UK Health Security Agency

Serious or severe adverse effects experienced by people taking doxycycline

A rapid review of systematic reviews

Contents

Main messages

1. This rapid review identified and summarised systematic reviews relating to serious or severe adverse effects experienced by people taking doxycycline for up to 30 days (search from January 2021 up to 12 August 2024). The review focused on serious or severe adverse events experienced by people taking doxycycline over a short to medium duration of use.

2. This review found 3 systematic reviews comparing doxycycline to other antibiotics or placebo for the treatment of medical conditions or as a preventive measure against infections. These included a total of 12 primary studies: 9 randomised controlled trials and 3 prospective non-randomised clinical trials. There was a total of 3,372 people included across all systematic reviews, with a mix of children and adults, males and females.

3. The review considered serious or severe adverse events as described by the included reviews. Where no definition of serious or severe adverse events was provided in the review, the definition of the European Medicines Agency for a serious or severe adverse event was used. The European Medicines Agency defines an adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect. Any adverse events reported to lead to discontinuation of doxycycline were also included.

4. One systematic review reported one serious adverse event. One person experienced a fixed drug eruption, an allergic skin reaction reoccurring in the same place upon re-administration of doxycycline. Two systematic reviews did not indicate any serious or severe adverse events related to doxycycline.

5. A small number of people reported by one systematic review experienced adverse events which led to the discontinuation of doxycycline. This systematic review reported that between 0.9% to 7% (measures of variance not reported) of people discontinued doxycycline because of an adverse event but did not report what the adverse events were.

6. Critical appraisal highlighted that most systematic reviews did not specify whether primary studies had stated financial conflict of interest, with some also not reporting the sources of funding for completing the systematic review. There was concern that some of the systematic reviews did not capture all the available literature due to poor search and screening methodology with a risk of selective reporting due to lack of pre-specified protocols. The systematic reviews only included a small number of primary studies each with small sample sizes. The overall number of people included may not have been large enough to find rare serious or severe adverse events.

7. All the systematic reviews generally reported high risk of bias in the primary studies they included. Two systematic reviews reported lack of blinding to which treatment people were taking (doxycycline, placebo, or different antibiotic). This lack of blinding may have affected people's reporting of adverse events due to their views of the treatment. It was also noted that some studies had incomplete data which can affect the study's ability to detect serious or severe adverse events.

8. Overall, there was limited systematic review evidence to suggest that use of doxycycline for short to medium duration of use leads to serious or severe adverse events. Some evidence suggested it may cause less severe adverse events which may lead to discontinuation of the drug.

Purpose

The purpose of this rapid review was to identify and summarise the available evidence from systematic reviews about serious or severe adverse effects experienced by people taking doxycycline for any dosing regimens.

Methods

The review question was:

1. What are the serious or severe adverse events experienced by people taking doxycycline for up to 30 days?

A rapid review was conducted, following streamlined systematic methods to accelerate the review process. A literature search was undertaken to look for relevant systematic reviews from January 2021 up to 12 August 2024. The search for systematic reviews was limited to January 2021 as a relevant review conducted in 2021 looking at the safety of antimicrobials including doxycycline was identified (1), and the summary of product characteristics (2) was last updated in 2021.

This review aimed to identify the following outcomes:

- severe or serious physiological (those that impact the normal function of an organ in the body) or neurological events (those that impact the central nervous system)
- any psychiatric symptom or mental health complaint (self-reported or diagnosed)

The review considered serious or severe adverse events as described by the included reviews, or the definition by the European Medicines Agency for a serious or severe adverse event was used, stated as an adverse reaction that results in death, is life-threatening, requires

hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect. Any adverse events reported to lead to discontinuation of the drug were also included.

Screening title and abstract was undertaken in duplicate by 2 reviewers for 20% of the eligible studies, with the remainder completed by one reviewer. Screening full text was undertaken by one reviewer and checked by a second. Data extraction was performed by one reviewer and checked by a second. Critical appraisal was conducted in duplicate by 2 reviewers using AMSTAR2, 'A MeaSurement Tool to Assess Systematic Reviews' (3).

A protocol was produced before the literature search was conducted, including the review question, the eligibility criteria, and all other methods. Full details of the methodology are provided in the protocol in Annexe A. There were no deviations from the protocol.

Evidence

In total, 897 records were screened at title and abstract and 126 records were screened at full text. Of these, 3 systematic reviews met the inclusion criteria, which included a total of 12 primary studies relevant to this review. Studies excluded during full text screening are available with the reasons why in Annexe C.

Two systematic reviews included randomised controlled trials (4, 5) and one included randomised controlled trials and prospective non-randomised clinical trials (6). Systematic reviews included studies of doxycycline as a treatment for Meibomian Gland Dysfunction which causes dry eyes (6), or as a preventive method for sexually transmitted infections (4, 5). There was an overlap of 3 primary studies in the reviews looking at sexually transmitted infections. Studies within the systematic review were conducted in Asia (6), Europe (4 to 6), the United States of America (4, 5) and Africa (4, 5).

Two systematic reviews looked at the use of doxycycline (one oral 200mg dose) to prevent sexually transmitted infections in people who have engaged in sexual behaviour without protection, compared to people receiving no preventative medicine (4, 5). One of these reviews by Sokoll 2024 synthesised 4 randomised controlled trials including a total of 1727 participants with an age range from 24 to 73 years. Seventy-three percent of participants were men who have sex with men, 1% were transgender women, and 26% were cisgender women (4). The systematic review reported that 90% of participants were also taking human immunodeficiency virus pre-exposure prophylaxis. People were followed for up to 14 months after receiving doxycycline. This systematic review did not provide a definition for serious adverse events and one of the primary studies included in this review did not report serious adverse events. The systematic review reported one serious adverse event attributed to doxycycline during the follow-up period, which was a fixed drug eruption, an allergic skin reaction reoccurring in the same place upon re-administration of the medication. The systematic review reported that

between 0.9% to 7% (measures of variance not reported) of people discontinued using doxycycline because of an adverse event, but they did not report what the adverse events were. The review reported that gastrointestinal-related events were the most common adverse events, but no further information was provided, and it was unclear whether gastrointestinal events were the reason for discontinuation. Critical appraisal did not reveal any serious limitations except that review authors did not report what sources of funding the primary studies used and therefore, the extent of financial conflict of interest in the primary studies could not be assessed.

In the second systematic review looking at doxycycline to prevent sexually transmitted infections by Szondy 2024, 3 randomised controlled trials were synthesised with a total of 1,182 participants (5). Age and sex were not reported, but the review included a large proportion of people taking human immunodeficiency virus pre-exposure prophylaxis, or people living with HIV infection. The 3 primary studies in this review were also included in the systematic review by Sokoll 2024 discussed above. This systematic review did not provide a definition for serious adverse events and did not report on discontinuation due to adverse events. People were followed for up to 12 months after receiving doxycycline. No serious adverse events were reported. In this systematic review, authors assessed the certainty of the included evidence with the Grading of Recommendations Assessment, Development, and Evaluations (7) and rated the certainty of the evidence on adverse events as low. Critical appraisal showed potential limitations in identification of the relevant evidence. Authors did not comprehensively describe how the literature was searched, nor did they provide information about the reasons for excluding studies. There was concern this systematic review did not include all the available evidence in the literature on doxycycline and serious adverse events. Review authors also did not report the sources of funding in the primary studies, meaning the extent of financial conflict of interest in the primary studies could not be assessed.

One systematic review by Ben Ephraim Noyman (2024), synthesised 5 primary studies with a total of 463 people (6). It included 2 randomised controlled trials and 3 prospective non-randomised clinical trials and aimed to test the efficacy and safety of doxycycline in treating people with Meibomian Gland Dysfunction. People receiving a total of 3.50 to 5.60 grams of doxycycline (either 100mg twice daily for 7 days and then 100mg daily for 21 days, or 100mg twice daily for 4 weeks) were compared to people receiving a total of 1.25 to 3.00 grams of Azithromycin. The review included both male and females, and ages ranged from 12 to 90 years. The treatment course for each antibiotic lasted for 4 weeks, after which, people were followed for up to 270 days. The systematic review did not provide a definition for serious adverse events. This review did not report any serious or severe adverse event from any of the included primary studies or discontinuation due to adverse events. The review did not comprehensively describe how the literature was searched, nor did it provide information about the reasons for excluding studies which raised concerns that relevant primary studies could have been missed. There was also concern about whether any conflict of interest existed as the authors did not report the funding source for primary studies, nor did they report their own conflict of interest or funding.

