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Review

Cross-protection of meningococcal B vaccines against gonorrhea: A systematic review and Meta-analysis

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ABSTRACT

Introduction: Gonorrhea remains a major global public health challenge due to its rising incidence, association with severe complications, and growing antibiotic resistance. Vaccine development against *N. gonorrhoeae* presents a promising solution, with particular focus on leveraging existing vaccines that offer potential cross-protective effects. This study evaluates the potential effectiveness of outer membrane vesicle (OMV)-based meningococcal B vaccines in preventing *N. gonorrhoeae* infections.

Methods: A systematic search was performed in PubMed, Embase and Scopus with no language restrictions until December 10th, 2024. Data were extracted independently by two researchers and effect estimates were synthesized using a random-effects model. We sought for odds ratios, relative risks, hazard ratios, or prevalence ratios of *N. gonorrhoeae* diagnoses between recipients of OMV-based vaccines and either unvaccinated individuals or those vaccinated with other vaccines. Vaccine effectiveness (VE) was calculated as (1 – Effect Size [ES]) x 100 %. Subgroup analyses by comparator, intervention (type of OMV-based MenB vaccine administered and number of doses) and type of effect estimate were conducted.

Results: Nine out of 814 screened items met the inclusion criteria; all of them were observational (three cohort and five case-control studies) except one randomized clinical trial (RCT). OMV-based meningococcal B vaccination was linked to a statistically significant reduction in *N. gonorrhoeae* diagnoses overall (pooled ES: 0.70, 95 % CI: 0.61–0.81, $p < 0.001$), namely pooled vaccine effectiveness (VE) estimated at 30 % (95 %CI: 19 %–39 %).

Conclusions and relevance: While randomized clinical trials are necessary, the findings of this systematic review and meta-analysis highlight the potential effectiveness of OMV-based vaccines in terms of gonorrhea prevention.

1. Introduction

Gonorrhea is among the most prevalent sexually transmitted diseases (STDs) globally [1]. *Neisseria gonorrhoeae* infections pose a significant public health challenge, as they are linked to severe complications, including infertility in women and pelvic inflammatory disease [2], with rising incidence rates [1]. According to the recent Centers for Diseases Control's (CDC) treatment guidelines for sexually transmitted infections it is the second most commonly reported bacterial communicable disease (available at https://www.cdc.gov/std/treatment-guidelines/gonorrhea-adults.htm). Over the last decade, the incidence of gonorrhea has nearly doubled in numerous countries [1], with an estimated 82 million new cases reported worldwide in 2020 [3]. This surge highlights the urgent need for effective control and prevention strategies.

Effective antibiotic treatment has historically been crucial in managing gonorrhea. However, *N. gonorrhoeae* has shown a remarkable ability to develop resistance to antibiotics, including ceftriaxone, the last remaining option for first-line empirical monotherapy [4]. This growing antimicrobial resistance, coupled with the limited availability of new

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antibiotics, highlights the critical necessity for innovative public health strategies. This situation is further exacerbated by the absence of novel antibiotics, creating an urgent need for alternative solutions.

One promising strategy is the development of a vaccine against *N. gonorrhoeae*, which could reduce infections and potentially prevent the development of resistant strains. However, several challenges impede this goal. The mechanisms of immune protection against *N. gonorrhoeae* infections are not yet fully understood, and natural immunity following infection is rare, as evidenced by the high rates of reinfection [5]. Leveraging existing vaccines that show cross-protection against *N. gonorrhoeae* could offer an immediate solution [6].

Recent research has suggested that the outer membrane vesicle (OMV) of *Neisseria meningitidis* serogroup B (MenB) vaccines might provide some protection against gonococcal infections [6–16]. Specifically, reductions in gonorrhea cases were observed after the implementation of vaccination campaigns with OMV-based MenB vaccines in Cuba, Canada and Norway [7,8,17]. The 4-component serogroup B meningococcal vaccine (4CMenB) is currently the sole OMV-based vaccine available for serogroup B meningococcal disease. Porin A (PorA) is considered the main immunogen of OMV regarding MenB [18]. The same OMVs from MenB were also included in older vaccines such as the New Zealand meningococcal vaccine (MeNZB) [19], the VA-MENGOC-BC in Cuba [7], and the MenBvac in Norway [20]. In addition to OMV, 4CMenB combines it with three recombinant antigenic proteins: Neisseria adhesin A (NadA), factor H binding protein (fHbp), and Neisserial Heparin Binding Antigen (NHBA). Notably, NHBA is the only one among these proteins that is expressed on the surface of *N. gonorrhoeae* [21].

We herein present a systematic review and meta-analysis aiming to perform a quantitative synthesis of the available evidence on the effectiveness of OMV-based MenB vaccines in reducing the risk of *N. gonorrhoeae* infections. By synthesizing the published data, we hope to provide a comprehensive assessment of the potential role of these vaccines in controlling *N. gonorrhoeae* infections, thereby informing future public health strategies and vaccination policies.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [22]; the PRISMA checklist is provided in Supplemental Table 1.

The study protocol was registered with PROSPERO (Registration No: CRD42024542628). We conducted a systematic search in PubMed, EMBASE, and Scopus databases (search concluded on December 10th, 2024). Detailed search algorithms for each database are included in the Supplemental Text. No language restrictions were applied. Reference lists of previously published systematic reviews and all eligible articles were systematically searched using a 'snowball' procedure.

All citations from each database were imported into a reference manager (Zotero) by two researchers independently, and duplicates were removed. Following initial screening of titles and abstracts, full texts of studies were assessed. Two authors independently selected studies; any disagreements were resolved by a senior author.

2.2. Eligibility

2.2.1. Inclusion criteria

We included studies involving any population having undergone MenB vaccination. Eligible study designs included quantitative studies such as randomized controlled trials, cohort studies, and case-control studies.

