vaccine effectiveness or vaccine efficacy estimate ([1-effect size measure] x 100) and 95% confidence intervals (CI) against gonorrhea and gonorrhea/chlamydia co-infection, intervention group (MenB-4C) and comparison/reference group (unvaccinated or a non-OMV-based vaccine), and reference group for gonorrhea. Estimates of effect size measure with a 95% confidence interval that did not include 1.0 were considered statistically significant. This systematic review and its findings were presented according to the PRISMA checklist (a reporting checklist for evaluating systematic reviews) (Supplementary Material Figure S1) [19].

We conducted a meta-analysis to estimate pooled MenB-4C vaccine effectiveness (≥ 1 dose of MenB-4C vaccine) against gonorrhea using the DerSimonian-Laird random-effects model [20]. We reported the τ^2 , Q-test, and the I^2 statistic to assess study heterogeneity. Egger’s test was used to assess publication bias [21]. We did not generate funnel plots because of the limitations of this technique in assessing publication bias with a small study sample (<10 studies) [22]. Because of the inherent differences in observational studies and randomized clinical trials (RCT) as well as the potentially underpowered sample size of the RCT included in this meta-analysis [17], we conducted a sensitivity analysis where we estimated pooled MenB-4C vaccine effectiveness using only estimates from observational studies. All analyses were conducted in Stata 18 statistical software [23]. This meta-analysis was reported according to the MOOSE checklist (a reporting checklist for meta-analyses of observational studies in epidemiology) (Supplementary Material Figure S2) [24]. This study was not reviewed by the Institutional Review Board of the CDC because it was a systematic review and meta-analysis of published studies.

RESULTS

Characteristics and summary of eligible studies

A total of 365 articles were identified by searching Medline, Embase, Global Health, CINAHL, and Scopus databases (Figure 1). After excluding 183 duplicate entries, we identified 162 unique references. We screened all 162 articles based on title and abstract and identified 13 articles. The full text of the thirteen articles were assessed for eligibility. Eight articles met the inclusion criteria [10–17] (Figure 1). Five articles were excluded because they did not report vaccine effectiveness estimates or reported effectiveness of a non-OMV-based MenB vaccine against gonorrhea. We reviewed the reference list of all eight eligible articles and did not identify additional articles eligible for inclusion in this systematic review. All eligible articles were published during 2022–2024.

Of the eight eligible studies, four studies analyzed data from jurisdictions in the United States (New York City and Philadelphia; Southern California; Oregon; and Northern California) [10–13]; two from South Australia, Australia [14, 15]; one from Milan, Italy [16]; and one from Paris, France [17] (Table 1). The data sources used in the eight studies included linked STI surveillance and immunization information system records [10, 12, 14, 15], electronic health records [11, 13, 16], and a RCT [17]. The unit of analysis of vaccine effectiveness was person-level for five studies [11, 12, 14–16] and infection-level for three studies [10, 13, 17].

The study design, data sources, and analytical samples differed between included studies (Table 1). Abara et al. (2022) conducted a retrospective cohort study that used STI surveillance data from New York City and Philadelphia to link gonorrhea and chlamydia cases and MenB-4C vaccination status (two-dose, one-dose, and unvaccinated) among persons aged 16–23 years-old and compared gonorrhea prevalence by vaccination group [10]. Bruxvoort et al. employed a matched case-control design to compare gonorrhea incidence rates among recipients of MenB-4C vaccine and recipients of MenACWY vaccine (a polysaccharide conjugate meningococcal vaccine targeting meningococcal serogroups A, C, W, and Y), aged 15–30 years, using electronic health record data from Kaiser Permanente Southern California [11]. Robison et al. conducted a case-control study to compare gonorrhea prevalence among recipients of MenB-4C vaccine and MenB-FHbp vaccine (a non-OMV-based serogroup B meningococcal vaccine), aged 18–29 years, following a serogroup B meningococcal disease outbreak at two universities in Oregon, USA [12]. Abara et al. (2024) conducted a retrospective cohort study that used electronic health records from Kaiser Permanente Northern California to compare gonorrhea prevalence among MenB-4C vaccinated persons and unvaccinated persons, aged 15–30 years [13].

Wang et al. conducted two case-control studies that used surveillance data from South Australia to assess the effectiveness of MenB-4C vaccine against gonorrhea in two studies [14, 15]. The first study (Wang et al., 2022) used surveillance data from adolescents and adults with a gonorrhea or chlamydia diagnosis who were born between February 1, 1998–February 1, 2005, and had a disease notification date between February 1, 2019–January 31, 2021 [14]. The second study (Wang et al., 2023) also used surveillance data from South Australian adolescents and adults with a gonorrhea or chlamydia diagnosis who were born

between January 31, 1998–April 30, 2006, and a disease notification date between February 1, 2019–January 31, 2021 [15]. Eligible gonorrhea and chlamydia case records were linked to MenB-4C vaccination records in both studies. Both case-control studies compared the odds of gonorrhea diagnosis in MenB-4C vaccinated persons and unvaccinated persons [14, 15].

