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

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Summary

Background Increased rates of sexually transmitted infections (STIs) are reported among men who have sex with men (MSM) and new interventions are needed. We aimed to assess whether post-exposure prophylaxis (PEP) with doxycycline could reduce the incidence of chlamydia or syphilis (or both) and whether the meningococcal group B vaccine (4CMenB) could reduce the incidence of gonorrhoea in this population.

Methods ANRS 174 DOXYVAC is a multicentre, open-label, randomised trial with a 2×2 factorial design conducted at ten hospital sites in Paris, France. Eligible participants were MSM aged 18 years or older, HIV negative, had a history of bacterial STIs within the 12 months before enrolment, and who were already included in the ANRS PREVENIR study (a cohort of MSM using pre-exposure prophylaxis with tenofovir and emtricitabine for HIV prevention). Participants were randomly assigned (2:1) to doxycycline PEP (two pills of 100 mg each orally within 72 h after condomless sex, with no more than three doses of 200 mg per week) or no PEP groups and were also randomly assigned (1:1) to the 4CMenB vaccine (GlaxoSmithKline, Paris, France; two intramuscular injections at enrolment and at 2 months) or no vaccine groups, using a computer-generated randomisation list with a permuted fixed block size of four. Follow-up occurred for at least 12 months (with visits every 3 months) up to 24 months. The coprimary outcomes were the risk of a first episode of chlamydia or syphilis (or both) after the enrolment visit at baseline for the doxycycline intervention and the risk of a first episode of gonorrhoea starting at month 3 (ie, 1 month after the second vaccine dose) for the vaccine intervention, analysed in the modified intention-to-treat population (defined as all randomly assigned participants who had at least one follow-up visit). This trial is registered with ClinicalTrials.gov, NCT04597424 (ongoing).

Findings Between Jan 19, 2021, and Sept 19, 2022, 556 participants were randomly assigned. 545 (98%) participants were included in the modified intention-to-treat analysis for the doxycycline PEP and no PEP groups and 544 (98%) were included for the 4CMenB vaccine and no vaccine groups. The median follow-up was 14 months (IQR 9–18). The median age was 40 years (34–48) and all 545 participants were male. There was no interaction between the two interventions (p≥0·1) for the primary outcome. The incidence of a first episode of chlamydia or syphilis (or both) was 8·8 per 100 person-years (35 events in 362 participants) in the doxycycline PEP group and 53·2 per 100 person-years (80 events in 183 participants) in the no PEP group (adjusted hazard ratio [aHR] 0·17 [95% CI 0·12–0·26]; p<0·0001). The incidence of a first episode of gonorrhoea, starting from month 3 was 58·3 per 100 person-years (103 events in 274 participants) in the 4CmenB vaccine group and 77·1 per 100 person-years (122 events in 270 participants) in the no vaccine group (aHR 0·78 [95% CI 0·60–1·01]; p=0·061). There were no deaths during the study. One drug-related serious adverse event (fixed-drug eruption) occurred in the doxycycline PEP group. Six (2%) participants in the doxycycline group discontinued doxycycline PEP because of gastrointestinal adverse events.

Interpretation Doxycycline PEP strongly reduced the incidence of chlamydia and syphilis in MSM, but we did not show efficacy of the 4CmenB vaccine for gonorrhoea. Doxycycline PEP should be assessed in other populations, such as heterosexual men and women, and its effect on antimicrobial resistance carefully monitored.

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For the French translation of the abstract see **Online** for appendix 1 (p 1)

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Introduction

Sexually transmitted infections (STIs) have a profound impact on sexual and reproductive health and remain a major public health challenge.[1,2] Increases in STI rates have been reported in several populations—eg, in men who have sex with men (MSM) with syphilis increasing

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See Online for appendix 2

Research in context

Evidence before this study

There is a rise in sexually transmitted infections (STIs) globally and new interventions aiming at reducing STI rates should be identified and if successful, implemented. We previously reported the efficacy of doxycycline post-exposure prophylaxis (PEP) for the high risk population of men who have sex with men (MSM) at reducing chlamydia and syphilis incidence, but not gonorrhoea. Antibiotic prophylaxis has been used for decades as a biomedical intervention to contain the spread of STIs with only short-term success for gonorrhoea because of the selection and dissemination of antibiotic resistant strains. Pending the availability of vaccines to prevent STIs or sustained changes in sexual behaviour, doxycycline PEP might be a useful tool to reduce STI rates. Confirmatory studies need to be conducted before implementation of this strategy. Additionally, observational studies have suggested that the meningococcal group B outer membrane vesicle vaccine, 4CMenB, could induce a cross protection against gonorrhoea but prospective data are not available. We searched PubMed on March 16, 2024, using the terms "post-exposure doxycycline" AND "sexually transmitted infections" for articles published from database inception to March 16, 2024. This search found 48 publications, but only three described randomised trials, including the initial study we reported in 2018. One trial published in 2023 among MSM and transgender women in the USA reported a significant reduction in chlamydia, syphilis, and gonorrhoea incidence after post-exposure prophylaxis with doxycycline. A trial in young women in Kenya showed no effectiveness of post-exposure doxycycline on chlamydia and gonorrhoea incidence, but adherence to doxycycline was low. A PubMed search on March 16, 2024, for "meningococcal B vaccination" AND "gonorrhoea" found 70 publications, but no prospective randomised trials.

Added value of this study

This study is the third randomised open-label trial, and the largest, to confirm the efficacy and safety of post-exposure doxycycline prophylaxis (200 mg within 24–72 h after sex) to reduce STI rates among MSM. We showed a significant reduction of syphilis and chlamydia incidence with this strategy in 556 MSM using pre-exposure prophylaxis for HIV prevention. There was also a significant relative reduction in gonorrhoea incidence, but post-exposure doxycycline was associated with an increase in high-level resistance of *Neisseria gonorrhoeae* to tetracycline. We could not show that the 4CMenB vaccine reduced the incidence of gonorrhoea. A lower effectiveness of this vaccine than previously shown in observational studies cannot be ruled out, but its clinical relevance and public health impact would be very small.

Implications of all the available evidence

Early data from implementation studies in the USA show the potential public health impact of this strategy in MSM and transgender women at reducing syphilis and chlamydia infections. Close monitoring of antimicrobial resistance remains warranted to detect emergence of STI resistance and to assess the effect on the microbiome. Indeed, contrary to *N gonorrhoeae*, no resistance to tetracycline has so far been reported for *Treponema pallidum* and *Chlamydia trachomatis*—bacteria that are less prone to develop antibiotic resistance. Additional studies are needed in other populations and countries to guide recommendations. Pending the results of ongoing trials (NCT04415424 and NCT04350138) with meningococcal group B vaccine against gonorrhoea, the evidence is low to recommend this vaccination against gonorrhoea and alternative vaccines should be developed.

at an alarming rate, in women with increasing numbers of congenital syphilis, along with a worsening of antimicrobial resistance for gonorrhoea.[3–6] New biomedical interventions, such as antibiotic prophylaxis and vaccines, need to be assessed to reduce the incidence of STIs.