All the systematic reviews included in this rapid review assessed risk of bias within their included studies and generally rated the evidence as having high risk of bias. Most systematic reviews identified blinding as a major source of bias whereby people might have been aware whether they were taking doxycycline, placebo, or another antibiotic. Some systematic reviews also reported there were studies with incomplete data, which can affect the extent to which these studies could accurately identify all serious or severe adverse events experienced by study participants.

Health inequalities

There was evidence of one occurrence of a fixed drug eruption in a systematic review that included men who have sex with men. In this sample, people took doxycycline within 3 days after having engaged in unprotected sexual intercourse and so were at a higher risk of becoming infected with a sexually transmitted infection, and at greater risk of needing antibiotic treatment. In these samples, the discontinuation rate of doxycycline ranged between 0.9% to 7%.

There was no other information on health inequalities relevant to the prespecified subgroups in the protocol including sex, ethnicity, pregnant women, children aged 18 years and below, and people with an alcohol dependency. One systematic review did include children, but they did not report results separately for children and adults, meaning we were unable to identify any inequalities between groups (6).

Limitations

This rapid review used streamlined systematic methods to accelerate the review process. Sources of evidence searched included databases of peer-reviewed research, but an extensive search of other sources was not conducted and most article screening was completed without duplication, so it is possible relevant evidence may have been missed.

None of the 3 included systematic reviews provided a definition for serious adverse events, meaning it was not possible to know what each review had considered as serious or severe. This definition may have therefore varied across studies and may explain why one study assessing the efficiency of doxycycline as post-exposure prophylaxis for sexually transmitted infections reported a serious adverse event, but the second study did not. Although not pre-specified as an aim of our protocol, no systematic review reported at which time point people experienced adverse events. Moreover, since the total sample sizes in each systematic review were relatively small it was not possible to know whether the absence of serious or severe adverse events was due to a good doxycycline safety profile or due to the lack of a sufficient number of people to be able to detect less frequent adverse events. Finally, there was concern about financial conflict of interest across most systematic reviews because they did not routinely

report or disclose sources of funding within the primary studies or for completing the systematic review. There was also concern that a couple of systematic reviews may have missed some relevant primary studies because of poor methodology in searching the literature. No systematic review specified whether studies used active monitoring or surveillance when collecting information regarding serious or severe adverse events.

Evidence gaps

There was limited recent evidence from systematic reviews investigating whether using doxycycline for 30 days is associated with any serious or severe adverse events. Where systematic reviews were available, the number of included studies and sample sizes may have been too small to be able to find such events.

Conclusion

There was limited evidence from recent systematic reviews investigating whether short to medium term use of doxycycline treatment for causes serious or severe adverse events. Of the systematic reviews that were available, there was one serious adverse event (4), and discontinuation due to adverse events was reported in one systematic review (4).

Overall, the available evidence base does not suggest doxycycline causes serious or severe adverse events, but this should be interpreted in light of several risks of bias identified. The systematic reviews included a small number of primary studies and total sample size, which may not have been sufficiently large to detect rare severe and serious adverse events. Moreover, review authors also did not report what sources of funding the primary studies used meaning the extent of financial conflict of interest in the primary studies could not be assessed. Authors did not comprehensively describe how the literature was searched, nor did they provide information about the reasons for excluding studies. Most systematic reviews reported lack of blinding to what treatment people were taking which may have affected people's reporting of adverse events due to their views of the treatment. It was also noted that some studies had incomplete data which can affect the study's ability to detect serious or severe adverse events. Both biases can have concerning implications in finding serious or severe adverse events from taking doxycycline, particularly in studies with relatively small samples. Therefore, that doxycycline does not seem to give serious or severe adverse events should be viewed in light of these sources of bias.

The evidence presented in this review aligns with that reported in the existing systematic review by Parker and others in 2021 (1) and the summary of product characteristics (2), and no new serious or severe adverse events were identified that were associated with taking doxycycline.

Acknowledgment

We would like to thank colleagues within the All Hazards Public Health Response division who either reviewed or input into aspects of the review.

Disclaimer

UKHSA's rapid reviews aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, unpublished reports and papers on preprint servers. Please note that the reviews:

- use accelerated methods and may not be representative of the whole body of evidence publicly available
- have undergone an internal, but not independent, peer review
- are only valid as of the date stated on the review

In the event that this review is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

References

1. Parker CM KA and others. 'Safety of Antimicrobials for Postexposure Prophylaxis and Treatment of Anthrax: A Review' Clinical Infectous Diseases 2022: volume 17, issue 75, supplement 3, pages S417 to S431
2. Authority HPR. 'Summary of Product Charecteristics' 2021
3. Beverley JS and others. 'AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both' BMJ 2017: volume 358, page j4008
4. Sokoll PR and others. 'Efficacy of postexposure prophylaxis with doxycycline (Doxy-PEP) in reducing sexually transmitted infections: a systematic review and meta-analysis' Sexually Transmitted Infections 2024: volume 3, page 3
5. Szondy I and others. 'Doxycycline prophylaxis for the prevention of sexually transmitted infections: a systematic review and meta-analysis of randomised controlled trials' International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 2024, page 107186
6. Ben Ephraim Noyman D and others. 'Systemic antibiotic treatment for meibomian gland dysfunction-A systematic review and meta-analysis' Acta Opthalmologica 2024: volume 102, issue 1, pages e1 to e10
7. TGW G. 'GRADE handbook for grading quality of evidence and strength of recommendations' 2013

Annexe A. Protocol

Review question

The review questions are:

1. What are the serious or severe adverse events experienced by people taking doxycycline for up to 30 days?

A search for systematic reviews to answer this review question will be conducted up to a. The Summary of Product Characteristics was last updated in 2021 and therefore the search for systematic reviews will be restricted between 2021 and 2024.

In this review:

Adverse events refer to any harmful event that a person experiences after taking doxycycline.

An exploratory approach will be performed synthesising all or any adverse events documented in the literature regardless of whether these had been prespecified as outcomes of interest in the original studies. Therefore, the exploratory approach will include spontaneously reported or prespecified adverse events documented in the original study.

The Cochrane Collaboration defines a systematic review as: A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question". It uses explicit, systematic methods that are selected with a view to minimising bias, thus providing more reliable findings from which conclusions can be drawn and decisions made. The key characteristics of a systematic review are:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology
- a systematic search that attempts to identify all studies that would meet the eligibility criteria
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies

The current rapid review aims to synthesise evidence on the adverse events associated with taking doxycycline. Since adverse events are often not primary outcomes but may be spontaneously reported and recorded in research studies and carry a specific set of biases needing a specific and separate critical appraisal, it is possible existing systematic reviews might not have routinely assessed the validity of study findings. Because of these reasons,

systematic reviews without explicit assessment of the validity of the findings such as risk of bias will be included, nonetheless.

This rapid review of systematic reviews will supplement a summary of existing tertiary reports and therefore it will not include literature from tertiary sources.

