

Stopping Syphilis: The HHS Summer Seminar Series

Doxycycline for Syphilis: Treatment and Prevention

Office of Infectious Disease and HIV/AIDS Policy
Office of the Assistant Secretary for Health

August 21, 2024



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for Health

Webinar Agenda

Topic
Welcome and Opening Remarks
Doxycycline for Syphilis Treatment
Doxycycline for Syphilis Prevention
Clinical Scenarios
Q&A Session
Close

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Doxycycline for Syphilis: Treatment and Prevention

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Doxycycline for Treatment and Prevention of Syphilis

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Centers for Disease Control and Prevention
National Center for HIV, Viral Hepatitis, STD, and TB Prevention



Doxycycline

- **Second-generation tetracycline, available since 1967**
- **Excellent bioavailability (i.e. oral absorption to plasma concentration)**
- **Excellent tissue penetration**
- **Bacteriostatic – inhibits protein synthesis so bacteria can't reproduce**
- **Pharmacologic and Economic Advantages**
 - Oral (IV sparing), allows for outpatient management or early discharge
 - No monitoring needed
 - Relatively inexpensive compared to other oral antibiotics
- **Well-tolerated, and excellent safety profile**
- **Used for many, many infections (next slide)**

- Peyriere, H et al, JAC 2018
- Chet Cunha doxycycline presentation at NACCHO's doxy PEP consultation Dec 2022

Optimal Use	Acceptable Use	Optimal Use	Acceptable Use
Lyme meningitis	Mycoplasma / legionella / encephalitis	Melioidosis	
		RMSF	Chloroquine resistant malaria
	Actino brain abscess	Lepto	Lymphatic filariasis
	“Neurosypphilis”	Lyme	
Bacterial sinusitis	Mastoiditis	Q fever	
Dental infections (including actino)		Brucellosis	
		Tularemia	
AECB (acute exacerbation of chronic bronchitis)	Peritonsillar abscess	Plague	
Laryngitis d/t C. pneumo		Anthrax	
Typical CAP – S. pneumo, H. flu, M. catarrhalis	Lung abscess	Anaplasmosis	
Atypical CAP (zoonotic) – psittacosis, tularemia, Q fever	Aspiration PNA	Ehrlichiosis	Traveler’s diarrhea
		Diverticulitis	Cholera
Atypical CAP (non-zoonotic) – legionella, mycoplasma, c. pneumoniae	Nocardia	Appendicitis	Whipple’s disease
Bioterrorism agents – anthrax, plague	Actino	Other pathogens	
		V. vulnificus	Atypical Mycobacteria (m. cheloniae, m. fortuitum)
Epididymitis		Animal bites	
Prostatitis (acute and chronic)		Acute cystitis (E coli, klebs, Enterobacter, indole + proteus,)	Acute pyelo (if susceptible)
PID, TOA, M. gen, etc.			

Recommendations for Doxycycline Use for Syphilis

	United States CDC	UK BAASH (2015)	European CDC	Australia
Indication	For patients with penicillin allergy and -early syphilis -late latent syphilis	Alternative Treatment for -early syphilis -late syphilis -neurosyphilis	For patients with early syphilis AND penicillin allergy or refusing IV/IM	For patients with penicillin allergy and -early syphilis -late / unknown duration
Dosages	-100mg BID x 14 days -100mg BID x 28 days	-100mg BID x 14 days -100mg BID x 28 days -200mg BID x 28 days	200mg daily x 14 days	-100 mg BID x 14 days -100mg BID x 28 days

Evidence for Efficacy for Syphilis Treatment



Open Forum Infectious Diseases

MAJOR ARTICLE



Syphilis Treatment: Systematic Review and Meta-Analysis Investigating Nonpenicillin Therapeutic Strategies

Gustavo Yano Callado,¹ Maria Celidonio Gutfreund,¹ Isabele Pardo,¹ Mariana Kim Hsieh,¹ Vivian Lin,¹ Mindy Marie Sampson,² Guillermo Rodriguez Nava,² Tássia Aporta Marins,³ Rodrigo Octávio Deliberato,^{4,5} Marinês Dalla Valle Martino,¹ Marisa Holubar,² Jorge L. Salinas,² and Alexandre R. Marra^{1,6}

¹Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, São Paulo, São Paulo, Brazil, ²Division of Infectious Diseases & Geographic Medicine, Stanford University, Stanford, California, USA, ³Faculdade de Medicina, Centro Universitário de Adamantina, Adamantina, São Paulo, Brazil, ⁴Department of Biomedical Informatics, University of Cincinnati College of Medicine, Cincinnati, OH, ⁵Carver College of Medicine



RESEARCH ARTICLE



Efficacy and Safety of Treatments for Different Stages of Syphilis: a Systematic Review and Network Meta-Analysis of Randomized Controlled Trials and Observational Studies

Meixiao Liu,^a Yuxin Fan,^a Jingjing Chen,^a Jiayu Yang,^a Li Gao,^a Xinya Wu,^a Xin Xu,^a Yu Zhang,^a Peng Yue,^a Wenjing Cao,^a Zhenhua Ji,^a Xuan Su,^a Shiyuan Wen,^a Jing Kong,^a Guozhong Zhou,^a Bingxue Li,^a Yan Dong,^a Aihua Liu,^{a,b} Fukai Bao^{a,b}

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^bYunnan Province Key Laboratory of Children's Major Diseases Research, The Affiliated Children Hospital, Kunming Medical University, Kunming, China

Meixiao Liu and Yuxin Fan contributed equally to the paper. The order was based on their contribution to the article.