Although antibiotic prophylaxis for gonorrhoea, including minocycline, has been abandoned due to the rapid selection of antibiotic resistance limiting treatment options, there is still no known resistance of *Chlamydia trachomatis* and *Treponema pallidum* to doxycycline despite five decades of use for treatment.[7–10] Doxycycline post-exposure prophylaxis (PEP) has been shown in two open-label randomised trials[11,12] to have a high efficacy in reducing the incidence of chlamydia and syphilis among MSM with conflicting results regarding gonorrhoea, and confirmation studies are needed. Observational studies have consistently reported a substantial, although moderate, reduction in gonorrhoea rate among individuals who received the meningococcal group B vaccine.[13–15] This cross-protection is most likely due to the genetic homology between outer membrane vesicle (OMV) proteins and recombinant Neisserial heparin binding antigen protein from *Neisseria meningitidis* group B and *Neisseria gonorrhoeae*.[16,17]

We aimed to assess whether the use of PEP with doxycycline could reduce the incidence of chlamydia or syphilis (or both) and whether the meningococcal group B vaccine (4CMenB) could reduce the incidence of gonorrhoea in MSM using pre-exposure prophylaxis (PrEP) for HIV prevention.

Methods

Study design and participants

ANRS 174 DOXYVAC is a multicentre, open-label, randomised trial with a 2×2 factorial design conducted at ten hospital sites in Paris, France. Eligible participants were MSM aged 18 years or older, HIV negative, and already included in the ANRS PREVENIR study (a cohort of MSM using PrEP with tenofovir and emtricitabine for

HIV prevention).[18] Participants had to have a history of bacterial STIs within the 12 months before enrolment into DOXYVAC. Main exclusion criteria were previous meningococcal group B vaccination, current treatment with doxycycline, and a doxycycline allergy or other contraindication for use. This trial was designed by academic investigators and the clinical trial unit led the conduct of the trial. An independent trial steering committee provided trial oversight and reviewed the safety data. The trial was approved by French health authorities (ANSM) and by an ethics committee (Comité de protection des personnes). All participants provided written informed consent. This trial is registered with ClinicalTrials.gov, NCT04597424 (ongoing).

Randomisation and masking

Participants were randomly assigned (2:1) to doxycycline PEP or no PEP groups and were also randomly assigned (1:1) to the 4CMenB vaccine or no vaccine groups. Overall, the four groups were: vaccine alone, vaccine plus doxycycline, doxycycline alone, and no intervention (no vaccine or doxycycline). Randomisation was done using a computer-generated randomisation list with a permuted fixed block size of four, only known by the trial statistician (MoO). Participants and study staff were not masked to treatment assignment.

Procedures

Participants in the doxycycline group received doxycycline (100 mg per pill; Mylan Génériques, Lyon, France) and were instructed to take two pills (200 mg) orally as PEP, within 72 h after condomless sex and preferably within 24 h, with no more than three doses of 200 mg per week. At enrolment and at each follow-up visit (ie, every 3 months for at least 12 months until 24 months after random assignment), participants received doxycycline pills to cover their use until the next visit. Participants in the vaccine group received two intramuscular injections of the meningococcal group B vaccine (4CMenB, Bexsero, GlaxoSmithKline, Paris, France) 2 months apart at enrolment and at 2 months after randomisation.

This trial was proposed to participants enrolled in the ANRS PREVENIR study when attending any scheduled visit. Visits in this trial were then scheduled at month 2 (only for those randomly assigned to the vaccine group to receive the second dose), month 3, and every 3 months thereafter. Unscheduled visits could also occur whenever participants had STI symptoms. At each visit participants had a physical examination and were asked about symptoms related to STIs.

At each visit, participants were tested for syphilis using serological assays (ie, treponemal and non-treponemal tests) and for chlamydial and gonorrhoeal infection with a specific PCR assay performed centrally on rectal and throat swabs and first-void urine samples, unless they refused.[11] Centralised cultures were also attempted for gonorrhoea and minimum inhibitory concentrations (MICs) were determined using the E-test method (bioMérieux, Marcy-l'Étoile, Lyon, France). Tetracycline resistance was defined according to European Committee on Antimicrobial Susceptibility Testing 2023 breakpoints (low-level resistance was defined as $MIC_{tetracycline}$>0·5 mg/L and high-level resistance was defined as $MIC_{tetracycline}$>8 mg/L).

For PCR samples positive for *C trachomatis*, another specimen was collected in Universal Transport Medium (Copan, Brescia, Italy) before treatment. Throat and rectal samples were centralised to the National Reference Centre for Chlamydia (Centre hospitalier de Bordeaux, Bordeaux, France) to perform cell culture for assessing tetracycline MICs in vitro.[19] Sequencing of the 16S rRNA of PCR positive swabs was performed to detect tetracycline resistance mutations.[19] All laboratory staff were masked to study treatment groups.

Syphilis was diagnosed according to the US Centers for Disease Control and Prevention (CDC) guidelines.[20] Chlamydial and gonorrhoeal infections were defined by a single positive PCR test from at least one site (throat, urine, or anus). All STI infections were reviewed by a masked event review committee and treated according to the US CDC guidelines.[20]

Adherence to doxycycline was assessed at each visit during face-to-face interviews with standard questions (self-reported use of doxycycline at the most recent sexual intercourse and timing of doxycycline use) by measuring pill count of unused returned medication and doxycycline concentration in plasma and urine in a subgroup of participants (due to time constraints) at baseline and month 6, as previously described.[11] The limit of quantification for doxycycline was 2·5 ng/mL in plasma and 50 ng/mL in urine.

Sexual behaviour was assessed at each visit and included the number of condomless sexual acts in the past 4 weeks and the number of sexual partners in the past 3 months. Adverse events were graded using the ANRS scale, regardless of relation to the study drugs.[21]

Outcomes

The coprimary outcomes were the risk of a first episode of chlamydia or syphilis (or both) after the enrolment visit at baseline for the doxycycline intervention and the risk of a first episode of gonorrhoea starting at month 3 (ie, 1 month after the second vaccine dose) for the vaccine intervention (4CMenB *vs* no vaccine groups). STIs diagnosed at the enrolment visit were not included in the assessment of the primary outcome (ie, not counted in the STI incidence).

The main secondary outcomes were the incidence of a first episode of gonorrhoea in the doxycycline PEP versus no PEP groups, cumulative incidence of gonorrhoea in all four study groups, incidence of symptomatic chlamydia and gonorrhoea, culture positive gonorrhoea, and site of infection (urine, anus, or throat) for chlamydia and gonorrhoea. In addition, the rates of detection of

For the **trial registration** see https://classic.clinicaltrials.gov/ct2/show/NCT04597424

methicillin-resistant *S aureus* (MRSA) in pharyngeal swabs and of extended-spectrum β-lactamase *E coli* in rectal swabs were assessed over time to measure the potential effect of doxycycline on multidrug-resistant bacteria. Other secondary endpoints such as the effectiveness of doxycycline PEP on *M genitalium*, the full assessment of doxycycline PEP on *N gonorrhoeae* and *S aureus* antimicrobial resistance, and the effectiveness of the 4CmenB vaccine and doxycycline PEP on *N meningitidis* pharyngeal carriage are still being analysed and are not reported in this manuscript.

