New Frontiers in the Prevention of Sexually Transmitted Infections

Ph.D. Thesis Booklet

István Szondy M.D.

Translational Medicine Program

Károly Rácz Conservative Medicine Doctoral School

SEMMELWEIS UNIVERSITY

Supervisor:	András Bánvölgyi M.D., Ph.D.
Official reviewers:	Prof. Lajos Kemény, M.D., Ph.D., D.Sc. Roxana Nedelcu, M.D., Ph.D.
Head of the Complex Examination Committee:	Andrea Harnos, Ph.D.
Members of the Complex Examination Committee:	Prof. Alan Irvine, M.D., Ph.D., D.Sc. Prof. Gábor Varga, Ph.D., D.Sc.

Budapest

2025

1. Introduction

1.1. What is the topic?

Sexually transmitted infections (STIs) represent a significant global health burden, with far-reaching personal, social, and economic consequences. The consistently high prevalence of bacterial STIs has highlighted the need for effective new preventive measures.

Consequently, doxycycline pre-exposure prophylaxis (doxy-PrEP) and doxycycline post-exposure prophylaxis (doxy-PEP) have been developed for the prevention of bacterial STIs, particularly targeting *Treponema pallidum* and *Chlamydia trachomatis*, both of which remain consistently susceptible to doxycycline. 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 sex.

At the same time, outer membrane vesicle (OMV) meningococcal vaccines have emerged as a potential

supplementary preventive strategy against gonorrhoea. The high degree of genetic and structural similarity between *Neisseria meningitidis* and *Neisseria gonorrhoeae*, particularly the similarities in the OMVs they produce, has led to the hypothesis that OMV meningococcal vaccines, including the most widely available 4CMenB vaccine, might offer cross-protection.

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. The burden of STIs disproportionately affects men who have sex with men (MSM) and transgender women (TGW), with syphilis prevalence estimated to be fifteen times higher, gonorrhoea nearly ten times higher, and chlamydia approximately four times higher among MSM compared to the general population.

1.3. What is the importance of the topic?

Developing effective preventive tools for bacterial STIs is critical to reducing their long-term health burden,

particularly by preventing new cases of early neurosyphilis, ocular syphilis and otosyphilis, which may lead to severe, irreversible complications. Furthermore, amidst high media attention, these interventions are becoming more popular among MSM and are being used without medical supervision, urging clinicians to take action.

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

Demonstrating the effectiveness of doxy-PrEP, doxy-PEP, and OMV meningococcal vaccines in preventing bacterial STIs could be followed by significant public health benefits. High-quality evidence generated from this research may support the development of international and national clinical guidelines, improve targeted prevention strategies for high-risk populations, and ultimately reduce the incidence of bacterial STIs at both individual and population levels.

2. Objectives

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

Our primary objective was to evaluate the effectiveness of doxy-PrEP and doxy-PEP in reducing the incidence of bacterial STIs, specifically syphilis, chlamydia, and gonorrhoea. Additionally, we aimed to assess patient adherence, the safety profile of doxycycline prophylaxis, and the potential risk of antimicrobial resistance (AMR) emerging in both STI-related and unrelated pathogens.

2.2. 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 evaluate the effectiveness of OMV meningococcal vaccines in preventing gonorrhoea, including the strength and consistency of protection, the duration of immunity, and differences in effectiveness between partial and complete vaccination.

3. Methods

Two systematic reviews and meta-analyses were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 and the Cochrane Handbook for Systematic Reviews of Interventions. Protocols were registered in PROSPERO (Study I: CRD42023478486; Study II: CRD42024530848).

3.1. Literature search

Systematic searches were carried out in PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). No filters or restrictions were used.

3.2. Eligibility criteria

Studies were eligible for inclusion if they matched the following Population – Intervention – Comparator – Outcome (PICO) frameworks. In study I, (P) sexually active adults; (I) Doxy-PrEP or Doxy-PEP) (C) no prophylaxis; (O) primary outcomes: the incidence of *N. gonorrhoeae*, *T. pallidum*, and *C. trachomatis*. Secondary outcomes: adverse events, emergence of new AMR, and

adherence to prophylaxis. Only randomised controlled trials (RCTs) were included. Grey literature was included.

In study II, (P) individuals eligible for meningococcal vaccines, (I) OMV meningococcal vaccine, (C) no OMV vaccine (no vaccine or non-OMV vaccine), (O) incidence of gonococcal infection. Grey literature was excluded.

3.3. Study selection and data extraction

After conducting the systematic search, all identified records were imported into a reference management software, EndNote 21. Duplicate entries were eliminated first automatically, then manually. Two reviewers independently screened the articles, first by examining the titles and abstracts, and then by reviewing the full texts using Rayyan software. Any discrepancies were resolved by a third reviewer.

For data extraction and synthesis, a standardised 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. Any discrepancies were resolved by a third reviewer.

3.4. Risk of bias and quality assessment

Risk of bias was assessed using the Risk of Bias 2 (RoB 2) tool for the RCTs included in Study I and Study II, and the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool for the non-randomised studies in Study II. Two independent reviewers performed the assessments, resolving disagreements with a third reviewer. Publication bias was assessed using funnel plots, and the overall quality of evidence was evaluated using GRADEpro, in accordance with Cochrane recommendations.

3.5. Data synthesis and analysis

All analyses were conducted in R using base functions, the meta package, and the dmetar package for additional diagnostics. A minimum of three studies was required for meta-analysis, with random-effects models applied throughout due to expected heterogeneity. In Study I, risk ratios (RRs) with 95% confidence intervals (CIs) were

calculated based on STI events per visit or per participant, depending on data availability. In Study II, odds ratios (ORs) were used, and vaccine effectiveness (VE) was calculated as (1 − OR) × 100%. ORs were derived from raw data or taken directly from publications when raw data were unavailable. Pooled RRs and ORs were calculated using the Mantel-Haenszel method, with the Paule-Mandel estimator for between-study variance. The results were displayed in forest plots, with prediction intervals also reported. Heterogeneity was assessed with the I^2 statistic proposed by Higgins and Thompson. Sensitivity analyses and subgroup comparisons were conducted to explore heterogeneity and assess robustness.

4. Results

4.1. Study I.

The systematic search yielded 552 records, and seven peer-reviewed articles and four conference abstracts representing six RCTs were included. The six studies comprised 1,766 participants and 602 incident STIs recorded across 4,612 visits. Five studies enrolled MSM or TGW, while one study included cisgender women (CGW).

When pooling data from doxy-PrEP and doxy-PEP studies, an STI was diagnosed in 9.6% of visits in the intervention groups compared to 17.7% in controls (RR = 0.44; 95% CI: 0.30-0.65; I^2 = 73%). For chlamydia, rates were 2.6% vs. 8.1% (RR = 0.24; 95% CI: 0.12-0.51; I^2 = 78%), and for syphilis, 1.0% vs. 4.1% (RR = 0.24; 95% CI: 0.18–0.32; I^2 = 0%). Gonorrhoea rates were 6.7% in the intervention group and 8.5% in controls (RR = 0.65; 95% CI: 0.41-1.04; I^2 = 59%).

Restricting the analysis 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%). 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. The pooled RR for gonorrhoea was 0.55 (95% CI: 0.34-0.87; I^2 = 41%).

Due to the limited number of available studies on doxy-PrEP, a separate meta-analysis could not be performed.

Doxy-PrEP and doxy-PEP were found to be safe, with most adverse events (AEs) reported as mild and self-limiting. Gastrointestinal symptoms were the most frequently observed drug-related AEs. No serious AEs were attributed to doxycycline use, and none of the included studies reported new HIV infections. Discontinuation rates due to AEs were low across studies.

One study observed an increase in tetracycline-resistant *N. gonorrhoeae*, commensal *Neisseria species*, and *S. aureus* within the doxy-PEP arm. However, it remains uncertain whether this reflects newly emergent resistance and to what extent it can be attributed to doxy-PEP exposure.

In the doxy-PrEP/PEP groups, 82% of participants (95% CI: 77%-86%) reported consistent use. One study evaluated hair samples for adherence and detected doxycycline at least once in 56% of participants.

Four included studies were assessed as having a low risk of bias, one had a moderate risk, and one had a high risk of bias. No evidence of publication bias was observed based on visual inspection of the funnel plots. The certainty of evidence was rated as moderate for the pooled analysis of doxy-PrEP and doxy-PEP, and high when limited to doxy-PEP studies involving MSM and TGW.

4.2. Study II.

The initial systematic search yielded 3,392 records, with an additional 100 records identified during an updated search. Eight retrospective case-control or cohort studies, three ecologic studies and one RCT met the inclusion criteria. Seven studies assessed the 4CMenB vaccine, two the VA-MENGOC-BC, two the MeNZB, and one assessed the MenBvac vaccine, all of which are OMV meningococcal vaccines.

The pooled OR was 0.62 (0.50-0.78; $I^2 = 55\%$), meaning a VE of 38 % (95% CI: 22%-50%; $I^2 = 55\%$). Restricting the analysis to the 4CMenB vaccine, the estimated VE was 41% (OR = 0.59; 95% CI: 0.46-0.76; $I^2 = 44\%$). Complete vaccination might be associated with a 24% greater VE compared to partial vaccination (OR = 0.76; 95% CI: 0.31-1.85; $I^2 = 86\%$).

The leave-one-out analysis identified one study as the main source of heterogeneity. Its exclusion yielded a pooled VE of 30% (OR = 0.70; 95% CI: 0.62-0.78) with substantially reduced heterogeneity ($I^2 = 0\%$).

The included studies reported highly variable follow-up durations, which prevented a quantitative analysis. Available evidence suggests that the protection offered by meningococcal vaccines diminishes over time and may become negligible after five years.

Four studies were rated as having low risk of bias, four as moderate, and four as having high risk of bias. Funnel plot analysis revealed no evidence of publication bias. The certainty of the evidence was rated as moderate.

5. Conclusions

Doxy-PEP has been shown to be a safe and effective method for preventing syphilis and chlamydia among high-risk MSM and TGW. It may also provide protection against gonorrhoea, particularly in settings with low prevalence of tetracycline resistance. Although there is currently no direct evidence linking doxy-PEP to the development of new AMR, ongoing monitoring is crucial. OMV meningococcal vaccines have demonstrated moderate effectiveness in preventing gonorrhoea, with protection sustained over a meaningful duration. Full vaccination appears to offer stronger protection compared to incomplete vaccination. Implementing a combined approach that includes both doxy-PEP and the 4CMenB vaccine in high-risk populations could significantly reduce the incidence of bacterial STIs at both the individual and community levels.

6. Bibliography

6.1. Publications related to the thesis

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

D1, IF: 3.5

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

Q1, IF: 4.3