RESEARCH ARTICLE

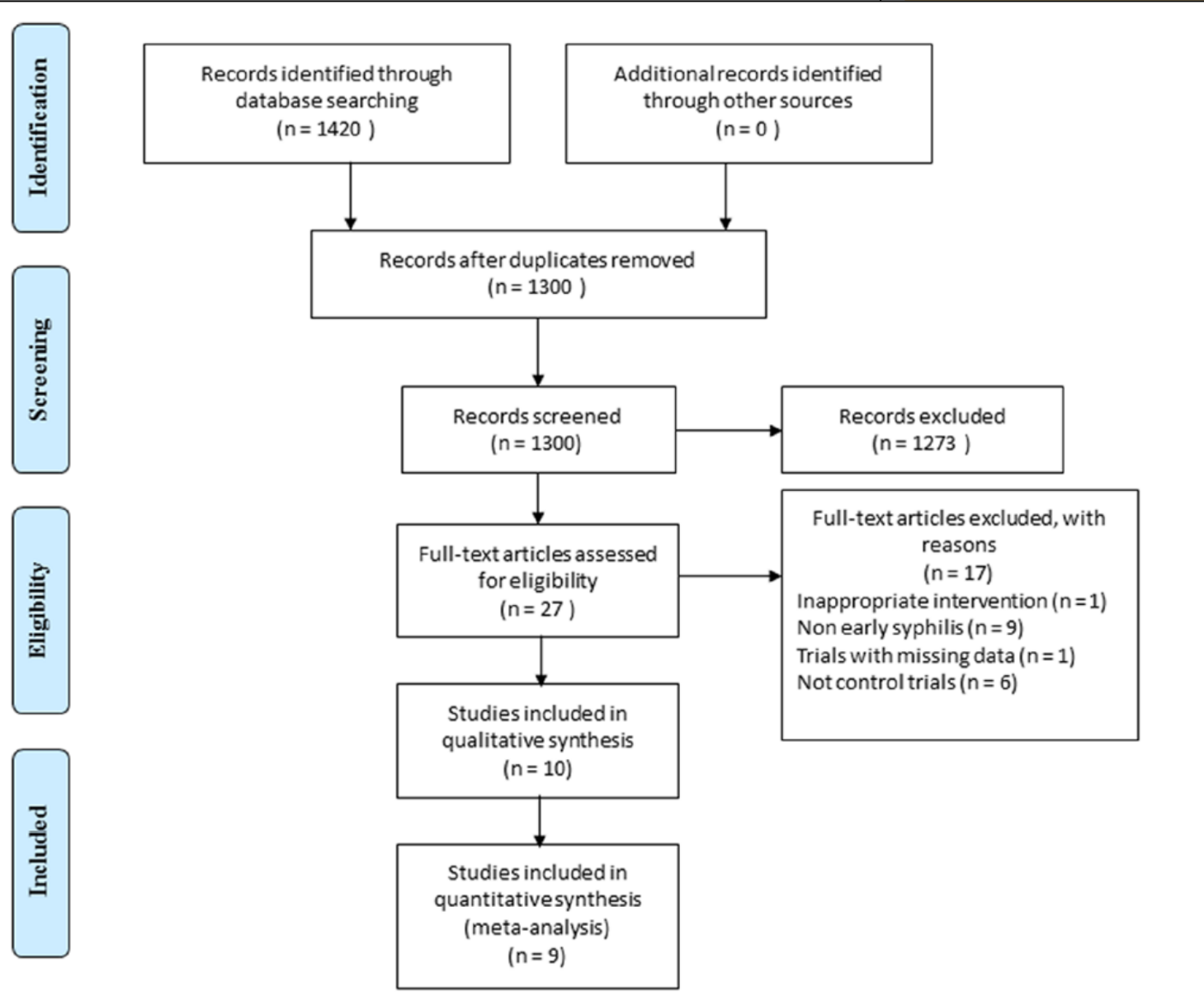
Comparison of efficacy of treatments for early syphilis: A systematic review and network meta-analysis of randomized controlled trials and observational studies

Hong-ye Liu^{1,2}, Yan Han¹, Xiang-sheng Chen¹, Li Bai², Shu-ping Guo², Li Li², Peng Wu³, Yue-ping Yin^{1*}

1 Reference STD Lab, National Center for STD Control, Chinese CDC, Institute of Dermatology, Chinese Academy of Medical Sciences, Peking Union Medical College, Jiangsu Key Laboratory of Molecular Biology for Skin Diseases and STIs, Nanjing, China, **2** Department of Dermatology and Venereology, First Affiliated Hospital of Shanxi Medical University, Taiyuan, China, **3** Health Statistics Teaching and Research Section, School of Public Health, Shanxi Medical University, Taiyuan, China

* yiny@ncstdlc.org

- Minor differences in inclusion criteria & outcome measured
- One only early syphilis, other all syphilis
- One study combined doxy & tetracycline
- Vary in included number of patients treated with doxy and penicillin
- All came to same conclusion



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N=2049 patients treated for early syphilis
Ceftriaxone = 115
Doxy/tetracycline = 267
Penicillin = 1667
Outcome = 12 month serologic response

Fig 1. PRISMA flow diagram for article screening and selection process.