Eligibility criteria

Table A.1 Inclusion and exclusion criteria

	Included	Excluded
Population	Anyone of any age taking doxycycline	Animals
Context	Any	None
Settings	Any	None
Intervention or exposure	Doxycycline taken orally only and in isolation of any dosage at any frequency for up to 30 days Doxycycline compared to placebo or no treatment or to other antibiotics	Any other antibiotic Doxycycline taken through any other route (for example, topically)
Outcomes	Systematic reviews explicitly stating that adverse events were outcomes of interest regardless of whether the primary research aim was to assess effectiveness of doxycycline Prevalence, incidence, risk (relative or absolute), or count data (individual or total) of any severe or serious adverse event ascribed to taking doxycycline • prespecified • spontaneously reported Type of outcomes as defined by the serious or severe adverse event (or reaction) or the suspected unexpected serious adverse reactions guidelines, or by the European Medicines Agency (an adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing	Systematic reviews that did not have adverse events as of one of their outcomes of interest Any beneficial outcome Any mild or moderate adverse event, for example • mild or moderate neurological symptoms (headaches, dizziness) • mild or moderate physiological events

	Included	Excluded
	hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect), or discontinuation due to adverse events, or as described by the review: • severe or serious physiological (those that impact the normal function of an organ in the body) or neurological events (those that impact the central nervous system) • any psychiatric symptom or mental health complaint (self-reported or diagnosed)	
Language	English	Any other language
Date of publication	From January 2021 up to 12 August 2024	Any record published prior to 2021
Study design	Systematic reviews with/without any type of meta-analysis (for example, standard or network) of: • any experimental study (for example, randomised controlled trials) • any observational study • a mix of both experimental and observational studies	• primary research • narrative reviews • literature reviews • systematic reviews of case reports or series • laboratory studies • scoping reviews
Publication type	Published peer-reviewed	• preprints • conference abstracts • editorials • letters • news articles • grey literature

Identification of studies

The following databases will be searched for systematic reviews published between January 2021 and 12 August 2024: Ovid Medline, Embase, Cochrane Database of Systematic Reviews and Epistemonikos. The search strategy is presented below.

Screening

Title and abstract screening will be undertaken in duplicate by 2 reviewers for at least 20% of the eligible studies, with the remainder completed by one reviewer. Disagreement will be resolved by discussion or with involvement of a third reviewer where necessary. Screening full text will be undertaken by one reviewer and checked by a second.

Data extraction

Summary information for each study will be extracted and reported in tabular form. Information to be extracted will include country, study period, study designs (for example, randomised controlled trials, cohort studies and so on), intervention, participants, results, and any relevant contextual data. This will be undertaken by one reviewer and checked by a second.

Systematic reviews that recorded any adverse events of any severity will be included; however, only data on adverse events as outcomes of interest in the systematic review will be extracted. This is because, studies do not always explicitly specify or record an adverse event as these may be rare. Primary studies may nonetheless report that no serious harm or adverse event occurred without defining the meaning of these, but such statements will not be recoded as “no adverse event” or “zero adverse event”. Therefore, extracting and recording data as “absence of harm” must have been outlined and stated in the original report.

Information to be extracted will include: study designs, population characteristics including age, sex, comorbidities, ethnicity, deprivation index and socioeconomic status, setting, sample size, intervention details including drug dosages, frequency and delivery route, comparator details, disease, reasons for taking doxycycline (like treatment or prophylaxis) and adverse events.

Meta-analytic results including summary point estimates such as hazard, odds, and risk ratios, means or mean differences (standardised or unstandardised) as well as indices of variance such as confidence intervals, standard errors, standard deviations and so on, will be extracted. Statistical indices of heterogeneity when available such as Q-2, I-2, H, prediction intervals and so on, will also be extracted alongside small-study effect results such as Egger’s test point estimates and *p* values and results from funnel plots when available.

Risk of bias assessment

Two reviewers will independently complete a risk of bias assessment for included studies, with disagreements resolved by discussion or with a third reviewer. Reviews will be assessed using the quality assessment tool AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both (3).

Synthesis

Where studies present data in a consistent format, a narrative synthesis will be produced to interpret the findings. The number of studies, the number of participants in each study, effect size (of the adverse event) and variance and a summary of the risk of bias across studies will be summarised and presented. Alternatively, if studies present methodological differences that would make synthesis inappropriate, a narrative summary of each study will be provided.

As each review would have synthesised evidence by using different selection criteria addressing different research questions, results will be presented at the review level by compiling any narrative or quantitative synthesis the review provides. Synthesis of each review's findings will involve combining review level narrative or quantitative results as well as risk of bias. Where systematic reviews present Grading of Recommendations Assessment, Development and Evaluation results, quantitative or qualitative findings from the review will be presented and interpreted in light of Grading of Recommendations Assessment, Development, and Evaluations assessment.

Review-level factors to explore heterogeneity may include but are not limited pregnant women, children aged 18 years and below, and people with an alcohol dependency as well as dose and frequency of doxycycline use. Any meta-analytic data will not be re-analysed.

Health inequalities

Variations across the following populations and subgroups will be considered, where evidence is available: sex, ethnicity, pregnant women, children aged 18 years and below, and people with an alcohol dependency whether self-reported or clinically diagnosed.

Search strategy

Database: Ovid MEDLINE(R) ALL <1946 to 9 August 2024>

1. Doxycycline/ (11189)
2. doxycyclin*.tw,kf. (17911)
3. doxycylin*.tw,kf. (166)
4. doxy-Caps.tw,kf. (1)
5. doxychel.tw,kf. (1)
6. doxytetracycline.tw,kf. (14)
7. "6-Deoxytetracycline".tw,kf. (31)
8. deoxymykoin.tw,kf. (2)
9. dossiciclina.tw,kf. (1)
10. doxiciclina.tw,kf. (33)
11. monodox.tw,kf. (2)

12. "564-25-0".tw,kf. (3)
13. vibramycin*.tw,kf. (198)
14. efracea.tw,kf. (0)
15. periosta.tw,kf. (0)
16. "6alpha-Deoxy-5-oxytetracycline".tw,kf. (1)
17. "6-alpha-Deoxy-5-oxytetracycline".tw,kf. (1)
18. "5-Hydroxy-alpha-6-deoxytetracycline".tw,kf. (1)
19. "alpha-6-Deoxy-5-hydroxytetracycline".tw,kf. (2)
20. "BMY-28689".tw,kf. (1)
21. liviatin.tw,kf. (1)
22. "CHEBI:50845".tw,kf. (156)
23. "(4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide".tw,kf. (0)
24. "2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)-".tw,kf. (1)
25. or/1-24 (21774)
26. Doxycycline/ae, to (916)
27. exp "Drug-Related Side Effects and Adverse Reactions"/ (136782)
28. ((adverse* or side or incidental or harm* or induced or severe* or serious*) adj2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result* or repercussion* or ramification* or impact*)).tw,kf. (1170366)
29. ((un-intended or un-expected or un-anticipated or un-foreseen or un-intentional* or un-desir* or un-planned or un-wanted) adj2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result or repercussion* or ramification* or impact*)).tw,kf. (40)
30. ((unintended or unexpected or unanticipated or unforeseen or unintentional* or undesir* or unplanned or unwanted) adj2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result or repercussion* or ramification* or impact*)).tw,kf. (45575)
31. (drug adj (reaction* or hypersensitiv* or sensitiv* or tolera* or safety or related or harm* or toxic*)).tw,kf. (82424)
32. safety profile*.tw,kf. (48806)
33. Patient Harm/ or Patient Safety/ (26637)
34. Prescription Drug Monitoring Programs/ (450)
35. Product Surveillance, Postmarketing/ (7754)
36. Pharmacovigilance/ (3703)
37. pharmacovigilance.tw,kf. (8539)
38. Adverse Drug Reaction Reporting Systems/ (9283)
39. ((person or personal or individual or patient* or public) adj experience*).tw,kf. (105989)
40. exp Risk Assessment/ (319761)
41. exp *Risk/ (43301)
42. (risk adj (assessment* or analys* or reduction)).tw,kf. (141308)
43. or/26-42 (1858248)
44. 25 and 43 (2601)
45. limit 44 to "reviews (best balance of sensitivity and specificity)" (441)

46. limit 45 to dt=20210101-20240812 (95)

