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Ph.D. értekezések

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SZONDY ISTVÁN

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című program

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NEW FRONTIERS IN THE PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS

Ph.D. Thesis

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“It is the nature of man to rise to greatness if greatness is expected of him.”

John Steinbeck

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1. LIST OF ABBREVIATIONS

AE	Adverse event
AMR	Antimicrobial resistance
CDC	Centers for Disease Control and Prevention
CENTRAL	Cochrane Central Register of Controlled Trials
CGW	Cisgender women
CI	Confidence interval
Doxy-PEP	Doxycycline post-exposure prophylaxis
Doxy-PrEP	Doxycycline pre-exposure prophylaxis
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HIV-PrEP	HIV Pre-exposure prophylaxis
IUSTI	International Union Against Sexually Transmitted Infections
LGBTQ	Lesbian, gay, bisexual, transgender, or queer/questioning
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
OLE	Open-label extension
OMV	Outer membrane vesicle
OR	Odds ratio
PLWH	People living with HIV
PICO	Population-Intervention-Comparator-Outcome
RCT	Randomised Controlled Trial
RoB 2	Risk of Bias 2

ROBINS-I	Risk Of Bias In Non-randomised Studies - of Interventions
RR	Risk ratio
STD	Sexually transmitted disease
STI	Sexually transmitted infection
TCN	Tetracycline
TGW	Transgender women
VE	Vaccine effectiveness
WHO	World Health Organization

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is a healthcare approach centred around proactive care to prevent sexually transmitted infections (STIs) and reduce associated complications. To realise this vision, my mission is to integrate evidence-based preventive strategies into routine clinical practice. My specific goals are to investigate the efficacy and safety of doxycycline in preventing STIs and to evaluate the potential role of meningococcal vaccines in the prevention of gonorrhoea.

2.2. Scientometrics

Number of all publications:	3
Cumulative IF:	12
Av IF/publication:	4
Ranking (SCImago):	D1: 2, Q1: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.8
Av IF/publication:	3.9
Ranking (Sci Mago):	D1: 1, Q1: 1
Number of citations on Google Scholar:	13
Number of citations on MTMT (independent):	8
H-index:	1

The detailed bibliography of the student can be found on page 63.

2.3. Future plans

My future plans include pursuing a career in dermatology alongside an active role in scientific research, with a focus on both translational and clinical investigations. I intend to first apply our research findings in clinical research settings and ultimately integrate them into clinical practice, with the goal of improving care for high-risk populations and contributing to the reduction of STI incidence in Hungary. In addition, I plan to conduct a separate systematic review and meta-analysis to investigate the prevalence of syphilis among sex workers, with the aim of identifying additional high-risk populations that could benefit from the interventions detailed in this thesis.

3. SUMMARY OF THE THESIS

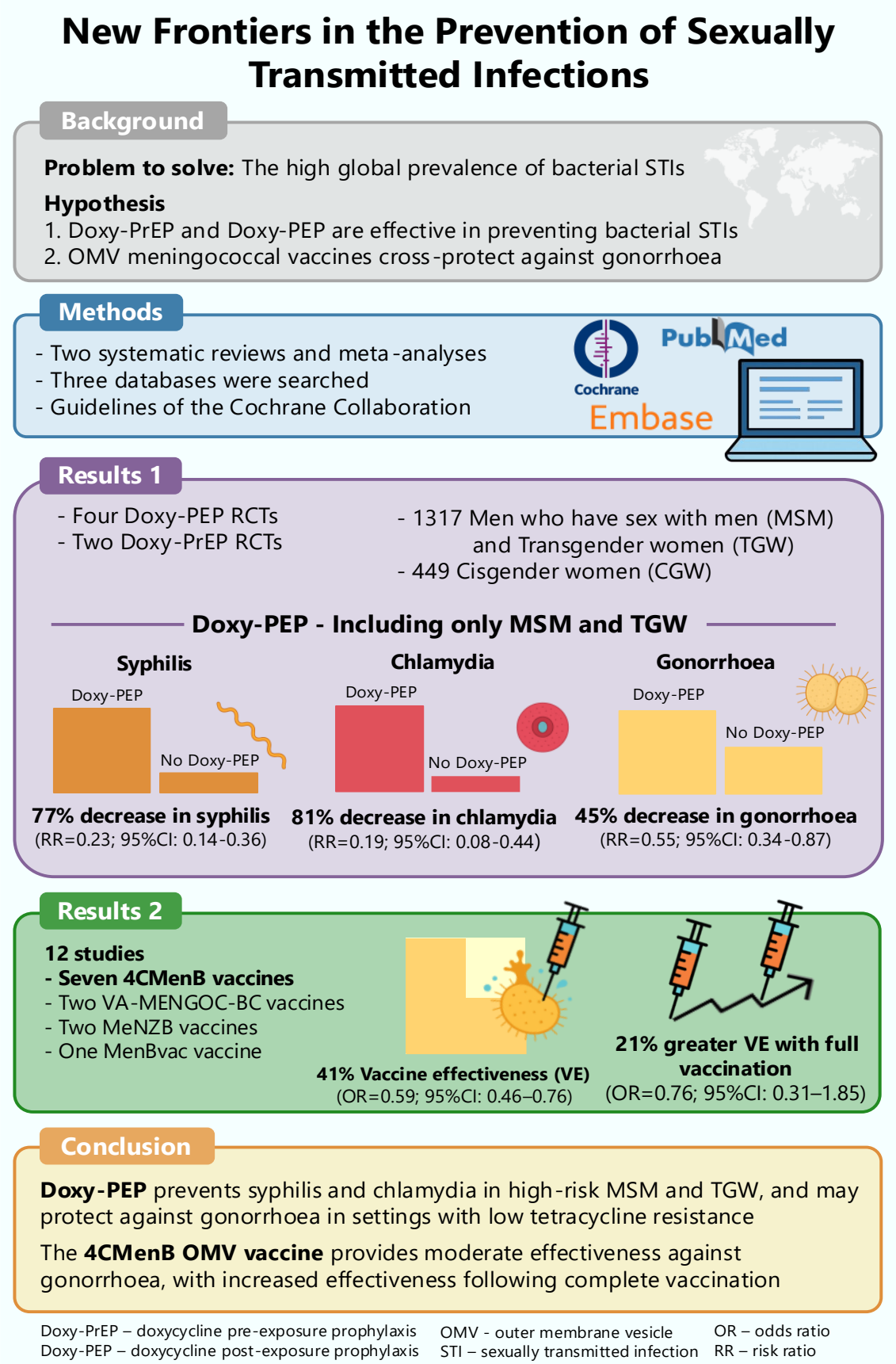
STIs represent a global health challenge, with rising rates of bacterial infections and subsequent complications such as neurosyphilis, which can lead to severe and irreversible neurological impairment. High-risk populations, including men who have sex with men (MSM) and transgender women (TGW), are disproportionately affected by this resurgence, offering a focus for targeted interventions. In response, doxycycline pre- and post-exposure prophylaxis (doxy-PrEP and doxy-PEP) have emerged as promising candidates for STI prevention, showing potential in reducing the incidence of syphilis and chlamydia. However, their effectiveness against gonorrhoea may be limited due to the widespread prevalence of tetracycline-resistant (TCN-resistant) *Neisseria gonorrhoeae*. In parallel, outer membrane vesicle (OMV) meningococcal vaccines, including the most widely available 4CMenB vaccine, have been proposed as an additional preventive approach, with evidence suggesting possible cross-protection against gonorrhoea.

Our research question was whether doxy-PrEP, doxy-PEP, and OMV meningococcal vaccines are effective in preventing bacterial STIs. To address this, we conducted two systematic reviews and meta-analyses, adhering to the methodological guidelines of the Cochrane Collaboration.

Our results showed that doxy-PEP is an effective and safe tool for preventing syphilis and chlamydia infections among high-risk MSM and TGW populations, while its effectiveness against gonorrhoea appears to depend on local antimicrobial resistance (AMR) patterns. Although the emergence of new AMR due to broader antibiotic use is a concern, current evidence on this issue remains limited and must be weighed against the substantial effectiveness and associated public health benefits of doxy-PEP. Not enough current evidence supports the use of doxy-PrEP. OMV meningococcal vaccines showed moderate effectiveness against gonorrhoea, with improved protection after full vaccination. They may complement doxy-PEP, particularly in settings where TCN-resistant *N. gonorrhoeae* is prevalent.

Implementing doxy-PEP among high-risk MSM and TGW populations, alongside targeted vaccination programs, could substantially reduce the individual risk of bacterial STIs and contribute to lowering incidence rates at the population level.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

STIs constitute a significant global public health burden, with far-reaching personal, social, and economic consequences. STIs may present with acute symptoms or remain asymptomatic, yet still progress to chronic health conditions, including serious reproductive complications. Beyond their physical symptoms, STIs can cause significant psychological distress by exposing individuals to stigma and discrimination, ultimately diminishing their quality of life (1).

The consistently high prevalence of STIs has highlighted the need for effective new preventive measures. Among the earliest proactive strategies was the introduction of HIV pre-exposure prophylaxis (HIV-PrEP), which has proven highly effective in reducing the risk of HIV acquisition (2). However, its widespread uptake has been accompanied by a rise in condomless anal sex among MSM, contributing to the already elevated rates of bacterial STIs in this population (3). This trend has created an urgent need for additional tools to combat other STIs, and also provided a model upon which similar preventive strategies could be developed for bacterial infections.

Consequently, two doxycycline-based strategies have been developed for the prevention of bacterial STIs, particularly targeting *Treponema pallidum* and *Chlamydia trachomatis*, both of which remain consistently susceptible to doxycycline. These strategies include doxy-PrEP and doxy-PEP. Doxy-PrEP involves the daily intake of 100 mg doxycycline by individuals at high risk, whereas doxy-PEP consists of a single 200 mg dose taken within 0 to 72 hours following condomless sexual intercourse, to prevent bacterial STIs.

However, as the effectiveness of doxycycline is primarily tied to the susceptibility of the pathogens, doxy-PrEP/PEP is not expected to be that effective against gonorrhoea, given the widespread TCN resistance exhibited by *N. gonorrhoeae* (4). Despite substantial efforts, creating an effective gonorrhoea vaccine has proven challenging, primarily due to the bacterium's pronounced antigenic variability, the lack of durable immunity following natural infection, and its complex immune evasion mechanisms (5).

Intriguingly, several vaccines already exist against *Neisseria meningitidis*, a close genetic relative of *N. gonorrhoeae*. The two species share 80-90% DNA primary sequence homology, with most virulence factors and antigens in one species having an equivalent in the other (6). This high degree of genetic and structural similarity is particularly relevant in the context of OMV vaccines developed for *N. meningitidis serogroup B*. The OMV components in these vaccines closely resemble those found in *N. gonorrhoeae*, which has led to the hypothesis that they may offer cross-protection against gonorrhoea (7).

5.1.2. What is the problem to solve?

In 2020, the World Health Organization (WHO) estimated 129 million cases of chlamydia, 82 million cases of gonorrhoea, and 7.1 million cases of syphilis infections globally (8). Presuming that neurological, ocular, and otic complications occur in 3%-5% of syphilis cases, this corresponds to approximately 213,000 to 355,000 cases of symptomatic neurosyphilis, ocular syphilis, and otosyphilis worldwide (9). The burden of STIs disproportionately affects MSM and TGW, who have been experiencing a concerning surge in bacterial STI incidence in recent years. Tsuboi et al. reported a fifteen-fold higher prevalence of syphilis among MSM compared to men in the general population (10). Additionally, a meta-analysis covering the period from 2000 to 2022 estimated that gonorrhoea rates were nearly ten times higher, and chlamydia rates approximately four times higher, among MSM compared to the general population (11).

5.1.3. What is the importance of the topic?

Developing effective preventive strategies for bacterial STIs is critical to reducing their health burden and could also help avert new cases of early neurosyphilis, ocular syphilis, and otosyphilis, thereby preventing severe and irreversible complications. Doxy-PrEP/PEP complemented with a vaccine effective against gonorrhoea may help address this need, covering a wide range of curable bacterial STIs.

Furthermore, while concerns and debates still persist regarding these methods, particularly due to fears about the development of new antibiotic resistance, doxy-PEP has gained significant media attention as evidence of its effectiveness continues to grow. Surveys indicate that doxycycline is already being used informally for STI prevention, often without medical supervision, and its use is becoming increasingly common within

the lesbian, gay, bisexual, transgender, or queer/questioning (LGBTQ) community (12, 13). This growing interest highlights the need for healthcare professionals to play an active role in guiding its use, as medical oversight is essential to ensure that doxy-PEP is implemented safely, with proper monitoring and clear clinical guidance, to minimise risks and maximise benefits.

5.1.4. What would be the impact of our research results?

Should our research confirm the effectiveness of doxy-PrEP, doxy-PEP and OMV meningococcal vaccines in reducing the incidence of bacterial STIs, the findings could have substantial public health implications. High-quality evidence supporting these interventions may inform international and national clinical guidelines, refine STI prevention strategies targeting high-risk populations, and ultimately contribute to a reduction in bacterial STI incidence at both individual and population levels.

5.2. Overview of relevant infections and preventive strategies

5.2.1. Syphilis

Treponema pallidum subspecies pallidum is a motile, spiral-shaped Gram-negative bacterium that is responsible for syphilis, a sexually transmitted disease (STD) with distinct clinical stages: primary, secondary, latent, and tertiary. The bacterium enters through mucosal surfaces or abraded skin and disseminates via the bloodstream. Primary syphilis typically presents with a painless chancre, followed by secondary syphilis, which is characterised by systemic manifestations such as rash and lymphadenopathy. One of the most serious complications is neurosyphilis, which can develop at any stage of the disease. While late-stage manifestations have become rare, early neurosyphilis continues to be reported and is not uncommon. Neuroinvasion occurs in up to 30% of early syphilis cases, though symptomatic neurosyphilis affects only 3-5% (9). Early forms may present as acute basilar meningitis with cranial nerve deficits or stroke. Ocular and otic syphilis, which should be treated by the same protocol as neurosyphilis, can occur at any stage and may present with eye pain, photophobia, or vision loss in the case of ocular involvement, and with tinnitus, hearing loss, or balance disturbances in otic involvement (14). If syphilis is left untreated, the tertiary stage can develop years later, leading to severe cardiovascular, neurological, or gummatous manifestations. Vertical transmission may result in foetal loss or congenital syphilis in the neonate. Diagnosis relies on serologic

testing using both treponemal and non-treponemal assays. Benzathine penicillin G remains the first-line treatment, while doxycycline serves as an alternative, with no resistance reported to date (15).