Raccagni et al. conducted a case-control study that used electronic health record data of Italian MSM, ≥ 18 years, living with HIV and in HIV care, and with a diagnosis of gonorrhea, chlamydia, syphilis, or anal human papilloma virus between July 2016–February 2021 [16]. Raccagni et al. linked STI records and MenB-4C vaccination records, and compared the odds of gonorrhea in MenB-4C vaccinated persons to unvaccinated persons to estimate MenB-4C vaccine effectiveness [16]. Molina et al. conducted a RCT that included MSM, ≥ 18 years, using HIV pre-exposure prophylaxis (PrEP), with a history of bacterial STIs (chlamydia, gonorrhea, or syphilis) in the past 12 months, and who were enrolled in the ANRS PREVENIR study cohort (a cohort of MSM using tenofovir and emtricitabine for HIV prevention) [17, 25]. They compared the risk of a first episode of gonorrhea among MenB-4C vaccinated persons to unvaccinated persons [17].

For all studies, gonococcal cases (the outcome of interest) were identified by a positive gonorrhea nucleic-acid amplification test (NAAT) or positive *N. gonorrhoeae* culture of urethral, rectal, or pharyngeal specimens. Four studies evaluated MenB-4C vaccine effectiveness against gonococcal mono-infection and gonorrhea/chlamydia co-infection [10, 13–15]. The RCT study reported efficacy estimates of MenB-4C against gonorrhea at anatomic-specific sites (urethra, rectum, and pharynx) [17]. No observational study examined anatomic-site vaccine effectiveness of MenB-4C against gonorrhea. Eligible studies reported various effect size measures to assess the effectiveness of MenB-4C vaccine against gonorrhea including odds ratio [12, 14–16], prevalence ratio [10, 13], or hazard ratio [11, 17].

Chlamydia was the reference group for gonorrhea in four studies [10, 13–15]. One study used a diagnosis of chlamydia, syphilis, or anal human papilloma virus as its reference group [16] (Table 1). Six studies incorporated a window period to allow for an optimal immune response to develop post-vaccination [10, 11, 13–15, 17]. STI diagnoses that occurred after this window period were considered to have occurred after vaccination. The post-vaccination window period was ≥ 14 days in three studies [13–15], and ≥ 30 days [10], ≥ 31 days [11], or ≥ 1 month [17]. Two studies did not report a post-vaccination window period [11, 12].

Menb-4C vaccine effectiveness against gonorrhea (positive NAAT or *N. Gonorrhoeae* culture)

Estimates of MenB-4C vaccine effectiveness against gonorrhea ranged from 23–47% from seven observational studies (Table 1). Three U.S. studies reported MenB-4C vaccine effectiveness (≥ 1 MenB-4C vaccine dose) estimates of 23% [13], 46% [11], and 47% [12] against gonorrhea among adolescents and young adults, aged 15–30 years. Two studies from South Australia demonstrated that two MenB-4C vaccine doses were 32–33% effective against gonorrhea in adolescents and young adults, aged 15–25 years old [14, 15]. Two

doses of MenB-4C were 44% effective against gonorrhea in a study of Italian MSM living with HIV, aged ≥ 18 -years-old, and in HIV care [16]. One study evaluated the dose-dependent association between MenB-4C vaccination and gonorrhea [10]. Compared to being unvaccinated, two doses of MenB-4C vaccine were 40% effective against gonorrhea and one dose was 26% effective. Data from the RCT did not show any efficacy of MenB-4C vaccine against gonorrhea [17].

Pooled vaccine effectiveness against gonorrhea after receipt of ≥ 1 MenB-4C dose was 32.4% (95% CI=26.2–38.7) (Figure 2) based on nine estimates from eight studies [10–17]. Egger's test showed no publication bias (t-value of Egger's test=1.14, $P=0.290$ and there was no study heterogeneity ($Q(8)=6.65$, $P=0.575$, $\tau^2=0.00$, $I^2=0.00\%$). In the sensitivity analysis where we excluded the RCT [17] and only included eight effectiveness estimates from seven observational studies [10–16], pooled vaccine effectiveness against gonorrhea after receipt of ≥ 1 MenB-4C dose was 33.5% (95% CI=26.9–40.1) (Figure 3). Egger's test showed no publication bias (t-value of Egger's test=1.32, $P=0.235$ and there was no study heterogeneity ($Q(7)=5.55$, $P=0.593$, $\tau^2=0.00$, $I^2=0.00\%$).

Menb-4C vaccine effectiveness against gonococcal mono-infection (positive NAAT or *N. Gonorrhoeae* culture only, and negative or undetected *Chlamydia trachomatis*)

Four studies assessed MenB-4C vaccine effectiveness against gonococcal mono-infections [10, 13–15] (Table 1). Two doses of MenB-4C vaccine were 31.6% [14] and 28.3% [15] effective against gonococcal mono-infections according to two studies by Wang et al [14, 15]. Abara et al. (2022) demonstrated that two doses and one dose of MenB-4C were 40% and 26% effective against gonococcal mono-infection, respectively [10]. Another study by Abara et al. (2024) showed that ≥ 1 dose of MenB-4C was 23% effective against gonococcal mono-infections [13].