The present search focused on studies that reported *N. gonorrhoeae* infection rates among individuals vaccinated with an OMV-based MenB vaccine compared to those who were either unvaccinated or vaccinated with a different meningococcal vaccine. We sought prevalence ratios, hazard ratios, odds ratios, and relative risks for *N. gonorrhoeae* infections between these groups.

2.2.2. Data extraction

The following study characteristics and outcomes were extracted by two researchers independently and any disagreement was resolved by consulting the senior authors: title, first author and publication year, location and date of study, study design, sample size, population characteristics, comparison group characteristics, participant age (mean, median and age range), definition of *N. gonorrhoeae* infections, type of MenB vaccine used, outcome measures and main results. Inter-rater agreement during study selection was assessed using Cohen's kappa. Any discrepancies in data extraction were resolved by discussion and consensus with the senior authors. In the case of missing or incomplete data the study authors were contacted via email in an effort to obtain any required information.

2.2.3. Quality and publication bias assessment

Two reviewers independently assessed study quality using the Newcastle-Ottawa Scale for observational studies (cohort and cross-sectional) and the Cochrane Risk of Bias 2.0 tool for randomized trials. Agreement between reviewers across all domains was high, with a Cohen's kappa of 0.94. Discrepancies were resolved through discussion and consensus with a senior author.

2.3. Statistical analysis

The pooled effect estimates and 95 % confidence intervals were estimated with the random effects (DerSimonian-Laird) model. Between-study heterogeneity was assessed by estimating Q-test and I^2 statistic. Odds ratios were converted to relative risks, as appropriate according to the Cochrane handbook [23]. Vaccine effectiveness (VE) was calculated as (1 – Effect Size [ES]) x 100 %. Subgroup analyses by comparator, intervention (type of OMV-based MenB vaccine administered and number of doses) and type of effect estimate were conducted. The level of statistical significance was set at 0.05. Statistical analysis was performed with STATA/SE version 16 (Stata Corp., College Station, TX, USA).

3. Results

Through our initial search, a total of 814 articles were retrieved; 199 from PubMed, 311 from Embase, and 304 from Scopus. After removing duplicates, 385 items were screened. Detailed information for each successive step in the selection of eligible studies is provided in the supplemental material (Supplemental Fig. 1 and Supplemental Table 2). Agreement between reviewers during the screening process was assessed using Cohen's kappa, which was estimated to be 0.92, indicating almost perfect agreement. Discrepancies (16 out of 385 studies) were resolved through consultation with a senior author. Ultimately, nine studies were included, eight of which were observational; three retrospective cohort studies [12,15,16], four case-control studies [6,11,13,14], and one study employing both cohort and case-control methodologies [10]. However, we only included data from the case-control part of the latter study, as it specifically explored the results of interest. Additionally, one randomized controlled trial (RCT) was included [9].

The first cohort study included 6641 recipients of 4CMenB versus 26,471 individuals receiving the tetravalent meningococcal vaccine MenACWY matched on age, sex, and year of index vaccination [15], the second one included 15,760 recipients of 4CMenB versus 15,212 recipients of a non-OMV-based MenB vaccine, the meningococcal serogroup B-factor H binding protein vaccine (MenB-FHbp) [12] and the third one included 51 people living with HIV (PLWH) and compared the

incidence rate of gonorrhea before and after vaccination [16].

The case-control studies included 30,904 cases of *N. gonorrhoeae* infection and 197,160 chlamydia controls in total (124,876 chlamydia controls [13], 12,487 chlamydia controls [6], 4935 chlamydia controls [10], 53,914 chlamydia controls [14] and 948 controls with either a chlamydia, syphilis or anal human papilloma virus (HPV) diagnosis [11]. Four case-control studies evaluated the 4CMenB vaccine [10,11,13,14], whereas one evaluated the MeNZB [6].

The RCT included 544 participants of which 274 received the 4CMenB vaccine (269 received two doses and 5 one dose) and 270 did not receive any vaccination [9].

All studies were conducted in high-income countries: four in the United States of America (USA) [12–15], two in Italy [11,16], one in France [9], one in Australia [10], and one in New Zealand [6]. The study characteristics are summarized in Table 1.

3.1. Results of the meta-analysis

Overall, nine studies were included in the quantitative synthesis: three studies reported adjusted odds ratios [6,10,11], which were converted to relative risks; two studies reported adjusted prevalence ratios [13,14]; two studies reported adjusted hazard ratios [9,15]; one study reported an unadjusted incidence rate ratio [16]; and one study provided *N. gonorrhoeae* case counts for OMV-based and non-OMV-based vaccine recipients [12], from which a relative risk was calculated. In seven studies, individuals vaccinated with OMV-based MenB vaccines were compared to unvaccinated individuals [6,9–11,13,14,16]; one study compared them to individuals vaccinated with the non-OMV-based MenB-FHbp vaccine [12], and another study compared them to individuals vaccinated with the MenACWY vaccine [15].

OMV-based MenB vaccination was associated with a statistically significant decrease in *N. gonorrhoeae* cases overall (pooled ES: 0.70, 95 % CI: 0.61–0.81, $p < 0.001$); vaccine effectiveness was consequently estimated at 30 % (95 % CI: 19 %–39 %) (Fig. 1).

Regarding subgroup analyses by type of MenB vaccine administered, a significant decrease in *N. gonorrhoeae* infections was observed for individuals vaccinated with two doses 4CMenB (pooled ES: 0.72, 95 % CI: 0.59–0.88, $p = 0.002$; pooled VE: 28 %, 95 %CI: 12 %–41 %, Fig. 1), more than one doses of 4CMenB vaccine (pooled ES: 0.65, 95 % CI: 0.50–0.85, p = 0.002; pooled VE: 35 %, 95 %CI: 15 %–50 %, Fig. 1) and individuals vaccinated with more than one doses of the MeNZB (pooled ES: 0.73, 95 % CI: 0.65–0.82, $p < 0.001$; pooled VE: 27 %, 95 %CI: 18 %–35 %, Fig. 1).

