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REVIEW

[Translated article] New Prevention Measures in Venereology: Evidence Review on the DoxiPrEP/PEP Antibiotic and the 4CMenB Vaccine

A. Català[a,b,c,*], **J. Riera**[a,b,c], **I. Fuertes de Vega**[a,b,c]

[a] *Servicio de Dermatología y Venereología, Hospital Clínic de Barcelona, Barcelona, Spain*
[b] *Programa de Salud Sexual, Servicio de Medicina Interna, Hospital Clínic de Barcelona, Barcelona, Spain*
[c] *Grupo Español de Investigación en ITS y VIH de la Academia Española de Dermatología y Venereología*

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Abstract Sexually transmitted infections (STIs) are increasing in Spain. The traditional strategy for STI control is mainly based on screening and treatment of STIs in patients with risky sexual practices. In recent years, new interesting primary and secondary prevention strategies are being studied to reduce the incidence rate of STIs in high-risk populations. The most interesting one, based on the evidence obtained, is the use of doxycycline and meningococcal B vaccines. Specialists in dermatology and venereology must be informed about these new developments that may have an impact on the way in which STIs are managed worldwide. This is a scientific evidence review of these new interesting primary and secondary prevention strategies to control STIs in a high-risk population.

PALABRAS CLAVE
ITS;
Clamidia;
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Vacuna meningocócica del grupo B;
Doxiciclina

Nuevas medidas de prevención en venereología: revisión de la evidencia existente sobre DoxiPrEP/PEP y vacuna 4CMenB

Resumen Las infecciones de transmisión sexual (ITS) están aumentando en España. La estrategia tradicional para el control de las infecciones venéreas se basa principalmente en el cribado y tratamiento de ITS en pacientes con prácticas sexuales de riesgo. En los últimos años, se están estudiando nuevas estrategias de prevención primaria y secundaria interesantes para reducir las ITS en poblaciones con elevado riesgo para su adquisición. Entre ellas, las de mayor interés por la evidencia obtenida son el uso de la doxiciclina y el de las vacunas meningocócicas B. Los

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* Corresponding author.
E-mail address: alcatala@clinic.cat (A. Català).

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especialistas en dermatología y venereología han de estar informados sobre estas novedades que pueden tener un impacto en el modo en el que se manejen las infecciones venéreas en todo el mundo. Se ha realizado una revisión de la evidencia científica actualizada de estas nuevas estrategias de prevención primaria y secundaria interesantes para controlar las ITS en poblaciones con elevado riesgo para su adquisición.

Introduction

Sexually transmitted infections (STIs) are on the rise in Spain,[1] particularly due to an increase in bacterial STIs. Cisgender men who have sex with men (MSM), transgender women, and sex workers are disproportionately affected.[2] The incidence of venereal infections is particularly high among individuals who engage in condomless sex. Condom use has declined dramatically in recent years, especially among certain groups such as users of HIV pre-exposure prophylaxis (PrEP), which protects against HIV but not against other STIs.

In addition to condom promotion, which is helpful but insufficient,[3] the traditional strategy for controlling venereal infections has relied on screening and treatment of STIs in patients with high-risk sexual practices.[4] In high-resource countries, quarterly serologies for syphilis and molecular testing for chlamydia and gonorrhea (and treatment if needed) form the basis of bacterial STI control in people at elevated risk.[5] However, in lower-resource settings, diagnosis tends to be syndromic and treatment empirical, due to lack of access to sensitive, rapid diagnostic tests. This empirical approach leaves asymptomatic patients – whose screening is crucial for controlling these infections – out of reach.[6]

In recent years, new strategies for primary and secondary STI prevention are being explored in high-risk populations. Of particular interest due to emerging evidence are the use of doxycycline and meningococcal B vaccines. We believe that dermatology and venereology specialists should be aware of these developments, which are already impacting the global management of venereal infections.

Doxy-PEP/Doxy-PrEP

Definition: Preventive intake of doxycycline before (Doxy-PrEP), during, or after (Doxy-PEP) high-risk sexual events, without prior sexual contact with someone diagnosed with an STI.

Usage: For Doxy-PEP,[7,8] a single dose of 200 mg doxycycline is taken within the first 24 h – and no later than 72 h – after unprotected oral/anal/vaginal sex. Doxy-PrEP[9,10] refers to continuous intake (100 mg every 24 h) of doxycycline to prevent STI acquisition.

Advantages: Doxycycline is a second-generation tetracycline with moderate spectrum, easy access, rapid absorption, and high bioavailability. It has a solid safety profile and is generally well tolerated.[12] It is the first-line therapy for *Chlamydia trachomatis*, second-line for syphilis, and shows activity against *Neisseria gonorrhoeae* in areas with low tetracycline resistance. Contraindications and drug interactions are limited.

What is the evidence for doxycycline in preventing bacterial venereal infections?