5.2.2. Chlamydia

C. trachomatis is a Gram-negative, obligate intracellular bacterium and the most commonly reported bacterial STI globally. It infects epithelial cells of the urogenital tract, rectum, and conjunctiva, often leading to asymptomatic cases, especially in women. When symptomatic, it may cause urethritis, cervicitis, pelvic inflammatory disease (PID), and infertility. In men, it causes urethritis and may lead to prostatitis or epididymitis. Vertical transmission can result in neonatal conjunctivitis or pneumonia. Diagnosis is typically made using nucleic acid amplification tests (NAATs). *C. trachomatis* is susceptible to doxycycline and macrolides, with doxycycline considered the first-line therapy (16). Resistance to this agent remains largely unknown, with only a few documented cases reported to date (17).

5.2.3. Gonorrhoea

N. gonorrhoeae is a Gram-negative diplococcus that frequently co-occurs with *C. trachomatis* infection (18). It infects mucosal surfaces of the urogenital tract, cervix, rectum, pharynx, and conjunctiva. It often presents as acute urethritis in men and is frequently asymptomatic in women, increasing the risk of ascending infection. Left untreated, gonorrhoea in men may progress to prostatitis or epididymo-orchitis, while in women it can lead to PID and infertility. Diagnosis relies on NAATs and culture, particularly for antimicrobial susceptibility testing (19). *N. gonorrhoeae* has developed extensive resistance to multiple antibiotic classes, including penicillins, fluoroquinolones, and TCNs, mainly through plasmid-encoded β-lactamases, efflux pumps, and target site mutations. Global TCN resistance is estimated at approximately 45%, with considerable variation across countries, ranging from 14.3% to 93.7% in Europe (4, 20). Current treatment guidelines recommend either ceftriaxone monotherapy or dual therapy with ceftriaxone and doxycycline or azithromycin to address co-infections (21).

5.2.4. Doxycycline

Doxycycline is a bacteriostatic, broad-spectrum antibiotic from the TCN class that inhibits protein synthesis by binding to the 30S ribosomal subunit, thereby blocking

protein synthesis. It is highly lipophilic, allowing effective penetration of both Gram-positive and Gram-negative bacterial membranes. It is widely used for various infections, including STIs and acne vulgaris therapy. Resistance to doxycycline can develop through several mechanisms, primarily ribosomal protection proteins such as Tet(O) and Tet(M), which displace the drug from its ribosomal binding site, allowing protein synthesis to resume. Additional resistance mechanisms include efflux pumps, enzymatic inactivation, and mutations in the ribosomal RNA. Doxycycline is generally well tolerated, with side effects including nausea, photosensitivity, and gastrointestinal (GI) upset. It is contraindicated during pregnancy and in paediatric patients (22).

5.2.5. Meningococcal vaccine

Meningococcal vaccines are used to prevent invasive disease caused by *N. meningitidis*, a pathogen responsible for bacterial meningitis and septicaemia. Among its multiple serogroups, A, B, C, W, and Y are the most clinically relevant. Based on these serogroups, two main categories of meningococcal vaccines are available: conjugate vaccines targeting serogroups A, C, W, and Y, and serogroup B vaccines, which include protein-based formulations and OMV vaccines. A recently developed pentavalent vaccine, MenABCWY, combines recombinant protein components for serogroup B with conjugate components for serogroups A, C, W, and Y in a single formulation. Notably, it does not include an OMV component (23).

OMVs are nanoscale particles naturally released by Gram-negative bacteria and possess well-established immunostimulatory properties, making them an effective and widely used platform in vaccine development. OMV vaccines are licensed or being developed against a number of pathogens, including *Haemophilus influenzae* and *N. meningitidis*. Earlier OMV-based meningococcal vaccines included VA-MENGOC-BC, developed by the Finlay Institute in Cuba, and MenBvac, developed by the Norwegian Institute of Public Health. Subsequently, MeNZB was developed by Novartis in collaboration with the Norwegian Institute of Public Health to control a meningococcal outbreak in New Zealand. The OMV component from MeNZB was later adapted for the development of 4CMenB (Bexsero), which combines OMVs with recombinant proteins, including NHBA, fHbp, and NadA (24, 25). Furthermore, 4CMenB is currently the only OMV meningococcal vaccine in routine use, accessible in more than 50 countries (26).

6. OBJECTIVES

6.1. Study I. – Investigating the efficacy and safety of doxycycline in preventing sexually transmitted diseases: a systematic review and meta-analysis

Our main objective was to evaluate the effectiveness of doxy-PrEP and doxy-PEP in reducing the incidence of bacterial STIs, specifically syphilis, chlamydia, and gonorrhoea. In addition, we sought to assess patient adherence to prophylactic regimens and to examine how levels of compliance may influence overall effectiveness. We also aimed to investigate the safety profile of doxycycline prophylaxis with particular attention to the incidence and nature of adverse events (AEs). Finally, we aimed to evaluate the potential risk for the emergence of antibiotic resistance in both STI-related and unrelated pathogens as a consequence of widespread prophylactic antibiotic use.

6.2. Study II. – Investigating the effectiveness of meningococcal vaccines in the prevention of gonorrhoea: a systematic review and meta-analysis

The aim of the study was to assess the effectiveness of OMV meningococcal vaccines against gonorrhoea. This included evaluating the magnitude and consistency of protection, the duration of immunity, and the differential impact of partial versus complete vaccination.

7. METHODS

Both systematic reviews and meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines and the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.4) (27, 28). The protocols for both studies were registered in the PROSPERO database, with registration numbers CRD42023478486 for Study I and CRD42024530848 for Study II. No amendments were made to either protocol following registration.

7.1. Literature search

We conducted systematic searches in three major medical databases: PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL).

In Study I, the search was performed on November 7, 2023, and the following search terms were used: in PubMed, the search key was (doxy*) AND ("pre-exposure" OR "PrEP" OR "post-exposure" OR "PEP"). In Embase and CENTRAL, we used the same search keys: (doxy*) AND ("pre-exposure" OR PrEP OR "post-exposure" OR PEP).

In Study II, an initial systematic search was performed on 10 April 2024, and a second search was performed on 10 July 2024. The same search key was used in both searches across all databases: (gonorrh* OR gonoc*) AND vaccin*.

Advanced search was used in Embase and CENTRAL. No filters or restrictions were applied to the search results. In addition, backward and forward citation chasing was performed to identify relevant studies not captured in the systematic search.

7.2. Eligibility criteria

In Study I, randomised controlled trials (RCTs) and RCT conference abstracts were included if they met the following Population-Intervention-Comparator-Outcome (PICO) framework: (P) sexually active adults; (I) Doxy-PrEP or Doxy-PEP; (C) no prophylaxis; (O) primary outcomes: the incidence of bacterial STIs, specifically *N. gonorrhoeae*, *T. pallidum*, and *C. trachomatis*. Secondary outcomes: AEs, emergence of new AMR, and adherence to prophylaxis. Where accessible, webcasts of conference presentations were also reviewed to supplement the data from abstracts.

In Study II, studies were eligible for inclusion if they matched the following PICO framework: (P) individuals eligible for meningococcal vaccine, (I) OMV meningococcal

vaccine, (C) no OMV vaccine (no vaccine or non-OMV vaccine), (O) incidence of gonococcal infection. Grey literature was excluded.

7.3. Study selection and data extraction

After conducting the systematic searches, all identified records were imported into a reference management software (EndNote 21, Clarivate Analytics, Philadelphia, PA, USA) (29). Duplicate entries were eliminated first automatically, then manually by comparing publication years, author names, and article titles. Two reviewers independently screened the articles, first by examining the titles and abstracts, and then by reviewing the full texts using Rayyan (Rayyan Systems, Cambridge, MA, USA) (30). Any disagreements were resolved by consulting a third reviewer.

For data extraction and synthesis, a standardised Excel form was used, which was developed based on the consensus of methodological and clinical experts. Two reviewers independently extracted key information from the included studies. In Study I, key information included the article title, first author, publication year, localisation, study settings, patient demographics, interventions, findings and reported outcomes. These outcomes included overall and specific STI incidence, AEs, AMR, and prophylaxis adherence. In Study II, data were collected, such as the study title, first author, year of publication, localisation, study settings, participant characteristics, key findings, duration of follow-up, and reported gonorrhoea incidence. Discrepancies were resolved by a third reviewer.

7.4. Risk of bias and quality assessment

The risk of bias in the included studies was evaluated using the Risk of Bias 2 (RoB 2) tool (31) for Study I, and for the sole RCT in Study II. For non-RCTs in Study II, the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool was used (31, 32). Two independent reviewers conducted the assessments, with any discrepancies resolved through consultation with a third independent reviewer. Potential publication bias was examined through visual inspection of funnel plots. The overall quality of evidence for each outcome was assessed using the GRADEpro, as recommended by the Cochrane Collaboration (33).

7.5. Data synthesis and analysis

All statistical analyses were conducted using R statistical software (version 4.1.2.). Base R functions were utilised alongside the meta package for standard meta-analytic computations and visualisations, and the dmetar package was employed for additional analyses, including influence diagnostics. A minimum of three studies was required to perform a meta-analysis. Due to the anticipated heterogeneity across studies, a random-effects model was applied in all cases to pool effect sizes.

In Study I, for dichotomous outcomes, risk ratios (RR) with corresponding 95% confidence intervals (CI) were calculated. These were based on the number of study visits in each group and the number of STI events observed during those visits in both the intervention and control arms. When data on the number of visits were not explicitly reported, the total number of visits was estimated based on the reported visit frequency and the duration of follow-up. The number of visits associated with an STI event was calculated by summing the reported cases of chlamydia, syphilis, and gonorrhoea. In instances where only the first occurrence of STIs was reported and participants were censored at first diagnosis, the number of participants was used instead of the number of visits for subsequent analyses. This substitution ensured consistency between the numerator (first infections) and the denominator (individuals at risk), as visit-based denominators are inappropriate when each participant contributes only one event. The detailed calculations for STI events and total visits can be found in the *Supplementary Material* of the original publication (34).

In Study II, for dichotomous outcomes, odds ratios (OR) with 95% CIs were used as the effect size measure. Vaccine effectiveness (VE) was calculated from the OR using the formula $(1 - \mathrm{OR}) \times 100\%$. In studies reporting raw data, ORs were derived from the number of gonorrhoea events and the total number of individuals in the intervention and control groups. Where raw data were not available, the reported ORs or VEs with corresponding CIs were used.

In both Study I and Study II, the pooled RRs and ORs were calculated using the Mantel-Haenszel approach (35, 36). To address studies with zero events in one or more cells, the exact Mantel-Haenszel method was applied without continuity correction. Between-study variance (τ^2) was estimated using the Paule-Mandel estimator (37). Statistical significance

was determined by examining whether the 95% CI excluded the null value. The results were presented in forest plots, and prediction intervals were reported to reflect the expected range of effect sizes in future studies. Heterogeneity across studies was quantified using the I^2 statistic proposed by Higgins and Thompson (38).

To further address heterogeneity, additional analyses were conducted. In Study I, subgroup analyses were performed based on the use of doxy-PrEP or doxy-PEP and sex assigned at birth. Additional sensitivity analyses using a leave-one-out approach were performed to assess the robustness of the results and to determine whether the exclusion of any individual study affected the statistical significance of doxy-PrEP or doxy-PEP. In Study II, further analyses included comparisons between full and partial vaccination and stratification by risk of bias. An additional leave-one-out analysis was also performed.

8. RESULTS

8.1. Study I

8.1.1. Study selection

The systematic search yielded 552 records. Following the selection process, six peer-reviewed articles and four conference abstracts were included, collectively representing six distinct RCTs (*Fig. 1*) (39-48). Webcasts were available for all four conference abstracts (41, 45, 46, 48). One of the included abstracts was published as a full-length article after the selection process; this publication was also incorporated into the final analysis (49).

8.1.2. Study characteristics

Five studies enrolled MSM or TGW, and one study included cisgender women (CGW). In the DOXYPEP study, two distinct cohorts were enrolled: one comprising people living with HIV (PLWH) and the other consisting of individuals receiving HIV-PrEP (42). As there was no overlap between the cohorts, each was treated as an independent study in our analysis. The characteristics of the included studies are summarised in *Table 1*.

8.1.3. Risk of bias assessment, certainty of evidence

For the primary outcome, four included studies were assessed as having a low risk of bias (40, 42, 46, 49), one had a moderate risk due to concerns regarding the randomisation process (47), and one was judged to have a high risk of bias owing to missing outcome data (48). Most studies were rated as having a moderate or high risk of bias for secondary outcomes. No evidence of publication bias was observed based on visual inspection of the funnel plots. The detailed results of the risk of bias assessments are presented in *Figures S11-S15* and *Tables S5-S8* of the original publication (34).

The overall certainty of evidence for the primary outcome was rated as low in studies evaluating doxy-PEP and very low in those evaluating doxy-PrEP. When restricting the analysis to doxy-PEP studies conducted among MSM and TGW, the certainty of evidence was rated as high. For secondary outcomes, the certainty of evidence was graded as low for AEs and very low for AMR and adherence. A detailed summary of the quality assessments is provided in the summary of findings table in the original publication (34).

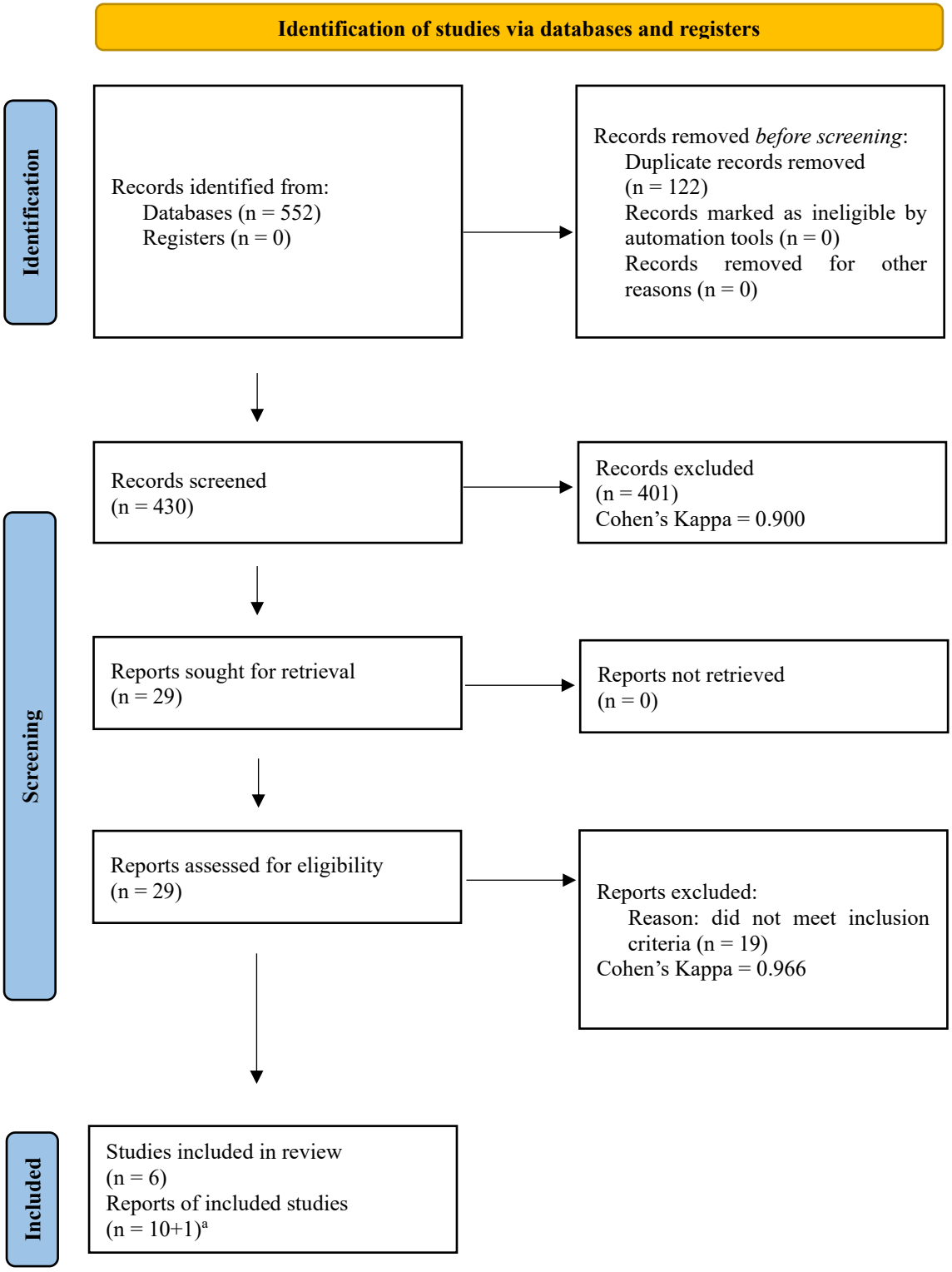


Figure 1. PRISMA flow diagram of the screening and selection process according to PRISMA 2020 guidelines.
a One report on an included study was published after the selection process. This figure is based on the figure by Szondy et al. (2024) (34).