In regard to subgroup analysis by comparator, when comparing vaccinated versus unvaccinated individuals a pooled ES of 0.73 (95 % CI: 0.63–0.85, p < 0.001, Supplemental Fig. 1) was observed. This decrease was also evident when comparing vaccinated individuals to recipients of the non-OMV-based MenB-FHbp vaccine (pooled ES: 0.53, 95 % CI: 0.32–0.86, $p = 0.011$, Supplemental Fig. 1) and to recipients of the MenACWY vaccine (pooled ES: 0.54, 95 % CI: 0.34–0.86, $p = 0.009$ Supplemental Fig. 1). However, the latter two subgroup analyses involved only one study each. Subgroup analyses by type of effect estimate (adjusted odds ratio [aOR], adjusted hazard ratio [aHR], adjusted prevalence ratio [aPR], risk ratio [RR]), are presented in Supplemental Fig. 2.

3.2. Evaluation of quality of studies and risk of bias

The evaluation of quality of the included studies is presented in Supplemental Tables 3–5. In the case-control studies, the quality was mainly compromised by the lack of data on dropouts (non-response rate). In cohort studies, quality was compromised by the lack of data on the completeness of follow-up. In the RCT low overall risk of bias was assessed.

4. Discussion

The findings of this systematic review and meta-analysis reveal a statistically significant decrease in *N. gonorrhoeae* infections comparing recipients of OMV-based MenB vaccines with either unvaccinated individuals or recipients of other meningococcal vaccines. All of the included studies, except for one, investigated the effectiveness of the 4CMenB vaccine, while one examined the effectiveness of the MeNZB vaccine; both are OMV-based, with the 4CMenB vaccine showing higher protection than the MeNZB vaccine.

The observed effectiveness likely stems from cross-protection between *N. meningitidis* and *N. gonorrhoeae*, both members of the *Neisseria* group [7], owing to significant similarities in their outer membrane vesicles due to high genetic homology [24–26]. Notably, enzyme-linked immunosorbent assays (ELISA) and Western blot analyses of the 4CMenB vaccine have demonstrated that immunized mice [27] and human serum [24] can recognize gonococcal proteins. Besides the MeNZB OMV, 4CMenB contains additionally three recombinant antigens, of which NHBA is the only one expressed on the surface of *N. gonorrhoeae*. 4CMenB may provide superior protection against gonorrhea compared to MeNZB, primarily due to the strong homology of MtrE, a highly conserved OMV component between the two species (96.4 %) [28,29], and secondarily due to NHBA, which has a homology of 68.8 % [24]. This observation highlights the need for further investigation into the role of minor OMV proteins in cross-protection.

The CDC recommends the 4CMenB vaccine as a public health measure for individuals aged 2 months to 10 years who are at increased risk for meningococcal disease in the USA [30]. Despite its primary aim to prevent invasive meningococcal disease (IMD) in toddlers, young children, adolescents, and young adults [30,31], some of whom are not typically at high risk for gonorrhea, the studies included in our analysis focused on age groups that are at risk for gonorrhea. The vaccine's potential benefit might pertain to high risk populations for gonorrhea; the latter may include men who have sex with men (MSM) [32]. although *N. meningitidis* serogroup C (MenC) is more common in outbreaks among MSM [33]. Since November 2023 the Joint Committee on Vaccination and Immunization (JCVI) has recommended the use of the 4CMenB vaccine for individuals at high risk of *Neisseria gonorrhoeae* infection, including MSM, transgender women, and sex workers in the United Kingdom [34].

The vaccine's effectiveness could nevertheless face challenges due to the variability of *N. gonorrhoeae's* membrane antigens [5]. While there have been indications of a sustained immunogenic response in vaccinated adolescents at 4 and 7.5 years [35], the waning immunogenicity over time remains a concern. This might underscore the potential necessity for booster doses to maintain effectiveness against evolving strains of the pathogen, a hypothesis that remains to be further investigated.

The findings of this study align partially with previous meta-analyses in the field. In 2024, Wang et al. reported a vaccine effectiveness of 34 % (95 % CI: 27–41 %) for OMV-based vaccines based on case-control studies, and 33 % (95 % CI: 9 %–56 %) based on cohort studies [36]. No overall estimate combining all study designs was provided, as case-control and cohort studies were analyzed separately. Similarly, Abara et al. reported a 4CMenB vaccine effectiveness of 32.4 % (95 % CI: 26.2–38.7 %) against gonorrhea in the same year [37]. It is worth noting, however, that neither study converted odds ratios to relative risks, which could potentially lead to an overestimation of vaccine effectiveness.

Several limitations should be considered when interpreting the results of the present systematic review and meta-analysis. First, most studies primarily enrolled younger participants and individuals who may have easier access to sexual health care services, potentially limiting the applicability of these findings to older populations or those facing barriers to accessing care. Second, the absence of site-specific data on *N. gonorrhoeae* infections (urethral, anal, pharyngeal)

Table 1
Characteristics of relevant studies concerning the vaccine effectiveness of OMV-based meningococcal vaccines on the prevention of *N.gonorrhoeae* infection.