Five randomized controlled trials[7–11] (RCTs) have been published on STI prevention with doxycycline in MSM, and in some cases, transgender women. Participants were either using HIV PrEP (PrEP-HIV) or had confirmed HIV infection (PLHIV).

Bolan et al.[9] presented a preliminary study with 30 PLHIV randomized into Doxy-PEP vs control. Molina et al.[7] published a 2018 study with 232 patients randomized to Doxy-PEP vs no intervention, allowing up to three doses of 200 mg doxycycline per week. Zhu et al.[10] conducted a dual-treatment study in 2021. The ''immediate group'' received HIV PrEP + Doxy-PrEP; the ''deferred group'', HIV PrEP and added Doxy-PrEP on week 25. Afterwards, Luetkemeyer et al.[8] enrolled a total of 501 participants categorized into two cohorts: HIV PrEP users and PLHIV. Ultimately, 374 were in the Doxy-PEP group vs 180 controls. Molina et al.[11] published 2023 open-label RCT results with 2:1 randomization (Doxy-PEP vs no prophylaxis) and 1:1 (2-dose meningococcal B vaccine vs no intervention), including 362 in Doxy-PEP vs 183 controls.

Efficacy against syphilis: Syphilis incidence decreased in all studies among Doxy-PEP users, with reductions between 73 and 87% vs controls. In the PLHIV subgroup, reductions of 73% and 77% were not statistically significant. Zhu et al.[10] reported a decrease from 8.2 to 0 per 100 person-years, though not statistically significant due to few syphilis diagnoses. In all PrEP-HIV cohorts,[7,8,11] the syphilis incidence reduction was statistically significant.

Efficacy against C. trachomatis: Incidence was significantly reduced in all studies[7,8,10,11] among doxycycline users vs controls, with reductions between 70% and 89%. This was observed in both PrEP-HIV and PWH users. None of the studies differentiated between D–K and L1–L3 *C. trachomatis* serovars.

Efficacy against N. gonorrhoeae: Gonorrhea incidence declined in all studies, though data were more heterogeneous. Reductions ranged between 17% and 57%, with statistical significance in only a few studies.[8,11] These results may reflect regional susceptibility of gonococci to tetracyclines.

Overall efficacy in bacterial STI prevention: Across all studies, a combined reduction in bacterial STI incidence was

noted. Molina et al.[11] reported an 83% combined reduction in syphilis and chlamydia. Other studies showed combined reductions ranging from 47% to 82%.

What concerns arise?

Adverse effects (AEs): GI AEs (nausea, vomiting, diarrhea) were among the most common in the RCTs[7–11] (Table 1 and supplementary data). However, no statistically significant differences were found regarding serious AEs between doxycycline and control groups.[7–11] Photosensitivity, a classic tetracycline-related AE, is a potential risk. Although specific evidence for doxycycline is limited, sun protection is recommended during its use.[13] Although hematological, liver, and kidney alterations are rare, analytical monitoring is advised for prolonged use.

Efficacy in cisgender women: The only study[14] that has investigated STI prevention with doxycycline in cisgender women did not observe a significant reduction in the incidence of venereal infections, which could be due to a different pattern of antibiotic resistance, as the study was conducted in Kenya (Africa). However, the authors also point to a possible low adherence to doxycycline by the participating women, which should be taken into consideration. Therefore, more studies are needed to evaluate the efficacy profile of this preventive measure in cisgender women.

Will patients adhere to doxycycline? In Luetkemeyer et al.,[8] a total of 86% of participants reported consistent Doxy-PEP adherence. A total of 71% said they never missed a dose during the study, with a median of 4 monthly doses (range, 1–10). It is unknown whether such adherence would be sustained long-term or if 4 monthly doses are sufficient in our populations.

What about antibiotic resistance? From a public health standpoint, the main concern about preventive doxycycline use is the potential to promote antimicrobial resistance – not only among STI pathogens but also in other bacteria or users' microbiomes:

- *N. gonorrhoeae*: In Luetkemeyer et al.,[8] 26.7% of baseline isolates showed tetracycline resistance. During the study, tetracycline resistance was higher in the Doxy-PEP vs the control (38.5% vs 12.5%). Molina et al.[7] found tetracycline resistance in all isolates (initial and during follow-up), with MIC >8 mg/L in 33.3% of Doxy-PEP isolates vs 18.9% in controls.
- *M. genitalium*: Molina et al.[7] ($n = 14$) reported no resistance differences across the groups.
- *C. trachomatis*: No resistance was detected, but prolonged use may risk strain selection.[15]
- *Staphylococcus aureus*: In the Molina et al.[7] study, the presence of methicillin-resistant *S. aureus* (MRSA) was investigated in pharyngeal swabs among participants. During the study, the two groups experienced an increase in MRSA detections, though the differences were non-significant. However, in the Luetkemeyer et al.[7] study, there were statistically significant differences and higher rates in the doxycycline group (month 6: 21.6% [doxycycline group] vs 10.3% [control group]; month 12: 16.1% vs 8.3%).
- *Escherichia coli* carrying extended-spectrum beta-lactamase (*E. coli ESBL*): In the Molina et al.[7] study, an increase in anorrectal *E. coli* ESBL was observed in the two groups, with no differences detected between them.
- *Microbiota*: Prolonged doxycycline intake seems to have moderate and transient effects on oral, respiratory, and GI flora; however, data on this topic are limited, mainly due to the relatively small size of the studies.[15]

What do experts recommend?

