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ANTIMICROBIAL RESISTANCE AND CLINICAL SAFETY OF DOXYCYCLINE POST-EXPOSURE PROPHYLAXIS FOR BACTERIAL SEXUALLY TRANSMITTED INFECTIONS: A SYSTEMATIC REVIEW

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ABSTRACT

Objectives: To evaluate antimicrobial resistance, microbiome/resistome changes and clinical safety during event-driven doxycycline post-exposure prophylaxis (doxy-PEP), distinguishing clinical outcomes from laboratory surrogates.**Methods:** PubMed, Europe PMC and ClinicalTrials.gov were searched on 11 October 2026. Primary human studies were eligible; companion publications were linked to study families. Outcome-specific appraisal used RoB 2, ROBINS-I or design-appropriate JBI tools, followed by GRADE. A single review workflow was used. Synthesis followed SWiM because analysis units, phenotypes, follow-up and exposure contrasts were incompatible with pooling. **Results:** After deduplication, 496 database records yielded 55 retained reports; three registry results brought the evidence map to 58 reports in 37 study families. Twenty-one reports from 11 families contributed target-outcome information. High-level gonococcal tetracycline-resistance signals arose in DOXYVAC and three observational settings, with very low certainty of causal effects. These culture-conditioned results do not estimate absolute resistant-infection incidence. One selected DoxyPEP substudy showed tetracycline-resistome enrichment. In IPERGAY, gastrointestinal adverse events occurred in 62/116 versus 47/116 participants (risk ratio 1.32, 95% CI 0.999–1.74; low certainty). King County reported greater resistant *S. aureus* and group A streptococcal carriage in exposed screening visits, with very low certainty. DOXYVAC documented one drug-related serious fixed drug eruption. Serious-event and laboratory data did not establish comparative safety equivalence. **Conclusions:** Doxy-PEP has documented intolerance and organism-specific resistance signals. The magnitude of any increase in absolute resistant-infection risk remains uncertain. Clinical interpretation and surveillance should preserve distinctions between patients, sampled organisms, molecular markers and exposure periods.

Keywords: doxycycline; post-exposure prophylaxis; antimicrobial resistance; sexually transmitted infections; adverse events; systematic review.

KEY MESSAGES

What is already known on this topic

Doxy-PEP prevents selected bacterial STIs, but resistant-infection risk and long-term safety remain incompletely characterised.

What this study adds

Linking overlapping reports and preserving denominators separates resistance among sampled organisms from clinical incidence, and identifies low or very low certainty for the principal harm estimates.

How this study might affect research, practice or policy

Surveillance should report absolute resistant-infection burden alongside susceptibility distributions, and distinguish all-cause serious events from drug-attributed reactions.

I. INTRODUCTION

Doxycycline post-exposure prophylaxis (doxy-PEP) adds an antibiotic-based option to sexual health prevention. Trials among men who have sex with men (MSM), with limited representation of transgender women, demonstrated reductions in chlamydia and syphilis; the effect on gonorrhoea varied across settings. The Kenyan trial in cisgender women did not demonstrate a reduction in the composite sexually transmitted infection (STI) outcome and documented low drug exposure in hair samples. These findings establish a population-specific benefit–harm question rather than a uniform indication across populations. [1, 2, 3, 4]

The 2026 World Health Organization guideline allows doxy-PEP to be offered within comprehensive sexual health care while emphasizing antimicrobial-resistance monitoring. Preventive efficacy alone does not resolve this concern. A resistant fraction can increase among breakthrough infections when prophylaxis preferentially prevents susceptible infections. Conversely, an unchanged fraction where resistance is already nearly universal may obscure shifts towards higher minimum inhibitory concentrations (MICs). Neither observation directly quantifies the absolute incidence of resistant disease. [5, 6]

Resistance outcomes also differ biologically. Phenotypic nonsusceptibility in a gonococcal isolate, carriage of a candidate resistance-associated mutation, and enrichment of antimicrobial-resistance genes (ARGs) in a metagenomic sample are not interchangeable clinical endpoints. Safety requires analogous distinctions: adverse-event severity, regulatory seriousness, investigator attribution and treatment discontinuation describe different events. [4, 7, 8]

Existing reviews have assessed prophylactic efficacy, longer-term doxycycline use and resistance across broader indications. The contribution of this review is a focused evaluation of event-driven human doxy-PEP evidence, including

recent microbiological and implementation reports, with explicit reconciliation of study families, outcome definitions and denominators. We asked what resistance and clinical-safety outcomes have been observed during doxy-PEP use compared with usual care, non-use or a defined pre-exposure period. We did not assume that a more recent publication necessarily provides the most appropriate randomized estimate. [9, 10]

II. METHODS

Protocol and eligibility

A reconstruction protocol was dated 11 October 2026 after earlier findings had been inspected; it was not prospectively registered. The protocol and amendment log accompany this review. Reporting was organized using PRISMA 2020, PRISMA-S and synthesis-without-meta-analysis principles. [11, 12, 13]

Eligible studies involved humans receiving event-driven oral doxycycline after sexual exposure for bacterial STI prevention. Randomized trials, comparative observational studies and cohorts with an identifiable denominator were considered. Cross-sectional surveys required quantitative safety or microbiological outcomes linked to actual use. Otherwise eligible intervention cohorts were retained when the target outcomes were not reported in the inspected material, to avoid interpreting non-reporting as absence of harm. Daily or weekly pre-exposure regimens, other antibiotics, therapeutic use, scheduled pharmacokinetic dosing, in-vitro studies, models, ecological-only analyses and denominator-free case reports were excluded from the direct evidence synthesis. Mixed regimens required separable PEP exposure.