First author (year)	Study Design	Participant Number	Region	Mean age (Age range)	Follow-Up	Population	Definition of gonococcal infections	Comparator	Type of OMV-based vaccine administered	Outcome Reported	Main results
Abara et al. 2022[13]	Retrospective case control study	18,099 cases of NG and 124,876 controls with CT	New York and Philadelphia USA	Age 16–23	Jan 1, 2016 to Dec 31, 2018	Data from immunization registries for Individuals aged 16–23 years. 65.5 % were female Cases: those who were NG-positive and controls as CT-positive only	Reported gonorrhea diagnoses by the STI surveillance system in New York City Department of Health and Mental Hygiene, and the Philadelphia Department of Public Health	Unvaccinated	4CMenB (≥1 dose; 4032 had received one dose, 3596 two doses and 64 at least three doses	Adjusted prevalence ratio for gonorrhea diagnoses comparing gonorrhea cases with chlamydia controls based on vaccination status. Multivariable models adjusted for race and ethnicity, gender, jurisdiction as covariates. Vaccine effectiveness (VE) was calculated as 100 × (1–Adjusted Prevalence Ratio)	VE: 40 % (95 % CI: 23–53) for full vaccination aPR: 0·60 (95 % CI: 0.47–0.77), $p < 0·0001$
Abara et al. 2024[14]	Retrospective case control study	68,454 participants with 85,393 STIs (10,638 cases of gonorrhea monoinfection and 53,914 cases of chlamydia monoinfection)	California, USA	Age 15–30	January 1, 2016–December 31, 2021	Electronic health records of Kaiser Permanente Northern California (KPNC). Reference group: Participants with chlamydia	Gonorrhea and chlamydia cases, whether occurring individually or as coinfections, were detected using NAAT.	Unvaccinated	4CMenB (≥1 Dose, 174 received 2 or more doses and 384 received 1 dose)	Adjusted for race/ethnicity, gender, insurance status, neighborhood deprivation index, and HIV status. (expanded)	aPR: 0.99 (0.79–1.25) (expanded)
Bruxvoort et al. 2023[15]	Matched Retrospective Cohort	6641 recipients of 4CMenB matched to 26,471 recipients of MenACWY	California, USA	18.8 (sd: 2.48) (MenB group) 18.6 (sd: 2.54) (MenACWY group)	Median follow-up: 1.90 (IQR: 1.16–2.97) (4CMenB group) 1.97 (IQR: 1.20–2.87) (MenACWY group)	Teens and young adults at Kaiser Permanente Southern California 3658 (55.1 %) Female (MenB group) 14,539 (54.9 %) female (MenACWY group)	Positive gonorrhea NAAT or NG culture from a genital or extragenital swab or urine sample and also any ICD-10 diagnosis for gonorrhea from all care settings from medical charts	Recipients of MenACWY vaccine	4CMenB (≥1 dose, no data on the exact number of participants who received one, two, or more doses)	Hazard ratios for incident gonorrhea comparing recipients of 4CMenB and recipients of MenACWY adjusted for Race/Ethnicity, Number of outpatient visits, HIV infection PrEP use and other STI diagnoses.	aHR: 0.54 (0.34–0.86)
Molina et al. 2024[9]	RCT	274 recipients of the 4CMenB vaccine and 270 unvaccinated individuals	France	Median age: 41 (IQR: 34–48) (4CMenB group) 40 (IQR: 34–49)	Jan 19, 2021, and Sept 19, 2022	MSM aged 18 years or older, HIV negative, already included in the ANRS	Gonorrhea infections were defined by a single positive PCR test from at least one	Unvaccinated	4CMenB (≥1 doses, 269 received 2 doses and 5	Adjusted hazard ratio for gonorrhea infection, adjusted for the	The incidence of a first episode of gonorrhea was 58.3 per 100 person-years

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Table 1 (*continued*)

First author (year)	Study Design	Participant Number	Region	Mean age (Age range)	Follow-Up	Population	Definition of gonococcal infections	Comparator	Type of OMV-based vaccine administered	Outcome Reported	Main results
				Unvaccinated group		PREVENIR study with a history of bacterial STIs within the 12 months before enrolment	site (throat, urine, or anus)		received one dose)	potential influence of doxycycline PEP	(PY) in the 4CMenB group and 77.1 per 100 PY in the no-vaccine group, with an adjusted hazard ratio (aHR) of 0.78 (95 % CI: 0.60–1.01).
Labate et al. 2024[16]	Retrospective cohort	51 PLWH	Italy	32 (IQR: 25–39) for the PLWH Data for MSM not available	2016–2023	PrEP users and PLWH who received at least one dose of 4CMenB vaccination and who had at least one STDs test before and after the vaccination between 2016 and 2023	Positive results for Gonorrhea	Unvaccinated	4CMenB (≥1 dose, no data on the exact number of participants who received one, two, or more doses)	Poisson regression model to compare the incidence rate of NG and other STDs before and after the vaccination, therefore reporting an IRR.	uIRR: 0.28 (95 % CI:0.11–0.71 $p = 0.0073$)
Petousis-Harris et al. 2017[6]	Retrospective case-control	14,730 cases and controls 1241 having NG only 12,487 having CT only 1002 co-infected with NG and CT	New Zealand	Age range: 15–30 (Majority: 49 % was 20–24)	Study period from Jan 1, 2004, to Dec 31, 2016	All people aged 15–30 years (born from Jan 1, 1984, to Dec 31, 1998) attending participating sexual health clinics who were diagnosed with NG or CT, or both, and eligible to receive the MeNZB vaccine in New Zealand during a mass immunization program from July 19, 2004, to June 30, 2006 Cases: those who were NG-positive only and controls as CT-positive only	Gonorrhea diagnosis by culture or NAAT	Unvaccinated	MeNZB (≥1 dose; 940 participants received at least one dose and 7429 received 3 doses)	Adjusted odds ratios for gonorrhea infections between cases and controls by vaccination status with MeNZB (complete vs. no vaccination) were calculated by logistic regression (adjusted for age group, ethnicity, sex, geographical location, and deprivation quintile.) VE was calculated as 100 × (1–OR). Only the results from sensitivity analysis were included, which established how much a change in classification and inclusion of coinfected individuals would	aOR: 0·71 (95 % CI: 0.62–0.80) $p < 0.0001$

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Table 1 (*continued*)