The International Union against Sexually Transmitted Infections (IUSTI)[16] issued a 2024 statement acknowledging the evidence supporting Doxy-PEP but noting concerns regarding resistance, public health impact, etc. IUSTI advises individualized decisions, considering the infection to be prevented, local health care capacity, ability to conduct public health surveillance, and patient engagement. Crucially, users must be informed about limitations in evidence and potential AEs. Other societies[17–19] oppose general prophylactic doxycycline use in sexually active individuals but allow Doxy-PEP in select cases.

The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC)[20] has stated that doxycycline is not approved for STI prevention and is thus considered off-label. SEIMC recommends individualized Doxy-PEP prescription in MSM or transgender women with repeated STIs in the past year, following shared decision-making with the patient.

Use of meningococcal B vaccines to prevent *N. gonorrhoeae* infection

A hard-to-control bacterium: *N. gonorrhoeae* has developed resistance to all antibiotic classes.[21] Pharyngeal and rectal infections are often asymptomatic,[22,23] facilitating resistance and transmission. In response to rising incidence, WHO aims to reduce gonorrhea by 90% by 2030.[24] Gonorrhea does not confer protective immunity,[25] and humans are its only natural host. There are no suitable animal models, complicating vaccine development. Four candidate vaccines failed to protect against gonorrhea in clinical trials.[25-28] However, recent epidemiological data[29–37] suggest that meningococcal B vaccines may provide cross-protection against gonorrhea.

Why might meningococcal B vaccines protect against *N. gonorrhoeae*?

Twelve serogroups of *Neisseria meningitidis* exist, based on polysaccharide capsules. Six (MenA, MenB, MenC, MenW, MenX, MenY) cause most invasive disease globally.[38] Conjugate vaccines are available for MenA, MenC, MenW, MenY. The Spanish Pediatric Association recommends routine vaccination against MenB, MenC, and MenACWY. Currently in Spain, eight inactivated meningococcal vaccines are available[39]: three monovalent vaccines against serogroup C; three tetravalent vaccines against serogroups A, C, W, and Y (MenACWY); and two monovalent vaccines against serogroup B.[39]

Two vaccines are available for invasive MenB disease[39]:

Table 1 Summary of randomized controlled trials (RCTs) on the use of doxycycline as a bacterial STI prevention method.

Study/year/location	*N*, inclusion criteria	Design	Intervention	Participants and follow-up	Syphilis efficacy	Chlamydia efficacy	Gonorrhea efficacy	Bacterial STI efficacy
Bolan et al.[9] (2015) Los Angeles (USA)	30 MSM or Trans-♀ + PLHIV + ≥2 syphilis episodes since HIV diagnosis	Open-label RCT Randomized 1:1 (intervention vs standard care with financial incentive to remain STI-free)	Doxy-PrEP:Doxycycline 100 mg/day for 36 weeks	15 Doxy-PrEP participants vs 15 standard care participants. Follow-up: Controls every 3 months for up to 48 weeks	Control group incidence: 7/49 visits (14.3%) Intervention group incidence: 2/53 visits (3.8%) Estimated efficacy: OR, 0.27 (95%CI, 0.04–1.73), $p = 0.16$	[a]	[a]	Control group incidence: 15/49 visits (30.6%) Intervention group incidence: 6/53 visits (11.3%) Estimated efficacy: OR 0.30 (95%CI, 0.08–1.09), $p = 0.07$
Molina et al.[7] (2017) ARNS IPERGAY Paris, Lyon, Nice, Nantes (France)	232 MSM or Trans-♀ + PrEP + unprotected anal and/or oral sex	Open-label RCT randomized on a 1:1 ratio (intervention vs no intervention)	Doxy-PEP: Doxycycline 200 mg single dose within 24–72 h after unprotected sexual encounter (AS or OS) Maximum 3 times/week	116 Doxy-PEP participants vs 116 control group participants. Follow-up: Controls every 2 months for up to 10 months. Mean follow-up: 8.7 months (IQR, 7.8–9.7)	Control group incidence: 12.9/100 person-years Intervention group incidence: 3.7/100 person-years Estimated efficacy: HR, 0.27 (95%CI, 0.07–0.98), $p = 0.047$	Control group incidence: 28.6/100 person-years Intervention group incidence: 8.7/100 person-years Estimated efficacy: HR, 0.30 (95%CI, 0.13–0.70), $p = 0.006$	Control group incidence: 34.5/100 person-years Intervention group incidence: 28.7/100 person-years Estimated efficacy: HR, 0.83 (95%CI, 0.47–1.47), $p = 0.52$	Control group incidence: 69.7/100 person-years Intervention group incidence: 37.7/100 person-years Estimated efficacy: HR, 0.53 (95%CI, 0.33–0.85), $p = 0.008$