Statistical analysis

The sample size was calculated to show vaccine efficacy. We assumed that the probability of gonorrhoea at 18 months would be 52%.[11] We needed to enrol 720 participants to show a hazard ratio of 0·70 with the 4CmenB vaccine (similar to that reported in the New Zealand study[13]), which would provide a power of 85% using a two-tailed log-rank test, a type I error of 5%, and a probability of loss to follow-up of 18%. This sample size assumed that doxycycline PEP had no statistically significant effect on gonorrhoea incidence.[11]

Analysis of the primary outcomes was performed in the modified intention-to-treat (mITT) population, which included all randomly assigned participants who had at least one follow-up visit regardless of adherence to medication. We used the Kaplan–Meier method to estimate the probability of the first coprimary outcome. A test for interaction between the two interventions using a Cox proportional hazards model including doxycycline PEP (yes *vs* no), 4CmenB vaccine (yes *vs* no), and the interaction term was performed to determine whether the comparison of each prevention strategy could be analysed independently of the other. In cases of $p_{interaction} \geq 0{\cdot}1$, adjusted hazard ratios (aHRs) and 95% CIs were estimated using a Cox proportional hazards model adjusting for the other intervention to compare the occurrence of the primary endpoint between groups. The assumption for the proportional hazards was examined. When assessing the effect of doxycycline PEP, time was counted from randomisation to occurrence of the first event or last follow-up, whichever occurred first and when assessing the effect of the 4CmenB vaccine, time was counted from month 3 visit to occurrence of the first event or last follow-up, whichever occurred first.

Poisson regression with a log link and person-years as the offset was used to assess the effect of vaccine or doxycycline PEP on cumulative episodes of gonorrhoea, chlamydia, and syphilis. As for the Cox model, we first assessed the interaction between the two interventions in a model including each intervention (yes or no) and the interaction term. In case of $p_{interaction} \geq 0{\cdot}1$ between the two prevention strategies, adjusted incidence rate ratios and 95% CIs were estimated using a Poisson regression model adjusting only for the other intervention. For these analyses, time was counted from randomisation to the last follow-up.

Subgroup analyses for each of the two coprimary outcomes were performed to assess the effect of each intervention across the subgroups defined at baseline (age; country of birth; ethnicity; education level; employment status; chemsex use at the most recent sex act; number of sexual partners in the past 3 months; number of condomless sex acts in the past 4 weeks; number of STIs in the past 12 months; and chlamydia, syphilis, or gonorrhoea in the past 12 months). Changes from baseline in the number of sexual partners in the past 3 months and in the number of condomless sexual acts in the past 4 weeks over time were compared between the doxycycline PEP and no PEP groups and the 4CmenB vaccine and no vaccine groups using a negative binomial regression model, while accounting for within-patient variability with an unstructured correlation structure, adjusted for the other intervention. These models included each intervention, time as a categorical variable, interaction between intervention of interest and time. We used χ^2 tests to compare the proportion of participants with detectable doxycycline concentration and the proportion of tetracycline resistant strains. The evolution of the proportion of MRSA detected in throat swabs and of extended-spectrum β-lactamase *E coli* detected in rectal swabs were compared between the doxycycline PEP and no PEP groups using a generalized estimating equation model with independent covariance structure, binomial distribution, and log link (including doxycycline, time, interaction between doxycycline and time, and vaccine as factors). Secondary and other analyses are described in the statistical analysis plan (appendix 2 p 15).

The study data were reviewed every 6 months by an independent data and safety monitoring board (DSMB). On Aug 5, 2022, after presentation of results from the Doxy-PEP study,[12] the DSMB requested a first unblinded interim analysis of the data (collected until July 15, 2022), which was presented on Sept 2, 2022. The interim analysis showed a statistically significant reduction in the incidence of a first episode of syphilis or chlamydia (or both) infection with doxycycline PEP ($p<0{\cdot}0001$) and a reduction in the incidence of a first gonorrhoea episode in participants who received the 4CMenB vaccine ($p=0{\cdot}016$). Based on this interim analysis, the DSMB recommended to stop enrolment of new participants and asked that all participants perform a final visit and are offered the two prevention strategies. This recommendation was endorsed by the scientific committee and ANRS Maladies Infectieuses Emergentes, and results from the interim analysis were presented on Feb 20, 2023.[22] When final results from this trial were available (data collected until Feb 28, 2023, and available for the funder from May 15, 2023), a discrepancy was found regarding the vaccine efficacy