No difference in serologic response

Table 5. Results of the head to head meta-analysis on serological response at 12-month follow-up.

Comparison of interventions	No. of studies	RR(95%CI)	Heterogeneity	
			<i>P</i> value	<i>I</i> ² (%)
Penicillin vs. ceftriaxone	5	1.01(0.90–1.14)	0.998	0
Penicillin vs. doxycycline/tetracycline	5	0.98(0.78–1.23)	0.999	0
Doxycycline/tetracycline vs. ceftriaxone	1	0.97(0.58–1.61)	-	-

RR, risk ratio; CI, confident interval

<https://doi.org/10.1371/journal.pone.0180001.t005>

All studies on doxycycline were observational.

N= 4485 patients with syphilis

Treatment Regimens:


Penicillin = 3083

Doxycycline = 222

Outcomes = 6 and 12 month serologic response



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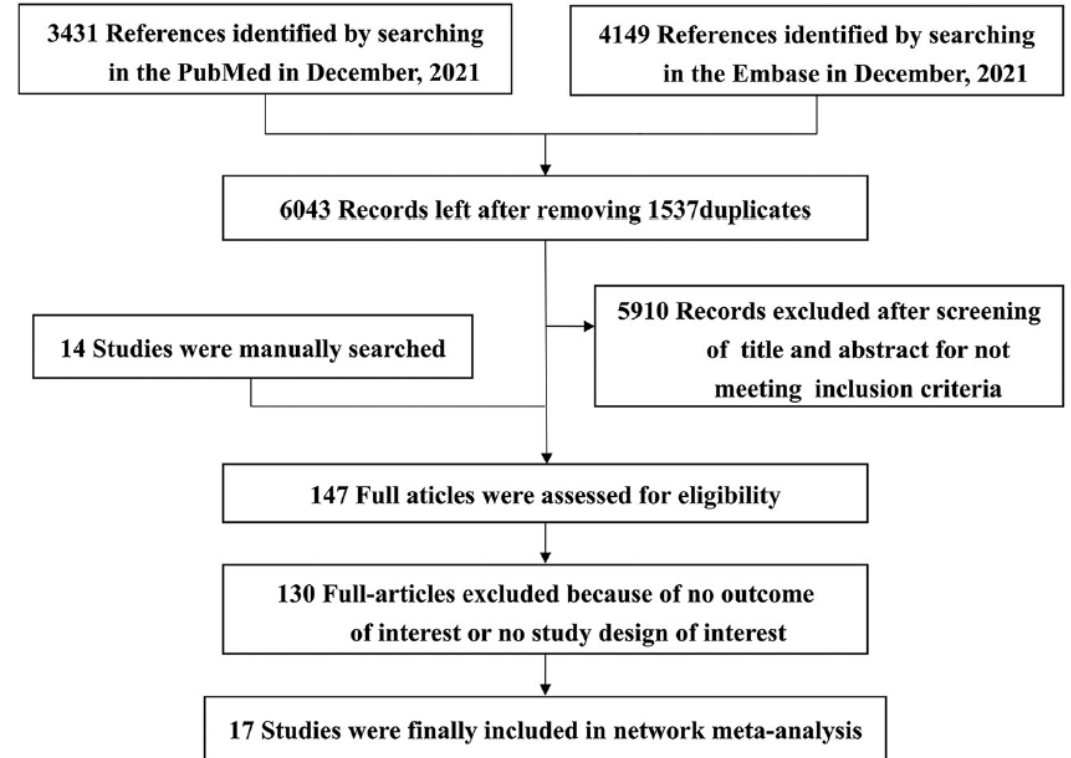
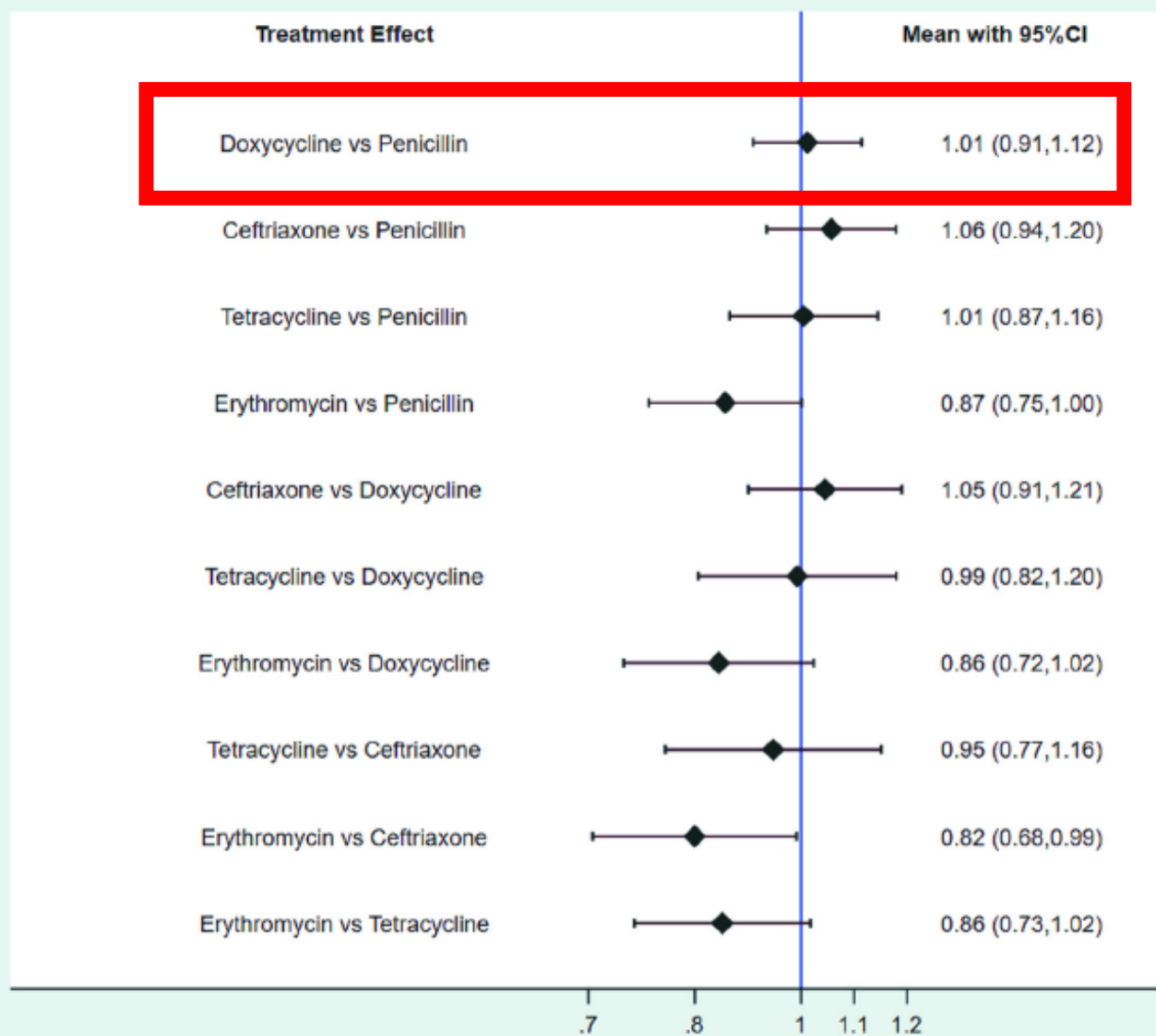