Table 1 (*Continued*)

Study/year/location	*N*, inclusion criteria	Design	Intervention	Participants and follow-up	Syphilis efficacy	Chlamydia efficacy	Gonorrhea efficacy	Bacterial STI efficacy
Zhu et al.[10] (DuDHS Dual HIV/STI PrEP – preliminary results, 2023) Vancouver (Canada)	52 MSM + syphilis in previous 36 months + unprotected sex in last 6 months	Single-blind RCT Randomized 1:1 (immediate group vs deferred group)	Immediate group: Daily emtric-itabine/ tenofovir + Doxy-PrEP Doxycycline 100 mg/day for 1–48 weeks Deferred group: Daily emtric-itabine/ tenofovir for 1–24 weeks, and emtric-itabine/tenofovir + Doxy-PrEP doxycycline 100 mg/day for 25–48 weeks	26 immediate group participants vs 26 deferred group participants. Follow-up: Controls every 3 months for up to 1 year	Control group incidence: 8.16/100 person-years Intervention group incidence: 0/100 person-years Estimated efficacy: $p = 0.98$	Control group incidence: 81.63/100 person-years Intervention group incidence: 0/100 person-years Estimated efficacy: $p = 0.001$	Control group incidence: 57.14/100 person-years Intervention group incidence: 31.37/100 person-years Estimated efficacy: $p = 0.505$	Control group incidence: 139.8/100 person-years Intervention group incidence: 33.9/100 person-years Estimated efficacy: OR, 0.18 (95%CI, 0.05–0.68)

Table 1 (*Continued*)

Study/year/location	*N*, inclusion criteria	Design	Intervention	Participants and follow-up	Syphilis efficacy	Chlamydia efficacy	Gonorrhea efficacy	Bacterial STI efficacy
Luetkemeyer et al.[8] (Doxy-PEP – 2023) Seattle and San Francisco (USA)	501 MSM or Trans-♀ + PrEP or PLHIV + ≥1 syphilis, gonorrhea or chlamydia in previous 12 months + unprotected sex	Open-label RCT Randomized 2:1 (intervention vs no prophylaxis) PrEP cohort and PLHIV cohort	Doxy-PEP: Doxycycline 200 mg single dose within 24–72 h after unprotected sexual encounter (AS or OS), up to daily use	374 Doxy-PEP participants (240 PrEP + 134 PLHIV) vs 180 control group participants (120 PrEP + 60 PLHIV). Follow-up: Controls every 3 months for up to 1 year	PrEP cohort Control group incidence: 7/257 quarterly visits (2.7%) Intervention group incidence: 2/570 quarterly visits (0.4%) Estimated efficacy: RR, 0.13 (95%CI, 0.03–0.59), $p = 0.008$ PLHIV cohort Control group incidence: 3/128 quarterly visits (2.3%) Intervention group incidence: 2/305 quarterly visits (0.7%) Estimated efficacy: RR 0.23 (95%CI, 0.04–1.29), $p = 0.095$	PrEP cohort Control group incidence: 31/257 quarterly visits (12.1%) Intervention group incidence: 8/570 quarterly visits (1.4%) Estimated efficacy: RR, 0.12 (95%CI, 0.05–0.25), $p < 0.001$ PLHIV cohort Control group incidence: 19/128 quarterly visits (14.8%) Intervention group incidence: 12/305 quarterly visits (3.9%) Estimated efficacy: RR, 0.26 (95%CI, 0.12–0.57), $p < 0.001$	PrEP cohort Control group incidence: 52/257 quarterly visits (20.2%) Intervention group incidence: 52/570 quarterly visits (9.1%) Estimated efficacy: RR, 0.45 (95%CI, 0.32–0.65), $p < 0.001$ PLHIV cohort Control group incidence: 26/128 quarterly visits (20.3%) Intervention group incidence: 27/305 quarterly visits (8.9%) Estimated efficacy: RR, 0.43 (95%CI, 0.26–0.71), $p = 0.001$	PrEP cohort Control group incidence: 82/257 quarterly visits (31.9%) Intervention group incidence: 61/570 quarterly visits (10.7%) Estimated efficacy: RR, 0.34 (95%CI, 0.24–0.46), $p < 0.001$ PLHIV cohort Control group incidence: 39/128 quarterly visits (30.5%) Intervention group incidence: 36/305 quarterly visits (11.8%) Estimated efficacy: RR, 0.38 (95%CI, 0.24–0.60), $p < 0.001$