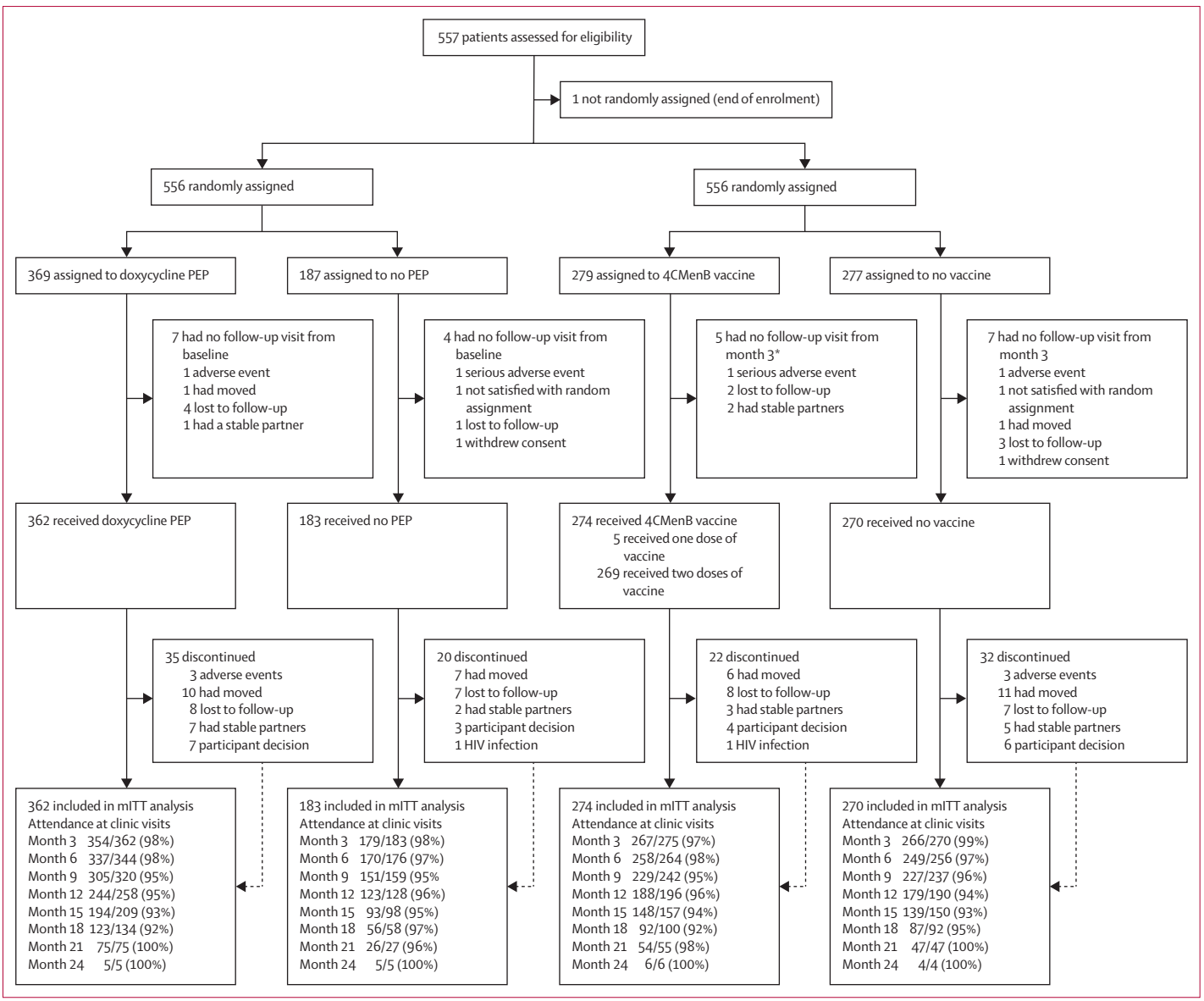

Figure 1: **Trial profile**
Attendance at clinic visits is shown for all participants who remained in the study. mITT=modified intention-to-treat. PEP=post-exposure prophylaxis. *One participant left the study before the month 3 visit (not included in vaccine efficacy but included in doxycycline PEP efficacy) due to having a stable partner.

reported in the interim analysis. This discrepancy prompted an audit of the clinical trial unit and an independent assessment of data collection and analysis which confirmed the final findings reported in this manuscript. Unfortunately, the audit found that several STI episodes (part of endpoints) had not been included accidentally by the statistician at the time of the interim analysis which misled the DSMB, the scientific committee, and the funder. The final analysis presented here included all events collected during the study. Analyses were conducted using Stata SE (version 13.0) and SAS software. All p values are two-sided with a significance threshold of 0·05.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Jan 19, 2021, and Sept 19, 2022, 557 adults were assessed for eligibility, and one was ineligible for random assignment. Of the 556 randomly assigned participants, 545 (98%) were included in the mITT analysis for the doxycycline PEP and no PEP groups and 544 (98%) were included for the 4CMenB vaccine and no vaccine groups. Overall, 66 (12%) of 556 randomly assigned participants

	Doxycycline PEP group (n=362)	No PEP group (n=183)	4CMenB vaccine group (n=274)*	No vaccine group (n=270)
Age, years	40 (34–49)	40 (34–48)	41 (34–48)	40 (34–49)
MSM	362 (100%)	183 (100%)	274 (100%)	270 (100%)
Race	361	183	274	269
White	316 (88%)	165 (90%)	244 (89%)	236 (88%)
Black	8 (2%)	5 (3%)	5 (2%)	8 (3%)
Asian	9 (2%)	4 (2%)	4 (1%)	9 (3%)
Other or unknown	28 (8%)	9 (5%)	21 (8%)	16 (6%)
Education level	267	135	202	199
2-year university degree or higher	237 (89%)	119 (88%)	181 (90%)	174 (87%)
High-school diploma	30 (11%)	16 (12%)	21 (10%)	25 (13%)
Employed	264	132	200	195
No	31 (12%)	15 (11%)	19 (10%)	27 (14%)
Yes	233 (88%)	117 (89%)	181 (91%)	168 (86%)
Place of residence	266	134	199	200
Outside Ile de France	1 (<1%)	2 (1%)	1 (1%)	2 (1%)
Ile de France (outside Paris)	64 (24%)	35 (26%)	48 (24%)	51 (26%)
Paris	201 (76%)	97 (72%)	150 (75%)	147 (74%)
Place of birth	361	183	274	269
North Africa	9 (2%)	2 (1%)	4 (1%)	7 (3%)
Sub-Saharan Africa	8 (2%)	5 (3%)	5 (2%)	8 (3%)
North America	2 (1%)	0	1 (<1%)	1 (<1%)
Latin America and the Caribbean	14 (4%)	6 (3%)	12 (4%)	8 (3%)
Asia	9 (2%)	4 (2%)	4 (1%)	9 (3%)
DOM-TOM	3 (<1%)	1 (<1%)	4 (1%)	0
Europe (outside France)	12 (3%)	16 (9%)	14 (5%)	14 (5%)
France (outside DOM-TOM)	304 (84%)	149 (81%)	230 (84%)	222 (83%)
PrEP† use for HIV prevention, months	32 (0–43)	36 (0–45)	31 (0–45)	33 (0–44)
Number of bacterial STIs in the past 12 months	2·0 (1·0–2·0)	1·5 (1·0–2·0)	2·0 (1·0–3·0)	2·0 (1·0–2·0)
Types of STIs	362	182	274	269
Gonorrhoea	245 (68%)	124 (68%)	185 (68%)	183 (68%)
Chlamydia	181 (50%)	88 (48%)	141 (52%)	127 (47%)
Syphilis	80 (22%)	33 (18%)	59 (22%)	54 (20%)
Sexual risk factors	361	182	273	269
Number of partners in the past 3 months	10 (5–20)	10 (5–20)	10 (5–20)	10 (5–20)
Condomless sexual intercourse in the past 4 weeks	4 (2–10)	4 (1–10)	4 (1–10)	4 (2–10)
Condom use during the most recent anal intercourse	101 (28%)	61 (33%)	81 (30%)	80 (30%)
Use of recreational drugs during the most recent sex act‡	79 (22%)	41 (22%)	54 (20%)	66 (24%)
Patients with bacterial STIs diagnosed at enrolment	362	183	274	270
Any STI§	82 (23%)	37 (20%)	56 (20%)	62 (23%)
Gonorrhoea	48 (13%)	23 (13%)	35 (13%)	35 (13%)
Chlamydia	36 (10%)	17 (9%)	25 (9%)	28 (10%)
Syphilis	7 (2%)	0	2 (1%)	5 (2%)

Data are median (IQR) or n (%). Denominators are shown for the data available in each category. DOM-TOM=Départements d'outre-mer, Territoires d'outre-mer (French overseas departments and territories). MSM=men who have sex with men. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection. *One participant discontinued follow-up at month 2 and was not included in the analysis of the vaccine intervention. †Use of oral tenofovir disoproxil and emtricitabine for HIV prevention. ‡Recreational drugs used for sex included ecstasy, crack, cocaine, gamma hydroxybutyrate, MDMA (3,4-methylenedioxymethamphetamine), and mephedrone. §Bacterial STIs included *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*.