Menb-4C vaccine effectiveness against gonorrhea/chlamydia co-infection

Four studies presented results of MenB-4C vaccine effectiveness against gonorrhea/chlamydia co-infection [10, 13–15] (Table 1). Two South Australian studies showed that two doses of MenB-4C were 32.7% and 44.7% effective against gonorrhea/chlamydia co-infection [14, 15]. Two U.S. studies concluded that MenB-4C was not effective against gonorrhea/chlamydia co-infection [10, 13].

Duration of protection of menb-4C vaccine effectiveness against gonorrhea

Wang et al. assessed the duration of protection of two doses of MenB-4C vaccine against gonorrhea by comparing the effectiveness of two doses of MenB-4C vaccine against gonorrhea within 6–36 months post-vaccination and >36 months post-vaccination [14] (Table 1). Effectiveness of two doses of MenB-4C against gonorrhea within 6–36 months post-vaccination (34.9%) was significantly higher than the effectiveness estimate >36 months post-vaccination (23.2%). Abara et al. [10] and Raccagni et al. [16] did not explicitly assess the duration of protection, however, the median duration of follow-up after vaccination, in both studies, were 3.1 years (37 months) and 3.8 years (45 months) with an observed two-dose vaccine effectiveness of 40% and 44%, respectively.

Risk of bias assessment

A risk of bias assessment was done for the case-control (Supplementary Material Table S1), cohort (Supplementary Material Table S2), and RCT studies (Supplementary Material Table S3) included in this systematic review. All studies included in this systematic review were of good quality. A sample size justification was not provided in any of the case-control or cohort studies [10–16]. However, the large analytical sample size of these studies (range=1,051–109,737) mitigated any concerns that these studies were underpowered to detect a difference in gonorrhea risk by MenB-4C vaccination status. A sample size justification for the RCT was provided [17]. However, enrollment in the RCT was prematurely discontinued based on results from an interim analysis that were later found to have used incomplete data. Because of this, the investigators suggest that the final analytical sample size may not have been sufficiently powered to detect moderate vaccine efficacy [17].

Gonorrhea and chlamydia can be asymptomatic and may not be detected without routine screening [26]. The RCT was the only study that employed routine screening to ascertain gonorrhea diagnoses. Because the cohort and case-control studies did not report routine gonorrhea or chlamydia screening before MenB-4C vaccination, misclassification bias is possible: infections might have been acquired before vaccination but detected only after vaccination. This may have decreased the observed estimate of vaccine effectiveness. Additionally, five studies assessed gonorrhea and chlamydia diagnosis at a single time point (person-level analysis) rather than at multiple time points (infection-level analysis). Estimating vaccine effectiveness by assessing gonorrhea or chlamydia at one time point and assigning case or reference group categorization based on this time point may have inadvertently missed subsequent gonorrhea or chlamydia diagnoses and introduced bias into the analysis. However, estimates of effectiveness from the studies that assessed MenB-4C vaccination status and gonorrhea diagnoses at a single time point are comparable to those that included diagnoses at multiple time points, suggesting that this type of bias is potentially minimal.

DISCUSSION

We systematically reviewed the peer-reviewed literature and identified seven observational studies that assessed the effectiveness of MenB-4C vaccine against gonorrhea [10, 12–16] and one RCT that assessed the efficacy of MenB-4C vaccine against gonorrhea. The analytical sample from all eligible studies included adolescents, young adults, MSM living with HIV, and HIV negative MSM on HIV PrEP with a history of bacterial STIs in the past 12 months. Receipt of ≥ 1 dose of MenB-4C vaccine was 23–47% effective against gonorrhea in observational studies. We also observed a dose-dependent association in vaccine effectiveness against gonorrhea [10]. The range in observed vaccine effectiveness (23–47%) may be attributed to differences in the composition of the analytical sample, differences in the reference group for gonorrhea, or differences in MenB-4C vaccination coverage in each study. MenB-4C vaccination was not protective against gonorrhea in the RCT although the vaccine efficacy estimate trended towards significance [17]. The RCT investigators posit that the lack of a protective effect may be attributable to a premature

discontinuation of enrollment which may have underpowered the sample size to detect a moderate vaccine efficacy [17]. Pooled vaccine effectiveness against gonorrhea after receipt of ≥ 1 MenB-4C dose was 32.4%. The high (80–90%) sequence identity between outer membrane proteins of *N. meningitidis* and *N. gonorrhoeae* [27, 28] and the ability of MenB-4C to induce anti-gonococcal antibodies and reduce genital gonococcal colonization load likely explains the cross-protection of MenB-4C against gonorrhea [29, 30].