FIG 1 Flow diagram for the referred reporting system for systemic reviews and meta-analysis (PRISMA).

All studies on doxycycline were observational.

B



No statistically significant difference between doxycycline and penicillin or ceftriaxone

B

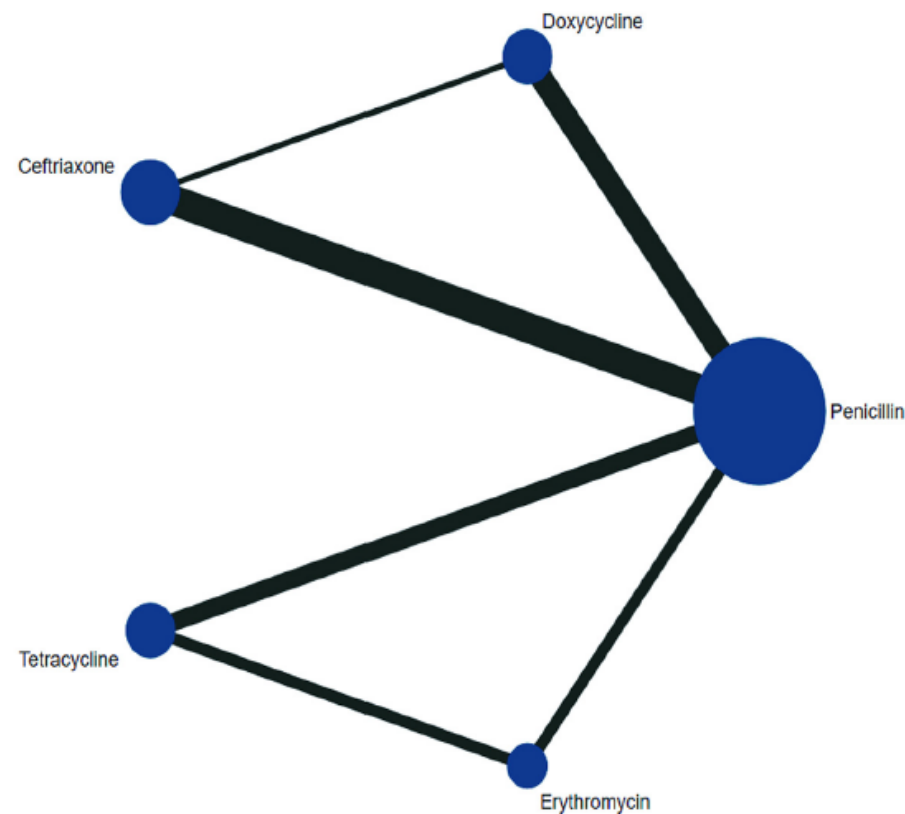


FIG 2 Network diagram of serological response rates for 6-month follow-up (A) and 12-month follow-up (B).

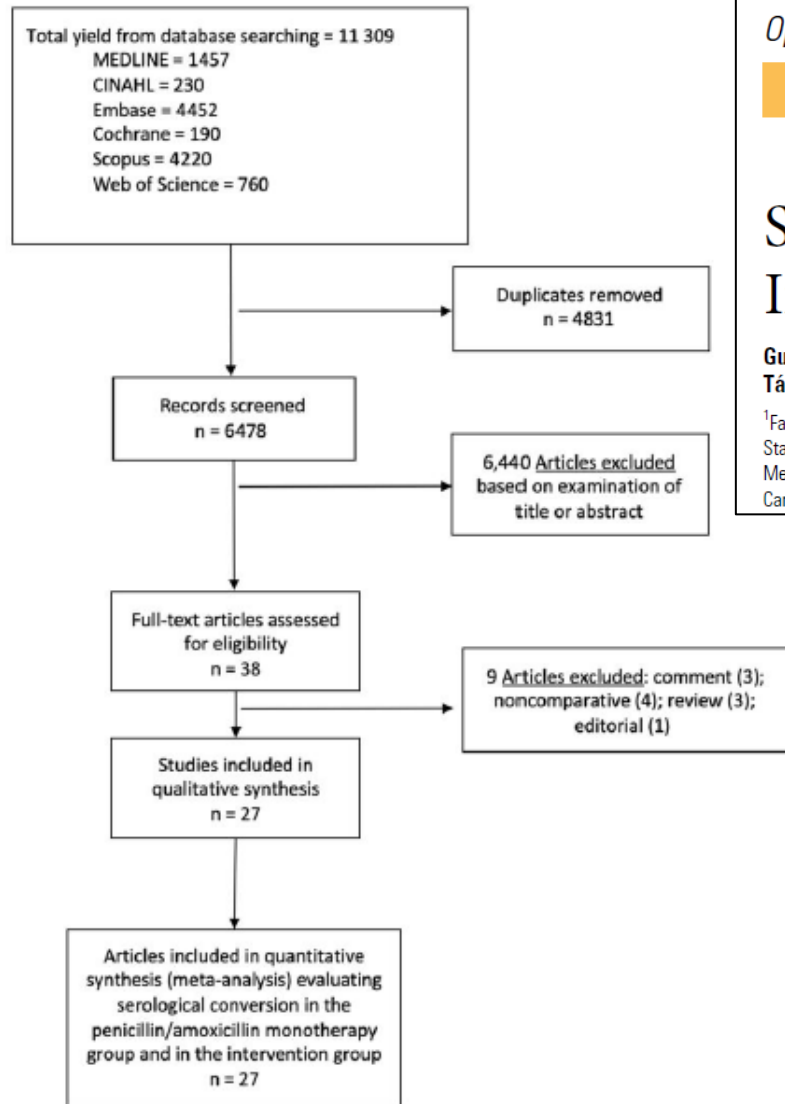
FIG 3 Summary of network meta-analyses of serological response rates at 6-month follow-up (A) and 12-month follow-up (B).

Identification

Screening

Eligibility

Included



Syphilis Treatment: Systematic Review and Meta-Analysis Investigating Nonpenicillin Therapeutic Strategies

Gustavo Yano Callado,^{1,6} Maria Celidonio Gutfreund,¹ Isabele Pardo,¹ Mariana Kim Hsieh,¹ Vivian Lin,¹ Mindy Marie Sampson,² Guillermo Rodriguez Nava,² Tássia Aporta Marins,³ Rodrigo Octávio Deliberato,^{4,5} Marinês Dalla Valle Martino,¹ Marisa Holubar,^{2,6} Jorge L. Salinas,² and Alexandre R. Marra^{1,6}

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N=6710 patients with non-neurologic syphilis

9 studies compared doxycycline to penicillin

n=496 treated with doxycycline

n=2118 treated with penicillin

Outcome = serologic response as defined by original study

All studies on doxycycline were observational.