First author (year)	Study Design	Participant Number	Region	Mean age (Age range)	Follow-Up	Population	Definition of gonococcal infections	Comparator	Type of OMV-based vaccine administered	Outcome Reported	Main results
										affect the estimates.	
Raccagni et al. 2023[11]	Case-control study	1051 (103 cases, 948 controls	Italy	44 (37–51)	Median follow-up was 3.8 years (2.1–4.3 years)	MSM living with HIV. Cases: individuals with ≥1 NG infection since July 2016, after receiving 2 doses of 4CMenB if vaccinated, Controls: people who had ≥1 syphilis, chlamydia, or anal HPV diagnosis since July 2016.	Gonorrhea infections were defined by gonococcal-specific cultures or NAAT	Unvaccinated	4CMenB (2 doses; all vaccinated individuals [349] received 2 doses)	Adjusted Odds ratios for gonorrhea infections between cases and controls by vaccination status (vaccinated with 4CMenB vs. unvaccinated) Adjusted for: CD8+ lymphocytes count, hepatitis coinfections, age, years of antiretroviral therapy, CD4+ lymphocytes count, HIV-RNA VE was calculated as (1 − OR) x 100.	aOR: 0.561 (95 % CI: 0.345 0.912) $p = 0.020$ VE: 44 % (95 % CI, 9 %–65 %), p = 0.020
Robison et al. 2023[12]	Retrospective cohort study	30,972 (15,760 recipients of 1 or more OMV-based MenB Vaccines and 15,212 recipients of 1 or more non–OMV-based MBV)	USA	Median age at vaccination: 19.3 (18–20) years for the OMV-based vaccine 19.4 (18–20) years for the non-OMV-based	1 month to 2 years after vaccination or study end (March 31, 2018)	Participants aged 18–29 years from the immunization registries in Oregon. 8510 (54 %) were females [54 %] for the OMV-based, and 8519 (56 %) were females for the non-OMV based)	Gonorrhea diagnoses from mandatory reporting in Oregon	Recipients of non-OMV based MenB vaccine MenB-FHbp	4CMenB (≥1 dose, no data on the exact number of participants who received one, two, or more doses))	VE was reported comparing gonorrhea cases between recipients of OMV-based MenB with recipients of non-OMV-based MenB vaccine.	VE: 47 % (95 % CI, 13 %–68 %) (Twenty-four cases of gonorrhea were reported in OMV-based MBV recipients vs 44 cases in non–OMV-based MBV recipients)
Wang et al. 2023[10]	Case-control study	823 cases of NG and 4935 CT controls	Australia	Follow-up for three years after the implementation of the vaccination program for gonorrhea (mean or median follow-up not reported)	36 months	Children, adolescents, and young adults targeted by the South Australia 4CMenB vaccination program Cases: those who were NG-positive only and controls as CT-positive only	Gonorrhea notification data were provided by the Communicable Disease Control Branch	Unvaccinated	4CMenB (2 doses: all vaccinated individuals included in this analysis received 2 doses, exact number not given)	Adjusted odds ratio comparing gonorrhea infections between cases and controls by vaccination status (vaccinated vs. unvaccinated) VE was calculated as 1 minus the odds ratio estimated from the model	aOR:0.717 (95 % CI: 0.552–0.930) $p = 0.012$ VE: 28.3 % (95 % CI: 7.0–44.8)

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Table 1 (*continued*)

First author (year)	Study Design	Participant Number	Region	Mean age (Age range)	Follow-Up	Population	Definition of gonococcal infections	Comparator	Type of OMV-based vaccine administered	Outcome Reported	Main results
										Adjusted according to changes in the incidence of gonorrhea in all three age cohorts of adolescents/ young adults who were not eligible to receive the free 4CMenB vaccine.	

aHR: adjusted hazard ratio; aOR: adjusted odds ratio; aPR: adjusted prevalence ratio; CI: confidence interval; CT: *Chlamydia Trachomatis*; HIV: Human Immunodeficiency Virus; HPV: Human Papillomavirus; HR: Hazard ratio; IQR: Interquartile range; MenACWY: Meningococcal Groups A, C, W, and Y vaccine, MenB: Meningococcal Group B vaccine, MenB-FHbp: Meningococcal serogroup B-factor H binding protein vaccine; NAAT: Nucleic Acid Amplification Tests; NG: *Neisseria gonorrhoeae*; OMV: outer membrane vesicle; OR: Odds Ratio; PR: Prevalence Ratio; PLWH: People living with HIV; USA: United States of America; VE: Vaccine effectiveness.

precluded a site-specific evaluation of vaccine effectiveness, potentially overlooking significant differences between sites. Third, most studies assessed vaccine effectiveness over a short period; however, there have been indications suggesting a potential decline in effectiveness over time [6,10], necessitating a longer-term approach to thoroughly investigate this phenomenon. Additionally, the inclusion of only 9 studies that have been published so far, somewhat limits the breadth of our analysis, but still provides valuable insights. Fourth, the observed VE was lower than 50 %, a commonly cited benchmark for VE evaluations, for instance in the COVID-19 pandemic [38]; nevertheless, the necessary VE for each vaccine takes into account the disease, the target population and overall public health goals. Furthermore, some of the included studies primarily focused MSM [9,11], that may have a distinct immunological reaction to the vaccine due to prior gonorrhea infections resulting in a potential anamnestic response against minor proteins that are part of the OMV vaccine. Moreover, the included studies lacked data on behavioral differences between vaccinated and unvaccinated individuals. Factors such as condom use and sexual health awareness may have influenced the observed vaccine effectiveness, but were not reported in the synthesized studies, as a rule. Additionally, the duration of follow-up varied across studies, with some covering the COVID-19 pandemic period. Social distancing measures and lockdowns during this time may have influenced sexual behavior and STD transmission, potentially impacting the observed vaccine effectiveness. Also, a key limitation is the variability in gonorrhea diagnosis and outcome measures across studies; while some used NAAT or culture [6,9,11,14,15], others did not specify their methods [10,12,13,16]. Similarly, variations such as the inclusion of throat swabs in Molina et al.'s study further impact comparability. Finally, key clinical details such as the interval between vaccine doses and how repeated gonorrhea infections were handled (e.g., as single or multiple events) were not consistently reported across the included studies, which could limit our ability to fully assess dosing effects or interpret outcome definitions, and may affect the generalizability of our findings.