Table 1. Characteristics of the included studies

Study name (First Author, Year of Publication)	Country	Publication Type	Study Design	Study population	Intervention	Control	Reported outcomes	Visit schedule, Follow-up time
IPERGAY (Molina, 2018) (39, 40)	France	Original article	RCT 1:1 ratio open-label	232 MSM and TGW on HIV-PrEP	Doxy-PEP	no prophylaxis	Occurrence of a first STI (syphilis, chlamydial, or gonorrhoeal infection after the enrolment visit), occurrence of all episodes of STIs, adherence (self-reported, plasma samples, pill count of returned medicine), TCN resistance (*N. gonorrhoea, C. trachomatis, Mycoplasma genitalium*[e]), adverse events	Participants were tested for STIs every two months over a follow-up period of 10 months.
DoxyPEP (Luetkemeyer, 2023) (41, 42)	USA	Original article	RCT 2:1 ratio open-label	PLWH Cohort 174 MSM and TGW living with HIV infection HIV-PrEP Cohort 327 MSM and TGW on HIV-PrEP	Doxy-PEP	no prophylaxis[c]	Incidence of at least one bacterial STI (gonorrhoea, chlamydia, or syphilis), adherence (self-reported), TCN resistance (*N. gonorrhoeae*, commensal *Neisseria spp. S. aureus),* adverse events	Participants were tested for STIs every three months over a follow-up period of 12 months, with additional interim visits as needed. Participants could contribute data on up to one incident infection per quarter.
dPEP Kenya (Stewart, 2023) (43-45, 49)	Kenya	Original article	RCT 1:1 ratio open-label	449 non-pregnant cisgender women on HIV-PrEP	Doxy-PEP	no prophylaxis[c]	Incidence of chlamydial and gonorrhoea infection, adherence (self-reported, hair samples), TCN resistance (*N. gonorrhoeae, C. trachomatis*), adverse events	Participants were tested for STIs every three months over a follow-up period of 12 months. Participants could contribute data on up to one incident infection per quarter.

DOXYVAC (Molina, 2023)[a] (46)	France	Conference abstract	RCT 2:1 ratio open-label	502 MSM on HIV-PrEP	Doxy-PEP and meningococcal B (4CMenB) vaccine[b]	no prophylaxis and no vaccine	Occurrence of first syphilis, chlamydia, gonorrhoea and mycoplasma infection, adherence (self-reported), TCN resistance (*N. gonorrhoea, C. trachomatis*), adverse events	Participants were tested for STIs every three months over a follow-up period of 12 months. Participant follow-up was right-censored at the time of the first STI.
DPMSM (Bolan, 2015) (47)	USA	Original article	RCT 1:1 ratio open-label	30 MSM and TGW living with HIV infection	Doxy-PrEP	incentive-based financial contingency management[d]	Contraction of syphilis, gonorrhoea and chlamydia, adherence (plasma samples), adverse events	Participants were tested for STIs every three months over a follow-up period of 48 weeks[f]
DuDHS (Grennan, 2021)[a] (48)	Canada	Conference abstract	RCT 1:1 ratio open-label	52 MSM and TGW on HIV-PrEP	Doxy-PrEP	no prophylaxis	Any incident chlamydia infection, gonorrhoea, or syphilis, adherence (self-reported), TCN resistance (*S. aureus)*	Participants were tested for STIs every three months over a follow-up period of 48 weeks[g]

This table is based on the table by Szondy et al. (2024) (34).
a Interim data
b Patients were randomised to receive doxy-PEP or no prophylaxis, then randomised to receive meningococcal vaccine or no vaccine, and there were no interactions between the interventions
c Reported as "standard care", defined as regular STI testing and treatment
d All participants were compensated $25 per visit. Participants in the control arm received an additional $50, $75, and $100 if they tested STD-free at weeks 12, 24, and 36, respectively
e Axillary study of the IPERGAY study
f Only STIs acquired up to 36 weeks were included, as after 36 weeks, none of the arms received doxy-PrEP
g Only STIs acquired up to 24 weeks were included, as after 24 weeks, both arms received doxy-PrEP
Doxy-PEP: doxycycline post-exposure prophylaxis; doxy-PrEP: doxycycline pre-exposure prophylaxis; MSM: men who have sex with men; TGW: transgender women; HIV-PrEP: HIV-Pre-Exposure-Prophylaxis; PLWH: persons living with HIV infection; TCN: tetracycline STI: sexually

8.1.4. Effectiveness

A total of six studies were included in our meta-analysis, comprising 1,766 participants and 602 incident STIs recorded across 4,612 visits. Four studies examined doxy-PEP, and two investigated doxy-PrEP. We assessed overall STI incidence and conducted separate analyses for chlamydia, syphilis, and gonorrhoea. One study was not sufficiently powered to assess syphilis independently (45, 49). We pooled data from both doxy-PEP and doxy-PrEP studies and performed separate analyses for doxy-PEP and doxy-PrEP among MSM and TGW. Due to the limited number of studies, a meta-analysis of doxy-PrEP alone was not feasible.

When pooling data from doxy-PrEP and doxy-PEP studies, at least one STI was diagnosed in 251 of 2,627 visits (9.55%) in the doxy-PrEP/PEP groups, compared to 351 of 1,985 visits (17.7%) in the control groups (RR = 0.44; 95% CI: 0.30-0.65; I^2 = 73%) (*Fig. 2a*). For chlamydia, 69 infections were diagnosed across 2,627 visits (2.63%) in the doxy-PrEP/PEP groups, versus 160 infections in 1,985 visits (8.06%) in the control groups (RR = 0.24; 95% CI: 0.12-0.51; I^2 = 78%) (*Fig. 2b*). Syphilis was identified in 17 of 1,773 visits (0.96%) in the doxy-PrEP/PEP groups and in 45 of 1,099 visits (4.09%) in the control groups (RR = 0.24; 95% CI: 0.18-0.32; I^2 = 0%) (*Fig. 2c*). Gonorrhoea was diagnosed in 175 of 2,627 visits (6.66%) in the doxy-PrEP/PEP groups, compared to 169 of 1,985 visits (8.51%) in the control groups (RR = 0.65; 95% CI: 0.41-1.04; I^2 = 59%) (*Fig. 2d*).

When the analysis was restricted to doxy-PEP studies, at least one STI was identified in 242 of 2,534 visits (9.55%) in the doxy-PEP groups, compared to 320 of 1,895 visits (16.9%) in the control groups (RR = 0.47; 95% CI: 0.29-0.77; I^2 = 80%) (*Fig. 2a*). For chlamydia, 68 infections were reported in 2,534 visits (2.68%) in the doxy-PEP groups, while 145 infections were recorded in 1,895 visits (7.65%) in the control groups (RR = 0.26; 95% CI: 0.10-0.68; I^2 = 84%) (*Fig. 2b*). Considering only the doxy-PEP studies, syphilis was diagnosed in 15 of 1,680 visits (0.89%) in the doxy-PEP groups and in 38 of 1,009 visits (3.77%) in the control groups (RR = 0.23; 95% CI: 0.14-0.36; I^2 = 0%) (*Fig. 2c*). Gonorrhoea was found in 169 of 2,534 visits (6.67%) in the doxy-PEP groups, compared to 160 of 1,895 visits (8.44%) in the control groups (RR = 0.66; 95% CI: 0.34-1.26; I^2 = 71%) (*Fig. 2d*).

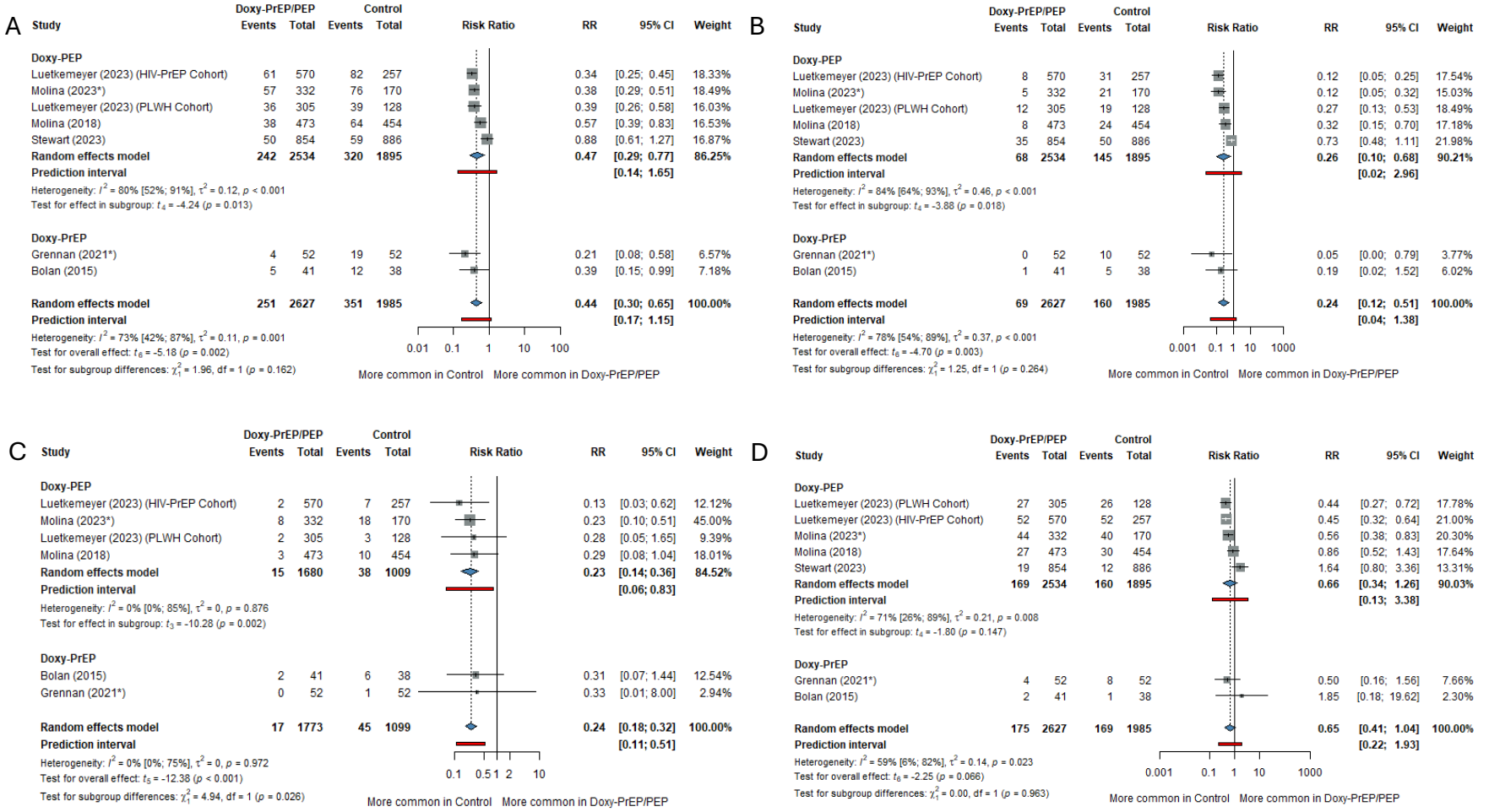


Figure 2. Forest plots for STI incidence; doxy-PrEP/PEP vs no prophylaxis, subgrouping by type of doxy-prophylaxis; (a) incidence of any STI (b) incidence of chlamydia (c) incidence of syphilis (d) incidence of gonorrhoea. Forest plots showing the total number of visits, and the number of visits with an STI in the doxy-PrEP/PEP and in the control groups. *Interim data. This figure is based on the figure by Szondy et al. (2024) (34).

When the analysis was further restricted to doxy-PEP studies involving only MSM and TGW, the pooled RR for overall STI acquisition was 0.40 (95% CI: 0.28-0.57; I^2 = 37%) (*Fig. 3a*). For chlamydia and syphilis, the pooled RRs were 0.19 (95% CI: 0.08-0.44; I^2 = 39%) and 0.23 (95% CI: 0.14.0.36; I^2 = 0%), respectively (*Figs. 3b and 3c*). The pooled RR for gonorrhoea acquisition was 0.55 (95% CI: 0.34-0.87; I^2 = 41%) (*Fig. 3d*).

The results for the leave-one-out analyses can be found in the *Supplementary Material* of the original publication (34).

8.1.5. Adverse events

Five studies, including a total of 1,026 participants in the doxycycline arm, reported on AEs (40, 42, 45-47, 49). GI side effects were the most commonly reported drug-related AEs. In the IPERGAY study, 29 GI AEs (25.0%) were attributed to doxycycline use, while only one drug-related GI AE was reported in the DPMSM study (40, 47). In the DoxyPEP, DOXYVAC, and dPEP Kenya studies, the number of drug-related AEs was 75 (8.00%), 19 (5.70%), and 156 (3.64%), respectively (42, 45, 46, 49). No serious AEs were associated with doxycycline use, and no new HIV infections were reported in any of the studies. Study discontinuation rates due to AEs were 6.67%, 7.00%, 2.00%, 0.90%, and 2.70% in the included trials. 44 participants (6% of follow-up visits) in the dPEP Kenya study discontinued doxy-PEP due to pregnancy (49).