No difference in serologic response

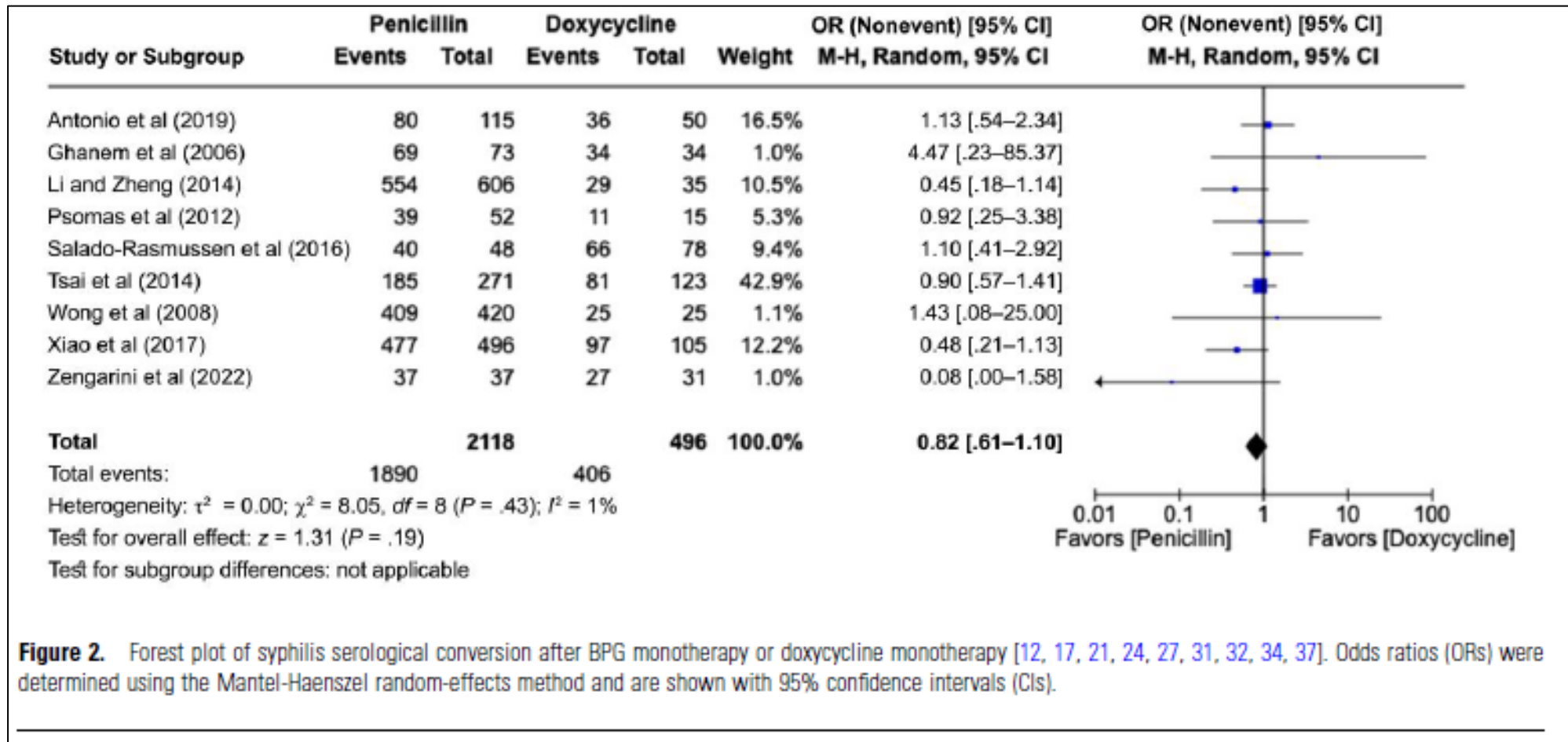


Figure 2. Forest plot of syphilis serological conversion after BPG monotherapy or doxycycline monotherapy [12, 17, 21, 24, 27, 31, 32, 34, 37]. Odds ratios (ORs) were determined using the Mantel-Haenszel random-effects method and are shown with 95% confidence intervals (CIs).

How well do patients adhere to doxycycline for syphilis treatment?

- No published studies for syphilis
- Doxycycline adherence for Chlamydia treatment
 - Poor adherence in several studies involving MEMS caps and self-report*
- However – all studies in systematic reviews were retrospective cohorts – “real world” compliance
- True dose and duration required for cure unknown

Take home:

Doxycycline has comparable effectiveness to penicillin for the treatment of syphilis.