Table 1 (*Continued*)

Study/year/location	*N*, inclusion criteria	Design	Intervention	Participants and follow-up	Syphilis efficacy	Chlamydia efficacy	Gonorrhea efficacy	Bacterial STI efficacy
Molina et al.[11] (2024) France	502 MSM + PrEP + previous STI in last year At-risk event: Unprotected sex	Open-label RCT Randomized 2:1 (Doxy-PEP intervention vs no prophylaxis) and 1:1 (two doses meningococcal B vaccine intervention vs no intervention)	Doxy-PEP: Doxycycline 200 mg single dose within 72 h after unprotected sexual encounter	362 Doxy-PEP participants vs 183 control group participants. Follow-up: Controls every 3 months for up to 96 weeks. Median of 9 months	Control group incidence: 14.5/100 person-years Intervention group incidence: 2.9/100 person-years Estimated efficacy: aHR, 0.21 (95%CI, 0.11–0.41), $p < 0.0001$	Control group incidence: 42.1/100 person-years Intervention group incidence: 5.9/100 person-years Estimated efficacy: aHR, 0.14 (95%CI, 0.09–0.23), $p < 0.0001$	Control group incidence: 68.4/100 person-years Intervention group incidence: 45.5/100 person-years Estimated efficacy: aHR, 0.67 (95%CI, 0.52–0.87), $p = 0.0025$	Control group incidence (syphilis + chlamydia): 53.2/100 person-years Intervention group incidence (syphilis + chlamydia): 8.8/100 person-years Estimated efficacy (syphilis + chlamydia): aHR, 0.17 (95%CI, 0.12–0.26), $p < 0.0001$

aHR: adjusted hazard ratio; RCT: randomized clinical trial; MSM: men who have sex with men; OR: odds ratio; PrEP: HIV pre-exposure prophylaxis; PLHIV: people living with HIV; RR: relative risk; AS: anal sex; OS: oral Sex; HIV: human immunodeficiency virus; Trans-♀: transgender woman.

[a] No data in the study.

- *Bivalent vaccine (fHbp, Trumenba®, Pfizer)*: Composed of two variants of factor H binding protein (fHbp). fHbp is a subcapsular protein essential for evading the host's immune response. It is expressed in almost all meningococcal B strains and can generate an antibody response in humans.
- *Tetravalent vaccine (4CMenB, Bexsero®, GSK)*: Contains three subcapsular antigens from meningococcus B (*N. meningitidis* adhesin A or NadA, fHbp, and the *Neisseria* heparin-binding antigen or NHBA) combined with outer membrane vesicles (OMV) from the *N. meningitidis* strain NZ 98/254.

N. meningitidis and *N. gonorrhoeae* belong to the same genus and share 80–90% genome sequence identity.[38] This similarity suggests that there might be cross-protection between serogroup B meningococcal vaccines and *N. gonorrhoeae*. A bioinformatics analysis has identified that a homolog of 20 out of 22 main meningococcal OMV proteins in the 4CMenB vaccine are present in *N. gonorrhoeae* (16 proteins have >90% identity and two proteins have >80% identity with the meningococcal vaccine antigen), and the 4CMenB antigen NHBA shares >67% identity with the NHBA of *N. gonorrhoeae* strains.[40]

Real-world evidence of meningococcal B vaccine efficacy against gonorrhea

Several real-world studies were conducted from 2009 through 2023[29–37] in countries such as Cuba, New Zealand, Norway, Canada, and the United States (Table 2). Most available results come from retrospective cohort studies, case–control studies, and ecological data from national epidemiological surveillance reports. The efficacy data for the meningococcal B vaccine are based on the reduction in the incidence rates of reported *N. gonorrhoeae* infections after vaccinating specific populations with OMV-containing vaccines (MeNZB™ from New Zealand, VA-MENGOC-BC from Cuba) or by comparing *N. gonorrhoeae* incidence rates after vaccination with 4CMenB vs MenACWY. Compared to other STSs, complete vaccination efficacy for gonorrhea prevention in the post-vaccination period went from 31% to 44%. The Paynter et al.[30] study showed that the efficacy rate of the MeNZB™ vaccine against gonorrhea hospitalization was 24%. Conversely, the Wang et al.[34] study observed lower vaccine efficacy rates after 36 months (23.2%; 95%CI, 0–47.5%) vs 6–36 months (34.9%; 95%CI, 15.0–50.1%) post-vaccination, and a reduced vaccine efficacy in patients with repeated gonococcal infections.

What is the real-world evidence for the efficacy of the 4CMenB vaccine in preventing gonorrhea infection in MSM?