MenB-4C vaccination was 44% protective against gonorrhea in Italian MSM living with HIV [16]. Most MSM in the Italian study were virally suppressed and all were in HIV care. This finding suggests that estimates of MenB-4C vaccine effectiveness against gonorrhea are comparable between virally suppressed persons who are living with HIV and persons who are not living with HIV. Although this vaccine effectiveness estimate is from one study, the cross-protective finding in this population is encouraging because gonorrhea may increase HIV transmission risk [31–33]. The effectiveness of MenB-4C vaccine against gonorrhea/chlamydia coinfection was mixed with two studies reporting a protective effect [14, 15] while two studies did not report a protective effect [10, 13]. We posit that the greater gonococcal load seen in gonorrhea/chlamydia co-infections [34, 35] may partly explain the differences in effectiveness seen in these studies. Differences in the analytical sample of cases of gonorrhea/chlamydia co-infections from Australia and the U.S. could also account for the varying effectiveness estimates. One study showed that the effectiveness of MenB-4C against gonorrhea was higher within 36 months post-vaccination compared to >36 months post-vaccination (35% effectiveness vs. 23% effectiveness) [15]. MenB-4C vaccine effectiveness against gonorrhea may begin to wane approximately 36 months post-vaccination. Because this estimated duration of protection is based on one study, more studies examining the duration of protection of MenB-4C vaccine against gonorrhea are needed. A serological correlate of MenB-4C vaccine-induced anti-gonococcal immunity is a more reliable indicator of vaccine-induced protection and monitoring levels of this correlate over time may be used to assess the duration of protection [7].

Findings about MenB-4C vaccine effectiveness and duration of protection presented in this review offer promise about the feasibility and public health impact of a gonorrhea vaccine after previous unsuccessful clinical trials [7]. Mathematical modeling studies suggest that a vaccine with moderate effectiveness and duration of protection like the estimates and duration of protection reported in this systematic review, can result in significant reductions gonorrhea incidence, prevalence, and gonorrhea-attributable healthcare costs, and mitigate the threat of antimicrobial resistant gonorrhea [36–40].

Data that are essential to our complete understanding of the cross-protective effect of the MenB-4C vaccine are still lacking. There is no known serological correlate of vaccine-induced protection. Identifying a serological correlate of protection is important to understanding the immunological basis of MenB-4C vaccine-induced anti-gonococcal immunity and duration of protection (12). Vaccine effectiveness estimates by anatomic sites (urogenital, rectal, and pharyngeal) are needed. Because extragenital *N. gonorrhoeae* is generally less susceptible to antimicrobial treatment and more likely to go undetected in the absence of routine screening [26, 41], anatomic-site vaccine effectiveness estimates are critical to evaluating the public health impact of a gonorrhea. Several ongoing clinical

2. United States Centers for Disease Prevention and Control. Sexually Transmitted Disease Surveillance 2022. Available at: <https://www.cdc.gov/std/statistics/2022/default.htm>. Accessed 20 November 2023
3. Cyr SS, Barbee L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1911–1916. [PubMed: 33332296]
4. Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: past, evolution, and future. Clin Microbiol Rev 2014; 27:587–613. [PubMed: 24982323]
5. Kirkcaldy RD, Harvey A, Papp JR, et al. *Neisseria gonorrhoeae* antimicrobial susceptibility surveillance—the gonococcal isolate surveillance project, 27 sites, United States, 2014. MMWR Surveill Summ 2016; 65:1–19.
6. Day M, Pitt R, Mody N, et al. Detection of 10 cases of ceftriaxone-resistant *Neisseria gonorrhoeae* in the United Kingdom, December 2021 to June 2022. Euro Surveill 2022; 27:2200803.
7. Abara WE, Jerse AE, Hariri S, Kirkcaldy RD. Planning for a gonococcal vaccine: a narrative review of vaccine development and public health implications. Sex Transm Dis 2021; 48:453–457. [PubMed: 33201019]
8. Greenberg L, Diena B, Ashton F, et al. Gonococcal vaccine studies in Inuvik. Can J Public Health 1974; 65:29–33. [PubMed: 4205640]
9. Tramont E, Sadoff J, Boslego J, et al. Gonococcal pilus vaccine. Studies of antigenicity and inhibition of attachment. J Clin Invest 1981; 68:881–8. [PubMed: 6116723]
10. Abara WE, Bernstein KT, Lewis FM, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis 2022; 22:1021–9. [PubMed: 35427490]
11. Bruxvoort KJ, Lewnard JA, Chen LH, et al. Prevention of *Neisseria gonorrhoeae* with meningococcal B vaccine: a matched cohort study in Southern California. Clin Infect Dis 2023; 76:e1341–e9. [PubMed: 35642527]
12. Robison SG, Leman RF. Association of Group B meningococcal vaccine receipt with reduced gonorrhea incidence among university students. JAMA Netw Open 2023; 6:e2331742-e.
13. Abara WE, Modaressi S, Fireman B, et al. Effectiveness of a group B meningococcal vaccine against gonorrhea. Vaccine 2024;
14. Wang B, Giles L, Andraweera P, et al. . Effectiveness and impact of the 4CMenB vaccine against invasive serogroup B meningococcal disease and gonorrhoea in an infant, child, and adolescent programme: an observational cohort and case-control study. Lancet Infect Dis 2022; 22:1011–20. [PubMed: 35427492]
15. Wang B, Giles L, Andraweera P, et al. 4CMenB sustained vaccine effectiveness against invasive meningococcal B disease and gonorrhoea at three years post program implementation. J Infection 2023; 87:95–102
16. Raccagni AR, Galli L, Spagnuolo V, et al. Meningococcus B vaccination effectiveness against *Neisseria gonorrhoeae* infection in people living with HIV: a case-control study. Sex Transm Dis 2023; 50:247–51. [PubMed: 36728240]
17. Molina J-M, Bercot B, Assoumou L, et al. Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2× 2 factorial design. Lancet Infect Dis 2024; 24:S1473–3099.
18. National Institutes of Health. Study Quality Assessment Tools. Available at: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>. Accessed 20 November 2023
19. PRISMA. PRISMA Checklist. Available at: <http://www.prisma-statement.org/>. Accessed 20 November 2023.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contem Clin Trials 2015; 45:139–45.
21. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–34. [PubMed: 9310563]
22. Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ 2006; 333:597–600. [PubMed: 16974018]
23. Stata. Available at: <https://www.stata.com/new-in-stata/>. Accessed 20 November 2023.

24. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000; 283:2008–12. [PubMed: 10789670]
25. Molina J-M, Ghosn J, Assoumou L, et al. Daily and on-demand HIV pre-exposure prophylaxis with emtricitabine and tenofovir disoproxil (ANRS PREVENIR): a prospective observational cohort study. *The Lancet HIV* 2022; 9:e554–e62. [PubMed: 35772417]
26. Abara WE, Llata EL, Schumacher C, et al. Extragenital gonorrhea and chlamydia positivity and the potential for missed extragenital gonorrhea with concurrent urethral chlamydia among men who have sex with men attending sexually transmitted disease clinics—Sexually Transmitted Disease Surveillance Network, 2015–2019. *Sex Transm Dis* 2020; 47:361–8. [PubMed: 32413018]
27. Marjuki H, Topaz N, Joseph SJ, et al. Genetic similarity of gonococcal homologs to meningococcal outer membrane proteins of serogroup B vaccine. *mBio* 2019; 10:e01668–19.
28. Tinsley C, Nassif X. Analysis of the genetic differences between *Neisseria meningitidis* and *Neisseria gonorrhoeae*: two closely related bacteria expressing two different pathogenicities. *Proc Natl Acad Sci* 1996; 93:11109–14. [PubMed: 8855317]
29. Semchenko EA, Tan A, Borrow R, Seib KL. The serogroup B meningococcal vaccine Bexsero elicits antibodies to *Neisseria gonorrhoeae*. *Clin Infect Dis* 2019; 69:1101–11. [PubMed: 30551148]
30. Leduc I, Connolly KL, Begum A, et al. The serogroup B meningococcal outer membrane vesicle-based vaccine 4CMenB induces cross-species protection against *Neisseria gonorrhoeae*. *PLoS pathogens* 2020; 16:e1008602.
31. Cohen MS, Council OD, Chen JS. Sexually transmitted infections and HIV in the era of antiretroviral treatment and prevention: the biologic basis for epidemiologic synergy. *J Int AIDS Soc* 2019; 22:e25355.
32. Guvenc F, Kaul R, Gray-Owen SD. Intimate relations: molecular and immunologic interactions between *Neisseria gonorrhoeae* and HIV-1. *Front Microbiol* 2020; 11:1299. [PubMed: 32582133]
33. Taylor M, Newman D, Gonzalez J, Skinner J, Khurana R, Mickey T. HIV status and viral loads among men testing positive for rectal gonorrhoea and chlamydia, Maricopa County, Arizona, USA, 2011–2013. *HIV Med* 2015; 16:249–54. [PubMed: 25230929]
34. Lovett A, Duncan JA. Human immune responses and the natural history of *Neisseria gonorrhoeae* infection. *Front Immunol* 2019; 9:3187. [PubMed: 30838004]
35. Vonck RA, Darville T, O'Connell C, Jerse AE. Chlamydial infection increases gonococcal colonization in a novel murine coinfection model. *Infect Immun* 2011; 79:1566–77. [PubMed: 21245268]
36. Craig AP, Gray RT, Edwards JL, et al. The potential impact of vaccination on the prevalence of gonorrhea. *Vaccine* 2015; 33:4520–5. [PubMed: 26192351]
37. Whittles LK, Didelot X, White PJ. Public health impact and cost-effectiveness of gonorrhoea vaccination: an integrated transmission-dynamic health-economic modelling analysis. *Lancet Infect Dis* 2022; 22:1030–41. [PubMed: 35427491]
38. Hui BB, Padeniya TN, Rebuli N, et al. A gonococcal vaccine has the potential to rapidly reduce the incidence of *Neisseria gonorrhoeae* infection among urban men who have sex with men. *J Infect Dis* 2022; 225:983–93. [PubMed: 34894134]
39. Whittles LK, White PJ, Didelot X. Assessment of the potential of vaccination to combat antibiotic resistance in gonorrhea: a modeling analysis to determine preferred product characteristics. *Clin Infect Dis* 2020; 71:1912–9. [PubMed: 31905399]
40. Régnier SA, Huels J. Potential impact of vaccination against *Neisseria meningitidis* on *Neisseria gonorrhoeae* in the United States: results from a decision-analysis model. *Hum Vaccin Immunother* 2014; 10:3737–45. [PubMed: 25483706]
41. Quilter LA, Cyr SBS, Hong J, et al. Antimicrobial susceptibility of urogenital and extragenital *Neisseria gonorrhoeae* isolates among men who have sex with men: Strengthening the US Response to Resistant Gonorrhea and Enhanced Gonococcal Isolate Surveillance Project, 2018 to 2019. *Sex Transm Dis* 2021; 48:S111–S7. [PubMed: 34475363]