Database: Embase <1974 to 9 August 2024>

1. exp doxycycline/ (71739)
2. exp doxycycline hyclate/ (1079)
3. doxycyclin*.tw,kf. (27418)
4. doxycylin*.tw,kf. (368)
5. doxy-Caps.tw,kf. (0)
6. doxychel.tw,kf. (3)
7. doxytetracycline.tw,kf. (12)
8. "6-Deoxytetracycline".tw,kf. (29)
9. deoxymykoin.tw,kf. (16)
10. dossiciclina.tw,kf. (0)
11. doxiciclina.tw,kf. (41)
12. monodox.tw,kf. (40)
13. "564-25-0".tw,kf. (2)
14. vibramycin*.tw,kf. (1698)
15. efracea.tw,kf. (3)
16. periosta.tw,kf. (0)
17. "6alpha-Deoxy-5-oxytetracycline".tw,kf. (0)
18. "6-alpha-Deoxy-5-oxytetracycline".tw,kf. (0)
19. "5-Hydroxy-alpha-6-deoxytetracycline".tw,kf. (0)
20. "alpha-6-Deoxy-5-hydroxytetracycline".tw,kf. (2)
21. "BMY-28689".tw,kf. (0)
22. liviatin.tw,kf. (0)
23. "CHEBI:50845".tw,kf. (149)
24. "(4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide".tw,kf. (1)
25. "2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)-".tw,kf. (0)
26. or/1-25 (75605)
27. exp doxycycline/ae, it, to, pv, tm [Adverse Drug Reaction, Drug Interaction, Drug Toxicity, Special Situation for Pharmacovigilance, Unexpected Outcome of Drug Treatment] (6272)
28. exp adverse event/ (1043415)
29. exp side effect/ (727011)
30. ((adverse* or side or incidental or harm* or induced or severe* or serious*) adj2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result* or repercussion* or ramification* or impact*)).tw,kf. (1744819)
31. ((un-intended or un-expected or un-anticipated or un-foreseen or un-intentional* or un-desir* or un-planned or un-wanted) adj2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result or repercussion* or ramification* or impact*)).tw,kf. (59)

32. ((unintended or unexpected or unanticipated or unforeseen or unintentional* or undesir* or unplanned or unwanted) adj2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result or repercussion* or ramification* or impact*)).tw,kf. (60455)
33. exp drug toxicity/ (165552)
34. (drug adj (reaction* or hypersensitiv* or sensitiv* or tolera* or safety or related or harm* or toxic*)).tw,kf. (131187)
35. safety profile*.tw,kf. (93378)
36. exp patient safety/ (177386)
37. exp pharmacovigilance/ (40328)
38. exp special situation for pharmacovigilance/ (32810)
39. pharmacovigilance.tw,kf. (17034)
40. exp postmarketing surveillance/ (40096)
41. exp personal experience/ (71173)
42. ((person or personal or individual or patient* or public) adj experience*).tw,kf. (170962)
43. exp risk assessment/ (777223)
44. exp risk reduction/ (137554)
45. sentinel event/ (884)
46. exp *risk/ (463100)
47. (risk adj (assessment* or analys* or reduction)).tw,kf. (191131)
48. or/27-47 (4240356)
49. 26 and 48 (16938)
50. limit 49 to "reviews (best balance of sensitivity and specificity)" (4019)
51. limit 50 to dc=20210101-20240812 (794)

Cochrane Database of Systematic Reviews

Date Run: 12 August 2024 12:38:17

ID	Search	Hits
#1	MeSH descriptor: [Doxycycline] explode all trees	1,330
#2	doxycyclin*	2,753
#3	doxycylin*	71
#4	"doxy-Caps"	1
#5	doxychel	2
#6	doxytetracycline	2
#7	"6-Deoxytetracycline"	3
#8	deoxymykoin	2
#9	dossiciclina	1
#10	doxiciclina	30
#11	monodox	10

ID	Search	Hits
#12	"564-25-0"	17
#13	vibramycin*	43
#14	efracea	3
#15	periosta	0
#16	"6alpha-Deoxy-5-oxytetracycline"	0
#17	"6-alpha-Deoxy-5-oxytetracycline"	0
#18	"5-Hydroxy-alpha-6-deoxytetracycline"	0
#19	"alpha-6-Deoxy-5-hydroxytetracycline"	0
#20	"BMY-28689"	2
#21	liviatin	1
#22	"CHEBI:50845"	0
#23	"(4S,4aR,5S,5aR,6R,12aR)-4-(dimethylamino)-1,5,10,11,12a-pentahydroxy-6-methyl-3,12-dioxo-4a,5,5a,6-tetrahydro-4H-tetracene-2-carboxamide"	0
#24	"2-Naphthacenecarboxamide,4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-, (4S,4aR,5S,5aR,6R,12aS)-"	0
#25		2,780
#26	MeSH descriptor: [Doxycycline] explode all trees and with qualifier(s): [adverse effects - AE, toxicity - TO]	190
#27	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	5,231
#28	((adverse* or side or incidental or harm* or induced or severe* or serious*) NEAR/2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result* or repercussion* or ramification* or impact*))	476,843
#29	(("un-intended" or "un-expected" or "un-anticipated" or "un-foreseen" or un NEXT intentional* or un NEXT desir* or "un-planned" or "un-wanted") NEAR/2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result or repercussion* or ramification* or impact*))	6
#30	((unintended or unexpected or unanticipated or unforeseen or unintentional* or undesir* or unplanned or unwanted) NEAR/2 (incident* or effect* or event* or consequenc* or outcome* or reaction* or result or repercussion* or ramification* or impact*))	7,517
#31	(drug NEAR/0 (reaction* or hypersensitiv* or sensitiv* or tolera* or safety or related or harm* or toxic*))	4
#32	safety NEXT profile*	27,092

ID	Search	Hits
#33	MeSH descriptor: [Patient Harm] explode all trees	6
#34	MeSH descriptor: [Patient Safety] explode all trees	1,082
#35	MeSH descriptor: [Prescription Drug Monitoring Programs] explode all trees	10
#36	MeSH descriptor: [Pharmacovigilance] explode all trees	42
#37	pharmacovigilance	3,294
#38	MeSH descriptor: [Adverse Drug Reaction Reporting Systems] explode all trees	185
#39	((person or personal or individual or patient* or public) NEAR/0 experience*)	45
#40	MeSH descriptor: [Risk Assessment] explode all trees	13,656
#41	(risk NEAR/0 (assessment* or analys* or reduction))	3
#42	MeSH descriptor: [Product Surveillance, Postmarketing] this term only	264
#43	MeSH descriptor: [Risk] this term only	4,696
#44	{OR #26-#43}	500,122
#45	#25 AND #44	1,039

Results from CDSR: 138 results

Date limited to 1 January 2021 to 12 August 2024 26 results

Epistemonikos

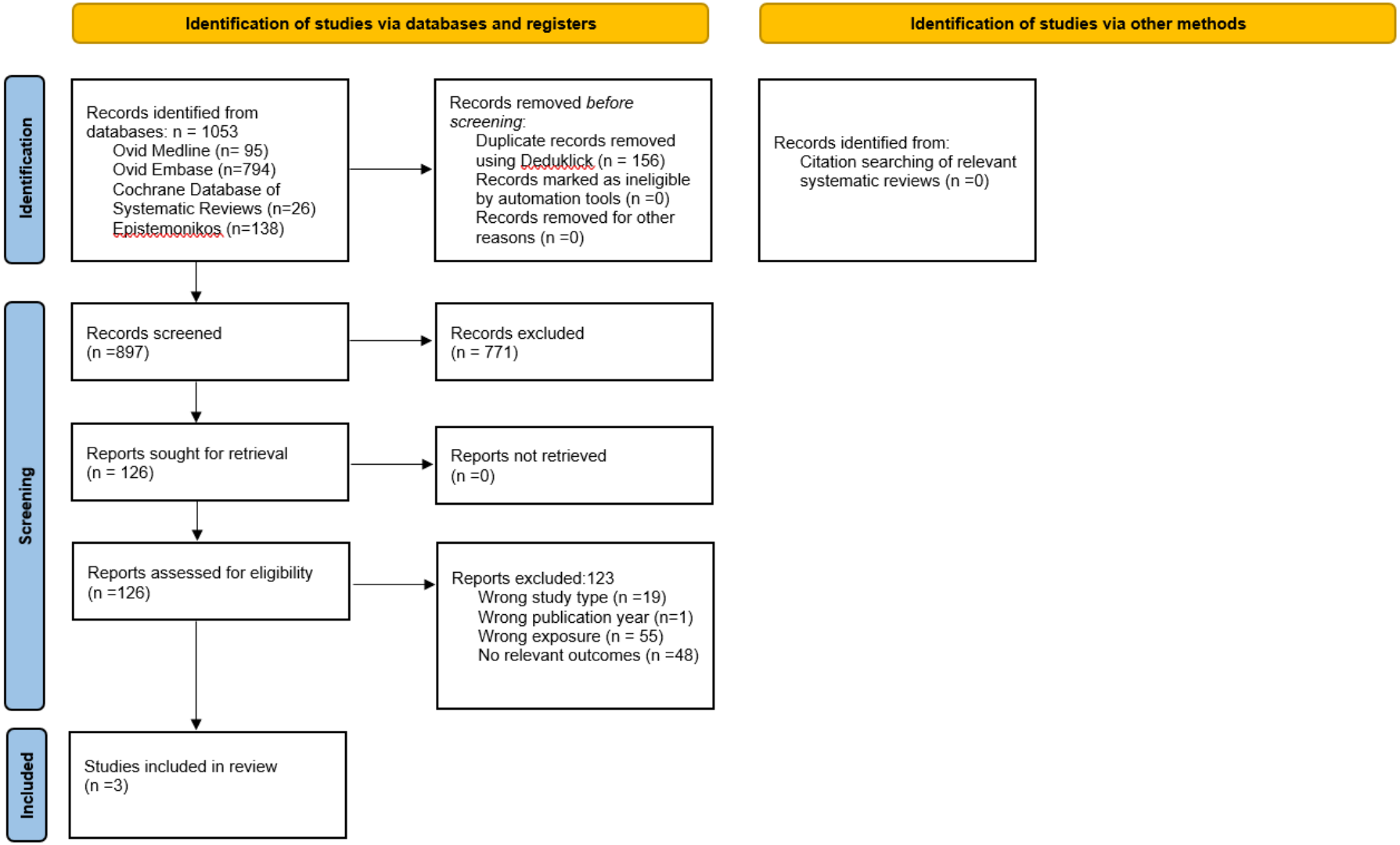
URL: https://www.epistemonikos.org/
Date: 12 August 2024