To date, data from two studies[11,41] have been published (Table 2). The study by Raccagni et al.,[41] an unmatched case–control study, evaluated the vaccine effectiveness (VE) of the 4CMenB vaccine against gonorrhea in PLHIV with a previous diagnosis of venereal infections. The study included a total of 1051 PLHIV (103 cases and 948 controls); 349 of 1051 (33%) received two doses of the 4CMenB vaccine. The median follow-up was 3.8 years (2.1–4.3 years). The unadjusted estimate of VE vs gonorrhea was 42% (95%CI, 6–64%; $p = 0.027$). Logistic regression showed that VE against gonorrhea remained significant (44%; 95%CI, 9–65%; $p = 0.020$) after adjusting for some factors.

Recently, the results of the DOXYVAC study from France[11] have been published. This is a multicenter, randomized, placebo-controlled, double-blind, phase 3 study to evaluate the efficacy of two doses of 4CMenB in preventing *N. gonorrhoeae* infection (whether symptomatic or asymptomatic), serum bactericidal activity vs meningococcus B and gonococcus, as well as vaccine tolerance. The study included a total of 720 participants aged 18–40, MSM on HIV PrEP who had been diagnosed with a bacterial STI in the previous 12 months. They were randomized in a 1:1 ratio to 4CMenB vs placebo. No statistically significant differences were observed in the cumulative incidence rates of gonorrhea at any site (anal, pharyngeal, or urethral).

Currently, several studies[42–46] are underway that will be able to provide better answers on the real efficacy (Table 2 of the additional data) in these populations in the near future.

What questions does this raise?

How often should patients be revaccinated? A probable short duration of vaccine-induced protection is assumed, calculated to be between 6 and 12 months.[36] Therefore, booster doses would be essential. In this regard, the group by Hui et al.[47] suggests a booster dose administered on average every 3 years.

Will it be effective vs asymptomatic infection? Studies on vaccines designed to protect vs meningococcal B disease have shown that they are very effective vs symptomatic invasive disease but do not have a real impact on carriers. If vaccination only reduces symptomatic *N. gonorrhoeae* infection, it could lead to fewer MSM seeking control/treatment for these infections, which would be counterproductive for transmission control.[48–50] It will be interesting to observe the impact of the vaccine on asymptomatic *N. gonorrhoeae* infection.[51]

Will it be effective against all strains? As with all vaccines, if the vaccine is not equally effective vs all *N. gonorrhoeae* strains, vaccination could introduce selective pressure favoring strains that are more difficult to prevent or treat.[48] This possibility makes close monitoring of *N. gonorrhoeae* strains essential if vaccination is implemented.

To whom should we offer the vaccine? Whittles et al.[52] recommended considering 4CMenB vaccination for MSM in sexual health clinics in England based on their individual risk. While this strategy might seem like the logical first step to radically reduce *N. gonorrhoeae* cases, this approach excludes many people who could benefit from the vaccine. An alternative approach would be to vaccinate adolescents, ideally before their sexual debut, which could contribute to protection vs gonorrhea and increase herd immunity vs *N. meningitidis*. However, this second strategy might have a lower impact on population-level gonorrhea diagnosis and would also be less efficient.[53]

Table 2 Summary of studies on the use of meningococcal B vaccine as a method for preventing gonococcal infection.