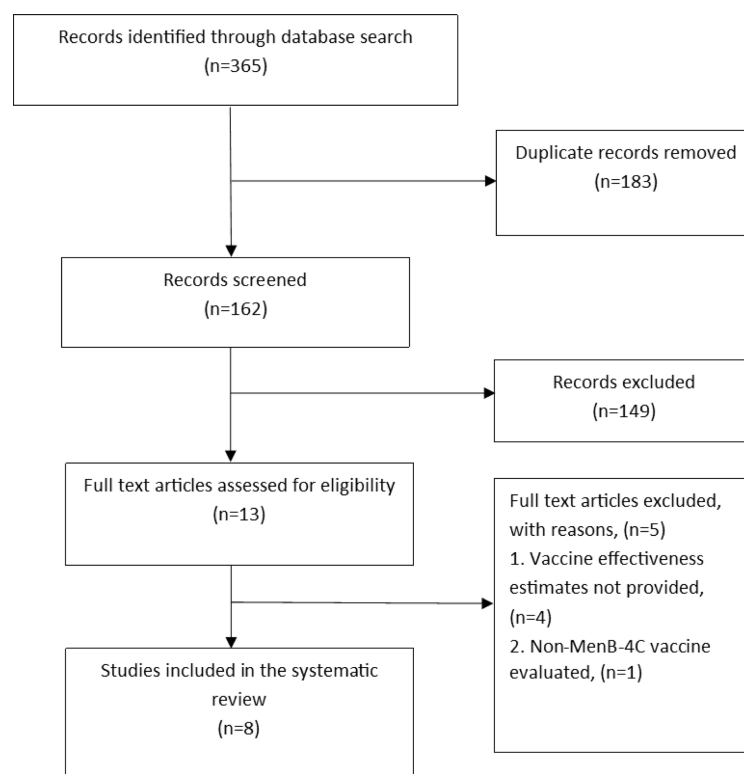


Figure 1.
Flow chart showing study selection for inclusion in systematic review

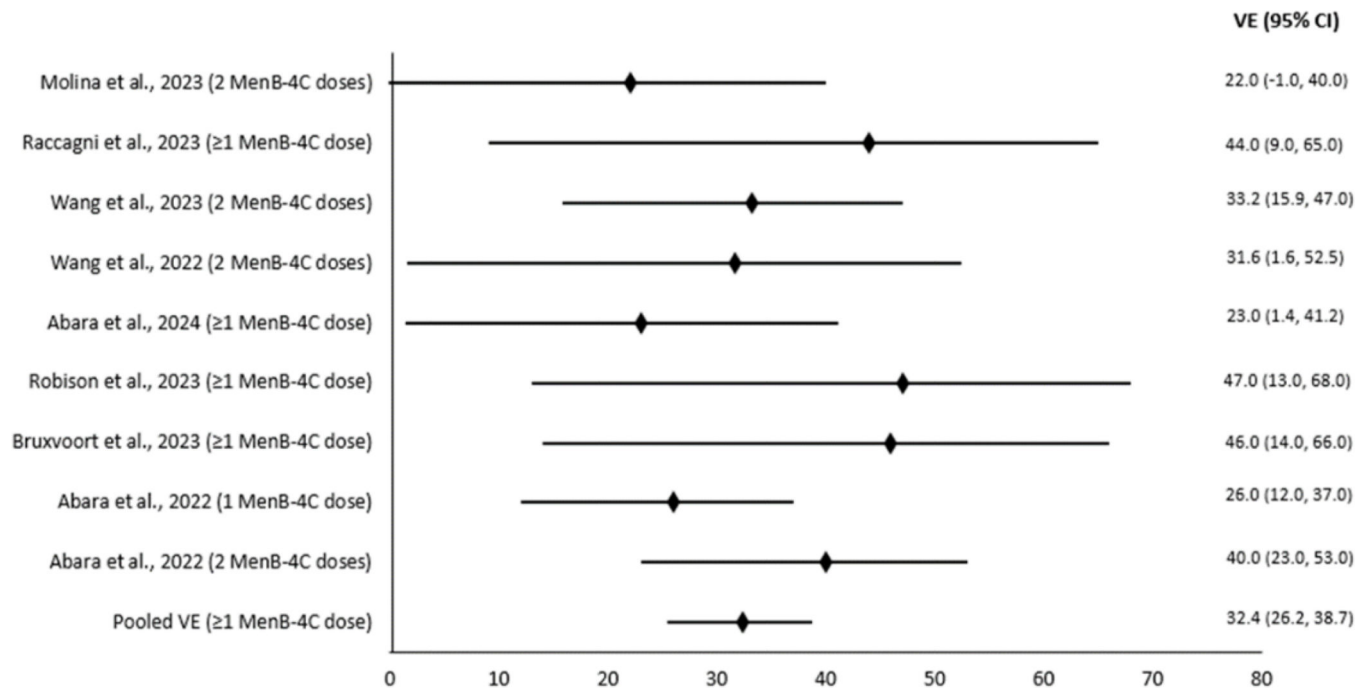


Figure 2.