Information sources and selection

PubMed was searched through NCBI E-utilities and Europe PMC through its core-record API on 11 October 2026. Searches combined doxycycline and doxy-PEP terms with post-exposure prophylaxis, DOXYVAC and IPERGAY, without outcome, language or date restrictions. The complete strings, raw search logs and record-level decisions are provided in Supplementary Methods. Europe PMC overlaps extensively with PubMed and was not treated as an independent MEDLINE source. A broad all-fields Europe PMC development search was superseded by a documented title/abstract search before record screening; both runs were preserved, and only the latter contributes to the flow diagram.

ClinicalTrials.gov was searched for doxycycline interventions and sexually transmitted conditions. Registry results were linked to publications where possible. Public scholarly searches and source references assisted retrieval and version checking, but citation searching was targeted rather than comprehensive. Embase was not searched because authorized access was unavailable; CENTRAL access could not be established. These are coverage limitations, not zero-result searches.

Records sharing a PMID or DOI were deduplicated while retaining source occurrences. Preprints and companion publications were linked rather than counted as independent trials. Screening and extraction used a single workflow; independent duplicate review was not performed. The selection procedure and source-verification record are described in Supplementary Methods. Uncertain eligibility was investigated using primary full reports, registries and identifiable companion reports; all report-level decisions are recorded.

Extraction and outcome hierarchy

Extraction recorded design, setting, population, exposure, comparator, follow-up, organism, assay, resistance threshold, analysis unit, numerator/denominator and source coverage. Within resistance, the hierarchy was resistant clinical infection, phenotypic resistance among tested infections or isolates, molecular determinants, commensal carriage and resistome composition. Within safety, all-cause serious adverse events, attributed serious reactions, adverse-event discontinuation and specific symptoms were distinguished. Missing values were recorded as not reported, not retrieved or unclear; none was coded as zero.

Randomized-phase results were separated from extension or exposure-defined comparisons. Repeated reports were not summed. A primary abstract was sufficient for inclusion where eligibility was explicit, but not for asserting that unmentioned harms had not occurred. Full reports and registries were used to check abstract compression and discrepancies. Report-level overlap and source conflicts are recorded in the supplement; potentially overlapping observational cohorts were not combined into a total participant denominator.

Appraisal and synthesis

Risk of bias was assessed for each selected result: RoB 2 for randomised assignment effects; ROBINS-I (2016) for observational intervention contrasts; and JBI checklists for descriptive prevalence, cross-sectional, cohort or specimen-series results. Conditional culture and within-arm molecular findings were not automatically treated as unbiased randomised effects. Signalling responses, including no information where appropriate, and reasoned overall judgments are supplied. GRADE profiles distinguish direct clinical effects from surrogate or descriptive endpoints. Judgments were completed within one workflow, without independent duplicate appraisal. [14, 15, 16, 17]

Pooling was assessed separately for each outcome. A common label such as “resistance” or “adverse events” was insufficient: population, comparator, threshold, unit, follow-up and analysis population also had to align. The available resistance comparisons differed in these features and included correlated isolates or episodes. Safety results mixed participant-level cumulative events, symptoms at repeated visits and investigator-attributed reactions, with incomplete comparator

data. Consequently, no new meta-analysis was performed. This is a current data-compatibility decision, not a claim that future outcome-specific pooling is intrinsically impossible.

For the complete participant-level gastrointestinal counts in IPERGAY, a study-specific risk ratio (RR) and 95% confidence interval were calculated using the logarithmic Wald method. Published adjusted odds ratios (aORs) were retained without conversion to RRs. No continuity correction, pooled diamond, funnel plot or trial-sequential analysis was applied. Descriptive plots display reported proportions and do not imply independent-binomial precision for recurrent isolates. Calculation code and input data are supplied.

III. RESULTS

Selection and evidence structure

PubMed returned 440 records and Europe PMC 477; removal of 421 duplicate occurrences left 496 unique records. After 398 title/abstract exclusions, 98 reports were assessed: 41 were excluded, two were linked earlier versions and 55 were retained. Three of 43 registry records supplied eligible results, yielding 58 reports in 37 study families (Figure 1). Twenty-one reports from 11 families contributed target-outcome information. The broader map includes cohorts without extractable harms and does not represent 37 independent harm studies.

Study characteristics, source coverage, companion-report linkage and outcome-specific contributor counts are provided in Supplementary Tables S1–S3 and the data files. IPERGAY, DoxyPEP, dPEP Kenya and DOXYVAC provide the randomised clinical framework. DoxyForward compared implementation strategies and was not treated as an additional pharmacological safety trial. Project PEACH did not separate harms by doxy-PEP exposure. The Bologna microbiological study recorded individual PEP use but supplied no separable PEP resistance estimate in the available report; its PrEP and aggregate-antibiotic comparisons were not used as PEP effects. [18, 19, 20]

Gonococcal susceptibility

Table 1 and Figure 2 distinguish any tetracycline resistance from high-level resistance. The initial randomised DoxyPEP report described 5/13 versus 2/16 culture-positive participants with tetracycline resistance. The final report described 8/29 among participants taking doxy-PEP versus 5/21 not taking it during the study. These overlapping results differ in follow-up and exposure definition and were not combined. Sparse culture recovery limits inference beyond the sampled participants. [2, 21]