Study/year/location	Design/objectives	Population	Results
Whelan et al.[29] (2016) Norway	Retrospective cohort study Association between meningococcal B vaccine coverage during 1988–1992 (63% of 13–15-year olds vaccinated) and national gonorrhea rates during 1993–2008	Individuals >16 years old Cohort of individuals, 63% born between 1973 and 1976 ($n = 93,611$)	Gonorrhea rates decreased among men (IRR, 0.68, 95%CI, 0.51–0.93) and women (IRR, 0.58, 95%CI, 0.42–0.8) aged 20–24 after vaccination campaign. No effect in other age groups.
Paynter et al.[30] (2017) New Zealand	Retrospective cohort study Efficacy of the New Zealand meningococcal B vaccine (81% of population aged 0–20 received vaccine in response to an epidemic) on gonorrhea hospitalization rates	Cohort of individuals born between 1984 and 1999 ($n = 935,496$)	Efficacy of the New Zealand meningococcal B vaccine vs hospitalization for gonorrhea was 24% (95%CI, 1–42%).
Petousis-Harris et al.[31] (2017) New Zealand	Retrospective case–control study in sexual health clinics Efficacy of the New Zealand meningococcal B vaccine vs gonorrhea	Young adults aged 15–30, born between 1984 and 1998 + diagnosed with gonorrhea or chlamydia, or both 14,730 cases and controls for the analyses	1241 gonorrhea cases, 12,487 chlamydia cases, and 1002 gonorrhea + chlamydia cases Fully vaccinated individuals were less likely to be cases than controls (511 [41%] vs 6424 [51%]; adjusted OR 0.69 [95%CI, 0.61–0.79]; $p < 0.0001$). New Zealand meningococcal B vaccine efficacy rate: 31% (95%CI, 21–39) (after adjusting for ethnicity, geographical area, and sex).
Longtin et al.[32] (2017) Canada	Retrospective cohort study Analyzed reported gonorrhea cases during pre- and post-vaccination periods with the 4CMenB vaccine In the Saguenay-Lac-Saint-Jean region of Quebec province (Canada), a large-scale vaccination campaign for individuals aged 6 months to 20 years was launched from May through December 2014. The overall vaccination coverage rate was 82% in the target group.	Individuals aged 6 months to 20 years in 2014. Cases reported to public health during the pre-vaccination period (January 2006 through June 2014) and post-vaccination (July 2014 through June 2017). Two age groups were analyzed: 14–20 years and ≥21 years.	Gonorrhea cases in individuals aged 14–20 decreased by 59% in the post-vaccination period, while cases in those ≥21 years increased. No statistically significant differences were reported (95%CI, ≥22% to 84%; $p = 0.1$) due to the small number of cases.
Azze[33] (2020) Cuba	Retrospective cohort study Collected serum, saliva, and oropharyngeal samples from high school students who had been previously vaccinated with VA-MENGOC-BC during their childhood. They were revaccinated with a 3rd dose during the study.	Individuals aged 3 months to 24 years from 1989 through 1993. Gonorrhea incidence rates were evaluated with respect to VA-MENGOC-BC vaccination: pre-vaccination (before 1989) and post-vaccination periods.	Epidemiological data showed a rapid decrease in gonorrhea incidence after a mass vaccination campaign (1988–1990) compared to other STIs. Incidence rates in unvaccinated age groups also decreased, likely due to herd immunity. Gonorrhea incidence decreased parallel to meningococcal disease from 1989 through 1993 (381.9 and 190.3 gonorrhea cases × 100,000 inhabitants, respectively) ($r = 0.9607$, $p = 0.001$). It then showed an upward trend again until 1995 (411.7 × 100,000), before decreasing again ($r = 0.9501$, $p = 0.008$).

Table 2 (*Continued*)

Study/year/location	Design/objectives	Population	Results
Wang et al.[34] (2022) Australia	Case–control study among patients adhering to the 4CMenB vaccination program initiated in 2018. Chlamydia controls were used to estimate VE in the primary analysis to control for potential confounding effects, such as high-risk sexual behavior associated with STIs. Vaccine impact was estimated using incidence ratios comparing the number of cases in each year after the start of the vaccination program vs cases in an equivalent age cohort during the years prior to vaccination.	Individuals adhering to the program: infants up to 12 months of age (3-dose 4CMenB schedule) and 10th-grade students (approximately 15 years of age receive two doses of 4CMenB).	Three years after the implementation of the infant vaccination program, the estimated efficacy of the 2-dose vaccine in adolescents was 33.2% (95%CI, 15.9–47.0%) for gonorrhea. Lower VE estimates were demonstrated after 36 months post-vaccination (23.2% [95%CI, 0–47.5%] >36 months post-vaccination vs 34.9% [95%CI, 15.0–50.1%] within 6–36 months). Higher VE estimates were found after excluding patients with repeated gonorrhea infections (37.3%, 95%CI, 19.8–51.0%). For gonorrhea cases coinfected with chlamydia, VE remained (44.7% [95%CI, 17.1–63.1%]).
Abara et al.[35] (2022) USA (New York City and Philadelphia)	Retrospective case–control study. Analyzed gonorrhea and chlamydia cases along with 4CMenB immunization records (full vaccination with 2 doses, partial vaccination with 1 dose, or no vaccination). Identified gonorrhea and chlamydia infections in individuals aged 16–23.	Young adults aged 16–23 with gonorrhea infection from January 1st, 2016 through December 31st, 2018. 18,099 gonorrhea infections. 12,4876 chlamydia infections. 24,731 gonorrhea and chlamydia co-infections in 109,737 individuals (7692 vaccinated, 4032 had received at least one dose, 3596 at least two doses, and 64 three doses).	Compared to no vaccination, full vaccination (APR, 0.60, 95%CI, 0.47–0.77; $p < 0.0001$) and partial vaccination (0.74, 0.63–0.88; $p = 0.0012$) protected vs gonorrhea. Full vaccination had an efficacy rate of 40% (95%CI, 23–53) and partial vaccination, 26% (12–37). MenB-4C did not protect vs gonorrhea and chlamydia co-infection in this study.
Bruxvoort et al.[36] (2022) USA (California)	Matched cohort study from 2016 through 2020 to examine the association of recombinant serogroup B meningococcal vaccine (4CMenB) containing OMV with gonorrhea infection among adolescents and young adults at Kaiser Permanente Southern California. 4CMenB recipients were matched 1:4 with recipients of the A, C, W, and Y serotype-targeted polysaccharide conjugate vaccine (MenACWY) who had not received 4CMenB and were followed for incident gonorrhea.	The association of gonorrhea and chlamydia infection was examined among 6641 4CMenB recipients and 26,471 MenACWY recipients, in adolescents and young adults.	During follow-up, gonorrhea incidence rates per 1,000 person-years (95%CI) were 2.0 (1.3–2.8) for 4CMenB recipients and 5.2 (4.6–5.8) for MenACWY recipients. In adjusted analyses, gonorrhea rates were 46% lower among those who received 4CMenB vs MenACWY (HR, 0.54; 95%CI, 0.34–0.86), but chlamydia rates were similar across the different vaccine groups (HR, 0.98; 95%CI, 0.82–1.17).