Table 1: **Baseline participant characteristics in the modified intention-to-treat population**

discontinued the study during follow-up or had no follow-up visit from baseline (figure 1). Median follow-up was 14 months (IQR 9–18) for all four groups combined. Baseline participant characteristics were well balanced between the groups in each factorial comparison (table 1). The median age was 40 years (34–48) and all 545 participants were male. Participants were White (481 [88%]), Black (13 [2%]), Asian, or other or unknown

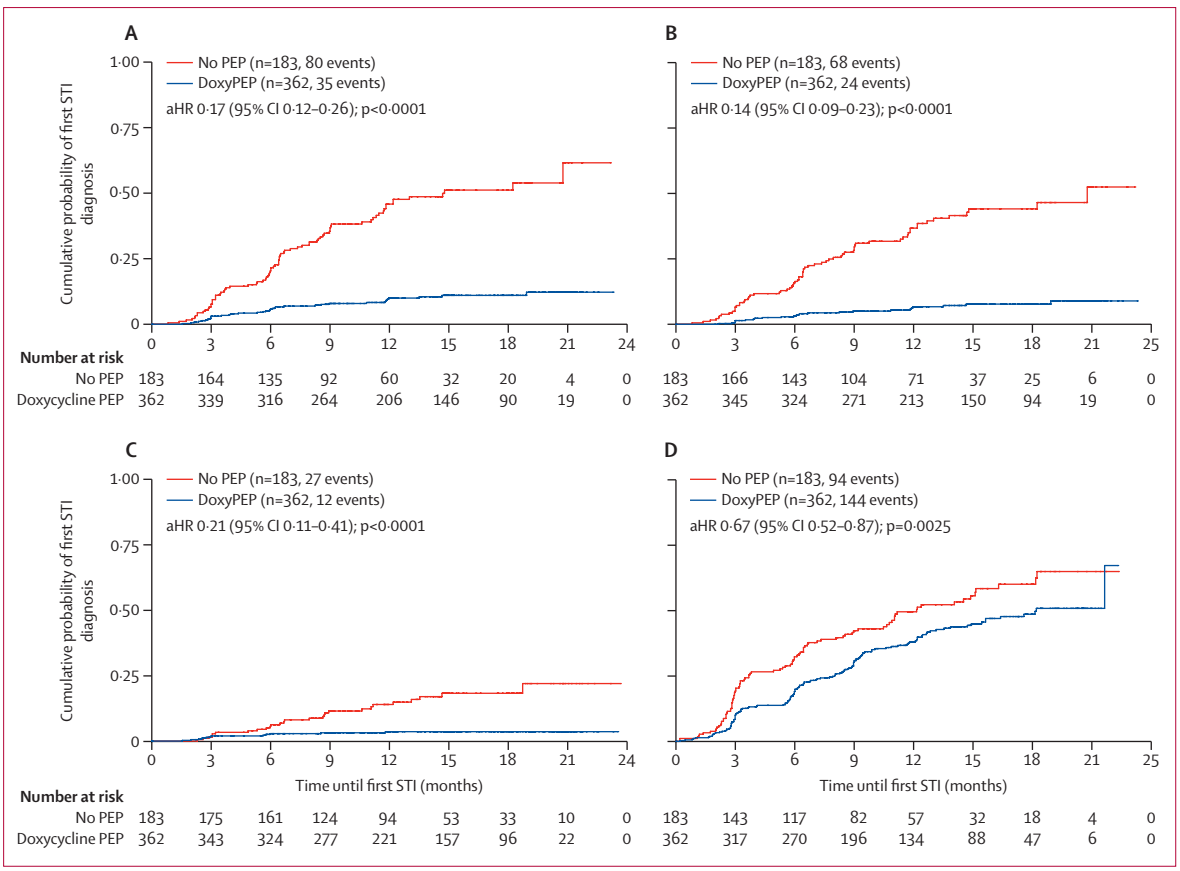

***Figure 2*: Kaplan–Meier analysis of the probability of the first episode of chlamydia, syphilis, and gonorrhoea in the modified intention-to-treat population**
Estimates of the probability of the first episode of chlamydia or syphilis (A); chlamydia (B); syphilis (C); and gonorrhoea (D). aHR=adjusted hazard ratio. PEP=post-exposure prophylaxis. STI=sexually transmitted infection.

(37 [7%]). The median number of STIs in the past 12 months was 2·0 (IQR 1·0–2·0) and the median number of partners in the past 3 months was 10 (5–20). Most interaction terms between the two interventions had a p≥0·1 (appendix 2 p 4), so the models used only included the doxycycline PEP intervention (yes *vs* no) and the 4CMenB vaccine intervention (yes *vs* no).

In the final analysis of the first coprimary outcome, the incidence of a first episode of chlamydia or syphilis (or both) was 8·8 per 100 person-years (35 events in 362 participants) in the doxycycline PEP group and 53·2 per 100 person-years (80 events in 183 participants) in the no PEP group (aHR 0·17 [95% CI 0·12–0·26]; p<0·0001; figure 2A; table 2).

Other key secondary endpoints show a similar reduction to the coprimary analysis in the incidence of a first episode and cumulative incidence of chlamydia (whether symptomatic or asymptomatic, irrespective of the site of infection) and syphilis between the doxycycline PEP and no PEP groups (table 2; figure 2B, C). The incidence of a first episode of gonorrhoea was 45·5 per 100 person-years (144 events in 362 participants) in the doxycycline PEP group and 68·4 per 100 person-years (94 events in 183 participants) in the no PEP group (aHR 0·67 [95% CI 0·52–0·87]; p=0·0025; figure 2D, table 2). Efficacy of doxycycline PEP was similar to the primary mITT analysis across prespecified subgroups (appendix 2 p 7).

Most chlamydia infections were rectal (86 [76%] of 113), 11 (10%) were pharyngeal, and 29 (26%) were urethral. Most gonorrhoea infections were pharyngeal (180 [58%] of 312) or rectal (176 [56%]), and 35 (11%) were urethral (data not shown). One participant acquired HIV infection in the no PEP group.

The median number of pills used per month per participant was 6 (IQR 3–13) in the doxycycline PEP group, self-reported use of doxycycline at the most recent sexual intercourse was more than 70% at each study visit, and median time to doxycycline intake after sex was 15 h (95% CI 5–30; appendix 2 p 9). 167 (62%) of 270 plasma and 188 (69%) of 272 urine samples had doxycycline concentrations above the limit of quantification at month 6 in the doxycycline PEP group compared with seven (5%) of 139 plasma and 12 (9%) of 136 urine samples from participants in the no PEP group (p<0·0001; appendix 2 p 9).