The DOXYVAC microbiological substudy assessed 78 cultured isolates and 233 NAAT-only samples. All cultured isolates were tetracycline resistant; high-level *tetM*-mediated resistance was reported in 35.5% versus 12.5% of the relevant doxy-

PEP and no-PEP isolate subsets. Decreased cefixime susceptibility associated with *penA34.007* was more frequent with doxy-PEP, although all isolates remained clinically susceptible to cefixime and ceftriaxone. These percentages were retained as reported; arm-specific counts were not inferred from rounded values. [6]

In Melbourne, among 1,020 isolates with known doxy-PEP status, any tetracycline resistance occurred in 107/120 exposed versus 695/900 unexposed isolates; high-level resistance occurred in 54.2% versus 29.7%. The decade-long parent surveillance series included 11,334 isolates, but that larger denominator is not the exposed–unexposed comparison. Multiple isolates could arise from the same individual, and the abstract did not supply an adjusted exposure effect. [22]

The Milan cohort included 318 people and 376 gonorrhoea episodes, of which 375 had the relevant susceptibility result. High-level tetracycline resistance occurred in 19/77 exposed versus 45/298 unexposed episodes (aOR 1.87, 95% CI 1.01–3.47). Decreased ceftriaxone susceptibility, defined as MIC >0.032 mg/L, occurred in 5/77 versus 3/298 (aOR 7.34, 95% CI 1.69–31.90). Only the latter association remained significant after multiple-comparison correction. There were eight such events and no ceftriaxone-resistant isolates; the estimate is therefore a sparse observational signal below the clinical resistance threshold. [23]

PRIDOX found tetracycline resistance in 6/14 exposed versus 25/54 comparator cultures. Cultures represented 14/47 versus 54/321 PCR-detected infections; similar resistant fractions cannot establish equivalence. In King County, >3 doses/month was associated with any resistance (RR 1.42, 95% CI 1.10–1.83) and high-level resistance (RR 1.45, 1.09–1.93). Any recent use had weaker estimates: RR 1.14 (0.93–1.39) and 1.16 (0.93–1.46), respectively. Calendar-month adjustment was described; the ecological high-level increase began before local prophylaxis guidance. [24, 25]

Molecular markers, commensals and the gut resistome

The Kenyan trial measured gonococcal tet(M) by PCR, despite the abstract's compressed reference to resistant isolates. The marker was detected at every tested baseline and follow-up visit in both groups; no tet(C) cassette was detected in 76 chlamydia samples. This is molecular evidence in a setting of high baseline resistance, not a cultured-isolate comparison establishing no selective effect. [3]

A separate IPERGAY laboratory report found no 16S rRNA mutations in 20 *C. trachomatis*-positive specimens from 18 participants (7 assigned doxy-PEP and 11 no-PEP). Nine had also received therapeutic doxycycline. Arm-specific specimen totals and a phenotypic resistance comparison were unavailable, so this finding does not establish absence of selection. The other clinical specimens and in vitro experiments in that mixed report were outside the intervention subset. [26]

The IPERGAY *Mycoplasma genitalium* substudy and a Taiwanese cohort identified candidate tetracycline-associated mutations, but these were not validated

clinical doxycycline-resistance endpoints. In Taiwan, the reported prevalence changed from 10.0% to 24.1% (P=0.28), with incomplete precision and denominator information in the abstract. A DOXYVAC syphilis substudy found no candidate doxycycline-resistance mutations in tested samples. Negative findings from small, selected molecular subsets cannot exclude emerging resistance. [8, 27, 28]

In the selected DoxyPEP sequencing substudy, 100 intervention and 50 control participants were chosen; usable DNA and RNA data came from different, smaller sample sets. Over six months, the reported proportional mass of tetracycline ARGs increased from 46% to 51% in DNA and from 4% to 15% in RNA in the intervention group. These are relative compositional measures, not percentages of patients acquiring resistant infection. Overall bacterial diversity did not show a corresponding detectable change. A subsequent change-point reanalysis used the same trial data and therefore supplies no independent replication or clinically validated "safe" dosing threshold. [7, 29]

King County distinguished overall carriage, resistant carriage and resistance among carriers. Tetracycline-resistant *S. aureus* occurred in 41/227 exposed versus 47/602 unexposed screening visits; among *S. aureus*-positive samples, the corresponding fractions were 41/62 and 47/216. Resistant group A Streptococcus (GAS) carriage occurred in 12/158 versus 11/352 visits, whereas resistance among GAS-positive samples was 12/15 versus 11/13. Thus, higher resistant carriage did not imply a higher resistant fraction among GAS carriers. Specimens could recur within individuals (Table 2). [25]

Clinical safety

Gastrointestinal intolerance was clinically relevant, but measurement differed (Table 3). In IPERGAY, 62/116 versus 47/116 participants reported any gastrointestinal adverse event: RR 1.32 (95% CI 0.999–1.74), an observed difference of 12.9 percentage points. The interval includes negligible difference through a substantial increase. This is not the narrower drug-attributed gastrointestinal endpoint. [1]

Kenya reported nausea at 7.2% versus 4.6% of follow-up visits and six adverse-effect discontinuations among 224 women assigned doxy-PEP. Repeated visits cannot be treated as independent people. Three participants discontinued because of social harms, a separate outcome from pharmacological toxicity. Registry adverse-event counts used a different reporting framework from the scheduled symptom questionnaire and were not substituted for its visit-based percentages. [3, 30]

The final DoxyPEP report described five grade 3 events and one grade 2 laboratory abnormality possibly or probably related to doxycycline, with no investigator-attributed serious adverse event. Its registry reported all-cause serious events in 3/326 observed doxy-PEP participants and 1/147 controls for an earlier

analysis set; non-serious events were not collected symmetrically in control arms. These registry counts neither contradict the attribution statement nor provide a valid all-adverse-event comparison. DOXYVAC reported one drug-related serious fixed drug eruption and six gastrointestinal discontinuations. [4, 21, 31]

The DoxyPEP post-hoc laboratory report tabulated alanine aminotransferase values above 40 U/L in 71/453 results (15.7%) in the HIV-negative PrEP stratum and 19/221 (8.6%) in the HIV-positive ART stratum. These are HIV-status strata within the monitored doxy-PEP population, not intervention and untreated-control arms. The report described generally mild laboratory abnormalities and no discontinuations attributable to the monitored abnormalities. However, the laboratory totals cannot be equated with unique exposed participants; only 100 of 195 controls had complete blood count data, and the authors did not present a meaningful comparative analysis. Inconsistencies in sampling times and neutrophil severity rows further preclude a participant-level risk estimate (Supplementary Table S8). The grade 2 transaminitis event cited from the parent trial was not counted again as an independent event. [32]

In observational evidence, the Taiwanese dermatology cohort recorded nine skin reactions among 671 users—eight fixed drug eruptions and one photosensitivity reaction—with all nine stopping prophylaxis. PRIDOX reported four mild-adverse-event discontinuations among 197 initiators, distinct from nine discontinuations for all reasons. A two-city Chinese survey reported possible side effects or adverse reactions in 7/38 actual users; event type, duration and clinical adjudication were insufficient for a comparative risk estimate. These findings add clinical context but should not be pooled into one adverse-event rate. [24, 33, 34]

Risk of bias and certainty of evidence

Outcome-level assessments were completed for 25 selected results. The three randomised safety comparisons had high overall risk of bias, driven by outcome completeness and/or cumulative concerns about open-label ascertainment and analysis reporting. Seven observational intervention contrasts had serious risk of bias, principally from confounding and post-exposure sampling. Fifteen descriptive appraisals identified restricted sampling, incomplete follow-up or unvalidated attribution. GRADE certainty was low for gastrointestinal symptoms and visit-level nausea, and very low for the graded resistance/carriage and serious-event effects. No certainty grade was assigned to an absent clinical effect estimate (Table 4; Supplementary Methods S5–S6).

Table 1. Gonococcal phenotypic resistance and susceptibility

Source / design	Endpoint and analysis unit	Result: doxy-PEP versus comparator	Key limitation
DoxyPEP initial; RCT [2]	Tetracycline MIC ≥2 µg/mL; culture-positive participants	5/13 versus 2/16	Small, selected culture-positive subset; not resistant-infection incidence.
DoxyPEP final; trial and extension [21]	Same resistance threshold; participants classified by study-period exposure	8/29 versus 5/21	Overlaps initial report; do not interpret as a new independent RCT.
DOXYVAC substudy [6]	High-level *tetM*-mediated tetracycline resistance; isolates	35.5% versus 12.5%; P=0.043; 78 cultures overall	Exact arm denominators not verified; all isolates resistant at the any-resistance threshold.
DOXYVAC substudy [6]	Decreased cefixime susceptibility linked to *penA34.007*	32.3% versus 10.0%; P=0.033	All isolates clinically susceptible to cefixime and ceftriaxone.
Melbourne; observational [22]	Tetracycline resistance; 1,020 isolates with exposure status	107/120 (89.2%) versus 695/900 (77.2%); high-level MIC >8 mg/L: 54.2% versus 29.7%	11,334 isolates in the parent surveillance series are not the comparison denominator; repeated isolates.
Milan; observational [23]	High-level tetracycline MIC >8 mg/L; episodes	19/77 (24.7%) versus 45/298 (15.1%); aOR 1.87 (1.01–3.47)	Not retained after multiplicity correction; residual confounding.
Milan; observational [23]	Ceftriaxone MIC >0.032 mg/L; episodes	5/77 versus 3/298; aOR 7.34 (1.69–31.90)	Eight events; susceptible-range signal; no resistant isolates.
PRIDOX; observational [24]	Tetracycline resistance among recovered cultures	6/14 (42.9%) versus 25/54 (46.3%)	Culture recovered in 14/47 exposed infections; differential sampling.

Source / design	Endpoint and analysis unit	Result: doxy-PEP versus comparator	Key limitation
King County; observational [25]	MIC ≥2 µg/mL (any); ≥16 µg/mL (high level); 286 infections with AMR/exposure data	>3 doses/month: RR 1.42 (1.10–1.83) any; RR 1.45 (1.09–1.93) high level. Any recent use: RR 1.14 (0.93–1.39) and 1.16 (0.93–1.46)	Calendar month included in reported modelling; other important confounders not controlled. 286/343 infections had both exposure and AMR data; ecological series is separate.

Values in parentheses after effect estimates are 95% CIs. aOR, adjusted odds ratio. The same study can contribute different endpoints, not independent effects. Figure 2 is descriptive; no pooled estimate is implied. King County used high-level MIC ≥16 µg/mL; Melbourne/Milan reported >8 mg/L. The initial and final DoxyPEP entries are overlapping, distinct analysis sets.

Table 2. Molecular markers, commensal carriage and resistome findings

Source	Measurement and sample structure	Observed finding	Interpretation
dPEP Kenya [3]	PCR tet(M); 16 baseline visits, 20 doxy-PEP and 12 control follow-up visits tested	100% tet(M) in all subsets; no tet(C) cassette in 76 *C. trachomatis* samples	Molecular determinants, not phenotypically tested cultures; no proof of absence of selection.
IPERGAY *C. trachomatis* [26]	20 specimens from 18 participants; 7 PEP/11 no-PEP participants; nine also received therapeutic doxycycline	No 16S rRNA mutations in sampled specimens	Selected positive specimens; arm-specific specimen totals unavailable; no phenotypic exclusion of resistance.
IPERGAY *M. genitalium* [27]	210 participants sampled at baseline and six months	Candidate 16S rRNA mutation in 12.5% of tested specimens; no arm difference in macrolide/fluoroquinolone resistance reported	Candidate genotype is not a validated doxycycline clinical-resistance outcome.
Taiwan *M. genitalium* [8]	325 doxy-PEP users; pre/post molecular analysis	Tetracycline-associated mutations 10.0% to 24.1%, P=0.28	Denominators and CIs not established from abstract; temporal comparison, not causal estimate.
DOXYVAC *T. pallidum* [28]	44 incident cases in 43 participants; 11 participants PCR positive	No tested candidate doxycycline-resistance mutation detected	Small selected molecular subset; no phenotypic resistance exclusion.
DoxyPEP gut substudy [7]	Selected 100/50 participants; DNA: 127 samples from 89 people; RNA: 86 samples from 70 people	Tetracycline ARG proportional mass: DNA 46→51%; RNA 4→15%; no detectable overall diversity change at six months	Different sample sets, compositional measures and selected higher-use participants; no resistant-infection outcome.

Source	Measurement and sample structure	Observed finding	Interpretation
DoxyPEP reanalysis [29]	Change-point analysis of the same six-month data	Reported resistome breakpoint approximately 65 cumulative doses	Exploratory reanalysis; no independent replication or validated safe dose threshold.
King County *S. aureus* [25]	838 screening specimens from 703 MSM; PEP status known for 829 visits (227/602); tetracycline MIC >8 µg/mL	Overall carriage: 62/227 vs 216/602. Resistant carriage: 41/227 vs 47/602. Resistant fraction among carriers: 41/62 vs 47/216	Convenience sample; repeat visits possible; no adjusted causal estimate. Nine visits had unknown exposure.
King County GAS [25]	512 screening specimens from 452 MSM; PEP status known for 510 visits (158/352); tetracycline MIC >8 µg/mL	Overall carriage: 15/158 vs 13/352. Resistant carriage: 12/158 vs 11/352. Resistant fraction among carriers: 12/15 vs 11/13	Resistant carriage differs from the resistant fraction among carriers. Two visits had unknown exposure; repeat visits possible.

ARG, antimicrobial-resistance gene; GAS, group A Streptococcus. No overall resistance effect is derived across organisms or assay types.

Table 3. Clinical safety with preserved denominators and attribution

Study	Endpoint and unit	Finding	Reporting boundary
IPERGAY [1]	Any gastrointestinal AE; participants	62/116 versus 47/116; RR 1.32 (95% CI 0.999–1.74)	Any GI endpoint; differs from drug-attributed symptoms. Comparative SAE counts were not extractable.
dPEP Kenya [3, 30]	Nausea; repeated visits. AE discontinuation; participants	7.2% versus 4.6% of visits; 6/224 AE discontinuations; 3/224 social-harm discontinuations	No attributed serious reaction; registry event reports and symptom surveys differ.
DoxyPEP final [21]	Attributed severity-graded events	Five grade 3 events and one grade 2 laboratory abnormality; no attributed SAE	Final study-period report includes extension exposure; not a complete comparative all-AE endpoint.
DoxyPEP laboratory post-hoc [32]	ALT >40 U/L; tabulated laboratory results by HIV-status stratum	HIV-negative PrEP: 71/453 (15.7%); HIV-positive ART: 19/221 (8.6%); no discontinuation attributed to monitored abnormalities	Both strata concern monitored doxy-PEP use. No untreated hepatic comparator; unique-person incidence unavailable. Timing and ANC-row discrepancies are recorded in Table S8.
DoxyPEP registry [31]	All-cause SAEs; participants with follow-up up to one year	3/326 doxy-PEP versus 1/147 controls	No-follow-up participants excluded; most registry non-completion was administrative at interim analysis. Non-serious events not collected in controls. Registry 641 assigned includes four who did not enroll; the publication reports 637 enrolled (Table S8).

Study	Endpoint and unit	Finding	Reporting boundary
DOXYVAC [4]	Drug-related SAE; GI discontinuation	One serious fixed drug eruption; six GI discontinuations; no deaths reported	Seriousness, attribution and GI cessation are distinct. Complete all-cause SAE arm counts were not extractable.
Taiwan skin cohort [33]	Dermatological reactions; users	9/671 (1.3%): 8 fixed drug eruptions, 1 photosensitivity; all stopped	Multicentre retrospective ascertainment; other harms not comprehensively measured.
PRIDOX [24]	AE discontinuation; initiators	4/197 (2.0%) due to mild AEs; 9/197 total discontinuations; no SAE reported	Nonrandomized cohort; all-cause cessation must not be called toxicity.
China two-city survey [34]	Self-reported possible reactions; actual users	7/38 (18.4%)	Broad self-report category; no validated timing/severity classification; not incidence.
Project PEACH registry [19]	AEs in entire prevention cohort	240 total cohort members; harms not separated by doxy-PEP exposure	No doxy-PEP-specific event rate calculated.

AE, adverse event; SAE, serious adverse event; GI, gastrointestinal. A zero explicitly reported by a source is distinct from an unreported endpoint. Rates from these rows must not be summed or averaged.

Table 4. Summary of Findings for priority outcomes

Outcome / comparison	Evidence and analysis unit	Effect or absolute observation	Certainty and principal reasons
Any GI adverse event; PEP vs no PEP in MSM using PrEP; median 8.7 months [1]	IPERGAY; 1 RCT; 232 participants (116/arm)	RR 1.32 (95% CI 0.999–1.74); 405/1000 comparator vs 534/1000 PEP; 129 more/1000 (illustrative CI 1 fewer to 301 more)	LOW; serious risk of bias and imprecision (G1).
All-cause SAE; assigned PEP vs control, observed follow-up up to 1 year [31]	DoxyPEP; 1 RCT registry; 473 observed participants (326/147)	3/326 vs 1/147; 9.2 vs 6.8/1000. No robust causal risk difference or pooled estimate	VERY LOW; incomplete safety set and only four events (G3).
High-level gonococcal tetracycline resistance among sampled infections [6, 22, 23, 25]	DOXYVAC plus 3 observational families; 78 cultures, 1020 isolates, 375 episodes and 286 infections respectively; not summed	DOXYVAC 35.5% vs 12.5%; Melbourne 54.2% vs 29.7%; Milan aOR 1.87 (1.01–3.47); King County >3 doses/month RR 1.45 (1.09–1.93)	VERY LOW in both design strata; selected cultures, confounding and limited precision. No common pooled effect (G4R/G4O).
Ceftriaxone MIC >0.032 mg/L; PEP use vs non-use [23]	Milan; 1 observational family; 375 episodes in 318 people	5/77 vs 3/298 episodes; aOR 7.34 (1.69–31.90). No ceftriaxone-resistant isolates	VERY LOW; confounding/selection and eight events. This is a susceptible-range MIC endpoint (G5).

Outcome / comparison	Evidence and analysis unit	Effect or absolute observation	Certainty and principal reasons
Tetracycline-resistant *S. aureus* carriage; recent PEP vs non-use [25]	King County; 1 observational family; 829 visits with exposure status; 703 people in full specimen cohort	41/227 (18.1%) vs 47/602 (7.8%); observed difference 10.3 percentage points	VERY LOW; unadjusted convenience sampling and repeated visits; no independent-binomial CI imposed (G6).
Tetracycline-resistant GAS carriage; recent PEP vs non-use [25]	King County; same study family; 510 visits with exposure status; 452 people in full specimen cohort	12/158 (7.6%) vs 11/352 (3.1%); observed difference 4.5 percentage points	VERY LOW; confounding, selected/repeated sampling and sparse events (G7).
Absolute incidence of resistant clinical infection	No suitable all-participant or person-time comparison extracted	Not estimable from conditional isolate proportions, candidate mutations or ARG abundance	NOT GRADED: no eligible effect estimate; absence of evidence is not very-low-certainty evidence of no effect (G12).

Doxy-PEP denotes event-driven exposure. Each row retains its own population, comparator and time horizon; this is a structured, non-pooled SoF. GI absolute CI uses the observed comparator risk multiplied by the RR limits and does not incorporate uncertainty in that baseline risk. Observational absolute differences are descriptive. Additional profiles for nausea, ARG composition, skin reactions and cessation, with all five GRADE domains and reasons, are in GRADE_evidence_profiles.csv. No overall patient total is calculated.

IV. DISCUSSION

Principal interpretation

The strongest practical message from the resistance evidence is the need to measure both the number of resistant infections per person-time and the resistance distribution among recovered organisms. The former addresses absolute clinical burden; the latter describes selection among sampled infections. Culture recovery, specimen site, treatment timing, repeat episodes and background susceptibility must be reported alongside both. In high-resistance settings, continuous MICs and high-level resistance may be more informative than a binary any-resistance threshold.

Clinical implications and novelty

Current preventive recommendations and microbiological uncertainty can coexist. WHO's 2026 guidance places doxy-PEP within comprehensive sexual health services and calls for resistance monitoring. The present synthesis supports counseling about gastrointestinal intolerance and cutaneous reactions and avoiding a blanket assertion that serious drug reactions never occur. The observed safety experience is primarily short- to medium-term and cannot establish tolerability over many years or in poorly represented populations. [4, 5, 33]

The laboratory post-hoc analysis extends the safety evidence beyond symptom reporting, but its implications are narrower than a comparison of monitored and unmonitored care. Routine laboratory surveillance was not randomized, hepatic monitoring was not symmetric between treatment arms, and the reported denominators do not establish person-level incidence. The observations are compatible with predominantly mild biochemical abnormalities in the monitored population; they cannot establish the absence of attributable toxicity or the safety of omitting monitoring across different comorbidity profiles. [32]

Compared with efficacy-centered syntheses, this review organizes the evidence around the precise harm being measured and the population in which it is estimated. Recent Melbourne, Milan, Taiwanese and DOXYVAC reports add organism-specific observations beyond the original trial abstracts. Its contribution is an updated separation of these clinically different endpoints, with outcome-specific appraisal and explicit study-family linkage. [6, 8, 9, 22, 23]

The Milan ceftriaxone finding merits replication with sufficient events and careful adjustment; it does not show ceftriaxone treatment failure. Similarly, changes in the gut resistome indicate altered antimicrobial ecology without demonstrating later resistant disease. A numerical breakpoint derived from a small secondary omics analysis is not an established maximum safe cumulative dose. Clinically useful follow-up studies need serial sampling after discontinuation and linkage of molecular changes to infections and treatment outcomes. [7, 23, 29]

Limitations of the evidence and review

Primary-study limitations include nonblinded symptom reporting, exposure misclassification, low adherence in some settings, sparse cultures, selection of higher-use sequencing participants, short follow-up and residual confounding. Conditioning analyses on infection or culture positivity can compromise randomized comparability. Nonrandomized exposure is also associated with STI risk, testing frequency and therapeutic antibiotic use. Adjustment for selected measured variables does not establish that these factors have been fully controlled.

Review limitations include overlapping bibliographic sources, unavailable Embase/CENTRAL access and incomplete comprehensive citation searching. Several reports could be assessed only through primary abstracts or companion conference material; missing assay, denominator and analysis details were retained as uncertainty in extraction and appraisal. The protocol followed prior knowledge of results, and independent duplicate review was not performed. These limitations constrain coverage and confidence given the search and appraisal constraints.

The intervention evidence map is larger than the harm-contributing subset. Unreported outcomes were not treated as absent events. Study-family linkage prevents obvious duplication within major trials, but independence across related observational clinic cohorts cannot be established for every participant. No overall exposed-person total was therefore calculated. Certainty applies to the specific endpoint and population, rather than to doxy-PEP as a single universally safe or unsafe intervention.

Research priorities

Future trials and cohorts should specify resistance assays and breakpoints, sampling completeness, individual exposure and therapeutic antibiotic use; report repeated-episode methods; and publish both absolute resistant-infection incidence and conditional resistance proportions. Safety reports should distinguish all-cause from attributed events, symptoms from serious reactions, and pharmacological from social harms. Longer follow-up, broader gender and geographic representation, and direct assessment of post-discontinuation persistence are needed to answer the remaining benefit–harm questions.

V. CONCLUSION

Event-driven doxy-PEP has documented gastrointestinal and cutaneous harms and is associated with organism-specific tetracycline-resistance signals. Available surrogate and culture-conditioned results do not establish the magnitude of an increase in absolute resistant-infection risk. Interpretation should remain specific to population, organism, assay and denominator. Laboratory observations provide additional tolerability information but do not establish comparative hepatic or hematological safety.

DECLARATIONS

Registration: not prospectively registered. Data availability: search strategies, bibliographic identifiers, screening decisions, extraction data and analysis code accompany this manuscript. No individual participant data were analyzed.

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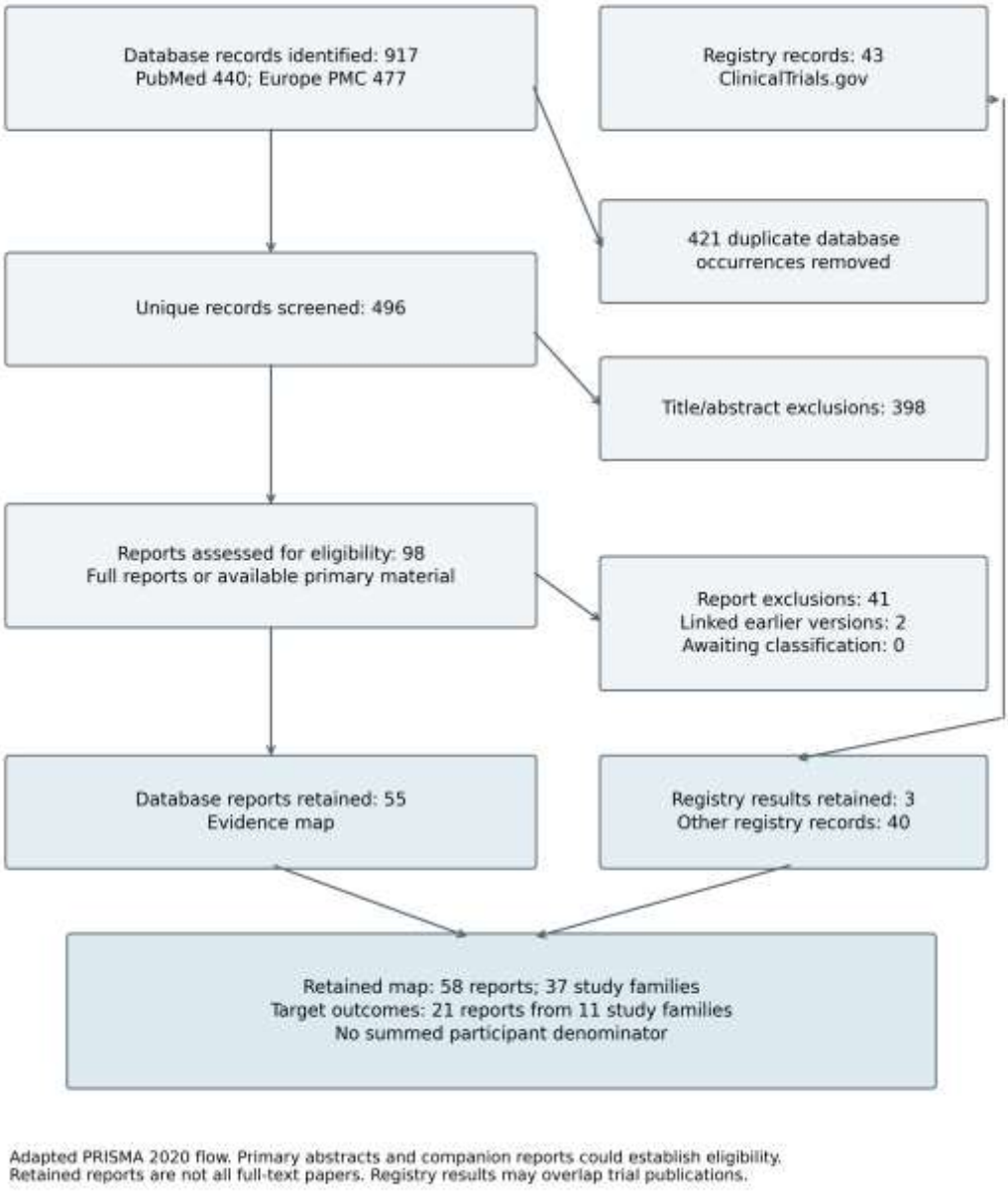


Figure 1. Adapted PRISMA 2020 selection flow. Counts derive from the executed 11 October 2026 searches and the reconciled report ledger. Eligibility could be established from primary abstracts or identifiable companion reports; "retained reports" does not mean all full-text papers were retrieved. Linked earlier versions and registry reports are not new independent studies. The 58-report map and the 21-report target-outcome subset answer different counting questions.

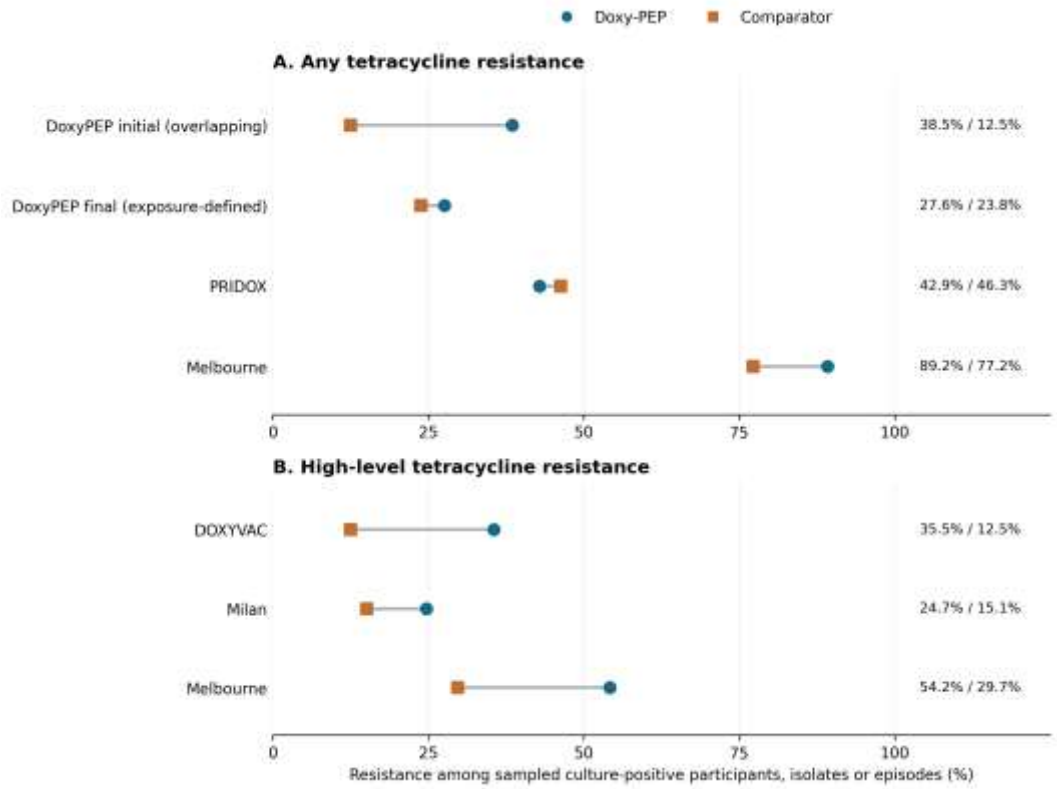


Figure 2. Descriptive resistance proportions among sampled culture-positive participants, isolates or episodes. Panels separate any and high-level tetracycline resistance; denominators, thresholds and sampling are specified in Table 1. Initial and final DoxyPEP reports overlap. The display gives no pooled estimate or independent-binomial uncertainty interval for correlated observations. Other published adjusted contrasts remain in Table 1.