Doxycyclin* OR doxyclin* OR doxychel OR doxytetracycline OR “6-Deoxytetracycline” OR deoxymykoin OR dossiciclina OR doxiciclina OR monodox OR “564-25-0” OR vibramycin OR efracea

Date limited by publication year 2021 to 2025
Limited to systematic reviews: 138 results

Annexe B. Study selection flowchart

Figure B.1. PRISMA diagram



Text version of Figure A.1. PRISMA diagram

A PRISMA diagram showing the flow of studies through this review, ultimately including 3 studies.

From identification of studies via databases and registers, n=1053 records identified from databases:

- Ovid Medline (n=95)
- Ovid Embase (n=794)
- Cochrane Database of Systematic Reviews (n=26)
- Epistemonikos (n=138)

From these, records removed before screening:

- duplicate records removed using Deduklick (n=156)
- duplicate records removed manually (n=0)
- records marked as ineligible by automation tools (n=0)
- records removed for other reasons (n=0)

n=897 records screened, of which n=771 were excluded, leaving n=126 papers sought for retrieval, of which n=0 were not retrieved.

No studies were identified from identification of studies via other methods.

Of the n=126 papers assessed for eligibility, n=123 reports were excluded:

- wrong study type (n=19)
- wrong publication year (n=1)
- wrong exposure (n=55)
- no relevant outcomes (n=48)

n=3 papers included in the review.

Annexe C. Excluded full texts

Wrong study type (n=19)

Anonymous and others. 'Antibacterial drugs for community-acquired pneumonia' Medical Letter on Drugs and Therapeutics 2021: volume 63, issue 1616, pages 10 to 14

Baloh CH and others. 'Inborn Errors of Immunity' Primary Care: Clinics in Office Practice 2023: volume 50, pages 253 to 268

Bhowmick S and others. 'Safety and Efficacy of Ivermectin and Doxycycline Monotherapy and in Combination in the Treatment of COVID-19: A Scoping Review' Drug Safety 2021: volume 44, issue 6, pages 635 to 644

Chen C and others. 'Do fluoroquinolones increase aortic aneurysm or dissection incidence and mortality? A systematic review and meta-analysis' Frontiers in Cardiovascular Medicine 2022: volume 9, article number 949538

De Macedo V and others. 'Doxycycline for Multidrug-Resistant Gram-Negative Bacterial Infection Treatment: A scoping review' Journal of Global Infectious Diseases 2023: volume 15, pages 95 to 100

Gouveia e Melo R and others. 'Doxycycline is not Effective in Reducing Abdominal Aortic Aneurysm Growth: A Mini Systematic Review and Meta-Analysis of Randomised Controlled Trials' European Journal of Vascular and Endovascular Surgery 2021: volume 61, pages 863 to 864

Hammerschlag MR and others. 'Azithromycin in the treatment of rectogenital Chlamydia trachomatis infections: end of an era?' Expert review of Anti-Infective Therapy 2021: volume 19, issue 4, pages 1 to 7

Hesse EM and others. 'Antitoxin Use in the Prevention and Treatment of Anthrax Disease: A Systematic Review' Clinical Infectious Diseases 2022: volume 75, pages S432 to S440

Jeon SM and others. 'Assessing the Labeling Information on Drugs Associated With Suicide Risk: Systematic Review' JMIR Public Health and Surveillance 2024: volume 10, e49755

Kory P and others. 'Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19' American Journal of Therapeutics 2021: volume 28, pages e299 to e318

Liu L and others. 'Efficacy of photodynamic therapy in cutaneous leishmaniasis: A systematic review' Photodiagnosis and Photodynamic Therapy 2023: volume 43

Mayer KH and others. 'Doxycycline Postexposure Prophylaxis and Sexually Transmitted Infections' Jama 2023: volume 330, pages 1381 to 1382

Monroy-Esquivel L and others. 'ALTERNATIVE INTRAVITREAL ANTIBIOTICS: A Systematic Review for Consideration in Recalcitrant or Resistant Endophthalmitis' Retina 2023: volume 43, pages 1,433 to 1,447

Rashuaman-Conche B and others. 'Efficacy and safety of pre-exposure of antibiotic prophylaxis for leptospirosis: Protocol for a systematic review and meta-analysis' medRxiv. 2021: volume 21

Rehman S and others. 'Pharmacological Management of Transthyretin Amyloid Cardiomyopathy: A scoping review' European Heart Journal Cardiovascular Pharmacotherapy 2024: volume 3, page 3

Shah P and others. 'The role of tetracycline-nicotinamide in management of bullous pemphigoid: A systematic review of the literature' British Journal of Dermatology 2020: volume 183, page 63

van der Linden MMD and others. 'Diagnosis and Treatment of Morbihan's Disease: A Practical Approach based on Review of the Literature' Journal of Clinical and Aesthetic Dermatology 2023: volume 16, issue 10, pages 22 to 30

Waitayangkoon P and others. 'Doxycycline Is Safe Over An Extended Exposure: A Systematic Review Of The Long-Term Safety Profiles Of Macrolides And Tetracyclines' Osteoarthritis and Cartilage 2023: volume 31, pages S413 to S414

Warren TA. 'Several Concerns With Doxycycline Meta-Analysis' Clinical Infectious Diseases 2023: volume 77, issue 4, pages 665 to 666

Wrong publication year (n=1)

Brett-Major DM and others. 'Antibiotics for leptospirosis' Cochrane Database of Systematic Reviews 2012: volume 2012

Wrong exposure (n=55)

Al Riyees L and others. 'Antibiotic prophylaxis against surgical site infection after open hernia surgery: A systematic review and meta-analysis' European Surgical Research 2021: volume 62, pages 121 to 133

Al-Haddad A and others. 'Regenerative endodontic treatment in mature teeth: a systematic review and meta-analysis' Giornale Italiano di Endodonzia 2022: volume 36, pages 151 to 165

Al-Hadidi SH and others. 'The Spectrum of Antibiotic Prescribing during COVID-19 Pandemic: A Systematic Literature Review' Microbial Drug Resistance 2021: volume 27, pages 1,705 to 1,725

Ameratunga D and others. 'Antibiotics prior to or at the time of embryo transfer in ART' Cochrane Database of Systematic Reviews 2023: issue 11