Tetracycline resistance was assessed on 78 available gonorrhoea cultures and all isolates were resistant to

	Doxycycline PEP group (n=362)*		No PEP group (n=183)*		Adjusted hazard ratio or IRR (95% CI)*	p value*	4CMenB vaccine group (n=274)†		No vaccine group (n=270)†		Adjusted hazard ratio or IRR (95% CI)†	p value†
	Person-years	Events (incidence per 100 person-years)	Person-years	Events (incidence per 100 person-years)			Person-years	Events (incidence per 100 person-years)	Person-years	Events (incidence per 100 person-years)		
First episode												
Chlamydia trachomatis or syphilis (or both)	397	35 (8·8)	151	80 (53·2)	0·17 (0·12–0·26)	<0·0001	..	..	..	..	..	..
C trachomatis	405	24 (5·9)	162	68 (42·1)	0·14 (0·09–0·23)	<0·0001	..	..	..	..	..	..
Rectal *C trachomatis*	409	17 (4·2)	170	56 (33·0)	0·13 (0·08–0·22)	<0·0001	..	..	..	..	..	..
Pharyngeal *C trachomatis*	419	3 (0·7)	201	7 (3·5)	0·21 (0·05–0·81)	0·024	..	..	..	..	..	..
Urethral *C trachomatis*	416	7 (1·7)	197	14 (7·1)	0·24 (0·10–0·59)	0·0020	..	..	..	..	..	..
Symptomatic *C trachomatis*	420	2 (0·5)	197	15 (7·6)	0·06 (0·01–0·27)	0·0002	..	..	..	..	..	..
Syphilis	412	12 (2·9)	187	27 (14·5)	0·21 (0·11–0·41)	<0·0001	..	..	..	..	..	..
Gonorrhoea	316	144 (45·5)	138	94 (68·4)	0·67 (0·52–0·87)	0·0025	177	103 (58·3)	158	122 (77·1)	0·78 (0·60–1·01)	0·061
Rectal gonorrhoea	370	68 (18·4)	159	64 (40·2)	0·47 (0·33–0·66)	<0·0001	206	61 (29·7)	193	64 (33·1)	0·90 (0·64–1·28)	0·57
Pharyngeal gonorrhoea	357	87 (24·3)	176	49 (27·9)	0·87 (0·62–1·24)	0·45	210	58 (27·6)	196	74 (37·7)	0·75 (0·53–1·05)	0·094
Urethral gonorrhoea‡	408	19 (4·7)	196	13 (6·6)	0·71 (0·35–1·44)	0·34	239	13 (5·4)	235	10 (4·3)	1·29 (0·56–2·94)	0·55
Symptomatic gonorrhoea	400	22 (5·5)	189	20 (10·6)	0·53 (0·29–0·97)	0·041	241	12 (5·0)	228	14 (6·1)	0·82 (0·38–1·78)	0·62
Culture positive gonorrhoea	316	27 (8·5)	138	29 (21·1)	0·42 (0·25–0·70)	0·0010	177	26 (14·7)	158	25 (15·8)	0·95 (0·55–1·65)	0·86
Cumulative incidence§												
C trachomatis or syphilis (or both)	421	36 (8·5)	207	116 (56·0)	0·15 (0·10–0·22)	<0·0001	..	..	..	..	..	..
C trachomatis	421	24 (5·7)	207	89 (43·0)	0·13 (0·08–0·21)	<0·0001	..	..	..	..	..	..
Rectal *C trachomatis*	421	17 (4·0)	207	69 (33·3)	0·12 (0·07–0·21)	<0·0001	..	..	..	..	..	..
Pharyngeal *C trachomatis*	421	3 (0·7)	207	8 (3·9)	0·18 (0·05–0·69)	0·013	..	..	..	..	..	..
Urethral *C trachomatis*	421	7 (1·7)	207	22 (10·6)	0·16 (0·07–0·37)	<0·0001	..	..	..	..	..	..
Symptomatic *C trachomatis*	421	2 (0·5)	207	17 (8·2)	0·06 (0·01–0·25)	<0·0001	..	..	..	..	..	..
Syphilis	421	12 (2·8)	207	27 (13·0)	0·22 (0·11–0·43)	<0·0001	..	..	..	..	..	..
Gonorrhoea	421	175 (41·6)	207	137 (66·2)	0·63 (0·50–0·79)	<0·0001	251	132 (52·6)	242	151 (62·4)	0·84 (0·67–1·07)	0·16
Rectal gonorrhoea	421	86 (20·4)	207	90 (43·5)	0·47 (0·35–0·63)	<0·0001	251	88 (35·1)	242	82 (33·9)	1·04 (0·77–1·40)	0·82
Pharyngeal gonorrhoea	421	103 (24·5)	207	77 (37·2)	0·66 (0·49–0·88)	0·0050	251	80 (31·9)	242	92 (38·0)	0·84 (0·62–1·13)	0·25
Urethral gonorrhoea‡	421	20 (4·7)	207	15 (7·2)	0·66 (0·34–1·28)	0·22	251	18 (7·2)	242	12 (5·0)	1·45 (0·70–3·01)	0·32
Symptomatic gonorrhoea	421	22 (5·2)	207	22 (10·6)	0·49 (0·27–0·89)	0·019	251	12 (4·8)	242	15 (6·2)	0·77 (0·36–1·65)	0·50
Culture positive gonorrhoea	421	28 (6·6)	207	38 (18·4)	0·36 (0·22–0·59)	<0·0001	251	29 (11·6)	242	28 (11·6)	1·00 (0·59–1·68)	1·00

IRR=incidence rate ratio. PEP=post-exposure prophylaxis. STI=sexually transmitted infection. *Incidence of the first episode of STI and cumulative incidence of STI between doxycycline PEP and no doxycycline PEP groups. STI episodes diagnosed at baseline were not considered. An STI with the same bacteria with multiple sites (anus, throat, or urine [or both]) diagnosed at the same date was counted as a single STI. For the first episode analysis, the follow-up began at baseline and continued until the end of the study, study discontinuation, loss to follow-up, or onset of STI of interest, whichever occurs first. For the cumulative incidence analysis, the entire follow-up was considered. In the presence of an interaction (p<0·10) between the two prevention strategies for the bacterial STI of interest, the effect of doxycycline PEP was assessed separately in each group (vaccine and no vaccine groups). †Episode and cumulative incidence of gonorrhoea from month 3 to the end of the study between the 4CMenB vaccine and no vaccine groups. Episodes of gonorrhoea diagnosed at baseline and up to month 3 were not considered. Gonorrhoea with multiple sites (anus, throat, or urine [or both]) diagnosed at the same date was counted as a single case of gonorrhoea. For the first episode analysis, the follow-up began at month 3 and continued until the end of the study, study discontinuation, loss to follow-up, or onset of STI of interest, whichever occurred first. For the cumulative incidence analysis, the entire follow-up from month 3 was considered. In the presence of an interaction (p<0·10) between the two prevention strategies for the bacterial STI of interest, the effect of 4CMenB vaccine was assessed separately in each group (doxycycline PEP and no PEP groups). ‡Indicates the presence of interaction between the two prevention strategies for urethral infection: $p_{interaction}$=0·034 for the first episode analysis and 0·072 for the cumulative incidence in the doxycycline PEP and no doxycycline PEP groups and $p_{interaction}$=0·077 for the first incidence and 0·040 for the cumulative incidence in the 4CMenB vaccine and no vaccine groups (appendix pp 4–6). §Adjusted IRR shown instead of hazard ratio.