Forest plot showing MenB-4C vaccine effectiveness (VE) (≥1 dose) against gonorrhea from nine VE estimates (eight studies) and pooled MenB-4C VE

Heterogeneity: $Q(8)=6.65$, $P=0.5753$; $\tau^2=0.00$; $I^2=0.00\%$

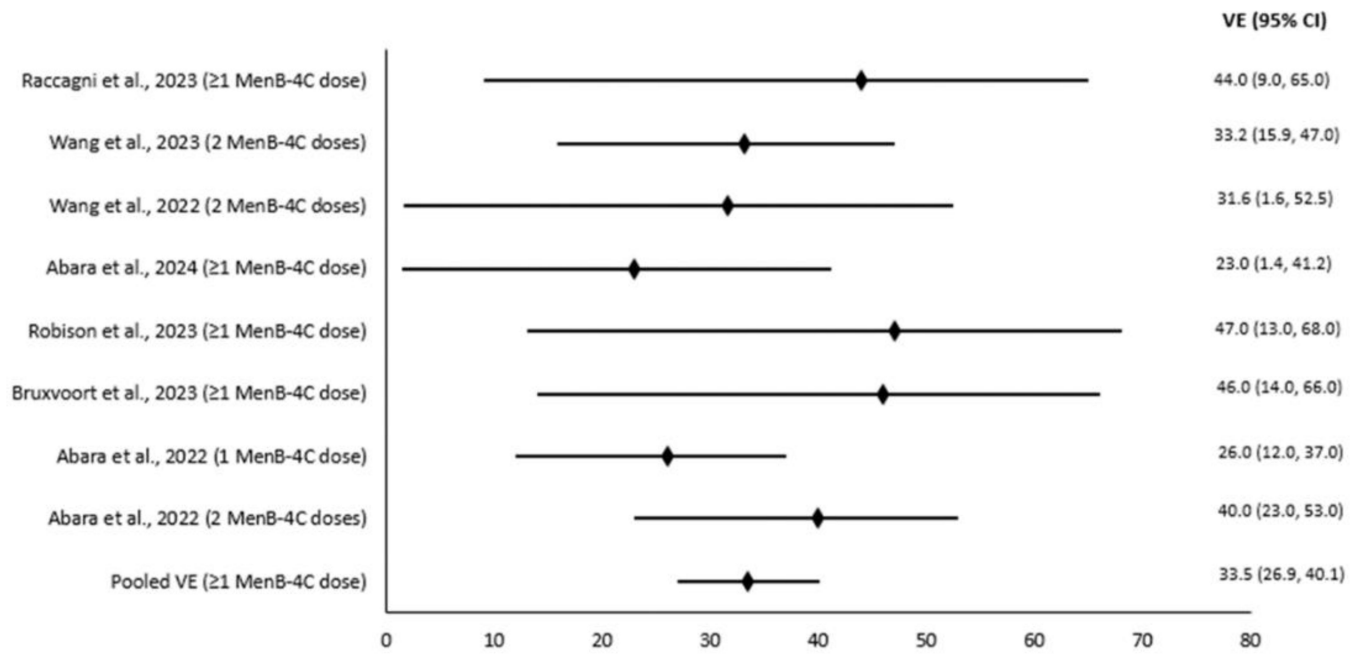


Figure 3.
Sensitivity analysis of forest plot showing MenB-4C vaccine effectiveness (VE) (≥1 dose) against gonorrhea from eight VE estimates (seven studies) and pooled MenB-4C VE
Heterogeneity: $Q(7)=5.55$, $P=0.5931$; $\tau^2=0.00$; $I^2=0.00\%$

Table 1.