8.1.6. Antimicrobial resistance

Four studies assessed TCN resistance in *N. gonorrhoeae* (40-42, 45, 46, 49). The DoxyPEP study reported a slight increase in TCN-resistant *N. gonorrhoeae* during the study period (41, 42). In both the DOXYVAC trial and the dPEP Kenya study, TCN resistance was already 100% at baseline and remained at this level throughout follow-up in both study arms (45, 46, 49). One study examined commensal *Neisseria species* and observed a relative increase in TCN resistance among these species in the doxy-PEP arm (41, 42). Three studies reported on *C. trachomatis*, and no TCN resistance was observed (40, 45, 46, 49). Two assessed *Staphylococcus aureus* carriage, and one reported a relative increase in TCN-resistant *S. aureus* in the doxy-PEP arm (41, 42, 48). One study tested participants for *Mycoplasma genitalium* and reported one TCN-resistant strain in both arms (39). The detailed methodology and findings on TCN resistance in each study are presented in *Table 2*.

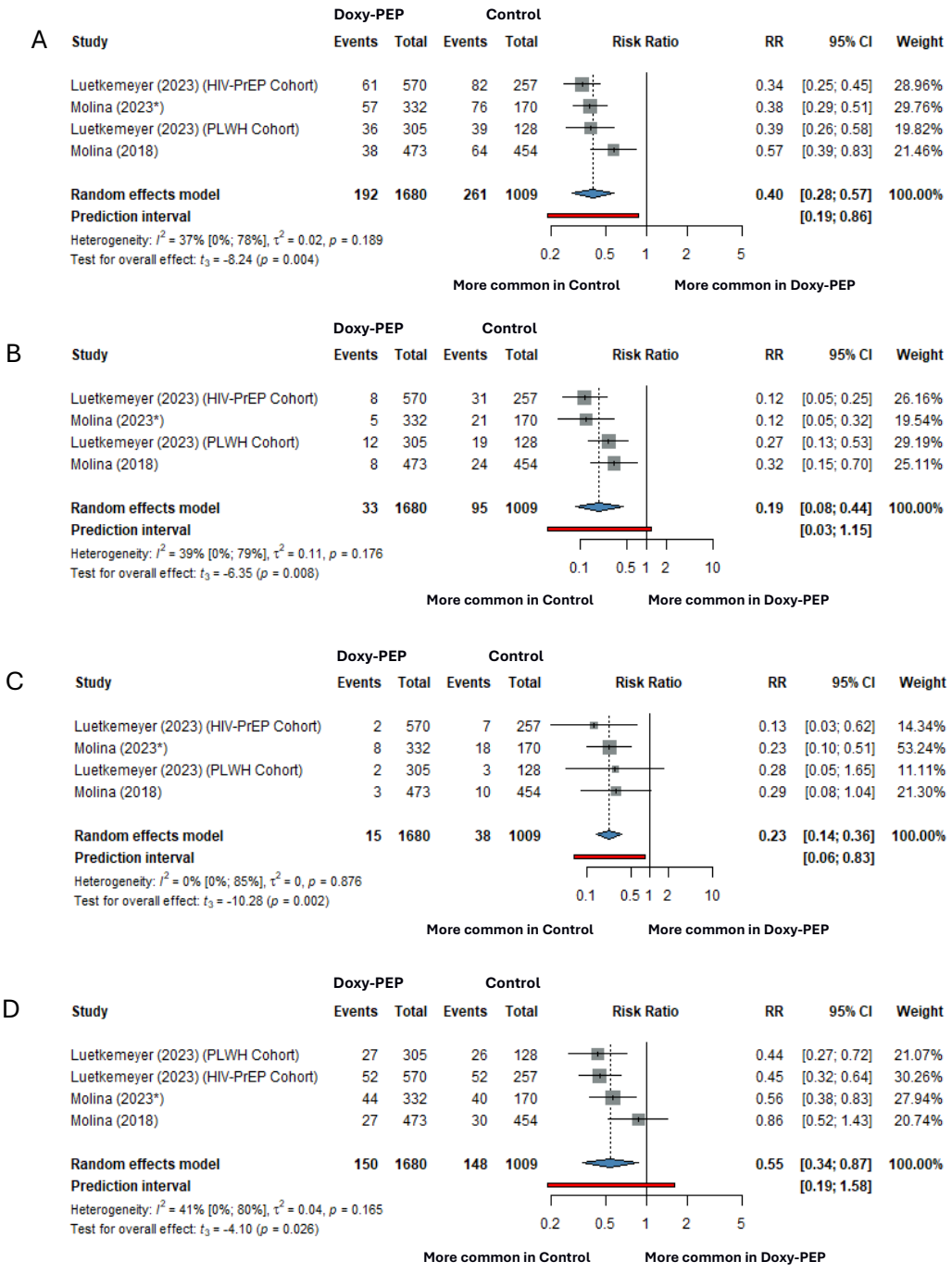


Figure 3. Forest plots for STI incidence; doxy-PEP vs no prophylaxis; including only MSM and TGW; (a) incidence of any STI (b) incidence of chlamydia (c) incidence of syphilis (d) incidence of gonorrhoea. Forest plots showing the total number of visits, and the number of visits with an STI in the doxy-PEP and in the control groups. *Interim data. This figure is based on the figure by Szondy et al. (2024) (34).

Table 2. Tetracycline resistance outcomes in the included studies

Study name (First Author, Year of Publication)	Bacterium	Methods	Baseline (number of resistant samples/total number of samples)		During follow-up (number of resistant samples/total number of samples)		Monthly doxycycline consumption (median, IQR)
			Doxycycline arm	Control arm	Doxycycline arm	Control arm	
IPERGAY (Molina, 2018) (39, 40)	*N. gonorrhoeae*	Culture. TCN resistance was defined as ≥1 mg/L and intermediate resistance as ≥0.5 mg/L with E-test. Molecular detection of the *tet*M gene, mutations in the *mtrR gene,* and *Val57Met* mutation in the *rpsJ* gene by PCR.	NA	NA	0/2 (0.00%)[b]	4/6 (0.67%)[b]	680 mg (280 mg - 1450 mg)
	M. genitalium	16S rRNA gene PCR.	0/3 (0.0%)	1/8 (12.5%)	1/2 (50.0%)	0/3 (0.00%)	
	C. trachomatis	Culture. Normal MIC range was defined as 0.12-0.25 mg/L.	NA	NA	0/2 (0.00%)	0/2 (0.00%)	
DoxyPEP (Luetkemeyer, 2023) (41, 42)	*N. gonorrhoeae*	Culture. TCN resistance was defined as MIC ≥2 mg/L by agar dilution.	2/7 (28.6%)	2/8 (25.0%)	5/13 (38.5%)	2/16 (12.5%)	800 mg (200 mg - 2000 mg)
	Commensal *Neisseria spp*	Culture. TCN resistance was defined as MIC ≥2 mg/L by E-test.	189/302 (62.6%)	92/153 (60.1%)	85/122 (69.7%)	25/56 (44.6%)	
	S. aureus (MSSA)	Culture. TCN resistance was defined as MIC ≥16 mg/L by E-test.	11/118 (9.30%)	9/67 (13.4%)	15/71 (21.1%)	3/47 (6.38%)	
	S. aureus (MRSA)		1/20 (5.00%)	4/9 (44.4%)	1/11 (9.09%)	2/6 (33.3%)	
dPEP Kenya (Stewart, 2023) (45, 49)	*N. gonorrhoeae*	Molecular detection of the *tet*M gene by PCR	16/16 (100%)		20/20 (100%)	12/12 (100%)	800 mg (0 mg - 1600 mg)
	C. trachomatis	Molecular detection of *tet*C gene by PCR.	0/20 (0.00%)		0/25 (0.00%)	0/31 (0.00%)	

DOXYVAC (Molina, 2023)[a] (46)	*N. gonorrhoeae*	Culture. TCN MICs were determined by E-test. TCN resistance was defined as >0.5 mg/L (High-level resistance >8 mg/L).		7/7 (100%)	21/21 (100%)[c]	37/37 (100%)[d]	700 mg (400 mg - 1100 mg)
	C. trachomatis	Culture.	NA	NA	NA	0/4 (0.00%)	
		16S rRNA PCR.	NA	NA	0/3 (0.00%)	0/50 (0.00%)[e]	
DPMSM (Bolan, 2015) (47)	NA	NA	NA	NA	NA	NA	NA
DuDHS (Grennan, 2021)[a] (48)	*S. aureus*	Culture. TCN MICs were determined by Kirby Bauer testing.	NA	NA	4/9 (44.4%)	1/2 (50.0%)[f]	NA

This table is based on the table by Szondy et al. (2024) (34).
The studies employed different breakpoints for TCN resistance testing in gonorrhoea. In the French studies, EUCAST recommendations were followed for assessing TCN resistance. During the IPERGAY study in 2018, the recommended breakpoint for resistance was 1 mg/L, which was revised to 0.5 mg/L in 2023, when the DOXYVAC study was conducted. In contrast, the DoxyPEP study conducted in the USA adhered to CLSI recommendations, defining TCN resistance at 2 mg/L.
a Interim data
b Nine isolates from eight participants. Intermediate TCN resistance was detected for three additional N. gonorrhoea isolates. *Tet*M was identified in one of the resistant isolates. All TCN-resistant strains carried the Val57Met mutation in the *rpsJ* gene and mutations associated with overexpression of the antibiotic efflux pump MtrCDE.
c 7/21 (33.3%) were high-level resistant.
d 7/37 (18.9%) were high-level resistant.
e 0/4 strains were resistant with culture.
f The control arm also received doxycycline from week 24.
MIC: minimal inhibitory concentration; MG: *Mycoplasma genitalium*; MRSA: Methicillin-Resistant *Staphylococcus aureus*; MSSA: Methicillin-Resistant *Staphylococcus aureus*; NA: not applicable; spp: species pluralis TCN: tetracyclin

8.1.7. Adherence

Adherence was self-reported in five studies (40, 42, 45, 46, 48, 49), with 82% (95% CI: 77%-86%) of participants in the doxy-PrEP/PEP groups reporting consistent use (*Fig. 4*). Three studies used additional objective measures to evaluate adherence to doxy-PrEP/PEP use. Of these, two studies assessed plasma doxycycline levels. In the DPMSM study by Bolan et al., detectable serum doxycycline concentrations were observed in 60.5% of visits in the doxycycline arm (47). Similarly, in the IPERGAY study, Molina et al. reported detectable plasma levels in 30% of participants in the doxycycline group and in 9% of those in the control group (40). The assay used was able to detect doxycycline in plasma up to 48 hours after intake. In the dPEP Kenya study, Stewart et al. randomly selected 50 participants from the doxy-PEP group to assess doxycycline concentrations in hair samples. Doxycycline was detected at least once in 28 participants (56.0%). Across all quarterly visits, the drug was present in 29.0% of samples, increasing to 32.6% when visits with suspended doxycycline use were excluded (49). Monthly doxycycline intake ranged from 0 to 1600 mg, as shown in *Table 2*.

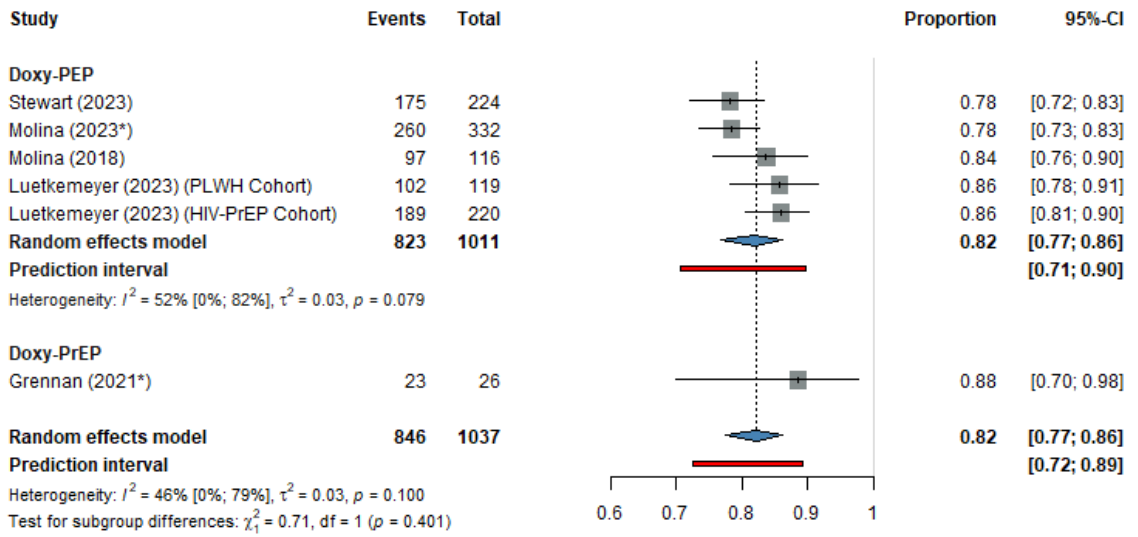


Figure 4. Forest-plot for self-reported adherence to doxy-PrEP/PEP; subgrouping by type of doxy-prophylaxis. The forest plot shows the percentage of participants who used doxycycline prophylaxis consistently. * Interim data. This figure is based on the figure by Szondy et al. (2024) (34).

8.2. Study II

8.2.1. Study selection

The initial systematic search yielded 3,392 records. After screening by title and abstract, followed by full-text assessment, 12 publications met the predefined inclusion criteria (50-61). A subsequent updated systematic search produced 100 additional records, of which one further study was found to be eligible (*Fig. 5*) (62). The studies by Wang et al. (Wang 2022 and Wang 2023) (55, 56), Rolando and Diaz (60, 61), and Petousis-Harris and Paynter (53, 57) assessed overlapping populations, with each pair of studies investigating the same population. Furthermore, one study included in the analysis had an associated erratum, which has been referenced alongside the original publication (51).

8.2.2. Study characteristic

The included studies comprised eight retrospective case-control or cohort studies, three ecologic studies, and one RCT. All investigated OMV meningococcal vaccines. Seven assessed the 4CMenB, two the VA-MENGOC-BC, two the MeNZB, and the MenBvac was assessed in one study. An overview of the main study characteristics and population details is presented in *Table 3*.

8.2.3. Risk of bias assessment, certainty of evidence

During our risk of bias assessment, the sole RCT was rated as having a low risk of bias (62). Three additional studies were also classified as low risk (50, 52, 54), while four were judged to have a moderate risk due to concerns regarding confounding and participant selection (53, 55-57). Another four studies were found to have a serious risk of bias, primarily due to concerns related to confounding and missing outcome data (58-61). Restricting the analysis to studies with a low risk of bias did not alter the magnitude or the significance of our findings. Funnel plot analysis revealed no evidence of publication bias. The detailed risk of bias assessment and the corresponding forest plot are available in the *Supplementary Material* of the original publication (63).

The certainty of the evidence was rated as moderate. Further information on the assessment of evidence certainty is provided in the *Supplementary Material* of the original publications (63).

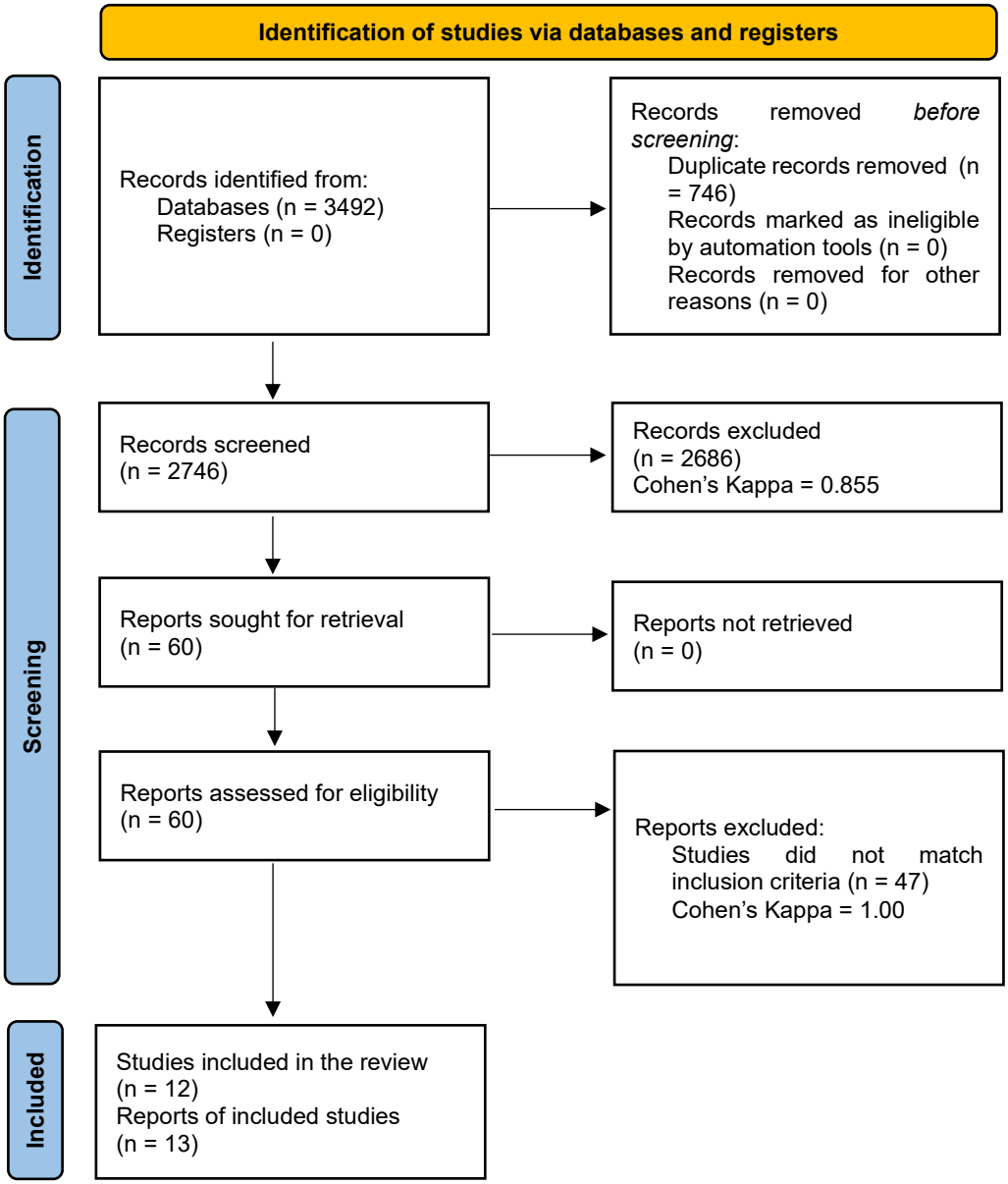


Figure 5. PRISMA flow diagram of the screening and selection process according to PRISMA 2020 guidelines. The diagram shows the merged results of the two systematic searches. This figure is based on the figure by Szondy et al. (2025) (63).

Table 3. Characteristics of the included studies

First author, year of publication	Study design, country, study period	Population details	Age	Sample size	Intervention	Control	Follow-up time	Vaccination status	Risk of bias	Included in the main analysis
Abara, 2022 (54)	Retrospective cohort study, USA, Jan 2016- Dec 2018	Gonorrhoea and chlamydia patients identified through the STI surveillance systems of the New York City Department of Health and Mental Hygiene and the Philadelphia Department of Public Health	16-23 years	42830 gonorrhoea cases among 109737 individuals, 7692 individuals were vaccinated (4032 received one dose, 3596 received two doses, and 64 received at least three doses)	One dose of 4CMenB[a] Two doses of 4CMenB[a]	No vaccine	Up to three years	Participants were considered vaccinated 30 days after the vaccinations. For fully vaccinated individuals, the second shot of the vaccine had to be administered between 30 and 180 days after the first shot of the vaccine.	Low	Yes
Bruxvoort, 2023 (50) (51)	Matched retrospective cohort study, USA, Jan 2016-Dec 2020	Individuals who received at least one dose of either the 4CMenB or MenACWY vaccine.	15-30 years	27 gonorrhoea cases among 6641 vaccinated individuals, and 295 gonorrhoea cases among 26471 controls	≥One dose of 4CMenB[a]	≥One dose of MenACWY[b]	Median 1.9 years (IQR: 1.16-2.97 years)	Individuals were considered vaccinated if they had received at least one dose of the 4CMenB vaccine with at least 31 days having elapsed since vaccination.	Low	Yes
Diaz, 2021 (61)	Ecologic study, Cuba, 1970-2018	Gonorrhoea incidence data from the statistical reports of the Public Health Ministry of Cuba were reviewed for all individuals vaccinated against *N. meningitidis* between 1970 and 2018, along with data related to the VA-MENGOC-BC vaccination program in Cuba.	NA	NA	VA-MENGOC-BC[c]	NA	NA	NA	Serious	No

Molina, 2024 (62)	Open-label RCT, France, Jan 2021- Feb 2023	HIV-negative MSM on PrEP aged 18 years or older and with a documented history of bacterial STIs within the 12 months prior to enrolment.	median 41 years (IQR: 34-48 years)	132 gonorrhoea cases among 274 vaccinated individuals, and 151 gonorrhoea cases among 270 controls	Two doses of 4CMenB[a]	No vaccine	Up to 24 months with a median follow-up of 14 months (IQR 9-18)	Individuals were considered vaccinated if they had received the second dose, and at least one month had elapsed since then.	Low	Yes
Paynter, 2019 (57)	Retrospective cohort study, New Zealand, 2004-2015	New Zealand residents born between 1984 and 1999 inclusive, who resided in New Zealand from 2004 until at least 2015.	≥13 years	261 cases of first hospitalisation due to gonorrhoea in 935496 individuals	One or two doses of MeNZB[d] Three doses of MeNZB[d]	No vaccine	Up to 11 years	Cohort members were considered fully vaccinated if they had received three doses of the MeNZB vaccine.	Moderate	No
Petousis-Harris, 2017 (53)	Retrospective case-control study, New Zealand, Jan 2004-Dec 2016	Individuals attending sexual health clinics who were diagnosed with gonorrhoea, chlamydia, or both, and who were eligible to receive the MeNZB vaccine in New Zealand during the mass immunisation programme from July 19, 2004, to June 30, 2006.	15-30 years	1192 gonorrhoea cases among 8369 vaccinated (940 partially, 7429 fully vaccinated) individuals and 1051 gonorrhoea cases among 6361 controls.	One or two doses of MeNZB[d] Three doses of MeNZB[d]	No vaccine	Up to 6 years[g] From 6, up to 11 years Up to 11 years	Individuals were considered fully vaccinated if they had received three doses of the vaccine at least six months prior to a gonorrhoea diagnosis. Those who had received one or two doses at least six months before a gonorrhoea diagnosis were considered partially vaccinated.	Moderate	Yes
Raccagni, 2023 (52)	Unmatched case-control study, Italy, Jul 2016-Feb 2021	MSM living with HIV with a diagnosis of gonorrhoea, syphilis, chlamydia, or anal human papillomavirus (HPV).	Median 44 years (IQR: 37-51 years)	24 gonorrhoea cases among 349 vaccinated, and 79 gonorrhoea cases among 702 controls	Two doses of 4CMenB[a]	No vaccine	Median 3.8 years (2.1-4.3 years)	Individuals were considered vaccinated if they had completed a two-dose 4CMenB vaccination schedule (doses administered at week 0 and week 8).	Low	Yes

Robison, 2023 (58)	Unmatched case-control study, USA, 2015-2018	University students.	18-29 years	24 gonorrhoea cases among 15760 vaccinated individuals and 44 gonorrhoea cases among 15212 controls	≥One dose of 4CMenB[a]	MenB-FHbp[e]	Up to 2 years	Individuals were considered vaccinated one month after receiving the vaccine.	Serious	Yes
Rolando, 2019 (60)	Ecologic study, Cuba, 1970-2017	National gonorrhoea incidence was evaluated before and after the mass vaccination campaign in 1989-1990.	3 months - 24 years	NA	VA-MENGOC-BC[c]	NA	NA	NA	Serious	No
Whelan, 2016 (59)	Ecologic study, Norway, 1993-2008	National gonorrhoea incidence was evaluated before and after the trial of MenBvac.	≥16 years	NA	MenBvac[f]	NA	NA	NA	Serious	No
Wang, 2022 (55)	Observational cohort and case-control study, Australia, 2019-2021 and 2019-2022	Individuals diagnosed with gonorrhoea or chlamydia.	15-25 years	512 gonorrhoea patients and 3140 controls	≥One dose of 4CMenB[a]	No vaccine	Up to 2 years	Individuals were considered vaccinated if they had received vaccine doses at least six months prior to a gonorrhoea diagnosis.	Moderate	Yes
Wang 2023 (56)				823 gonorrhoea patients, 4935 controls			Up to 3 years		Moderate	No

This table is based on the table by Szondy et al. (2025) (63).
a 4CMenB vaccine: OMV vaccine with three additional recombinant proteins (fHbp, NHBA, NadA) against *N. meningitidis* serogroup B by GSK
b MenACWY vaccine: non OMV vaccine against *N.Meningitidis* serogroups A, C, W-135 and Y by GSK
c VA-MENGOC-BC vaccine: OMV vaccine developed by National Center for Meningococcal Vaccine Development in Havana against *N. Meningitidis* serogroup B
d MeNZB vaccine: non-OMV, recombinant protein-based vaccine developed against *N.Meningitidis* serogroup B by a partnership involving the New Zealand Ministry of Health, the University of Auckland, the Institute of Environmental Science and Research (ESR), Chiron (now Novartis Vaccines and Diagnostics), the NIPH and the WHO.
e MenB-FHbp vaccine: non-OMV, recombinant protein-based vaccine developed against *N. Meningitidis* serogroup *B* by Pfizer Inc.
f MenBvac vaccine: OMV vaccine developed by the National Institute of Public Health in Norway against *N. Meningitidis* serogroup B
g The study of Petousis-Harris et al. reported multiple follow-up time points. The 'up to 6 years' follow-up time was used in the main analysis.
HIV: human immunodeficiency virus, HPV: human papillomavirus, IQR: Interquartile range, MSM: men who have sex with men, NA: not applicable, RCT: randomised controlled trial, STI: sexually transmitted infection, USA: United States of America

8.2.4. Vaccine effectiveness

8.2.4.1. Quantitative analysis

Seven articles were included in the quantitative analysis (50, 52-55, 58, 62). In four of these studies, all participants received the complete vaccination series. In the remaining three studies, participants included both fully and partially vaccinated individuals. One study reported that 57% of participants completed the full vaccination series, another reported 86.4%, while the third reported that all participants had received at least one dose but did not specify the proportion who completed the full series. The pooled OR was 0.62 (0.50-0.78; I^2 = 55%), corresponding to a VE of 38 % (95 % CI: 22 %-50 %; I^2 = 55%) (*Fig. 6.*).

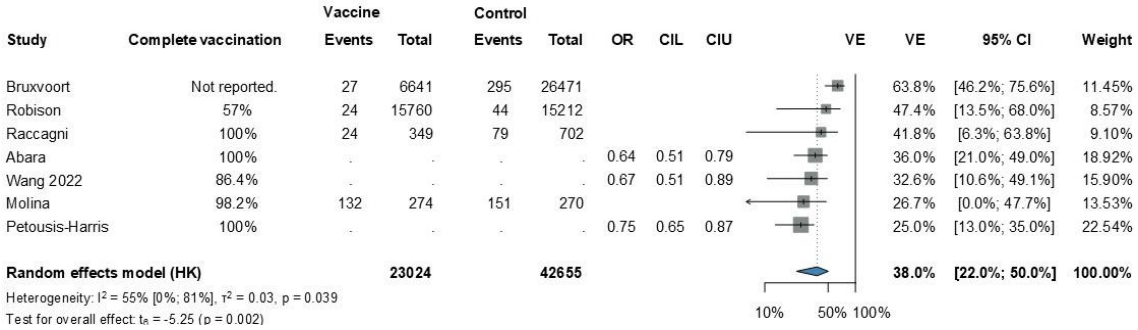


Figure 6. Forest plot for vaccine effectiveness. The numbers of gonorrhoea cases and total cases are shown, where available, for both the OMV vaccine and control groups. In the absence of these data, the reported odds ratios are displayed instead. The study of Abara et al. used prevalence ratios instead of odds ratios. This figure is based on the figure by Szondy et al. (2025) (63).

Three studies evaluated the VE of both partial and complete vaccination (53, 54, 58). Our analysis suggested that complete vaccination is associated with 24% greater effectiveness compared to partial vaccination (OR = 0.76; 95% CI: 0.31-1.85; I^2 = 86%) (Fig. 7).

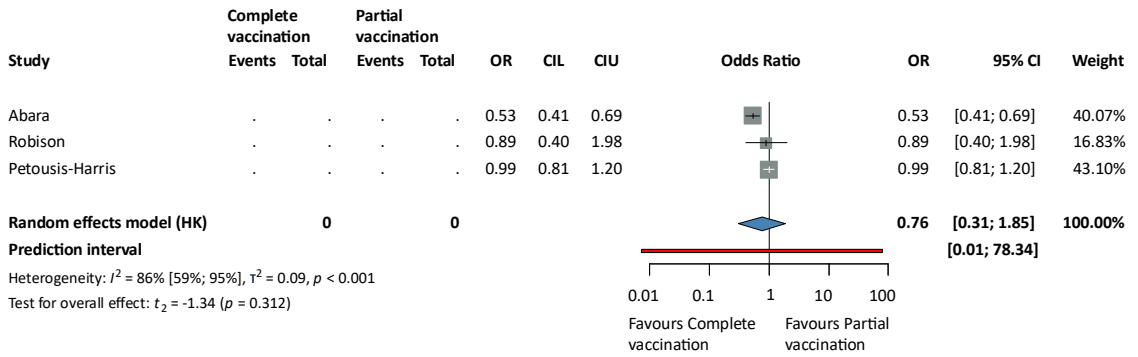


Figure 7. Forest plot for complete vs partial vaccination. The forest plot shows the pooled odds ratio for acquiring gonorrhoea with complete vs partial vaccination. The study of Abara et al. used prevalence ratios instead of odds ratios. This figure is based on the figure by Szondy et al. (2025) (63).

The leave-one-out sensitivity analysis aimed at identifying sources of heterogeneity indicated that the study by Bruxvoort et al. (50) was the main contributor to statistical heterogeneity. When this study was excluded, the pooled VE was 30% (OR = 0.70; 95% CI: 0.62-0.78; I^2 = 0%) (*Fig. 8*). Including only studies assessing the 4CMenB vaccine, the estimated VE was 41% (OR = 0.59; 95% CI: 0.46-0.76; I^2 = 44%) (*Fig. 8*).

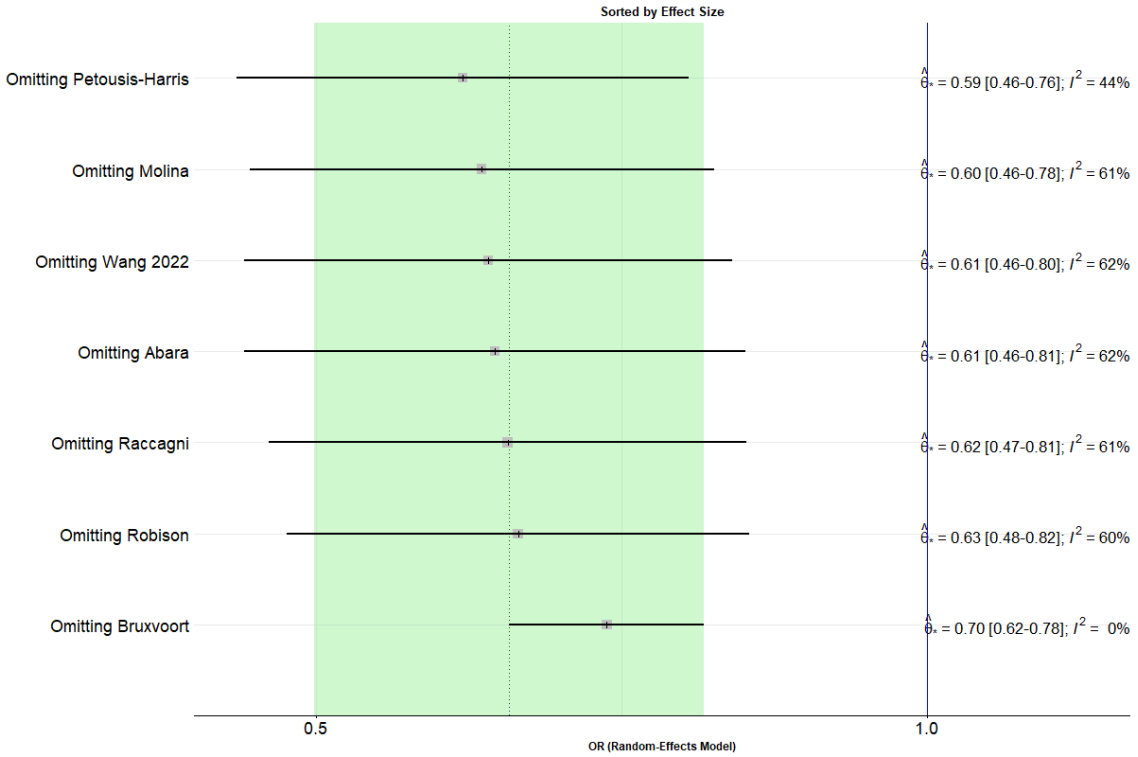


Figure 8. Sensitivity analysis; leave-one-out analysis.
This figure is based on the figure by Szondy et al. (2025) (63).

8.2.4.2. Qualitative analysis

Evidence from ecological studies complements the results of case-control and cohort studies. Whelan et al. studied the incidence of gonorrhoea in Norway after the MenBvac OMV vaccine trial conducted among adolescents between 1988 and 1992. Their findings indicated a correlation between increased vaccine uptake and decreased gonorrhoea rates in both sexes (59). In Cuba, Rolando et al. and Diaz et al. assessed the effects of the VA-MENGOC-BC OMV vaccine on gonorrhoea trends. A phase III trial involving adolescents aged 10 to 16 was initiated in 1987, followed by a broader immunisation program between 1989 and 1990 that initially included individuals aged 3 months to 20 years, later expanded to 24 years. Between 1989 and 1993, gonorrhoea cases declined

markedly - from 381.9 to 190.3 per 100,000 people - parallel to reductions in meningococcal disease, while other STIs showed upward trends. Vaccine coverage during this campaign ranged between 75% and 95% (60, 61).

One study assessed the effectiveness of an OMV vaccine not through direct prevention of gonorrhoea infection, but indirectly by evaluating its impact on gonorrhoea-related hospitalisations. After adjusting for potential confounding factors, the MeNZB vaccine was estimated to reduce the risk of hospitalisation due to gonorrhoea by 24% (95% CI: 1-42%) (57).

The studies included in this review reported varying follow-up durations, as detailed in *Table 3*. The studies did not report exact follow-up times for individual participants. Instead, they described a vaccination period during which participants were followed, without specifying when each was vaccinated within that timeframe; however, three studies evaluated VE at distinct intervals. The study with the longest follow-up was conducted by Petousis-Harris et al., which followed participants for up to 11 years (53). When restricted to the first six years, the estimated VE was 25% (95% CI: 13%-35%), but this declined to 8% (95% CI: 0%-19%) when considering only the 6-11 year follow-up interval (53). Wang et al. assessed VE at two- and three-year post-vaccination. The initial analysis reported a VE of 32.7% (95% CI: 8.3%-50.6%) within the first three years, which declined to 23.2% (95% CI: 0%-47.5%) after 36 months (55, 56). In Cuba, studies by Díaz et al. and Rolando et al. observed a sharp decline in gonorrhoea incidence following the introduction of the mass vaccination campaign in 1989, with the lowest rates recorded in 1993. However, incidence began to rise again in the subsequent years (60, 61).

9. DISCUSSION

9.1. Summary of findings

In Study I, we investigated the novel approach of doxy-PrEP/PEP for the prevention of bacterial STIs. The rationale was the persistently high prevalence of bacterial STIs, particularly the alarming rates of syphilis among MSM (10).

Thus, the most important finding of our meta-analysis is the marked effectiveness of doxy-PEP in preventing syphilis. The pooled analysis demonstrated a statistically robust 77% relative reduction in syphilis incidence among MSM and TGW. Although we did not have direct data on early neurosyphilis, it is reasonable to assume that its incidence would decline proportionally, averting irreversible neurological complications. Additionally, doxy-PEP was associated with an 81% reduction in the incidence of chlamydia. Unexpectedly, a statistically significant 45% reduction in gonorrhoea incidence was also observed with the use of doxy-PEP among MSM and TGW, highlighting the influence of regional TCN resistance patterns on its effectiveness.

Subsequent to our meta-analysis, the full article of the DOXYVAC study and the open-label extension (OLE) of the DoxyPEP study have been published (62, 64). In the final analysis of the DOXYVAC study, the effectiveness of doxy-PEP against syphilis and chlamydia remained consistent, whereas the estimated effectiveness against gonorrhoea showed a modest reduction (62). In the OLE phase of the DoxyPEP study, participants from the standard-care group who initiated doxy-PEP experienced a reduction in STI incidence comparable to that observed in the doxy-PEP group during the randomised phase (64). Real-world studies further support the effectiveness of doxy-PEP in clinical settings, aligning with trial data showing high efficacy against syphilis and chlamydia and variable effectiveness against gonorrhoea. These studies from California and Italy reported reductions in bacterial STI rates associated with doxy-PEP use, with chlamydia declining by 79% to 87%, syphilis by 80% to 83%, and gonorrhoea by 12% to 74% (65-67).

To date, evidence supporting the effectiveness of doxy-PEP has been limited to MSM and TGW, as the only trial conducted among CGW yielded null results. Nonetheless, there is no historical evidence that doxycycline efficacy is influenced by sex, and Haaland et al recently demonstrated high penetration in both female and male urogenital and rectal

tissues (68). This dPEP Kenya study - conducted in a setting with nearly 100% TCN resistance in *N. gonorrhoeae* and low syphilis prevalence - was unlikely to demonstrate efficacy against gonorrhoea and was not adequately powered to detect differences in syphilis incidence (49, 69). Notably, doxy-PEP also failed to show effectiveness against chlamydia, suggesting that poor adherence may be a more plausible explanation for the lack of effect. Although self-reported adherence was comparable to that in other included trials, doxycycline levels measured in hair samples indicated that up to 44% of participants in the doxy-PEP group might not have taken the prophylaxis (49). This approach, previously validated in HIV-PrEP research, is regarded as a reliable measure of long-term adherence (70).

Due to the limited number of studies, a pooled analysis of doxy-PrEP was not feasible. However, since the completion of our meta-analysis, the full-length article of the DuDHS study and one additional study have been published, and the available data suggest that its effectiveness is comparable to that of doxy-PEP (71, 72). Doxy-PrEP may offer advantages in specific contexts where individuals face sustained short-term risk, such as among seasonal sex workers or during festivals. Nonetheless, the cumulative doxycycline exposure is substantially higher with doxy-PrEP than with doxy-PEP, increasing the potential risks of adverse effects and AMR development. Therefore, based on current evidence, doxy-PEP should be preferred over doxy-PrEP in most settings.

In Study II, the rationale was the high incidence of gonorrhoea and the ineffectiveness of doxy-PEP against TCN-resistant strains. We reviewed all available evidence on all OMV-based meningococcal vaccines evaluated for protection against gonorrhoea. Both MeNZB and 4CMenB studies were included in the main analysis, as the OMV component in 4CMenB is derived from the same *N. meningitidis* strain used in MeNZB and is believed to be responsible for cross-protection irrespective of the specific formulation. For practical relevance, we also conducted a subgroup analysis focusing exclusively on the 4CMenB vaccine, which is the most widely available. This sensitivity analysis, restricted to studies evaluating 4CMenB, demonstrated a statistically significant VE of 41%. However, statistical heterogeneity remained high. A leave-one-out analysis identified the study by Bruxvoort et al. (50) as the primary source of heterogeneity, as it reported an exceptionally high VE of 63.8%. Excluding this study reduced heterogeneity to zero percent, while the statistical significance of the overall VE was preserved.

According to the Food and Drug Administration (FDA), full immunisation with the 4CMenB vaccine for healthy adolescents and young adults requires two doses administered six months apart (73). Our analysis indicated that completing the full two-dose schedule may provide an estimated 24% greater protection compared to receiving only a single dose, although this difference did not reach statistical significance due to the limited number of studies. The observed estimated difference aligns with findings reported by Jesús Castilla et al., who observed a similar distinction between full and partial vaccination in children vaccinated against invasive meningococcal disease caused by any *N. meningitidis*. In their study, full vaccination with 4CMenB conferred 76% protection, while partial vaccination offered 54% protection (74).

Moreover, complete vaccination may offer longer-lasting protection. Due to the lack of precise data on follow-up durations, we were unable to pool estimates on the duration of protection. Nevertheless, findings from longer-term studies suggest that VE wanes over time and may become negligible after five years. Wang et al. reported a VE of 32.7% during the first 3 years of the vaccination programme, which declined to 23.2% at 36 months. In a subsequent analysis, a similar VE of 26.2% was estimated four years post-vaccination (55, 56, 75). Additionally, findings from the study by Petousis-Harris et al. and from ecological studies indicate that VE declined to negligible levels five years after the initial vaccination programme (53) (60, 61).

Two studies evaluated VE in high-risk MSM populations, which may serve as key targets for future vaccination strategies (52, 62). Several modelling studies have also explored the impact of vaccinating high-risk MSM populations, projecting substantial public health benefits. One analysis estimated that administering 4CMenB with 31% effectiveness lasting 18 months could prevent approximately 110,200 gonorrhoea cases over a decade in England (76). Another model suggested that a gonococcal vaccine with 50% efficacy could reduce gonorrhoea prevalence by 62% within two years if 30% of MSM are vaccinated at the time of STI testing (77).

To date, the concurrent use of doxy-PEP and an OMV meningococcal vaccine is limited to a single clinical trial conducted by Molina et al., in which the effectiveness of each intervention was reported separately, without an analysis of their joint impact. Although the study did not demonstrate a statistically significant benefit of 4CMenB, this result can

be explained by methodological limitations. The trial was originally designed with a longer follow-up period to ensure sufficient power to detect meaningful effects on gonorrhoea incidence, but was terminated early, substantially reducing its statistical power. Despite the shortened duration, the findings indicated a non-significant trend toward a decline in gonorrhoea incidence among vaccine recipients (62, 78).

Both doxy-PrEP/PEP and meningococcal vaccines demonstrate a favourable safety profile, and potential AEs do not appear to pose significant limitations to their use. The most commonly reported side effects of doxycycline include GI disturbances, nausea, and photosensitivity, all of which are typically mild and self-limiting. While no serious AEs were reported in the included studies, one case of fixed drug eruption was documented in the full-length publication of the DOXYVAC trial (62). Discontinuation due to AEs was rare. All participants were either PLWH or taking HIV-PrEP, and no new HIV infections were documented, which highlights the importance of ensuring that doxy-PEP is accompanied by HIV-PrEP to prevent HIV acquisition. Similarly, OMV meningococcal vaccines are generally well tolerated, with the most frequently reported adverse effects being local injection site reactions, headache, and transient fever (79).

Besides safety considerations, doxy-PEP faces another significant limitation; its potential impact on AMR, which may critically affect its long-term viability as a public health strategy. Although doxycycline has been used for decades in the treatment of acne vulgaris and for malaria prophylaxis, with limited evidence suggesting a meaningful contribution to resistance development, renewed concern has emerged with the introduction of doxy-PEP.

Both *N. gonorrhoeae* and *S. aureus* (Including Methicillin-resistant *Staphylococcus aureus*, MRSA) exhibit a high potential for developing TCN resistance (80). In the DoxyPEP trial, a modest relative increase in TCN-resistant strains of both species was observed among doxy-PEP recipients (41, 42). However, this likely reflects the limited efficacy of doxycycline against pre-existing resistant strains rather than the emergence of new resistance.

Based on global resistance trends, a further plausible concern is the development of TCN resistance in *Streptococcus species*, *Mycoplasma species*, and Gram-negative intestinal bacteria, although no evidence currently links doxy-PEP use to the emergence of

resistance in *Mycoplasma* or *Streptococcus spp*. On the other hand, as part of a secondary objective in the DoxyPEP study, Chu et al. employed DNA and RNA metagenomic sequencing to investigate AMR dynamics following doxy-PEP use, and their analysis revealed an increase in TCN resistance genes from baseline to month six (81).

In contrast, *C. trachomatis* and *T. pallidum* are unlikely to develop TCN resistance, as no cases of TCN-resistant *T. pallidum* have been reported to date, and only isolated case reports exist for resistant *C. trachomatis* (17). Consistently, none of the studies included in this analysis reported any evidence of resistance in these pathogens.

Of the listed pathogens, *Mycoplasma spp*, streptococci and MRSA are of actual clinical relevance, as they constitute the primary contexts in which doxycycline is routinely used in current medical practice. Nevertheless, the potential for AMR selection must be weighed against the exceptional effectiveness of doxy-PEP and its associated public health benefits. Combining the doxy-PEP approach with the OMV vaccination could further mitigate the potential for resistance selection in gonorrhoea, as the vaccine is effective against gonorrhoea, regardless of AMR.

9.2. International comparisons

Our study was the first systematic review and meta-analysis to assess doxy-PEP, including a separate subgroup analysis among MSM and TGW. Following our publication, two further meta-analyses were published: one evaluating both doxy-PrEP and doxy-PEP, and another focusing exclusively on doxy-PEP (82, 83). These studies applied similar methods and reported comparable findings. A key distinction of our analysis was the dedicated subgroup evaluation among MSM and TGW, which showed that, in addition to its high effectiveness against syphilis and chlamydia, doxy-PEP is also effective against gonorrhoea in settings with low to moderate TCN resistance.

Regarding meningococcal vaccines for gonorrhoea prevention, two additional systematic reviews and meta-analyses have been published alongside our own, reporting similar findings (84, 85). Abara et al. focused exclusively on the 4CMenB vaccine, whereas Wang et al. evaluated all OMV-based vaccines, consistent with the scope of our analysis. However, our study was the only one to pool effect size estimates comparing complete versus partial vaccination, suggesting a trend in favour of complete vaccination.

9.3. Strengths

In this thesis, we systematically reviewed all available evidence on the novel preventive approaches of doxy-PEP, doxy-PrEP and OMV vaccines. We rigorously followed the guidelines of the Cochrane Collaboration, ensuring the highest standards of methodological quality, transparency, and replicability.

In Study I, we included only RCTs, which represent the highest level of clinical evidence. Our pooled analysis produced a statistically robust estimate of doxy-PEP effectiveness against syphilis. Furthermore, we were able to provide statistically significant estimates of doxy-PEP among MSM and TGW with high certainty.

In Study II, we performed a meta-analysis that pooled data from studies conducted in diverse settings, yielding a statistically significant estimate of VE. Through leave-one-out analysis, we were able to substantially reduce heterogeneity, thereby increasing the reliability of the results. Although no RCTs were available, the relatively large number of eligible studies provides strong evidence for the effectiveness of the 4CMenB vaccine.

9.4. Limitations

Both of our studies are subject to several limitations. In Study I, two of the six studies included in the analysis had not been published at the time of assessment, only interim data from conference abstracts were available. Moreover, the number of available studies was insufficient to perform a separate quantitative analysis for doxy-PrEP. At present, the evidence supports the recommendation of doxy-PEP only for MSM and TGW, although it is likely to be effective in other populations as well. Due to different methodologies and relatively short follow-up times, data on antibiotic resistance were insufficient to discard potential threats.

In Study II, the majority of included studies were retrospective and therefore not suitable for establishing causal relationships. The only prospective RCT, the DOXYVAC study, did not demonstrate a statistically significant VE (62). Considerable heterogeneity was observed across studies in terms of design, population characteristics, definitions of cases and controls, follow-up duration, vaccine formulations, and criteria for determining complete vaccination. Furthermore, due to limited data and high heterogeneity, the analysis comparing complete versus partial vaccination should be regarded as exploratory rather than conclusive. The generally short and imprecisely reported follow-up periods

further limited our ability to accurately assess the duration of protection. Lastly, due to the absence of data on the combined use of doxy-PEP and OMV-based vaccines, conclusions regarding their joint effects are currently limited to theoretical assumptions.

10. CONCLUSIONS

In our study, we demonstrated that doxy-PEP is an effective and safe intervention for the prevention of syphilis and chlamydia infections among high-risk MSM and TGW and may also be effective against gonorrhoea in settings with low prevalence of TCN resistance. No direct evidence currently links doxy-PEP to the emergence of AMR; however, continued surveillance remains essential. OMV meningococcal vaccines demonstrated moderate effectiveness, with a reasonably sustained duration of protection against gonorrhoea. Completing the full vaccination series appears to offer greater protection than partial vaccination. A combined strategy involving doxy-PEP and vaccination with the 4CMenB vaccine in high-risk groups has the potential to substantially reduce the burden of bacterial STIs at both the individual and population levels.

11. IMPLEMENTATIONS FOR PRACTICE

The rapid translation of research findings into clinical practice is of utmost importance (86, 87). In the case of doxy-PEP, the local incidence of syphilis and the prevalence of TCN-resistant gonorrhoea must be thoroughly understood and taken into account when considering its use. Clinicians should counsel all high-risk MSM and TGW on the potential benefits and risks of doxy-PEP, and its use should be offered through shared decision-making. Restricting its use to individuals living with HIV or those receiving HIV-PrEP may help minimise the risk of HIV acquisition. Additionally, doxy-PEP prescriptions should be linked to routine STI screening, which allows for the timely detection of breakthrough infections and provides an opportunity to regularly reassess the ongoing need for prophylaxis. Given its limited effectiveness against gonorrhoea, co-administration with a meningococcal vaccine should always be recommended. Beyond individual-level interventions, vaccination campaigns targeting high-risk populations should be considered in settings with a high incidence of gonorrhoea. While doxy-PrEP may offer advantages over doxy-PEP in certain settings, it entails greater cumulative doxycycline exposure, and current evidence does not support its use in general practice; doxy-PEP should be preferred.

12. IMPLEMENTATION FOR RESEARCH

Robust evidence supports the effectiveness of doxy-PEP; however, current data are primarily limited to MSM and TGW. To ensure the generalisability of this intervention, additional RCTs are needed among CGW and men who have sex with women. In contrast, evidence for doxy-PrEP remains limited, highlighting the need for further research to assess its benefit-risk profile. Additional RCTs should also investigate the potential protective effect of OMV meningococcal vaccines against gonorrhoea. Beyond VE, long-term follow-up is essential to determine the duration of protection and to establish the optimal timing for booster doses as immunity wanes. Future studies should explore the potential co-benefits of combining doxy-PEP with vaccination, reflecting real-world scenarios in which these interventions may complement one another. Additionally, a standardised method for assessing the impact on resistance emergence is needed to generate consistent and reliable data across studies.

13. IMPLEMENTATION FOR POLICYMAKERS

The Centers for Disease Control and Prevention (CDC) issued a guideline recommending that clinicians counsel all high-risk MSM and TGW about doxy-PEP and offer it as a preventive option, while the International Union Against Sexually Transmitted Infections (IUSTI) has also acknowledged its potential benefits (88, 89). Following these developments, local clinical guidelines should be developed, as the applicability of doxy-PEP largely depends on the local epidemiology of bacterial STIs and the prevalence of TCN-resistant gonorrhoea. Additionally, upscaling resistance surveillance systems is essential to detect emerging resistance trends in time and re-evaluate the use of doxy-PEP accordingly. National-level targeted vaccination campaigns should be considered for high-risk groups in settings with high gonorrhoea incidence. In addition, public communication strategies aimed at the general population could support broader understanding and informed decision-making regarding these interventions, with particular emphasis on the importance of medical oversight and the potential risks associated with unsupervised use.

14. FUTURE PERSPECTIVES

Although considerable progress has been achieved over the past decades, the prevention and control of STIs remain an ongoing public health challenge that will continue to require sustained efforts. The novel approaches of doxy-PEP and OMV meningococcal vaccines against gonorrhoea hold promise for significantly reducing the burden of STDs in the near future, provided they are implemented effectively. Doxy-PEP is increasingly adopted, particularly in the United States and several European countries, while the United Kingdom is expected to become the first country to launch a national meningococcal vaccination campaign to prevent gonorrhoea among MSM (90).

We aim to introduce these practices into clinical and public health settings in Hungary. Building on our current research, we intend to identify additional core populations, beyond MSM and TGW, who may benefit from such interventions. Furthermore, we plan to assess the awareness, acceptability, and uptake of doxy-PEP and meningococcal vaccination for gonorrhoea within the Hungarian context.

15. REFERENCES

1. Elendu C, Amaechi DC, Elendu ID, Elendu TC, Amaechi EC, Usoro EU, et al. Global perspectives on the burden of sexually transmitted diseases: A narrative review. Medicine (Baltimore). 2024;103(20):e38199.
2. E OM, Marshall L, Teljeur C, Harrington P, Hayes C, Moran P, et al. Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. BMJ Open. 2022;12(5):e048478.
3. Traeger MW, Schroeder SE, Wright EJ, Hellard ME, Cornelisse VJ, Doyle JS, et al. Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018;67(5):676-86.
4. Hooshiar MH, Sholeh M, Beig M, Azizian K, Kouhsari E. Global trends of antimicrobial resistance rates in Neisseria gonorrhoeae: a systematic review and meta-analysis. Front Pharmacol. 2024;15:1284665.
5. Maurakis SA, Cornelissen CN. Recent Progress Towards a Gonococcal Vaccine. Front Cell Infect Microbiol. 2022;12:881392.
6. Tinsley CR, 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 U S A. 1996;93(20):11109-14.
7. Marjuki H, Topaz N, Joseph SJ, Gernert KM, Kersh EN, Wang X. Genetic Similarity of Gonococcal Homologs to Meningococcal Outer Membrane Proteins of Serogroup B Vaccine. mBio. 2019;10(5).
8. WHO. Sexually transmitted infections (STIs) 2020 [Internet]. 29 May 2025. Available from: https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections-(stis). Accessed: 20.07.2025.
9. Hamill MM, Ghanem KG, Tuddenham S. State-of-the-Art Review: Neurosyphilis. Clin Infect Dis. 2024;78(5):e57-e68.
10. Tsuboi M, Evans J, Davies EP, Rowley J, Korenromp EL, Clayton T, et al. Prevalence of syphilis among men who have sex with men: a global systematic review and meta-analysis from 2000-20. Lancet Glob Health. 2021;9(8):e1110-e8.

11. Davies EP, Tsuboi M, Evans J, Rowley J, Korenromp EL, Clayton T, et al. A global meta-analysis of gonorrhoea and chlamydia prevalence among men who have sex with men from 2000 to 2022. Int J STD AIDS. 2025:9564624251333489.
12. Villanueva Baselga S, Ruben M, Luis V. A practice already in use: a snapshot survey on the use of doxycycline as a preventive strategy (Doxy-PEP and Doxy-PrEP) in the GBMSM population in Spain. Infection. 2025;53(1):437-41.
13. Hornuss D, Mathé P, Usadel S, Zimmermann S, Müller M, Rieg S. Already current practice? A snapshot survey on doxycycline use for prevention of sexually transmitted infections in parts of the German MSM community. Infection. 2023;51(6):1831-4.
14. Ghanem KG, Ram S, Rice PA. The Modern Epidemic of Syphilis. N Engl J Med. 2020;382(9):845-54.
15. Janier M, Unemo M, Dupin N, Tiplica GS, Potočnik M, Patel R. 2020 European guideline on the management of syphilis. J Eur Acad Dermatol Venereol. 2021;35(3):574-88.
16. Malhotra M, Sood S, Mukherjee A, Muralidhar S, Bala M. Genital Chlamydia trachomatis: an update. Indian J Med Res. 2013;138(3):303-16.
17. Somani J, Bhullar VB, Workowski KA, Farshy CE, Black CM. Multiple drug-resistant Chlamydia trachomatis associated with clinical treatment failure. J Infect Dis. 2000;181(4):1421-7.
18. Ball LM, Bronstein E, Liechti GW, Maurelli AT. Neisseria gonorrhoeae drives Chlamydia trachomatis into a persistence-like state during in vitro co-infection. Infect Immun. 2024;92(1):e0017923.
19. Unemo M, Seifert HS, Hook EW, 3rd, Hawkes S, Ndowa F, Dillon JR. Gonorrhoea. Nat Rev Dis Primers. 2019;5(1):79.
20. Unemo M, Cole MJ, Kodmon C, Day M, Jacobsson S. High tetracycline resistance percentages in Neisseria gonorrhoeae in Europe: is doxycycline post-exposure prophylaxis unlikely to reduce the incident gonorrhoea cases? Lancet Reg Health Eur. 2024;38:100871.
21. Unemo M, Ross J, Serwin AB, Gomberg M, Cusini M, Jensen JS. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2020:956462420949126.

22. Chopra I, Roberts M. Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol Mol Biol Rev. 2001;65(2):232-60.
23. CDC. About Meningococcal Vaccines 2023 [Internet]. July 14, 2025. Available from: https://www.cdc.gov/vaccines/vpd/mening/hcp/about-vaccine.html. Accessed: 20.07.2025.
24. Micoli F, Adamo R, Nakakana U. Outer Membrane Vesicle Vaccine Platforms. BioDrugs. 2024;38(1):47-59.
25. Semchenko EA, Tan A, Borrow R, Seib KL. The Serogroup B Meningococcal Vaccine Bexsero Elicits Antibodies to Neisseria gonorrhoeae. Clin Infect Dis. 2019;69(7):1101-11.
26. Abitbol V, Martinón-Torres F, Taha MK, Nolan T, Muzzi A, Bambini S, et al. 4CMenB journey to the 10-year anniversary and beyond. Hum Vaccin Immunother. 2024;20(1):2357924.
27. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Available from www.training.cochrane.org/handbook. Accessed: 20.07.2025.
28. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.
29. Team TE. EndNote. EndNote 21 ed. Philadelphia, PA: Clarivate; 2013.
30. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
31. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
32. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj. 2016;355:i4919.
33. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University and Evidence Prime, 2025. Available from gradepro.org.

34. Szondy I, Meznerics FA, Lőrincz K, Kemény LV, Walter A, Mohammed AA, et al. Doxycycline prophylaxis for the prevention of sexually transmitted infections: A systematic review and meta-analysis of randomized controlled trials. International Journal of Infectious Diseases. 2024;147:107186.

35. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-48.

36. Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol. 1986;124(5):719-23.

37. Paule RC, Mandel J. Consensus Values and Weighting Factors. J Res Natl Bur Stand (1977). 1982;87(5):377-85.

38. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.

39. Berçot B, Charreau I, Rousseau C, Delaugerre C, Chidiac C, Pialoux G, et al. High Prevalence and High Rate of Antibiotic Resistance of Mycoplasma genitalium Infections in Men Who Have Sex With Men: A Substudy of the ANRS IPERGAY Pre-exposure Prophylaxis Trial. Clin Infect Dis. 2021;73(7):e2127-e33.

40. Molina JM, Charreau I, Chidiac C, Pialoux G, Cua E, Delaugerre C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis. 2018;18(3):308-17.

41. Anne F.Luetkemeyer DD, Julia C.Dombrowski, Stephanie Cohen, Cole Grabow, Clare Brown, Cheryl Malinksi, Sharon K.Martens, Alison Cohee, Veronica Viar, Phong Pham, Susan P.Buchbinder, Diane V.Havlir, Connie L.Celum, Olusegun O.Soge. DOXYPEP & ANTIMICROBIAL RESISTANCE IN N. GONORRHOEAE, COMMENSAL NEISSERIA & S. AUREUS. Seattle, Washington, USA, 2023. Available from https://www.croiconference.org/abstract/doxypep-antimicrobial-resistance-in-n-gonorrhoeae-commensal-neisseria-s-aureus/. Accessed: 20.07.2025.

42. Luetkemeyer AF, Donnell D, Dombrowski JC, Cohen S, Grabow C, Brown CE, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med. 2023;388(14):1296-306.

43. Oware K, Adiema L, Rono B, Violette LR, McClelland RS, Donnell D, et al. Characteristics of Kenyan women using HIV PrEP enrolled in a randomized trial on

doxycycline postexposure prophylaxis for sexually transmitted infection prevention. BMC Womens Health. 2023;23(1):296.

44. Stewart J, Bukusi E, Sesay FA, Oware K, Donnell D, Soge OO, et al. Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis: study protocol for an open-label randomized trial. Trials. 2022;23(1):495.

45. Jenell Stewart KO, Deborah Donnell, Lauren R.Violette, Josephine Odoyo, Caitlin W.Scoville, Olusegun O.Soge, Victor Omollo, Felix Mogaka, Fredricka A.Sesay, R. Scott McClelland, Elizabeth A.Bukusi, Jared M.Baeten. DOXYCYCLINE POSTEXPOSURE PROPHYLAXIS FOR PREVENTION OF STIs AMONG CISGENDER WOMEN. CROI; Seattle, Washington, USA, 2023. Available from: https://www.croiconference.org/abstract/doxycycline-postexposure-prophylaxis-for-prevention-of-stis-among-cisgender-women/. Accessed: 20.07.2025.

46. Jean-Michel Molina BB, Lambert Assoumou, Algarte-Genin Michele, Emma Rubenstein, Gilles Pialoux, Christine Katlama, Laure Surgers, Cecile Bebear, Nicolas Dupin, Jean-Paul Viard, Juliette Pavie, Claudine Duvivier, Jade Ghosn, Dominique Costagliola. ANRS 174 DOXYVAC: AN OPEN-LABEL RANDOMIZED TRIAL TO PREVENT STIs IN MSM ON PrEP. CROI; Seattle, Washington, USA, 2023. Available from https://www.croiconference.org/abstract/anrs-174-doxyvac-an-open-label-randomized-trial-to-prevent-stis-in-msm-on-prep/. Accessed: 20.07.2025.

47. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. Sex Transm Dis. 2015;42(2):98-103.

48. Troy Grennan MH, Saira Mohammed, Tessa Tattersall, Joshua Edward, Amit Gupta, Michelle K. Dennehy, Marc Romney, Muhammad Morshed, Wendy Zhang, Sidhant Guliani, Jason Trigg, Viviane D. Lima, Julio S. Montaner, Reka Gustafson. DAILY DOXYCYCLINE IN MSM ON PrEP FOR PREVENTION OF SEXUALLY TRANSMITTED INFECTIONS. CROI; Virtual, 2021. Available from https://www.croiconference.org/abstract/daily-doxycycline-in-msm-on-prep-for-prevention-of-sexually-transmitted-infections/. Accessed: 20.07.2025.

49. Stewart J, Oware K, Donnell D, Violette LR, Odoyo J, Soge OO, et al. Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women. N Engl J Med. 2023;389(25):2331-40.
50. Bruxvoort KJ, Lewnard JA, Chen LH, Tseng HF, Chang J, Veltman J, et al. Prevention of Neisseria gonorrhoeae With Meningococcal B Vaccine: A Matched Cohort Study in Southern California. Clin Infect Dis. 2023;76(3):e1341-e9.
51. Correction to: Prevention of Neisseria gonorrhoeae With Meningococcal B Vaccine: A Matched Cohort Study in Southern California. Clin Infect Dis. 2023;76(3):561.
52. Raccagni AR, Galli L, Spagnuolo V, Bruzzesi E, Muccini C, Bossolasco S, 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.
53. Petousis-Harris H, Paynter J, Morgan J, Saxton P, McArdle B, Goodyear-Smith F, 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.
54. Abara WE, Bernstein KT, Lewis FMT, Schillinger JA, Feemster K, Pathela P, 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.
55. Wang B, Giles L, Andraweera P, McMillan M, Almond S, Beazley R, 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(7):1011-20.
56. Wang B, Giles L, Andraweera P, McMillan M, Almond S, Beazley R, et al. 4CMenB sustained vaccine effectiveness against invasive meningococcal B disease and gonorrhoea at three years post programme implementation. J Infect. 2023;87(2):95-102.
57. Paynter J, Goodyear-Smith F, Morgan J, Saxton P, Black S, Petousis-Harris H. Effectiveness of a Group B Outer Membrane Vesicle Meningococcal Vaccine in Preventing Hospitalization from Gonorrhea in New Zealand: A Retrospective Cohort Study. Vaccines (Basel). 2019;7(1).

58. 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.
59. Whelan J, Kløvstad H, Haugen IL, Holle MR, Storsaeter J. Ecologic Study of Meningococcal B Vaccine and Neisseria gonorrhoeae Infection, Norway. Emerg Infect Dis. 2016;22(6):1137-9.
60. Azze RFO. A meningococcal B vaccine induces cross-protection against gonorrhea. Clin Exp Vaccine Res. 2019;8(2):110-5.
61. Reyes Díaz LM, Lastre González M, Cuello M, Sierra-González VG, Ramos Pupo R, Lantero MI, et al. VA-MENGOC-BC Vaccination Induces Serum and Mucosal Anti Neisseria gonorrhoeae Immune Responses and Reduces the Incidence of Gonorrhea. Pediatr Infect Dis J. 2021;40(4):375-81.
62. Molina JM, Bercot B, Assoumou L, Rubenstein E, Algarte-Genin M, Pialoux G, 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.
63. Szondy I, Lőrincz K, Walter A, Mohammed AA, Hegyi P, Kiss N, et al. Evaluating cross-protection: Meningococcal vaccines show effectiveness in gonorrhoea prevention - A systematic review and meta-analysis. Vaccine. 2025;56:127188.
64. Luetkemeyer AF, Donnell D, Cohen SE, Dombrowski JC, Grabow C, Haser G, et al. Doxycycline to prevent bacterial sexually transmitted infections in the USA: final results from the DoxyPEP multicentre, open-label, randomised controlled trial and open-label extension. Lancet Infect Dis. 2025.
65. Raccagni AR, Diotallevi S, Lolatto R, Bruzzesi E, Catalano G, Mainardi I, et al. DoxyPEP: real-life effectiveness in a cohort of men who have sex with men in Milan, Italy. Lancet Infect Dis. 2025;25(1):e1-e3.
66. Traeger MW, Leyden WA, Volk JE, Silverberg MJ, Horberg MA, Davis TL, et al. Doxycycline Postexposure Prophylaxis and Bacterial Sexually Transmitted Infections Among Individuals Using HIV Preexposure Prophylaxis. JAMA Intern Med. 2025;185(3):273-81.

67. Spinelli MA, Heise MJ, Roman J, Bena J, Barry MP, Buchbinder SP, et al. Sustained Effectiveness of Doxycycline Post-Exposure-Prophylaxis in a Large Sexual Health Clinic over 96 Weeks: An Interrupted Time Series Analysis. Clin Infect Dis. 2025.
68. Haaland RE, Fountain J, Edwards TE, Dinh C, Martin A, Omoyege D, et al. Pharmacokinetics of single dose doxycycline in the rectum, vagina, and urethra: implications for prevention of bacterial sexually transmitted infections. EBioMedicine. 2024;101:105037.
69. Soge OO, Issema R, Bukusi E, Baeten JM, Mujugira A, Celum C, et al. Predominance of High-Level Tetracycline-Resistant Neisseria gonorrhoeae in Kenya: Implications for Global Implementation of Doxycycline Postexposure Prophylaxis for Prevention of Sexually Transmitted Infections. Sex Transm Dis. 2023;50(5):317-9.
70. Hickey MD, Salmen CR, Tessler RA, Omollo D, Bacchetti P, Magerenge R, et al. Antiretroviral concentrations in small hair samples as a feasible marker of adherence in rural Kenya. J Acquir Immune Defic Syndr. 2014;66(3):311-5.
71. Abe S, Mizushima D, Ando N, Kawashima A, Uemura H, Shibata S, et al. Doxycycline pre-exposure prophylaxis prevents sexually transmitted infections without affecting vaginal bacterial flora in female sex workers. JAC Antimicrob Resist. 2025;7(2):dlaf054.
72. Grennan T, Mohammed S, Edward J, Tattersall T, Gupta AK, Seto J, et al. A pilot, randomized controlled trial of Dual Daily HIV and sexually transmitted infection pre-exposure prophylaxis using tenofovir disoproxil fumarate/emtricitabine and doxycycline in gay, bisexual and other men who have sex with men and transgender women: The DuDHS Study. Clin Infect Dis. 2025.
73. Schillie S, Loehr J, Chen WH, Moser CA, Cooper G, Isenhour C, et al. New Dosing Interval and Schedule for the Bexsero MenB-4C Vaccine: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, October 2024. MMWR Morb Mortal Wkly Rep. 2024;73(49):1124-8.
74. Castilla J, García Cenoz M, Abad R, Sánchez-Cambronero L, Lorusso N, Izquierdo C, et al. Effectiveness of a Meningococcal Group B Vaccine (4CMenB) in Children. N Engl J Med. 2023;388(5):427-38.
75. Wang B, Giles L, Andraweera P, McMillan M, Beazley R, Sisnowski J, et al. Long-term 4CMenB Vaccine Effectiveness Against Gonococcal Infection at Four Years

Post-Program Implementation: Observational Case-Control Study. Open Forum Infect Dis. 2025;12(1):ofae726.

76. 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(7):1030-41.

77. Hui BB, Padeniya TN, Rebuli N, Gray RT, Wood JG, Donovan B, 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(6):983-93.

78. White PJ, Leng T, Nikitin D, Whittles LK. The potential role of the 4CMenB vaccine in combating gonorrhoea: the need for nuance in interpreting the DOXYVAC trial. Lancet Infect Dis. 2024;24(9):e543.

79. Marshall GS, Abbing-Karahagopian V, Marshall HS, Cenci S, Conway JH, Occhipinti E, et al. A comprehensive review of clinical and real-world safety data for the four-component serogroup B meningococcal vaccine (4CMenB). Expert Rev Vaccines. 2023;22(1):530-44.

80. Soge OO, Thibault CS, Cannon CA, McLaughlin SE, Menza TW, Dombrowski JC, et al. Potential Impact of Doxycycline Post-Exposure Prophylaxis on Tetracycline Resistance in Neisseria gonorrhoeae and Colonization With Tetracycline-Resistant Staphylococcus aureus and Group A Streptococcus. Clin Infect Dis. 2025;80(6):1188-96.

81. Chu VT, Glascock A, Donnell D, Grabow C, Brown CE, Ward R, et al. Impact of doxycycline post-exposure prophylaxis for sexually transmitted infections on the gut microbiome and antimicrobial resistome. Nat Med. 2025;31(1):207-17.

82. Sokoll PR, Migliavaca CB, Döring S, Traub U, Stark K, Sardeli AV. Efficacy of postexposure prophylaxis with doxycycline (Doxy-PEP) in reducing sexually transmitted infections: a systematic review and meta-analysis. Sex Transm Infect. 2025;101(1):59-67.

83. Boschiero MN, Sansone NMS, Matos LR, Marson FAL. Efficacy of Doxycycline as Preexposure and/or Postexposure Prophylaxis to Prevent Sexually Transmitted Diseases: A Systematic Review and Meta-Analysis. Sex Transm Dis. 2025;52(2):65-72.

84. 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. 2025;231(1):61-70.
85. 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 Infect. 2024;89(3):106225.
86. Hegyi P, Erőss B, Izbéki F, Párniczky A, Szentesi A. Accelerating the translational medicine cycle: the Academia Europaea pilot. Nat Med. 2021;27(8):1317-9.
87. Hegyi P, Petersen OH, Holgate S, Erőss B, Garami A, Szakács Z, et al. Academia Europaea Position Paper on Translational Medicine: The Cycle Model for Translating Scientific Results into Community Benefits. J Clin Med. 2020;9(5).
88. Bachmann LH, Barbee LA, Chan P, Reno H, Workowski KA, Hoover K, et al. CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024. MMWR Recomm Rep. 2024;73(2):1-8.
89. Sherrard J, Gokengin D, Winter A, Marks M, Unemo M, Jensen JS, et al. IUSTI Europe position statement on use of DoxyPEP: June 2024. Int J STD AIDS. 2024;35(13):1087-9.
90. Wise J. Gonorrhoea: England rolls out "world first" vaccination programme. Bmj. 2025;389:r1064.

16. BIBLIOGRAPHY

16.1. Publications related to the thesis

Szondy, I., Meznerics, F. A., Lőrincz, K., Kemény, L. V., Walter, A., Mohammed, A. A., … Bánvölgyi, A. (2024). Doxycycline prophylaxis for the prevention of sexually transmitted infections: a systematic review and meta-analysis of randomised controlled trials. *INTERNATIONAL JOURNAL OF INFECTIOUS DISEASES*, *147*. http://doi.org/10.1016/j.ijid.2024.107186

SJR: Q1, IF: 4.3

Szondy, I., Lőrincz, K., Walter, A., Mohammed, A. A., Hegyi, P., Kiss, N., … Bánvölgyi, A. (2025). Evaluating cross-protection: Meningococcal vaccines show effectiveness in gonorrhoea prevention - A systematic review and meta-analysis. *VACCINE*, *56*. http://doi.org/10.1016/j.vaccine.2025.127188

SJR: D1, IF: 3.5

16.2. Publications not related to the thesis

Mohammed, A. A., Lengyel, A. S., Meznerics, F. A., Szondy, I., Walter, A., Szabó, B., … Kurgyis, Z. (2025). Efficacy and Safety of JAK Inhibitors in the Management of Vitiligo: A Systematic Review and Meta-analysis. *DERMATOLOGY AND THERAPY*, *15*(7), 1657–1679. http://doi.org/10.1007/s13555-025-01397-z

SJR: D1, IF: 4.2

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