Doxy as Prevention

Doxycycline PEP (200mg taken after sex) studies show reduced STI incidence among MSM and transgender women

Chlamydia

Reduced
70-89%

Gonorrhea

Reduced
0-57%

Syphilis

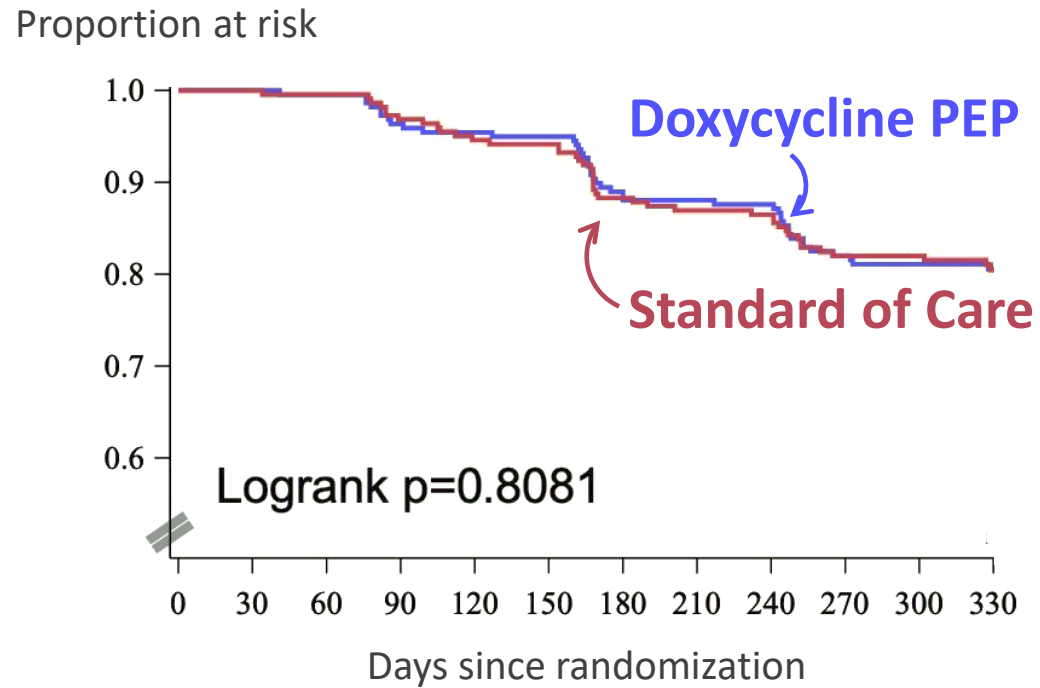
Reduced
73-87%

Note: No significant difference was observed in the Ipergay study for gonorrhea; No significant difference in time to first incident STI between study groups in DPEP study.

Molina JM. Lancet Infect Dis 2018;18:308-17. Luetkemeyer AF, et al. NEJM 2023;388:1296-306. Jean-Michel Molina, CROI 2023. Jenell Stewart, DO, MPH, CROI 2023 | 18

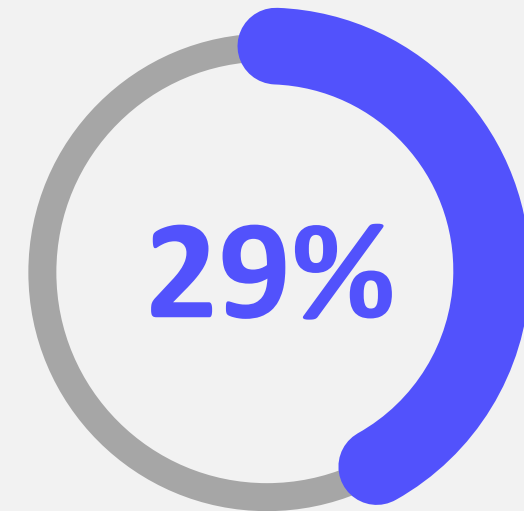
dPEP study: DoxyPEP did not show reduced STI incidence among women

Time to first incident STI



Probable reason is adherence

Testing indicated only:



of quarterly visits had doxycycline detectable in hair samples

CDC doxy PEP Guidelines

U.S. Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 73 / No. 2

June 6, 2024

CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024

<https://www.cdc.gov/mmwr/volumes/73/rr/rr7302a1.htm#:~:text=Administration%20and%20Dosage,200%20mg%20every%2024%20hours>

Doxy PEP Guidelines

Providers should counsel

- Gay, bisexual, and other men who have sex with men
- Transgender women

with

A history of at least **one bacterial STI*** in the **last 12 months.**

**i.e. gonorrhea, chlamydia or syphilis*

about the benefits and harms of doxy PEP

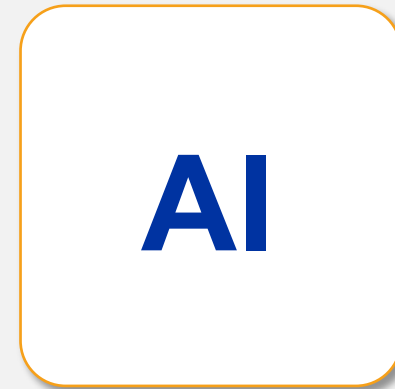
&

prescribe doxy PEP through shared decision-making



Doxycycline 200mg taken once orally within 72 hours of oral, vaginal or anal sex

Strength of recommendation and quality of evidence



Doxy PEP Guidelines: Additional Guidance

- Any formulation of doxycycline is acceptable
- Providers should prescribe enough doxycycline based on individual need to last until their next visit in 3-6 months
- Providers should assess ongoing need for doxy PEP every 3-6 months