Anothaisintawee T and others. 'Efficacy of drug treatment for severe melioidosis and eradication treatment of melioidosis: A systematic review and network meta-analysis' PLoS Neglected Tropical Diseases [electronic resource] 2023: volume 17, issue 6, article e0011382

Armstrong AW and others. 'Oral Tetracyclines and Acne: A Systematic Review for Dermatologists' Journal of Drugs in Dermatology: JDD 2020: volume 19, pages s6 to s13

Asilian A and others. 'Interventions for bullous pemphigoid: An updated systematic review of randomized clinical trials' Medical Journal of The Islamic Republic of Iran 2021: volume 35, page 111

Assiri A and others. 'Efficacy of Low-Dose Isotretinoin in the Treatment of Rosacea: A Systematic Review and Meta-Analysis' Cureus 2024: volume 16, issue 3, e57085

Chan PA and others. 'Safety of Longer-Term Doxycycline Use: A Systematic Review and Meta-Analysis With Implications for Bacterial Sexually Transmitted Infection Chemoprophylaxis' Sexually Transmitted Diseases 2023: volume 50, issue 11, pages 701 to 712

Chen F and others. 'Moxifloxacin monotherapy for treatment of uncomplicated pelvic inflammatory disease: A systematic review and meta-analysis with trial sequential analysis of randomized controlled trials' Pharmacoepidemiology and Drug Safety 2023: volume 32, pages 1,189 to 1,199

Cheng Q and others. 'Comparative efficacy and safety of pharmacological interventions for severe COVID-19 patients: An updated network meta-analysis of 48 randomized controlled trials' Medicine 2022: volume 101, issue 41, e30998

Chiu MN and others. 'Safety profile of COVID-19 drugs in a real clinical setting' European Journal of Clinical Pharmacology 2022: volume 78, pages 733 to 753

Cruz GS and others. 'Percutaneous treatments of primary aneurysmal bone cysts: systematic review and meta-analysis' European Journal of Orthopaedic Surgery and Traumatology 2021: volume 31, pages 1,287 to 1,295

Del Rosso JQ and others. 'Effective Treatment of Inflammatory Lesions of Rosacea with Subantibiotic Dose Doxycycline Irrespective of Patient Weight or Baseline Lesion Count Severity' The Journal of Clinical and Aesthetic Dermatology 2022: volume 15, issue 11, pages 69 to 74

Dichman ML and others. 'Antibiotics for uncomplicated diverticulitis' Cochrane Database of Systematic Reviews 2022: issue 6

Fernandes S and others. 'Sclerosing agents in the management of lymphatic malformations in children: A systematic review' Journal of Pediatric Surgery 2022: volume 57, pages 888 to 896

Gael M and others. 'Efficacy of dupilumab in chronic prurigo and chronic idiopathic pruritus: a systematic review of current evidence and analysis of response predictors' Journal of the European Academy of Dermatology and Venereology 2022: volume 36, pages 1,541 to 1,551

Genovese G and others. 'A Systematic Review of Treatment Options and Clinical Outcomes in Pemphigoid Gestationis' Frontiers in Medicine 2020: volume 7

Gingold-Belfer R and others. 'Rifabutin triple therapy for first-line and rescue treatment of Helicobacter pylori infection: A systematic review and meta-analysis' Journal of Gastroenterology and Hepatology (Australia) 2021: volume 36, pages 1392 to 1402

Gingold-Belfer R and others. 'Susceptibility-guided versus empirical treatment for Helicobacter pylori infection: A systematic review and meta-analysis' Journal of Gastroenterology and Hepatology (Australia) 2021: volume 36, pages 2649 to 2658

Gordon M and others. 'Antibiotics for the induction and maintenance of remission in ulcerative colitis' Cochrane Database of Systematic Reviews 2022: issue 5

Gupta T and others. 'Hydroxychloroquine in the treatment of coronavirus disease 2019: Rapid updated systematic review and meta-analysis' Reviews in Medical Virology 2022: volume 32

Hanscheid T and others. 'Repurposing of anti-malarial drugs for the treatment of tuberculosis: realistic strategy or fanciful dead end?' Malaria Journal 2024: volume 23

Hernandez-Rodriguez P and others. 'Combination Therapy as a Strategy to Control Infections Caused by Multi-resistant Bacteria: Current Review' Current Drug Targets 2022: volume 23, pages 260 to 265

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Jin XX and others. 'Efficacy and safety of tetracyclines for pemphigoid: a systematic review and meta-analysis' Archives of Dermatological Research 2022: volume 314, issue 2, pages 191 to 201

Jung F and others. 'Systematic review of the efficacies and adverse effects of treatments for pityriasis lichenoides' British Journal of Dermatology 2020: volume 183, pages 1026 to 1032

Keragala ARKK and others. 'Efficacy and safety of co-trimoxazole in eradication phase of melioidosis; systematic review' Annals of Clinical Microbiology and Antimicrobials 2023: volume 22

Kow CS and others. 'The association between the use of ivermectin and mortality in patients with COVID-19: a meta-analysis' Pharmacological Reports 2021: volume 73, pages 1473 to 1479

Masson R and others. 'Treatments for Dissecting Cellulitis of the Scalp: A Systematic Review and Treatment Algorithm' Dermatology and Therapy 2023: volume 13, pages 2487 to 2526

Murchu EO and others. 'Interventions in an Ambulatory Setting to Prevent Progression to Severe Disease in Patients With COVID-19: A Systematic Review' Annals of Pharmacotherapy 2022: volume 56, pages 309 to 318

Nascimento Silva S and others. 'Efficacy of antibiotic prophylaxis to preventing brucellosis in accidental exposure: A systematic review' Tropical Medicine and International Health 2024: volume 29, issue 6, pages 454 to 465

Nibali L and others. 'Adjunctive effect of systemic antibiotics in regenerative/reconstructive periodontal surgery- a systematic review with meta-analysis' Antibiotics 2022: volume 11

Nickles MA and others. 'Topical dapsone in the treatment of acne: a systematic review' International Journal of Dermatology 2022: volume 61, issue 11, pages 1,412 to 1,421

Nugent SM and others. 'A Systematic Review of Therapeutic Interventions and Management Strategies for Gulf War Illness' Military medicine 2021: volume 186, issue 1, pages e169 to e178

Onghanseng N and others. 'Oral antibiotics for chronic blepharitis' Cochrane Database of Systematic Reviews 2021: volume 6, CD013697

Palomera-Tejeda E and others. 'Prophylactic Antibiotics Do Not Prevent Infectious Complications of Endoscopic Ultrasound Fine-Needle Aspiration of Pancreatic Cysts: A Systematic Review and Meta-Analysis' Pancreas 2021: volume 50, pages 667 to 672

Parker CM and others. 'Safety of Antimicrobials for Postexposure Prophylaxis and Treatment of Anthrax: A Review' Clinical Infectious Diseases 2022: volume 75, pages S417 to S431

Pucker AD and others. 'LipiFlow for the treatment of dry eye disease' Cochrane Database of Systematic Reviews 2024: volume 2, CD015448

Rago Z and others. 'Results of a systematic review and meta-analysis of early studies on ivermectin in SARS-CoV-2 infection' GeroScience 2023: volume 45, pages 2,179 to 2,193

Sampath A and others. 'Use of baricitinib in treatment of COVID-19: a systematic review' Medicinal Research Reviews 2023: volume 43, pages 1,322 to 1,345

Silva SN and others. 'Efficacy and safety of therapeutic strategies for human brucellosis: A systematic review and network meta-analysis' PLoS Neglected Tropical Diseases [electronic resource] 2024: volume 18, issue 3, e0012010

Singh S and others. 'Interventions for bullous pemphigoid' Cochrane Database of Systematic Reviews 2023: volume 8, CD002292

Verburgt CM and others. 'Antibiotics in pediatric inflammatory bowel diseases: a systematic review' Expert review of gastroenterology and hepatology 2021: volume 15, issue 8, pages 891 to 908

Vockel J and others. 'Pharmacological anti-inflammatory treatment in children and adolescents with depressive symptoms: A systematic-review and meta-analysis' European Neuropsychopharmacology 2024: volume 78, pages 16 to 29