Our study exhibits several strengths. A notable advantage is that it represents the most up-to-date meta-analysis to quantitatively synthesize vaccine effectiveness of OMV-based MenB vaccines against *N. gonorrhoeae* infections. Furthermore, a significant portion of the included studies used chlamydia cases as controls, thereby minimizing confounding factors such as differences in sexual behaviors and access to healthcare. This approach is justified as gonorrhea and chlamydia share similar risk factors and are commonly screened for together in both jurisdictions. Our study also benefits from transforming odds ratios into relative risks, which helps mitigate the potential exaggeration of effects inherent in odds ratios—a method not previously implemented in past meta-analyses. This is a timely topic with significant public health impact and currently RCTs are being conducted in the field; two in Australia [39,40], one in USA [41], and one in China [42].

In an era marked by rising *N. gonorrhoeae* infections, the development of effective prevention strategies is of great importance. A modeling study has shown that even a *N. gonorrhoeae* vaccine with a non-waning effectiveness of 20 %, namely substantially lower than that observed in our study, could still lead to a significant reduction in *N. gonorrhoeae* infections [43]. Another model indicated that vaccinating high-risk groups, such as men who have sex with men, with a vaccine of effectiveness of 31 % for 2–4 years (similar to that observed in our meta-analysis) could lead to a significant decrease in *N. gonorrhoeae* infections from 45 to 75 % until 2030 within this demographic [44]. A recent cost-effectiveness study demonstrated that vaccinating MSM in England with the 4CMenB meningococcal vaccine, using one or two primary doses, saves costs and improves health outcomes, particularly when targeting strategies align with *N. gonorrhoeae* risk and diagnosis [45], that can be compromised by the associated social stigma, anxiety and perception of discrimination in getting tested. Finally, as the 4CMenB vaccine effectiveness was found to be 30 % and as there are genetic similarities of 80–90 % homology in the primary genetic

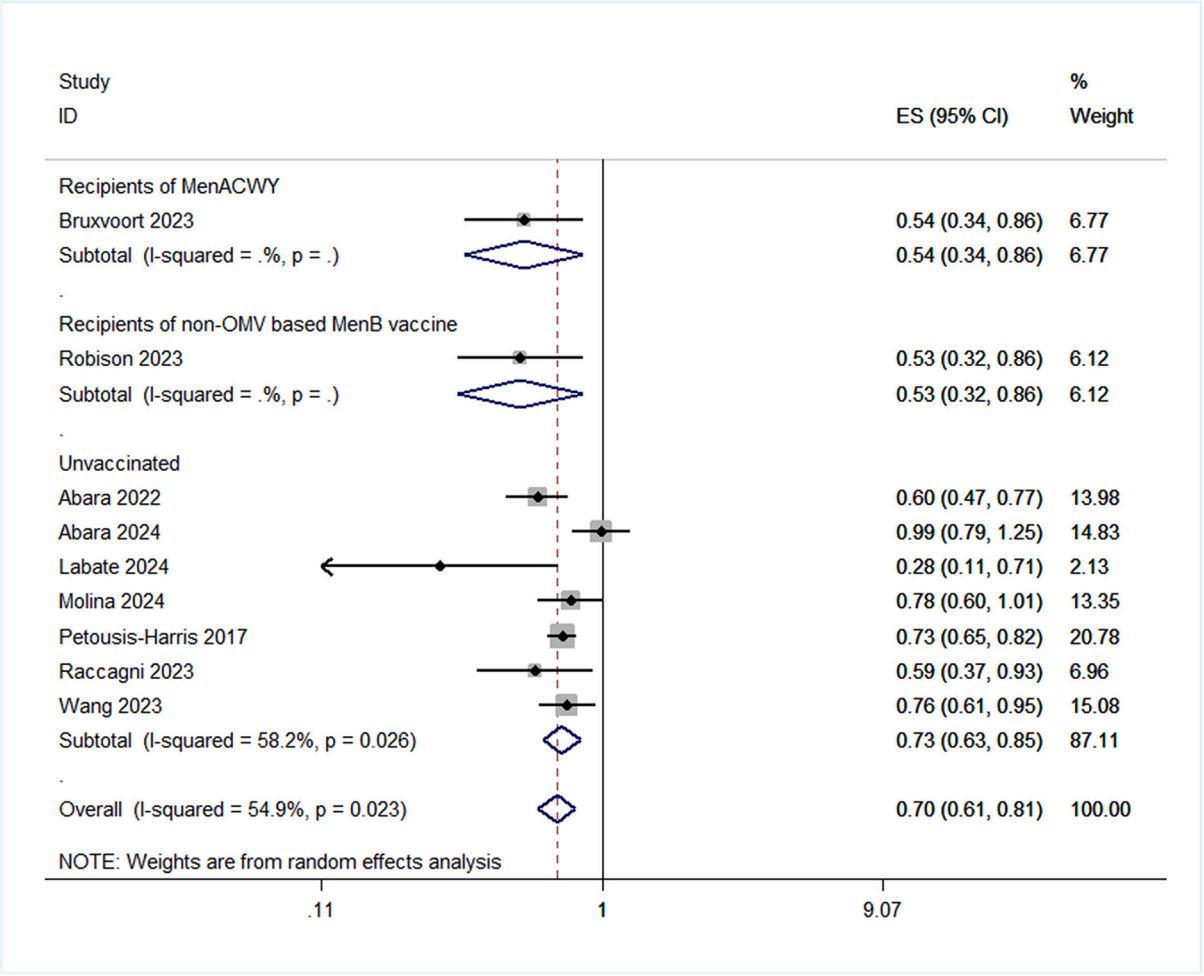

Fig. 1. Forest plot describing the association between OMV-based MenB vaccination and *N. gonorrhoeae* infection diagnoses. Subgroup analyses by intervention (type of OMV-based MenB vaccine and number of doses administered) are presented. CI: Confidence Interval; ES: Effect Size; RR: Relative Risk.

sequences between *N. gonorrhoeae* and *N. meningitidis* [25,46], there is a need of further robust, multidisciplinary research towards the development of an effective vaccine in order to enhance the sexual health outcomes of individuals globally.