Table 2 (*Continued*)

Study/year/location	Design/objectives	Population	Results
Robinson et al.[37] (2023) Portland (Oregon) (USA)	Matched cohort study to examine the association of recombinant serogroup B meningococcal vaccine (4CMenB) containing OMV with gonorrhea infection among students, staff, and some medical personnel at the University of Oregon and Oregon State University. Evaluated whether receiving OMV-based vaccine was associated with lower gonorrhea prevalence than receiving non-OMV-based vaccine. Gonorrhea cases were determined from 1 month to 2 years post-vaccination (2015) until the end of the study (March 31st, 2018).	University students aged 18–29 (♀ and ♂). 15,760 recipients of >1 doses of OMV-based vaccines vs 15,212 recipients of >1 doses of non-OMV-based vaccines.	24 gonorrhea cases among OMV-based vaccine recipients vs 44 cases among non-OMV-based vaccine recipients. The OMV-based vaccine had an efficacy rate of 47% (95%CI, 13–68%) in preventing gonorrhea among recipients aged 18–29.
Raccagni et al.,[41] (2023) Italy	An unmatched case–control study evaluated the effectiveness of the 4CMenB vaccine (from 2016 to 2021) vs gonorrhea in MSM PLHIV who had a previous diagnosis of STIs.	Cases: MSM PLHIV who had experienced at least 1 episode of gonorrhea. Controls: MSM PLHIV with at least infection of syphilis, chlamydia, or anal human papillomavirus (HPV). In total, 1051 MSM PLHIV were included (103 cases and 948 controls). Of these, 349 (33%) received two doses of the 4CMenB vaccine. The median follow-up period for the study was 3.8 years (2.1–4.3 years).	The unadjusted VE vs gonorrhea was estimated at 42% (95%CI, 6–64%; $p = 0.027$). Logistic regression further showed that the VE vs gonorrhea remained significant at 44% (95%CI, 9–65%; $p = 0.020$) after adjusting for various factors.
Molina et al.[11] (2024) France	Open-label RCT Patients randomized 2:1 (Doxy-PEP intervention vs no prophylaxis) and 1:1 (two doses 4CMenB vaccine intervention vs no intervention).	544 MSM + PrEP + previous STI in the last year + unprotected sex.	225 infected subjects. 122 in the no-vaccine arm (incidence 77.1/100 person-years) vs 103 in the 4CMenB vaccine arm (incidence 58.3/100 person-years). Interim analysis showed no statistically significant differences in cumulative gonorrhea incidence rates, aHR, 0.78 (95%CI, 0.80–1.01, $p = 0.061$).

4CMenB: 4-component meningococcal serogroup B vaccine; aHR: adjusted hazard ratio; APR: adjusted prevalence ratios; RCT: randomized clinical trial; VE: vaccine efficacy/effectiveness; MSM: men who have sex with men; IRR: incidence rate ratios; PLHIV: people living with HIV; HIV: human immunodeficiency virus.

Conclusions

Although evidence continues to grow, long-term consequences of prophylactic doxycycline and 4CMenB vaccination for *N. gonorrhoeae* prevention remain uncertain. In Spain, both measures are off-label.

Leading institutions suggest that Doxy-PEP prescription should be considered on an individualized basis for MSM or

transgender women who've experienced repeated venereal infections in the last year. This decision needs to be supported by appropriate monitoring and research activities. It's also recommended to monitor the impact of antibiotic prophylaxis regarding the emergence of antimicrobial resistance, potential changes in the microbiome, and possible shifts in the epidemiological dynamics of STIs.

On the other hand, current evidence indicates that vaccinating at-risk populations with the 4CMenB vaccine could significantly impact gonorrhea incidence in these groups, even if protection is only partial. However, we still need more information on the vaccine potential differential impact on asymptomatic vs symptomatic infection, as well as on its effectiveness at various infection sites.

Given these points, we believe that the suitability of using both measures should be individually assessed for selected users at high risk of acquiring venereal infections, such as some PrEP users.

Conflicts of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.ad.2025.06.014.

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