Table 2: **Efficacy outcomes**

tetracycline at baseline and during follow-up (11 [36%] of 31 in the doxycycline PEP group and five [13%] of 40 exhibiting high-level resistance in the no PEP group; p=0·043; appendix 2 p 10). Also, four strains of *C trachomatis* in the no PEP group (none in the doxycycline PEP group) were tested for tetracycline resistance in tissue culture and no resistance was found. 68 (54%) of 126 of *C trachomatis* PCR positive swabs were sequenced, and no tetracycline-resistance associated mutation was found in the 16S rRNA (eight sequences were from the doxycycline PEP group; data not shown). The rate of detection of MRSA in pharyngeal swabs slightly increased during follow-up in both groups but the difference between the doxycycline PEP and no PEP

groups was not statistically significant (appendix 2 p 11). Similarly, the rate of detection of extended-spectrum β-lactamase producing *E coli* in rectal swabs remained unchanged during follow-up in both groups with no statistically significant difference between groups (data not shown; appendix 2 p 11).

In the final analysis of the second coprimary outcome, the incidence of a first episode of gonorrhoea, starting from month 3 was 58·3 per 100 person-years (103 events in 274 participants) in the 4CMenB vaccine group and 77·1 per 100 person-years (122 events in 270 participants) in the no vaccine group (aHR 0·78 [95% CI 0·60–1·01; p=0·061; figure 3). Responses were similar to the primary mITT analysis across prespecified subgroups (appendix 2 p 8). The cumulative incidence of gonorrhoea was 52·6 per 100 person-years (132 events in 274 participants) in the 4CMenB vaccine group and 62·4 per 100 person-years (151 events in 270 participants) in the no vaccine group (adjusted incidence rate ratio 0·84 (95% CI 0·67–1·07, p=0·16; table 2). Gonorrhoea incidence in the four study groups is shown in appendix 2 (p 12).

In a prespecified analysis, sexual practices did not change overall during the study compared with baseline and there were no significant differences between intervention groups in the number of condomless sex acts in the past 4 weeks before each visit or the number of sexual partners in the past 3 months before each visit (appendix 2 pp 13–14).

There were no significant differences between the study groups in the frequency of serious adverse events (65 [18%] of 369 participants in the doxycycline PEP *vs* 27 [14%] of 187 in the no PEP groups and 52 [19%] of 279 in the 4CMenB vaccine *vs* 40 [14%] of 277 in the no vaccine groups) or grade 3 or 4 adverse events (21 [6%] *vs* 10 [5%] and 20 [7%] *vs* 11 [4%], respectively; table 3). None of the participants died during the study. There was a single drug-related serious adverse event in one participant in the doxycycline PEP group who presented with fixed-drug eruption. Six (2%) participants in the doxycycline group discontinued doxycycline PEP because of gastrointestinal adverse events. Drug-related adverse events were reported in 25 (7%) participants in the doxycycline PEP group and 134 (48%) in the 4CMenB vaccine group. Most frequent drug-related adverse events were nausea or vomiting (11 [3%] of 369), abdominal pain (seven [2%]), and diarrhoea (four [1%]) in the doxycycline PEP group and injection site reactions (129 [46%] of 279), headaches (nine [3%]), and asthenia (17 [6%]) in the 4CMenB vaccine group.

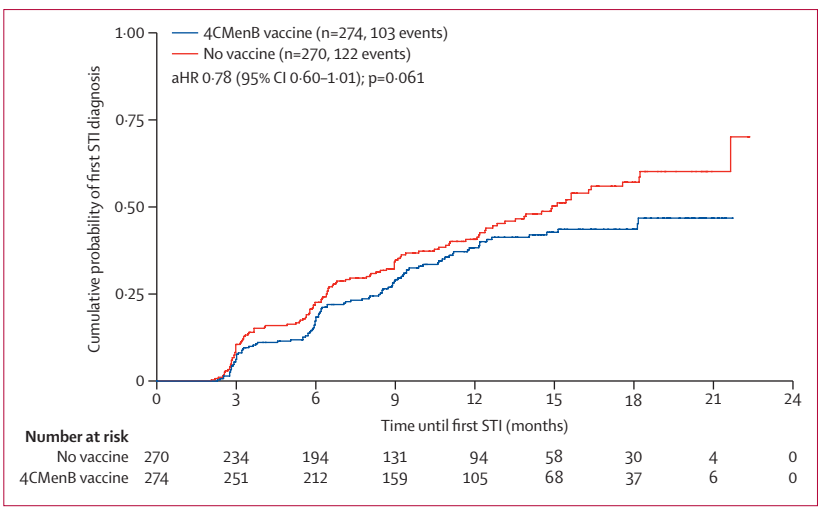

***Figure 3*: Kaplan–Meier analysis of the probability of the first episode of gonorrhoea in the modified intention-to-treat population**

The analysis started at month 3 (ie, 1 month after the second dose of the 4CMenB vaccine). aHR=adjusted hazard ratio. STI=sexually transmitted infection.

Discussion

This study showed that doxycycline PEP reduces the incidence of chlamydia and syphilis in MSM using PrEP for HIV prevention (aHR 0·17 [95% CI 0·12–0·26]; p<0·0001) with a median use of only 600 mg of doxycycline per month. Our results are consistent with those seen in the recent doxycycline PEP trial,[12] which showed a statistically significant relative risk reduction for chlamydia (0·12 [0·05–0·25]; p<0·0001) and syphilis (0·13 [0·03–0·59]; p=0·0084) in participants receiving PrEP. Here, we also showed moderate efficacy (aHR 0·67 [0·52–0·87]; p=0·0025) against gonorrhoea compared with the relative risk reduction (0·45 [0·32–0·65]; p<0·0001) shown in a trial conducted in the USA.[12] This lower efficacy against gonorrhoea in our study can be related to the fact that all strains of *N gonorrhoeae* were resistant to tetracycline in our population. In addition, there was a significant increase in high-level resistance to tetracycline in the doxycycline group, suggesting that efficacy against gonorrhoea might be less protective against strains with tetracycline resistance and might wane with time. However, this same strategy was not successful at reducing chlamydia incidence (relative risk with doxycycline PEP 0·73 [0·47–1·13]) and gonorrhoea incidence (1·64 [0·78–3·47]) in young women in Kenya,[23] possibly because of high resistance of *N gonorrhoeae* to tetracycline and low PEP adherence. Nevertheless, a study in healthy volunteers showed adequate doxycycline concentrations in cervical and vaginal secretions, supporting additional studies in women.[24] Indeed, women would benefit the most from this strategy since reducing STIs might reduce infertility, pelvic inflammatory disease, and congenital syphilis. Doxycycline PEP would also need to be assessed in the high risk population of men who have sex with women. This strategy of doxycycline PEP has entered guidelines in 2023, but is currently only considered for MSM or transgender women with a history of STIs.[25] Early observational data in the USA have reported a 50% (95% CI 38–59) decline in the number of cases of chlamydia infections within 1 year since the release of these guidelines, and a 51% (43–58) decline in the number of cases of syphilis during