CRediT authorship contribution statement

Nikolaos Georgiadis: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andreas Katsimpris:** Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Georgina Tzanakaki:** Writing – review & editing, Validation, Supervision, Data curation, Conceptualization. **Sotirios Tsiodras:** Writing – review & editing, Validation, Supervision, Data curation, Conceptualization. **Apostolos Beloukas:** Writing – review & editing, Validation, Supervision, Conceptualization. **Tonia Vassilakou:** Writing – review & editing, Project administration, Investigation, Data curation, Conceptualization. **Theodoros N. Sergentanis:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

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Drs Georgiadis, Katsimpris and Sergentanis have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127180.

Data availability

All data of included articles is available in each article seperately and also in table 1.

References

[1] Kirkcaldy RD, Weston E, Segurado AC, Hughes G. Epidemiology of gonorrhea: a global perspective. Sex Health 2019;16(5):401–11. https://doi.org/10.1071/SH19061.

[2] Unemo M, Seifert HS, Hook EW, Hawkes S, Ndowa F, Dillon JAR. Gonorrhoea Nat Rev Dis Primer 2019;5(1):79. https://doi.org/10.1038/s41572-019-0128-6.

[3] Sexually transmitted infections (STIs). Accessed June 26, 2024, https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis); 2024.

[4] Unemo M, Lahra MM, Cole M, et al. World health organization global gonococcal antimicrobial surveillance program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts. Sex Health 2019;16(5):412–25. https://doi.org/10.1071/SH19023.

[5] Jerse AE, Bash MC, Russell MW. Vaccines against gonorrhea: current status and future challenges. Vaccine 2014;32(14):1579–87. https://doi.org/10.1016/j.vaccine.2013.08.067.

[6] Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet 2017;390(10102):1603–10. https://doi.org/10.1016/S0140-6736(17)31449-6.

[7] Azze RFO. A meningococcal B vaccine induces cross-protection against gonorrhea. Clin Exp Vaccine Res 2019;8(2):110–5. https://doi.org/10.7774/cevr.2019.8.2.110.

[8] Whelan J, Klovstad H, Haugen IL, MRDRB Van Holle, Storsaeter J. Ecologic Study of Meningococcal B Vaccine and Neisseria gonorrhoeae Infection, Norway. Emerg Infect Dis 2016;22(6):1137–9. https://doi.org/10.3201/eid2206.151093.

[9] Molina JM, 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(10):1093–104. https://doi.org/10.1016/S1473-3099(24)00236-6.

[10] Wang B, Giles L, Andraweera P, et al. 4CMenB sustained vaccine effectiveness against invasive meningococcal B disease and gonorrhoea at three years post programme implementation. J Inf Secur 2023;87(2):95–102. https://doi.org/10.1016/j.jinf.2023.05.021.

[11] 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(5):247–51. https://doi.org/10.1097/OLQ.0000000000001771.

[12] Robison SG, Leman RF. Association of Group B Meningococcal Vaccine Receipt with Reduced Gonorrhea Incidence among University Students. JAMA Netw Open 2023;6(8):e2331742. https://doi.org/10.1001/jamanetworkopen.2023.31742.

[13] Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. Lancet Infect Dis 2022;22(7):1021–9. https://doi.org/10.1016/S1473-3099(21)00812-4.

[14] Abara WE, Modaressi S, Fireman B, et al. Effectiveness of a serogroup B meningococcal vaccine against gonorrhea: a retrospective study. Vaccine 2024;42(26):126312. https://doi.org/10.1016/j.vaccine.2024.126312.

[15] 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 Off Publ Infect Dis Soc Am 2023;76(3):e1341–9. https://doi.org/10.1093/cid/ciac436.

[16] Labate L, Marelli C, Guarise E, et al. OC-24 effectiveness of MenB vaccination against gonorrhoeae among PrEP users and PWH. Sex Transm Infect 2024;100(Suppl. 1):A24–5. https://doi.org/10.1136/sextrans-ICAR-2024.22.

[17] Longtin J, Dion R, Simard M, et al. Possible impact of wide-scale vaccination against serogroup B Neisseria Meningitidis on gonorrhea incidence rates in one region of Quebec, Canada. Open Forum Infect Dis 2017;4(Suppl. 1):S734–5. https://doi.org/10.1093/ofid/ofx180.002.

[18] Viviani V, Fantoni A, Tomei S, et al. OpcA and PorB are novel bactericidal antigens of the 4CMenB vaccine in mice and humans. Npj Vaccines 2023;8(1):1–15. https://doi.org/10.1038/s41541-023-00651-9.

[19] Holst J, Oster P, Arnold R, et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV). Hum Vaccin Immunother 2013;9(6):1241–53. https://doi.org/10.4161/hv.24129.

[20] Bjune G, Iby EAHO, JKGO Nnesby, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. Lancet 1991;338(8775):1093–6. https://doi.org/10.1016/0140-6736(91)91961-S.

[21] Esposito V, Musi V, de Chiara C, et al. Structure of the C-terminal domain of Neisseria heparin binding antigen (NHBA), one of the Main antigens of a novel vaccine against Neisseria meningitidis. J Biol Chem 2011;286(48):41767–75. https://doi.org/10.1074/jbc.M111.289314.

[22] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71.

[23] Cochrane Handbook for Systematic Reviews of Interventions. Accessed June 26, 2024, https://training.cochrane.org/handbook/current; 2024.

[24] Semchenko EA, Tan A, Borrow R, Seib KL. The serogroup B meningococcal vaccine Bexsero elicits antibodies to Neisseria gonorrhoeae. Clin Infect Dis Off Publ Infect Dis Soc Am 2019;69(7):1101–11. https://doi.org/10.1093/cid/ciy1061.