Characteristics of eligible studies

Author	Study site/ jurisdiction	Sample size	Study design	Study period (year)	Data source	Inclusion criteria	Unit of analysis	MenB-4C vaccine effectiveness against GC	MenB-4C vaccine effectiveness against GC/CT co-infection	Reference group for GC (outcome of interest)
Abara et al., 2022 ¹⁰	Philadelphia & New York City, USA	109,737 persons with 167,706 sexually transmitted infections (18,099 GC cases; 124,876 CT cases; 24,731 GC/CT coinfection cases)	Retrospective cohort	2016– 2018	Linked STI surveillance records and MenB-4C immunization information system records	Persons aged 16– 23 years with a GC or CT diagnosis from 1/1/2016– 12/31/2018	Infection- level	2 MenB-4C doses: 15% (95% CI: –13%– 36%); not significant 1 MenB-4C dose: 26% (95% CI: 12%–37%) Reference group: unvaccinated persons	2 MenB-4C doses: 15% (95% CI: –13%– 36%); not significant 1 MenB-4C dose: 0.06% (95% CI: –28%–12%); not significant Reference group: unvaccinated persons	CT
Bruxvoort et al., 2023 ¹¹	Kaiser Permanente Southern California, USA	33,112 persons (6,641 MenB-4C vaccine recipients; 26,471 MenACWY vaccine recipients)	Matched case- control	2016– 2020	Electronic health records	Persons aged 15– 30 years who received ≥1 MenB-4C dose or ≥1 MenACWY dose from 1/1/2016– 12/12/2019	Person- level	≥1 MenB-4C vaccine dose: 46% (95% CI=14%– 66%) Reference group: MenACWY vaccinated persons	Not reported	No case diagnosis reported. Analysis compared GC incidence among MenB-4C vaccinated persons with MenACWY vaccinated persons.
Robison et al., 2023 ¹²	Oregon, USA	30,972 persons (15,760 MenB-4C vaccine recipients; 15,212 MenB- FHbp vaccine recipients)	Case-control	2015– 2018	Linked immunization information system records and GC surveillance case reports	Persons aged 18– 29 years who received ≥1 dose of MenB-4C or MenB-FHbp from 2015–3/3/2018	Person- level	≥1 MenB-4C vaccine dose: 47% (95% CI=13%– 68%) Reference group: MenB-FHbp vaccinated persons	Not reported	No case diagnosis reported. Analysis compared GC prevalence among MenB-4C vaccinated persons with MenB-FHbp vaccinated persons
Abara et al., 2024 ¹³	Kaiser Permanente Northern California, USA	68,454 persons (10,638 persons with 13,000 GC cases; 53,914 persons with 68,008 CT cases; 3,902 persons with	Retrospective cohort	2016– 2021	Electronic health records	Persons aged 15– 30 years with a GC or CT diagnosis from 1/1/2016– 12/31/2021	Infection- level	≥1 MenB-4C vaccine dose: 23% (95% CI=1%– 41%) Reference group: unvaccinated persons	≥1 MenB-4C vaccine dose: –0.01% (95% CI=–47%–31%); not significant Reference group:	CT

Author	Study site/ jurisdiction	Sample size	Study design	Study period (year)	Data source	Inclusion criteria	Unit of analysis	MenB-4C vaccine effectiveness against GC	MenB-4C vaccine effectiveness against GC/CT co-infection	Reference group for GC (outcome of interest)
		4,385 GC/CT co-infection cases)							unvaccinated persons	
Wang et al., 2022 ¹⁴	South Australia, Australia	3,652 persons (512 persons with 575 GC cases; 3,140 persons with 3,847 CT cases)	Case-control	2019– 2021	Linked STI surveillance records and MenB-4C immunization register	Persons with GC or CT diagnosis, born between 2/1/1998–2/1/2005 and a disease notification date between 2/1/2019– 1/31/2021	Person- level	Two MenB-4C vaccine doses: 31.6% (95% CI=1.6%–52.5%) Reference group: unvaccinated persons	Two MenB-4C vaccine doses: 32.7% (95% CI=8.3%– 50.6%) ≥1 MenB-4C vaccine doses: 32.6% (95% CI=10.6%– 49.1%) Reference group: unvaccinated persons	CT
Wang et al., 2023 ¹⁵	South Australia, Australia	5,758 persons (823 GC cases; 4,935 CT cases)	Case-control	2019– 2021	Linked STI surveillance records and MenB-4C immunization register	Persons with GC or CT diagnosis, born between 1/31/1998– 4/30/2006 and a disease notification date between 2/1/2019– 1/31/2021	Person- level	Two MenB-4C vaccine doses: 33.2% (95% CI=15.9%– 47.0%) Reference group: unvaccinated persons	Two MenB-4C doses: 44.7% (95% CI: 17.1%–63.1%) Reference group: unvaccinated persons	CT
Raccagni et al., 2023 ¹⁶	Milan, Italy	1,051 persons (103 GC cases; 948 CT cases)	Case-control	2016– 2021	Electronic health records	Men who have sex with men living with HIV and in HIV care, ≥18 years, and with a diagnosis of GC, CT, syphilis, or anal human papilloma virus	Person- level	≥1 MenB-4C vaccine dose: 44% (95% CI=9%– 65%) Reference group: unvaccinated persons	Not reported	Syphilis, CT, or anal human papillomavirus diagnoses
Molina et al., 2024 ¹⁷	Paris, France	556 persons	Randomized clinical trial	2021– 2023	Clinical trial data	Men who have sex with men (MSM), ≥18 years, HIV negative, a history of bacterial sexually transmitted infections in the 12 months before enrollment, and in the ANRS PREVENIR study	Infection- level	2 MenB-4C doses: 22% (95% CI=–1–40); not significant Reference group: unvaccinated persons	Not reported	No case diagnosis reported. Analysis compared incidence of first GC episode among MenB-4C vaccinated persons with unvaccinated persons

GC/CT: gonorrhea/chlamydia co-infection

CT: chlamydia

GC: gonorrhea

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript