

INPLASY

Doxycycline post-exposure prophylaxis (Doxy-PEP) and antimicrobial resistance in non-target organisms: a two-tier systematic review protocol

INPLASY2026100055

doi: 10.37766/inplasy2026.10.0055

Received: 12 October 2026

Published: 12 October 2026

Nemec, EC; Custeau, EC; Gallant, AJ; Rose, SJ.

Corresponding author:

Eric Nemec

nemece@sacredheart.edu

Author Affiliation:

Sacred Heart University.

ADMINISTRATIVE INFORMATION**Support** - N/A.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - No external funding was received for this review. The work is conducted as part of a graduate capstone project in the Sacred Heart University Physician Associate Program. No funder or sponsor had any role in the design, conduct, or reporting of this review, or in the decision to submit this protocol.**INPLASY registration number:** INPLASY2026100055**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 October 2026 and was last updated on 12 October 2026.**INTRODUCTION**

Review question / Objective Primary question: Among humans receiving doxycycline, what effects does intermittent doxycycline post-exposure prophylaxis (Doxy-PEP) for prevention of bacterial sexually transmitted infections (STIs) have on colonization and tetracycline-class resistance in non-target (bystander) organisms, and how do these effects compare with resistance patterns observed during systemic doxycycline use for other clinical indications? PICOS framework: - Population: Humans aged 18 years or older. Tier 1: persons receiving Doxy-PEP for bacterial STI prevention (expected predominantly men who have sex with men and transgender women). Tier 2: persons receiving systemic doxycycline for any indication other than STI prophylaxis. - Intervention: Tier 1: intermittent oral doxycycline post-exposure prophylaxis (any dose or schedule). Tier 2: systemic doxycycline for any other clinical

indication (any dose, schedule, or duration). - Comparator: no doxycycline; placebo; standard care; the participant's own pre-exposure baseline (self-controlled designs); or groups differing in doxycycline frequency, cumulative exposure, or duration. - Outcomes: Primary: phenotypic tetracycline-class resistance in bystander organisms. Secondary: bystander-organism colonization/carriage; genotypic resistance determinants; resistome composition; microbiome changes; cross-resistance or co-selection. - Study designs: randomized and non-randomized comparative designs, including single-arm self-controlled before-after studies. The comparison between exposure groups is a structured, qualitative comparison of resistance patterns: direction of effect, organisms affected, resistance mechanisms, and exposure-response gradients, rather than a head-to-head comparison of effect sizes. Populations, regimens, and effect sizes are not assumed to be equivalent between Doxy-PEP and other doxycycline exposures.

Rationale Doxy-PEP (oral doxycycline taken shortly after condomless sexual exposure) reduces incident bacterial STIs and has been incorporated into clinical guidance in the United States. Because it exposes healthy individuals to repeated, intermittent antibiotic courses, its principal safety concern is selection of antimicrobial resistance in organisms that are not the intended prevention target (bystander organisms), including *Staphylococcus aureus*, group A *Streptococcus*, commensal *Neisseria* spp., and skin and gut microbial communities. Direct evidence on bystander effects of Doxy-PEP remains limited and derives largely from microbiologic sub-studies nested within the early trials. A prior systematic review (Usuanlele et al., Sexually Transmitted Diseases, 2026) synthesized the 2013–2023 literature; the bystander-resistance question remains incompletely characterized, and resistance outcomes may emerge over years at a population level. Because Doxy-PEP is a relatively new exposure, this review uses a prespecified two-tier design. Tier 1 captures all direct Doxy-PEP evidence on bystander organisms. Tier 2 assembles the much larger human literature on systemic doxycycline used for other indications (for example, acne, rosacea, and malaria prophylaxis), in which resistance, colonization, and microbiome outcomes have been studied for decades, in order to evaluate whether the limited direct Doxy-PEP findings are biologically consistent with the broader doxycycline literature. Tier 2 evidence is interpreted with explicit attention to differences in dosing frequency, cumulative exposure, treatment duration, population, and organism, and is not treated as a substitute for direct Doxy-PEP evidence. A prespecified baseline and contextual evidence stream (pre-Doxy-PEP carriage and resistance-prevalence data in relevant populations) provides reference points for interpreting observed changes. This review updates the prior synthesis: database searches are restricted to records published from January 2023 onward, and earlier evidence is incorporated through the prior review's included studies and reference lists via citation searching.

Condition being studied The health condition of interest is antimicrobial resistance and colonization change in non-target (bystander) bacteria, organisms that are not the intended treatment or prevention target of the doxycycline exposure under study. For Doxy-PEP, bystander organisms include *Staphylococcus aureus* (including methicillin-resistant strains), group A and other streptococci, commensal *Neisseria* spp., *Cutibacterium acnes*, enterococci,

Enterobacteriaceae, and skin, oropharyngeal, rectal, and gut microbial communities; bacterial STI pathogens (e.g., *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) are the intended prevention targets. Measured outcomes include phenotypic tetracycline/doxycycline resistance (including minimum inhibitory concentrations), tetracycline resistance determinants (e.g., tet genes), resistome composition, microbiome composition, and colonization or carriage prevalence. STI-pathogen resistance is not a primary outcome of this review and is retained only as context.

METHODS

Search strategy Four databases are searched: PubMed (National Library of Medicine), CINAHL Ultimate (EBSCOhost), Cochrane Central Register of Controlled Trials (CENTRAL; via EBSCOhost Cochrane Collection Plus), and Academic Search Premier (EBSCOhost). Searches use concept-block structures combining controlled vocabulary (MeSH in PubMed; CINAHL headings) with title/abstract keywords, truncation, and, on EBSCOhost, proximity operators; strategies are adapted per database and peer-reviewed against the PRESS 2015 checklist by a health sciences librarian. Searches are restricted to records published from January 1, 2023 to the search date, updating the prior review (Usuanlele et al., 2026), which synthesized the 2013–2023 literature; the window deliberately overlaps the prior review's coverage to avoid missing records indexed near its search cutoff. Evidence published before 2023 is incorporated through the prior review's included studies and reference lists via citation searching. No language, publication-type, or peer-review limiters are applied. Two search sets are run in each database, with no NOT operator. The Tier 1 set (direct Doxy-PEP evidence) searches Doxy-PEP terminology (e.g., “doxy pep”, doxypep, doxycycline post-exposure prophylaxis, and proximity constructions of doxycycline with postexposure prophylaxis) OR (doxycycline terms AND post-exposure prophylaxis AND STI terms), without any outcome filter. The Tier 2 set searches doxycycline terms AND a resistance/colonization/microbiome outcome block AND a clinical-exposure-context block AND two precision elements that mirror the Tier 2 eligibility criteria: a human-study restriction (PubMed: Humans [Mesh]) and a bystander-organism/flora block. Overlapping records from the two sets are merged, deduplicated, and classified as Tier 1 or Tier 2 at full-text screening. Searches will be rerun immediately before final analyses, with full line-by-line strategies, dates, and yields reported per PRISMA-S.

Participant or population Humans aged 18 years or older. Tier 1: persons receiving doxycycline post-exposure prophylaxis for prevention of bacterial STIs, expected to be predominantly adult men who have sex with men and transgender women; any clinical or community setting; any country. Tier 2: persons receiving systemic doxycycline for any indication other than STI prophylaxis (e.g., acne, rosacea, periodontal disease, malaria prophylaxis, other infections), with the clinical indication identifiable. Studies enrolling mixed-age populations (for example, dermatology cohorts including adolescents) are eligible only when results for participants aged 18 or older are reported separately. The baseline and contextual evidence stream includes human populations relevant to the review (e.g., men who have sex with men, sexual-health-clinic attendees, Tier 2 treatment populations) sampled predominantly before widespread Doxy-PEP implementation or without doxycycline exposure.

Intervention Intermittent oral doxycycline administered as post-exposure prophylaxis against bacterial sexually transmitted infections (Doxy-PEP), of any dose, schedule, or cumulative exposure; dose, frequency, and cumulative exposure are recorded. For Tier 2, systemic (oral or intravenous) doxycycline for any clinical indication other than STI prophylaxis, of any dose, schedule, or duration. Chronic continuous doxycycline prophylaxis (Doxy-PrEP) is excluded from Tier 1.

Comparator Any of: no doxycycline; placebo; standard care; the participant's own pre-exposure (baseline) measurements in self-controlled before-after designs; or exposure groups differing in doxycycline frequency, cumulative exposure, or duration. Single-arm self-controlled studies with a prespecified outcome measured before and after a clearly defined exposure are eligible. Purely descriptive studies with no comparison group and no baseline measurement are excluded.

Study designs to be included Randomized controlled trials (including nested microbiologic substudies); quasi-experimental studies; prospective and retrospective cohorts; case-control, cross-sectional, and surveillance studies; and single-arm before-after (self-controlled) studies with a prespecified resistance, colonization, or resistome outcome.

Eligibility criteria Inclusion: peer-reviewed journal articles with primary data; human participants aged 18 years or older; a clearly identifiable systemic doxycycline exposure (Tier 1: intermittent Doxy-PEP for STI prevention; Tier 2: any other

clinical indication); at least one colonization, carriage, phenotypic-resistance, resistance-determinant, microbiome, or resistome outcome in a non-target organism, flora, or microbial community; a comparison (a concurrent comparison group or the participant's own pre-exposure baseline); an English full text; records published from January 2023 forward, with pre-2023 evidence incorporated through the prior review's included studies and reference lists via citation searching. Exclusion: conference abstracts, preprints, editorials, commentaries, letters without primary data, theses, and trial-registry records without a published report; animal or in-vitro-only studies; mathematical modeling studies; topical or otherwise non-systemic doxycycline; tetracycline-class exposure in which doxycycline cannot be identified separately; studies with no microbiologic outcome; studies reporting only intended-target-pathogen outcomes with no bystander-organism data; purely descriptive studies with no comparison group and no baseline measurement; and chronic continuous doxycycline prophylaxis (Doxy-PrEP) in Tier 1. Baseline and contextual evidence stream (prespecified secondary stream): human carriage or resistance-prevalence studies, or temporal resistance trends, in bystander organisms or STI pathogens, from populations relevant to the review, with data collected predominantly before widespread Doxy-PEP implementation or in unexposed populations. Mathematical modeling studies and reviews are excluded from this stream. Studies retained in this stream are enumerated separately, appraised with the JBI prevalence checklist, and are not counted in the primary PRISMA flow diagram or synthesis.

Information sources Electronic databases: PubMed (National Library of Medicine), searched in place of MEDLINE; CINAHL Ultimate (EBSCOhost); Cochrane Central Register of Controlled Trials (CENTRAL, via EBSCOhost Cochrane Collection Plus); and Academic Search Premier (EBSCOhost) for supplemental interdisciplinary coverage. All databases are searched for records published from January 1, 2023 to the search date, updating the prior review by Usuanlele et al. (2026), which synthesized the 2013–2023 literature; no language, publication-type, or peer-review limiters are applied. Evidence published before 2023 is identified through the prior review's included studies and reference lists rather than through new database searching. Database searches were executed beginning October 7, 2026, and will be rerun immediately before final analyses. Supplemental searches: backward citation searching of the reference lists of all included

studies and of the prior review; forward citation searching of all included studies in Google Scholar; and trial-registry searching of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, using the Doxy-PEP terminology from the search strategy. Registry records are reported separately and enter the synthesis only if a full published report with sufficient outcome data exists. Embase, Scopus, and Web of Science are unavailable through institutional subscriptions; CENTRAL provides access to Embase-derived trial records, and this limitation will be acknowledged. Search strategies are peer-reviewed by a health sciences librarian against the PRESS 2015 checklist before final execution.

Main outcome(s) Primary outcome: tetracycline-class phenotypic resistance in non-target (bystander) organisms, including doxycycline-specific minimum inhibitory concentrations (MICs) where reported, and high-level tetracycline resistance where reported, measured before versus after doxycycline exposure, or compared between exposure groups. Effect measures: event counts with denominators, absolute proportions, and reported comparative estimates (risk ratio, odds ratio, prevalence ratio, or risk difference) with 95% confidence intervals; MIC distributions, MIC50/MIC90, geometric mean MICs, and fold-changes as reported. The unit of analysis (participant, specimen, or isolate) is recorded. Timing: baseline versus post-exposure comparisons and between-group comparisons at reported follow-up points. Certainty will be assessed with GRADE, judged separately by tier.

Additional outcome(s) (a) Colonization or carriage prevalence of bystander organisms; (b) genotypic resistance determinants (e.g., tet genes) and their prevalence; (c) resistome composition and antimicrobial-resistance gene abundance, including any exposure-response relationships with cumulative doxycycline exposure; (d) microbiome composition changes; and (e) cross-resistance or co-selection of resistance to other antimicrobial classes. Each outcome is analyzed and presented separately rather than combined into a single resistance category. Tetracycline-class and doxycycline-specific resistance are distinguished and reported separately whenever studies permit. Resistance definitions and breakpoints are accepted as reported, with differences noted in the synthesis.

Data management All records are imported into Covidence for a round of automated duplicate detection, with residual duplicates removed manually. Titles and abstracts are screened

independently by two reviewers against prespecified eligibility criteria; full-text assessment is likewise dual, with exclusions documented with reasons. Reports are classified at full text as Tier 1, Tier 2, or baseline/contextual evidence, and multiple reports of one parent study are grouped by their common identifier before eligibility assessment. Data are extracted with a standardized extraction form in Covidence, piloted on two studies (one per tier) before full extraction; extraction is performed independently by two reviewers, with discrepancies resolved by discussion and adjudication by a third reviewer (the faculty mentor) when unresolved. Database export files and deduplication logs are archived as the audit trail for the PRISMA 2020 flow diagram.

Quality assessment / Risk of bias analysis Risk of bias is assessed with the tool matched to the analysis evaluated, not solely the parent study design: the Cochrane Risk of Bias 2 (RoB 2) tool for randomized comparisons in which the analyzed exposure reflects the randomized allocation; ROBINS-I for non-randomized comparative analyses, including microbiologic substudies analyzed by actual (cumulative) exposure or based on selected subsets; the JBI critical appraisal checklist for quasi-experimental studies for single-arm self-controlled before-after designs; and the JBI checklist for prevalence studies for the baseline and contextual evidence stream. Two reviewers assess risk of bias independently; disagreements are resolved by discussion, with a third reviewer adjudicating unresolved judgments. Domain-level judgments are reported for each study; studies at high risk of bias are retained, and their influence on findings is described narratively.

Strategy of data synthesis A meta-analysis is not planned: included studies are expected to differ substantially in populations, doxycycline exposures, organisms, specimen sites, laboratory methods, outcome definitions, and units of analysis, and statistical pooling would obscure these differences. A structured narrative synthesis will be conducted and reported in accordance with the SWiM (Synthesis Without Meta-analysis) reporting guideline. Tier 1 and Tier 2 evidence will be synthesized separately before any cross-tier comparison. Within each tier, findings will be grouped by organism, specimen site, phenotypic versus genotypic outcome, exposure pattern (intermittent versus continuous; dose, duration, and cumulative exposure), and outcome timing, and tabulated in structured synthesis tables and evidence matrices (study, population, exposure, organism, outcome, unit of analysis, result, risk of bias, parent-study identifier). Direction and

magnitude of findings will be summarized; vote-counting by statistical significance will not be used. We will evaluate cross-tier convergence or divergence against differences in dosing frequency, cumulative exposure, duration, population, specimen site, organism, and method; convergence will be interpreted as strengthening the biological plausibility of doxycycline selection pressure, not as proof of causation or regimen equivalence. The baseline and contextual stream will be summarized in a separate, labeled table. Certainty will be assessed with GRADE for two prespecified critical outcomes (phenotypic bystander resistance; genotypic determinants or resistome), judged separately by tier.

Subgroup analysis No formal statistical subgroup analyses are planned. Within the narrative synthesis, findings are grouped descriptively by organism, specimen site, phenotypic versus genotypic outcome, exposure pattern (intermittent versus continuous; dose, duration, and cumulative exposure), outcome timing, and tier. Cumulative-exposure and dose-response analyses are extracted and reported separately from fixed-dose comparisons, because they address a distinct aspect of the review question.

Sensitivity analysis Sensitivity analyses are not applicable because no meta-analysis is planned. The influence of study quality is handled narratively: risk-of-bias judgments are reported for every study, findings from studies at high risk of bias are retained with their influence on apparent patterns described, and the synthesis states explicitly where high-risk-of-bias studies drive findings. Certainty of evidence is assessed with GRADE for the two prespecified critical outcomes, judged separately for Tier 1 and Tier 2 evidence.

Language restriction No language limits are applied in the searches. English full text is required for data extraction, assessed at screening.

Country(ies) involved United States.

Other relevant information Conduct and reporting standards: the review is conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, version 6.5, where applicable to a review composed predominantly of observational exposure-outcome evidence, and reported per the PRISMA 2020 statement; the searches are reported per PRISMA-S; and the narrative synthesis follows the SWiM reporting guideline. Final search strategies, with all search lines, dates, interfaces, and record counts, will be reported in the final manuscript. Search

strategies are peer-reviewed by a health sciences librarian against the PRESS 2015 checklist before final execution, and searches are rerun immediately before final analyses. Because the review updates a prior systematic review (Usuanlele et al., 2026), evidence published before January 2023 is drawn from the prior review's included studies and reference lists; any pre-2023 study not identified by the prior review's search may be missed, and we will acknowledge this limitation. No formal calibration exercise precedes screening; both screeners jointly review the eligibility criteria and the operational tier and bystander-organism definitions before screening begins, and unresolved screening, extraction, and risk-of-bias disagreements are adjudicated by a third reviewer (the faculty mentor). Any amendments to this protocol made after registration will be documented and reported in the final manuscript.

Keywords doxycycline; Doxy-PEP; post-exposure prophylaxis; antimicrobial resistance; tetracycline resistance; bystander organisms; colonization; microbiome; resistome; systematic review protocol.

Dissemination plans Results will be presented at the Sacred Heart University graduate capstone symposium and submitted for publication in a peer-reviewed journal focused on sexually transmitted infections, antimicrobial resistance, or clinical pharmacology. Findings are intended to inform clinician-patient communication and antimicrobial-stewardship conversations about the collateral resistance effects of Doxy-PEP. No individual participant data will be reported.

Contributions of each author

Author 1 - Results will be presented at the Sacred Heart University graduate capstone symposium and submitted for publication in a peer-reviewed journal focused on sexually transmitted infections, antimicrobial resistance, or clinical pharmacology. Findings are intended to inform clinician-patient communication and antimicrobial-stewardship conversations about the collateral resistance effects of Doxy-PEP. No individual participant data will be reported.

Email: nemece@sacredheart.edu

Author 2 - Emma Custeau.

Email: custeau@mail.sacredheart.edu

Author 3 - Andre Gallant.

Email: gallanta2@mail.sacredheart.edu

Author 4 - Suzanne Rose .

Email: srose@stamhealth.org