[25] Hadad R, Jacobsson S, Pizza M, et al. Novel meningococcal 4CMenB vaccine antigens - prevalence and polymorphisms of the encoding genes in Neisseria gonorrhoeae. APMIS Acta Pathol Microbiol Immunol Scand 2012;120(9):750–60. https://doi.org/10.1111/j.1600-0463.2012.02903.x.

[26] 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(5). https://doi.org/10.1128/mBio.01668-19. e01668–19.

[27] 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 Pathog 2020;16(12):e1008602. https://doi.org/10.1371/journal.ppat.1008602.

[28] Wang S, Xue J, Lu P, et al. Gonococcal MtrE and its surface-expressed loop 2 are immunogenic and elicit bactericidal antibodies. J Inf Secur 2018;77(3):191–204. https://doi.org/10.1016/j.jinf.2018.06.001.

[29] Ruiz García Y, Sohn WY, Seib KL, et al. Looking beyond meningococcal B with the 4CMenB vaccine: the Neisseria effect. Npj Vaccines 2021;6(1):1–10. https://doi.org/10.1038/s41541-021-00388-3.

[30] Vaccines for Meningococcal | CDC. June 26, 2024. Accessed July 5, 2024, https://www.cdc.gov/vaccines/vpd/mening/index.html; 2024.

[31] Vaccine Scheduler | ECDC. Accessed July 5, 2024, https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=48&SelectedCountryIdByDisease=-1; 2024.

[32] Fairley CK, Hocking JS, Zhang L, Chow EPF. Frequent transmission of gonorrhea in men who have sex with men. Emerg Infect Dis 2017;23(1):102–4. https://doi.org/10.3201/eid2301.161205.

[33] Taha MK, Claus H, Lappann M, et al. Evolutionary events associated with an outbreak of meningococcal disease in men who have sex with men. PLoS One 2016;11(5):e0154047. https://doi.org/10.1371/journal.pone.0154047.

[34] JCVI advice on the use of meningococcal B vaccination for the prevention of gonorrhoea. GOV.UK. https://www.gov.uk/government/publications/meningococcal-b-vaccination-for-the-prevention-of-gonorrhoea-jcvi-advice-10-november/jcvi-advice-on-the-use-of-meningococcal-b-vaccination-for-the-prevention-of-gonorrhoea. [Accessed 13 March 2025].

[35] Martinón-Torres F, Nolan T, Toneatto D, Banzhoff A. Persistence of the immune response after 4CMenB vaccination, and the response to an additional booster dose in infants, children, adolescents, and young adults. Hum Vaccin Immunother 2019;15(12):2940. https://doi.org/10.1080/21645515.2019.1627159.

[36] Wang B, Mohammed H, Andraweera P, McMillan M, Marshall H. Vaccine effectiveness and impact of meningococcal vaccines against gonococcal infections: a systematic review and meta-analysis. J Inf Secur 2024;89(3). https://doi.org/10.1016/j.jinf.2024.106225.

[37] Abara WE, Kirkcaldy RD, Bernstein KT, Galloway E, Learner ER. Effectiveness of MenB-4C vaccine against gonorrhea: a systematic review and Meta-analysis. J Infect Dis 2024:jiae383. https://doi.org/10.1093/infdis/jiae383. Published online July 31.

[38] Vaccine efficacy, effectiveness and protection. Accessed July 9, 2024, https://www.who.int/news-room/feature-stories/detail/vaccine-efficacy-effectiveness-and-protection; 2024.

[39] Thng C, Semchenko EA, Hughes I, O'Sullivan M, Seib KL. An open-label randomised controlled trial evaluating the efficacy of a meningococcal serogroup B (4CMenB) vaccine on Neisseria gonorrhoeae infection in gay and bisexual men: the MenGO study protocol. BMC Public Health 2023;23(1):607. https://doi.org/10.1186/s12889-023-15516-y.

[40] Seib KL, Donovan B, Thng C, et al. Multicentre double-blind randomised placebo-controlled trial evaluating the efficacy of the meningococcal B vaccine, 4CMenB (Bexsero), against Neisseria gonorrhoeae infection in men who have sex with men: the GoGoVax study protocol. BMJ Open 2024;14(4):e081675. https://doi.org/10.1136/bmjopen-2023-081675.

[41] Study Details. Efficacy of Immunization With 4C-MenB in Preventing Experimental Urethral Infection With *Neisseria Gonorrhoeae* | ClinicalTrials.gov. Accessed July 6, 2024, https://clinicaltrials.gov/study/NCT05294588?cond=Gonorrhoea&intr=4CMenB&rank=7; 2024.

[42] Study Details. Efficacy Trial on Meningococcal B Vaccine for Preventing Gonorrhea Infections | ClinicalTrials.gov. Accessed July 6, 2024, https://clinicaltrials.gov/study/NCT05766904?cond=Gonorrhoea&intr=4CMenB&rank=5; 2024.

[43] Craig AP, Gray RT, Edwards JL, et al. The potential impact of vaccination on the prevalence of gonorrhea. Vaccine 2015;33(36):4520–5. https://doi.org/10.1016/j.vaccine.2015.07.015.

[44] 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 Off Publ Infect Dis Soc Am 2020;71(8):1912–9. https://doi.org/10.1093/cid/ciz1241.

[45] Nikitin D, Whittles LK, Imai-Eaton JW, White PJ. Cost-effectiveness of 4CMenB vaccination against gonorrhea: importance of dosing schedule, vaccine sentiment, targeting strategy, and duration of protection. J Infect Dis 2024. https://doi.org/10.1093/infdis/jiae123. Published online April 17, 2024:jiae123.

[46] Perrin A, Bonacorsi S, Carbonnelle E, et al. Comparative genomics identifies the Genetic Islands that distinguish Neisseria meningitidis, the agent of cerebrospinal meningitis, from other Neisseria species. Infect Immun 2002;70(12):7063. https://doi.org/10.1128/IAI.70.12.7063-7072.2002.