Waitayangkoon P and others. 'Long-Term Safety Profiles of Macrolides and Tetracyclines: A Systematic Review and Meta-Analysis' Journal of Clinical Pharmacology 2024: volume 64, issue 2, pages 164 to 177

Walker J and others. 'A systematic review of pharmacological and cell-based therapies for the treatment of lymphoedema (2010 to 2021)' Journal of Vascular Surgery. Venous and Lymphatic Disorders 2022: volume 10, issue 4, pages 966 to 975

Xi W and others. 'Effect of antibiotic therapy in patients with ulcerative colitis: a meta-analysis of randomized controlled trials' Scandinavian Journal of Gastroenterology 2021: volume 56, pages 162 to 170

Yang W and others. 'The Efficacy and Safety of Disease-Modifying Osteoarthritis Drugs for Knee and Hip Osteoarthritis-a Systematic Review and Network Meta-Analysis' Journal of General Internal Medicine 2021: volume 36, issue 7, pages 2,085 to 2,093

Yu PA and others. 'Safety of antimicrobials during pregnancy: A systematic review of antimicrobials considered for treatment and postexposure prophylaxis of plague' Clinical Infectious Diseases 2020: volume 70, pages S37 to S50

Zhang H and others. 'Efficacy and safety of oritavancin for the treatment of acute bacterial skin and skin-structure infections: a systematic review and meta-analysis' Journal of Global Antimicrobial Resistance 2021: volume 25, pages 380 to 389

Zhang X and others. 'Efficacy and safety of antibiotic therapy for post-Lyme disease? A systematic review and network meta-analysis' BMC infectious diseases 2023: volume 23, issue 1, page 22

Zhao J and others. 'Doxycycline and minocycline in Helicobacter pylori treatment: A systematic review and meta-analysis' Helicobacter 2021: volume 26, issue 5, article e12839

Zeng B-S and others. 'The efficacy and tolerability of antibiotics in scrub typhus: an updated network meta-analysis of randomized controlled trials' International Journal of Infectious Diseases 2022: volume 122, pages 461 to 468

No relevant outcomes (n=48)

Avraham S and others. 'Treatment of ocular rosacea: a systematic review' Journal der Deutschen Dermatologischen Gesellschaft 2024: volume 22, issue 2, pages 167 to 174

Cai F and others. 'Effectiveness and safety of tetracyclines and quinolones in people with Mycoplasma pneumonia: a systematic review and network meta-analysis' eClinicalMedicine 2024: volume 71

Callado GY and others. 'Syphilis Treatment: Systematic Review and Meta-Analysis Investigating Nonpenicillin Therapeutic Strategies' Open Forum Infectious Diseases 2024: volume 11, issue 4, ofae142

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Chen C-Y and others. 'The effect of additional antimicrobial therapy on the outcomes of patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis' Respiratory Research 2021: volume 22, issue 1, page 243

Chen L-F and others. 'Efficacy of doxycycline versus azithromycin for the treatment of rectal chlamydia: a systematic review and meta-analysis' The Journal of Antimicrobial Chemotherapy 2021: volume 76, issue 12, pages 3,103 to 3,110

Chitsuthipakorn W and others. 'Treatments of Epistaxis in Hereditary Hemorrhagic Telangiectasia: Systematic Review and Network Meta-Analysis' Current Allergy and Asthma Reports 2023: volume 23, issue 12, pages 689 to 701

Choi S-H and others. 'Efficacy of Doxycycline for Mild-to-Moderate Community-Acquired Pneumonia in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials' Clinical Infectious Diseases 2023: volume 76, issue 4, pages 683 to 691

Dersch R and others. 'Treatment of post-treatment Lyme disease symptoms-a systematic review' European Journal of Neurology 2024: volume 31

Dersch R and others. 'Efficacy and safety of pharmacological treatments for Lyme neuroborreliosis: An updated systematic review' European Journal of Neurology 2023: volume 30, pages 3,780 to 3,788

Desai SR and others. 'Microencapsulated Benzoyl Peroxide for Rosacea in Context: A Review of the Current Treatment Landscape' Drugs 2024

Fan W and others. 'Efficacy of azithromycin in treating Ureaplasma urealyticum: a systematic review and meta-analysis' BMC infectious diseases 2023: volume 23, issue 1, page 163

Furukawa Y and others. 'Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: A systematic review and duration-effect meta-analysis' BMJ Open 2023: volume 13

Geng RSO and others. 'Efficacy of Treatments in Reducing Inflammatory Lesion Count in Rosacea: A Systematic Review' Journal of Cutaneous Medicine and Surgery 2024: 12034754241253195

Grimes DA and others. 'Antibiotic prophylaxis for intrauterine contraceptive device insertion' Cochrane Database of Systematic Reviews 1999: volume 2012

Gupta N and others. 'Doxycycline vs azithromycin in patients with scrub typhus: a systematic review of literature and meta-analysis' BMC Infectious Diseases 2023: volume 23, issue 1, page 884

Gupta N and others. 'Leptospirosis in India: a systematic review and meta-analysis of clinical profile, treatment and outcomes' Le infezioni in medicina 2023: volume 31, issue 3, pages 290 to 305

Guzmán Pérez M and others. 'Current Evidence on the Antimicrobial Treatment and Chemoprophylaxis of Human Leptospirosis: A Meta-Analysis' Pathogens (Basel, Switzerland) 2021: volume 10, issue 9

Jakab A and others. 'Tick borne relapsing fever - a systematic review and analysis of the literature' PLoS Neglected Tropical Diseases 2022: volume 16

Ji Z and others. 'Efficacy and safety of antibiotics for treatment of leptospirosis: a systematic review and network meta-analysis' Systematic Reviews 2024: volume 13, issue 1, page 108

Kabir KI and others. 'Macrolides versus other antibiotics in pediatric scrub typhus: A meta-analysis' Indian Journal of Medical Microbiology 2023: volume 46

Kharb P and others. 'A Systematic Review of the Prospective Studies on Adverse Drug Reactions Reported with Anti-Microbials among Indian Patients' International Journal of Academic Medicine and Pharmacy 2022: volume 4, pages 253 to 265

Khaslavsky S and others. 'Treatment of pediatric ocular rosacea: A systematic review' Annales de Dermatologie et de Venereologie 2023: volume 150, pages 199 to 201

Khattri S and others. 'Adjunctive systemic antimicrobials for the non-surgical treatment of periodontitis' Cochrane Database of Systematic Reviews 2020: volume 2020

Khurana N and others. 'Novel Therapies for Kidney Disease in People With Diabetes' Journal of Clinical Endocrinology and Metabolism 2022: volume 107, issue 1, pages e1 to e24

Kim DH and others. 'A comparison of doxycycline and conventional treatments of refractory chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis' European archives of Oto-Rhino-Laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2024: volume 281, issue 8, pages 3,949 to 3,957

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Liu M and others. 'Efficacy and Safety of Treatments for Different Stages of Syphilis: a Systematic Review and Network Meta-Analysis of Randomized Controlled Trials and Observational Studies' Microbiology Spectrum 2022: volume 10, issue 6, article e0297722

Lodi and others. 'Antibiotics to prevent complications following tooth extractions' Cochrane Database of Systematic Reviews 2021: issue 2

Lu D and others. 'Evaluation of the Therapeutic Effect of Antibiotics on Scrub Typhus: A Systematic Review and Network Meta-Analysis' Frontiers in Public Health 2022: volume 10, 883945

Medikeri S and others. 'Effectiveness of Tetracycline Drugs in the Non Surgical Treatment of Peri-implantitis: A Systematic Review and Meta-analysis' Journal of Clinical and Diagnostic Research 2022: volume 16, pages ZE01 to ZE07

Miranda LHL and others. 'Systematic review of pharmacological management in Creutzfeldt-Jakob disease: no options so far?' Arquivos de Neuro-Psiquiatria 2022: volume 80, issue 8, pages 837 to 844

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Nelwan EJ and others. 'Association of G6PD status and haemolytic anaemia in patients receiving anti-malarial agents: a systematic review and meta-analysis' Malaria Journal 2023: volume 22