Doxycycline 200mg taken once orally within 72 hours of oral, vaginal or anal sex

**Strength of recommendation
and quality of evidence**

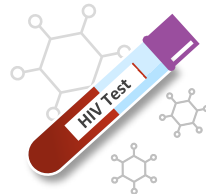
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Doxy PEP Guidelines: Additional Guidance

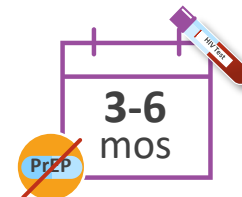
MSM/TGW who are prescribed doxycycline as STI PEP **should undergo bacterial STI testing at anatomic sites of exposure at baseline and every 3-6 months** thereafter



HIV screening should be performed **for HIV-negative MSM/TGW on HIV PrEP** according to current recommendations*



For **individuals** without HIV who are **not receiving HIV PrEP**, consider screening for **HIV every 3-6 months**



Doxy PEP, when offered, should be implemented in the context of a **comprehensive sexual health approach**



*For details, visit: <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf>

Counseling For Patients Prescribed Doxy PEP:

- 1** A **discussion of the potential benefits** as well as **known and unknown harms** of doxycycline PEP including:
 - Potential side effects (phototoxicity, esophagitis and esophageal discomfort, gastrointestinal intolerance) and methods to mitigate side effects
 - Potential for development of antimicrobial resistance in other pathogens and commensals
 - The unknown risks on the microbiome
- 2** The need to **take doxycycline exactly as prescribed** and only for its intended purpose
- 3** **Potential drug interactions**

Doxy PEP Guidelines



No recommendation can be given at this time on the use of doxycycline as PEP for:

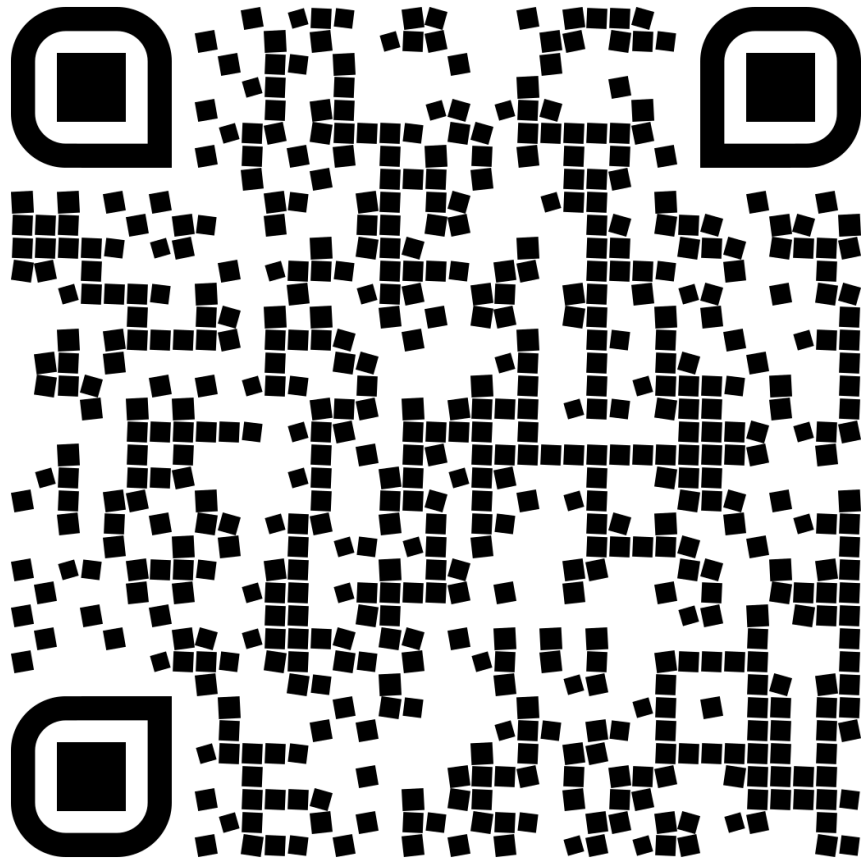
- **Cisgender women**
- **Cisgender heterosexual men**
- **Transgender men**
- **Other queer and nonbinary individuals**

Strength of recommendation and quality of evidence

Insufficient

There is insufficient evidence to assess the balance of benefits and harms of the use of doxycycline as PEP

Additional Resources and Information



Scan the QR Code to see:

- Webinar schedule
- Various resources related to the series including:
 - **Slide decks from each webinar**
 - **Federal agency funding flexibilities**
 - **Professional and clinical resources for syphilis and congenital syphilis**

Thank You and Contact Information

For more information, or if you have any questions or feedback, contact the HHS Sexually Transmitted Infections Inbox at STI@hhs.gov

Notify CDC's DSTDP (stdshortages@cdc.gov) of any shortage or low inventories of STI treatments in your jurisdiction so CDC can continue monitoring treatment availability.

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