	Doxycycline PEP group (n=369; 423 person-years)		No PEP group (n=187; 208 person-years)		p value	4CMenB vaccine group (n=279; 321 person-years)		No vaccine group (n=277; 310 person-years)		p value
	Events	n (%)	Events	n (%)		Events	n (%)	Events	n (%)	
Any serious adverse event	67	65 (18%)	29	27 (14%)	0·57	55	52 (19%)	41	40 (14%)	0·21
Any drug-related serious adverse event	1	1 (<1%)	..	..	..	0	0	..	..	..
Fixed drug eruption	1	1 (<1%)	..	..	..	0	0	..	..	..
Any grade 3 or 4 adverse event	22	21 (6%)	14	10 (5%)	0·45	24	20 (7%)	12	11 (4%)	0·063
Grade 3 or 4 drug-related adverse event	0	0	..	..	..	1	1 (<1%)	..	..	..
Asthenia	0	0	..	..	..	1	1 (<1%)	..	..	..
Treatment discontinuation due to an adverse event*	6	6 (2%)	..	..	..	0	0	..	..	..
Diarrhoea	3	3 (1%)	..	..	..	0	0	..	..	..
Abdominal pain	1	1 (<1%)	..	..	..	0	0	..	..	..
Vomiting	1	1 (<1%)	..	..	..	0	0	..	..	..
Unspecified	1	1 (<1%)	..	..	..	0	0	..	..	..
Drug-related adverse events	28	25 (7%)	..	..	..	202	134 (48%)	..	..	..
Drug-related adverse events in three or more patients										
Injections site reactions	0	0	..	..	..	171	129 (47%)	..	..	..
Headache	0	0	..	..	..	10	9 (3%)	..	..	..
Asthenia	1	1 (<1%)	..	..	..	17	17 (6%)	..	..	..
Nausea or vomiting	11	11 (3%)	..	..	..	2	2 (<1%)	..	..	..
Abdominal pain	7	7 (2%)	..	..	..	1	1 (<1%)	..	..	..
Diarrhoea	4	4 (1%)	..	..	..	2	2 (<1%)	..	..	..
Redness	0	0	..	..	..	10	9 (3%)	..	..	..
Fever	0	0	..	..	..	7	7 (3%)	..	..	..
Chills	0	0	..	..	..	5	5 (2%)	..	..	..
Myalgia	0	0	..	..	..	4	4 (1%)	..	..	..
Pruritus	0	0	..	..	..	3	3 (1%)	..	..	..
Body aches	0	0	..	..	..	3	3 (1%)	..	..	..

All participants also received tenofovir and emtricitabine for HIV pre-exposure prophylaxis. In this analysis, the entire follow-up was considered (ie, from baseline until the end of the study, study discontinuation, or loss to follow-up, whichever occurred first). p values were adjusted for the vaccine intervention. PEP=post-exposure prophylaxis. *Discontinuation due to adverse events related to doxycycline PEP or 4CMenB vaccine.

Table 3: **Adverse events in the intention-to-treat population**

the same period among MSM and transgender women.[26] Although there is a theoretical concern that this strategy could also induce resistance to tetracycline among *T pallidum* and *C trachomatis*, such resistance has not emerged despite five decades of tetracycline use for the treatment of these two infections, and reduction of antibiotic use for the treatment of STIs will result in an overall reduction of antibiotic use in this population.[9,10] Another concern with antibiotic prophylaxis is the impact on the microbiome, although data are scarce and there is little evidence so far of a strong effect of doxycycline PEP on the microbiome.[27] Studies on the microbiome and monitoring of antimicrobial resistance for bacterial STIs should continue to fully assess this strategy. The safety and tolerability of doxycycline prophylaxis was good overall with few gastrointestinal and cutaneous (one serious adverse event of fixed drug eruption) adverse events in this study.

Unfortunately, our study did not show a statistically significant reduction of at least 30% in gonorrhoea incidence with the 4CMenB vaccine (defined as the threshold for vaccine efficacy to be considered for public health implementation) when assessing the incidence of the first episode, and there was also no statistically significant reduction in cumulative episodes and symptomatic infections although the number of events was small. These results are consistent with the absence of effectiveness of 4CMenB vaccines on meningococcal carriage in the throat contrary to conjugate vaccines, since most *N gonorrhoeae* infections in our study were asymptomatic and should foster research for an alternative vaccine for gonorrhoea such as the ongoing trial using *N gonorrhoeae* OMV proteins (NCT05630859).[28,29]

Our study has several limitations. We only included MSM, and this trial design was open-label, but the use of centrally assessed laboratory-based outcomes reduced the likelihood of substantial bias. In addition, because this study was prematurely discontinued after results from the interim analysis and before enrolment of the projected sample size, it might have been underpowered to show a moderate vaccine efficacy against gonorrhoea. Modelling studies have reported that even a vaccine with

modest efficacy could have a strong impact on the epidemic within a community if the uptake is high.[30] Also, since most infections were asymptomatic, particularly pharyngeal infections, this study was not powered to assess vaccine efficacy against symptomatic infections. We also excluded participants with no follow-up visit (2% of participants) from the mITT analysis, but we do not think that this exclusion could have affected our estimates of efficacy. The results of ongoing randomised trials (NCT04415424 and NCT04350138) using the same 4CMenB vaccine in the USA, Thailand, and Australia will hopefully provide a definitive answer regarding its efficacy against gonorrhoea.

In conclusion, our study has shown that doxycycline PEP could strongly reduce the incidence of chlamydia and syphilis in MSM but did not show statistically significant efficacy of the 4CMenB vaccine for gonorrhoea.

Contributors

J-MM, DC, and LA designed and led the study. J-MM wrote the first draft of the manuscript. LA, MoO, and DC were responsible for the statistical analysis. LA, DC, BB, CB, ND, MoO, MA-G, JG, and J-MM analysed the data. MA-G and LA coordinated the study and oversaw data management. LG did the doxycycline assays. BB, CB, and ND performed the STI tests. J-MM, JG, ER, GP, CK, LSu, LSl, JP, CD, and BL did the study at the respective sites. DC, LA, MoO, MA-G, and J-MM had full access to all the data in this study and had final responsibility for the decision to submit for publication. All authors critically reviewed and approved the manuscript.

Declaration of interests

J-MM received support as an adviser for Gilead Sciences, Merck, Abbott, and ViiV; consulting fees from Aelix; and research grants from Gilead Sciences and Merck. GP received consulting fees from AstraZeneca, Gilead Sciences, Merck, and ViiV. JG received consulting fees from Gilead Sciences and ViiV. DC received personal fees from Pfizer for a lecture outside of the submitted work. CD, CK, and LSl received consulting fees from Gilead Sciences, Merck, and ViiV. LG received support from Novartis and consulting fees from AbbVie, Promise, Ipsen, and Takeda. All other authors declare no competing interests.

Data sharing

Data requests can be submitted to the scientific committee of the ANRS 174 DOXYVAC Study (corresponding author; jean-michel.molina@aphp.fr) and need to be approved by the French data protection authority (la Commission Nationale de l'Informatique et des Libertés [CNIL]) and ANRS Maladies Infectieuses Emergentes. French law requires that those who wish to access cohort or clinical study data require permission from CNIL by completing a form that can be provided by the coauthor LA (lambert.assoumou@iplesp.upmc.fr). The scientific committee will evaluate each proposal for compatibility with general objectives, ethical approval, and informed consent forms of the ANRS 174 DOXYVAC project, and for possible overlap with ongoing work. De-identified participant data, the study protocol (including informed consent forms), and statistical analysis plan can be made available upon request, 1 year after publication of this manuscript.

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