Oren-Shabtai M and others. 'Treatment of Bullous Pemphigoid in People Aged 80 Years and Older: A Systematic Review of the Literature' Drugs and Aging 2021: volume 38, pages 125 to 136

Saraswati K and others. 'Systematic review of the scrub typhus treatment landscape: Assessing the feasibility of an individual participant-level data (IPD) platform' PLoS Neglected Tropical Diseases [electronic resource] 2021: volume 15, issue 10, e0009858

Schiefer-Niederkorn A and others. 'Necrobiosis lipoidica in childhood: a review of literature with emphasis on therapy' JDDG - Journal of the German Society of Dermatology 2023: volume 21, pages 1,120 to 1,129

Sethi NJ and others. 'Antibiotics for secondary prevention of coronary heart disease' Cochrane Database of Systematic Reviews 2021: issue 2

SeyedAlinaghi S and others. 'Ocular manifestations of COVID-19: A systematic review of current evidence' Preventive Medicine Reports 2024: volume 38

Spinks a and others. 'Antibiotics for treatment of sore throat in children and adults' Cochrane Database of Systematic Reviews 2021: issue 12

Vanbaelen T and others. '45 years of tetracycline post exposure prophylaxis for STIs and the risk of tetracycline resistance: a systematic review and meta-analysis' BMC Infectious Diseases 2024: volume 24

Vernhardsdottir RR and others. 'Antibiotic treatment for dry eye disease related to meibomian gland dysfunction and blepharitis - A review' The Ocular Surface 2022: volume 26, pages 211 to 221

Wagenlehner F and others. 'Systematic review on estimated rates of nephrotoxicity and neurotoxicity in patients treated with polymyxins' Clinical Microbiology and Infection 2021: volume 27, pages 671 to 686

Win TZ and others. 'Antibiotics for treatment of leptospirosis' Cochrane Database of Systematic Reviews 2024: volume 3, CD014960

Win TZ and others. 'Antibiotic prophylaxis for leptospirosis' Cochrane Database of Systematic Reviews 2024: volume 3, CD014959

Xiao W and others. 'Efficacy and safety of antibiotic agents in the treatment of rosacea: a systemic network meta-analysis' Frontiers in Pharmacology 2023: volume 14, 1169916

Yang J and others. 'Forty Years of Evidence on the Efficacy and Safety of Oral and Injectable Antibiotics for Treating Lyme Disease of Adults and Children: A Network Meta-Analysis' Microbiology Spectrum 2021: volume 9, issue 3, e0076121

Zhou G and others. 'Antibiotic prophylaxis for prevention against Lyme disease following tick bite: an updated systematic review and meta-analysis' BMC infectious diseases 2021: volume 21, issue 1, article number 1,141

Annexe D. Data extraction tables

SAE: serious adverse event, AE: adverse event, IQR: interquartile range, USA: United States of America, DoxyPEP: doxycycline post exposure prophylaxis, DoxyPrEP: doxycycline pre-exposure prophylaxis, STI: sexually transmitted infections, HIV-PrEP: human immunodeficiency virus pre-exposure prophylaxis, GRADE: Grading of Recommendations Assessment, development, and Evaluation

Study	Study design of included primary studies	Country, time period	Population	Intervention	Outcomes
Ben Ephraim Noyman 2024	5 meeting inclusion criteria, 2 were randomised control trials and 3 prospective clinical trials. Aim of primary studies was to assess the effect of oral doxycycline antibiotics or macrolides in treating moderate to severe meibomian gland dysfunction.	4 studies in India, one in Spain, 2014 to 2022	463 participants treated for moderate-severe Meibomian Gland Dysfunction • age: where reported within the primary studies between 12 and 90 years old • sex: males and females • other demographics not reported	Review interested in any interventional study comparing oral doxycycline to macrolides in treating meibomian gland dysfunction and assessing clinical outcomes. Typical treatment consisted of oral doxycycline for 4 weeks with a total cumulative dose of 3.5 to 5.6 grams per participant. Compared to 5-day treatment with Azithromycin with a total cumulative dose of 1.25 to 3.00 grams per participant. Route of administration not reported.	No serious adverse events (SAE) were found in any of the studies. Follow up period of all 5 studies was between 60 and 270 days. GRADE evaluation not performed. The review did not report on how SAEs were collected, or whether active monitoring or surveillance was used.
Sokoll 2024	4 primary studies in the review All randomised control trials Aim of primary studies was to assess if DoxyPEP could reduce the incidence of sexually transmitted infections (STIs).	2 studies in France, one in USA and one in Kenya, 2015 to 2022	1,727 total participants taking doxycycline (DoxyPep) or control, for sexually transmitted infections after condomless sex (1,041 in the intervention group and 686 in control groups) • age: median age ranged from 24 to 73 years, all over age of 18 • 73% men who have sex with men, 1% transgender women and 26% cisgender women • 90% of participants were also taking HIV PrEP) ◦ other demographics not reported	Review interested in any RCT that evaluated the efficacy of Doxy-PEP within 72 hours after condomless sex. All participants across studies were given a single dose of oral 200 milligrams doxycycline within 72 hours after condomless sex, compared to no prophylaxis.	One doxycycline-related SAE was reported, which was a fixed drug eruption. Follow up lasted 14 months after intervention (IQR 9 to18) for this study and was conducted in men who have sex with men. Two studies found no SAEs. One study did not report on SAEs. Follow up in all studies occurred between 8.7 to 14 months. Percentage of discontinuation due to drug related AEs varied from 0.9% to 7% (8 out of 116 in one study, 7 out of 339 in second, 6 out of 362 in third, 6 out of 224 in final). Authors reported gastrointestinal related adverse events as being the most common. GRADE was not performed on our outcome of interest. The review did not report on how SAEs were collected, or whether active monitoring or surveillance was used.

Study	Study design of included primary studies	Country, time period	Population	Intervention	Outcomes
Szondy 2024	3 meeting our inclusion criteria All original articles of randomised control trials. Aim of primary studies was to assess if DoxyPEP or DoxyPrEP could reduce the incidence of sexually transmitted infections (STIs).	One in France, one in USA, one in Kenya, time period not reported	1,182 total participants taking DoxyPep or control for the prevention of STI • included 449 women on HIV-PrEP, 559 men who have sex with men, and transgender women on HIV-PrEP and 174 men who have sex with men, and transgender women with HIV infection • other demographics not reported	Review interested in any RCT where sexually active adults took Doxy-PrEP or Doxy-PEP to prevent the occurrence of a sexually transmitted infection (STI). All participants across studies took a single oral 200 milligrams dose of doxycycline within 72 hours of having condomless sex, compared to no prophylaxis.	No SAEs were found in any of the studies. Follow up period in studies was between 10 and 12 months. Outcomes evaluated with GRADE-Pro indicating the certainty of evidence for the included studies on adverse events was low. 3 included studies overlap with Sokoll 2024. The review did not report on how SAEs were collected, or whether active monitoring or surveillance was used.

Annexe E. Critical appraisal

Table E.1. Critical appraisal of studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16
Ben Ephraim Noyman, 2024	No	Yes	Yes	No	Yes	Yes	No	No	Yes	No	N/A	N/A	Yes	Yes	N/A	No
Sokoll, 2024	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	N/A	N/A	Yes	Yes	N/A	Yes
Szondy, 2024	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	N/A	N/A	Yes	Yes	N/A	Yes

Q= question. The AMSTAR2 tool was used.

Q1: Did the research question and inclusion criteria for the review include the components of PICO?
Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
Q3: Did the review authors explain their selection of the study designs for inclusion in the review?
Q4: Did the review authors use a comprehensive literature search strategy?
Q5: Did the review authors perform study selection in duplicate?
Q6: Did the review authors perform data extraction in duplicate?
Q7: Did the review authors provide a list of excluded studies and justify the exclusions?
Q8: Did the review authors describe the included studies in adequate detail?
Q9: Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?
Q10: Did the review authors report on the sources of funding for the studies included in the review?
Q11: If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
Q13: Did the review authors account for RoB in individual studies when interpreting or discussing the results of the review?
Q14: Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the results of this review?
Q15: If they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

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