DoxyPEP for bacterial STI
Do not prescribe!

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Disclaimer

This presentation was prepared by Maria Prins upon invitation by the chairs of the meeting. The opinions expressed in this presentation do not necessarily reflect her view and the view of the Public Health Service of Amsterdam or Amsterdam University Medical Centers, the Netherlands

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE | ARCHIVE

A Trial of Minocycline Given after Exposure to Prevent Gonorrhea

Authors: William O. Harrison, M.D., Richard R. Hooper, M.D., Paul J. Wiesner, M.D., Axel F. Campbell, M.D., Walter W. Karney, M.D., Gladys H. Reynolds, Ph.D., Oscar G. Jones, B.S., and King K. Holmes, M.D., Ph.D. Author Info & Affiliations

Published May 10, 1979 | N Engl J Med 1979;300:1074-1078 | DOI: 10.1056/NEJM197905103001903

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Abstract

In a prospective evaluation of antibiotic prophylaxis against gonorrhea, 1080 men were given 200 mg of oral minocycline or placebo after sexual intercourse with prostitutes in a Far Eastern port. Later, at sea, gonococcal infection was detected in 57 of 565 men given placebo and 24 of 515 men given minocycline ($P<0.001$). Minocycline prophylaxis completely prevented infection by gonococci susceptible to 0.75 μg or less of tetracycline per milliliter, reduced the risk of infection or prolonged the incubation period in men exposed to gonococci susceptible to 1.0 to 2.0 μg per milliliter, but did not prevent infection or prolong incubation in men exposed to gonococci resistant to 2.0 μg. Minocycline did not increase the proportion of asymptomatic infections. Minocycline prophylaxis would probably have limited effectiveness as a public-health measure because of the tendency to select resistant gonococci. (N Engl J Med 300:1074-1078,1979)

DoxyPEP and STI acquisition

Evidence from 6 RCTs evaluating the efficacy of DoxyP(r)EP, mainly in MSM and TGW

Two systematic reviews: Meta-analyses pooling data from about 1750 individuals included in these RCTs

Doxy

Red

- an

Except for syphilis, no strong evidence that DoxyPEP reduces STI acquisition
Most infections are asymptomatic
These bacterial STIs are curable with short treatment durations

- Chlamydia	65% - 74%	low
- Syphilis	77%[1,2]	high[1]
- Gonorrhoea	no effect[1,2]	very low[1]
	only effect in regions with low TCN resistant gonorrhoea prevalence[2]	

1. Sokoll et al, Sex Transm Infect 2024; 2. Szondy et al, Int Journal of Infect Dis 2024

Weaknesses study design

These RCTs on DoxyP(r)EP

- In most RCTs participants & personnel were aware of the intervention (DoxyPEP/control) to which participants were assigned: performance bias

- Follow-up duration was limited: 8-14 months: long-term effect unknown

- Number of RCTs ar

- The primary outco
  outcome it was oft

Insufficient evidence that DoxyPrEP works

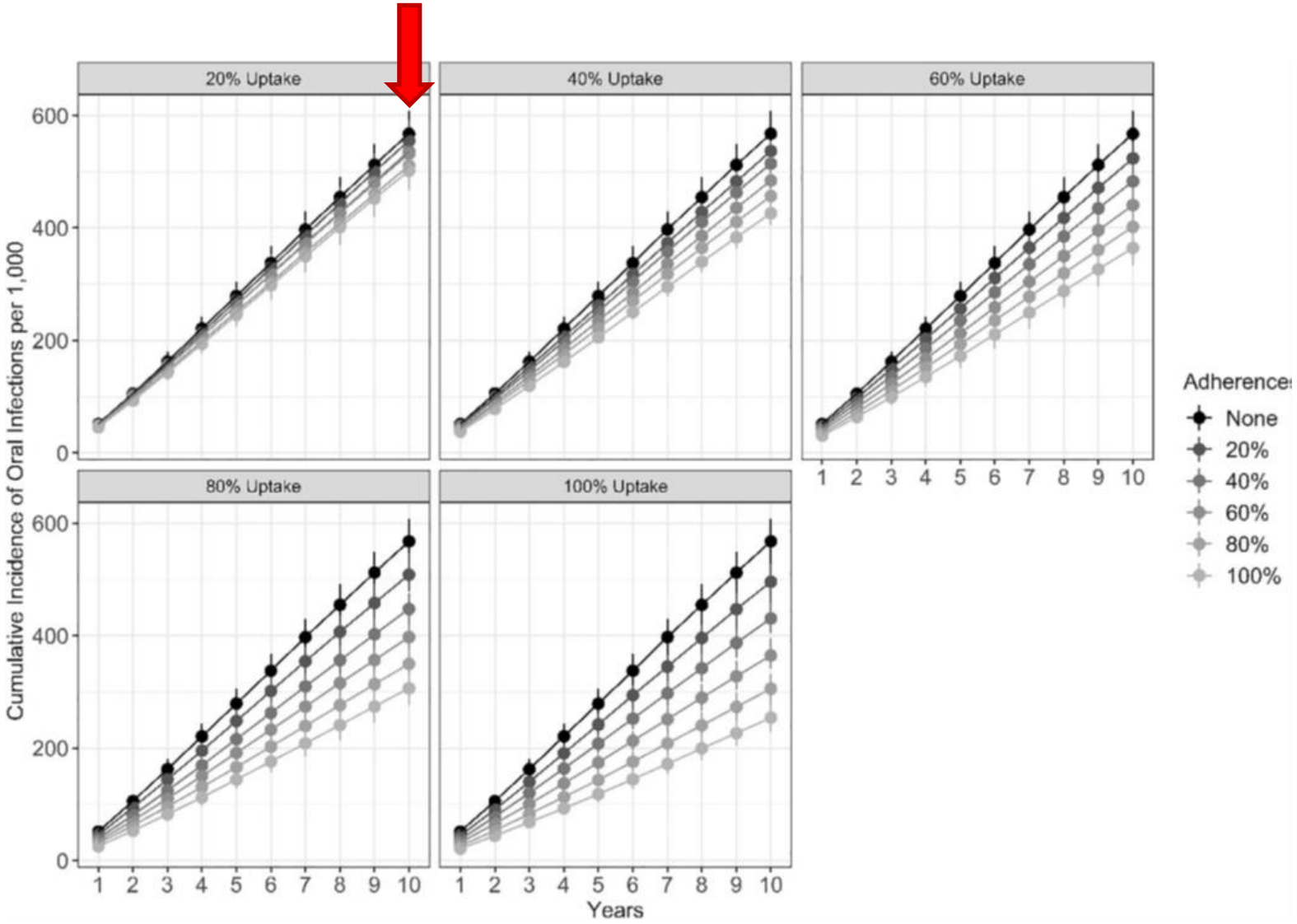
So far, evidence limited to RCTs

- Effect has not been measured in real-life settings
- Effect on population level is unknown, except findings from modelling studies

Population effect: Evidence from modelling studies not convincing

Modest impact of DoxyPEP on syphilis incidence among sexual minority men in the US

Even under high DoxyPrEP adherence levels with a reasonable uptake level of 20%, only 10% reduction in syphilis incidence over 10 year



Tran et al, Int J STD AIDS 2022

Bacterial antimicrobial resistance (AMR)

- on the rise worldwide
- a leading cause of death globally: highest burden in low-resource settings
- a top global health threat

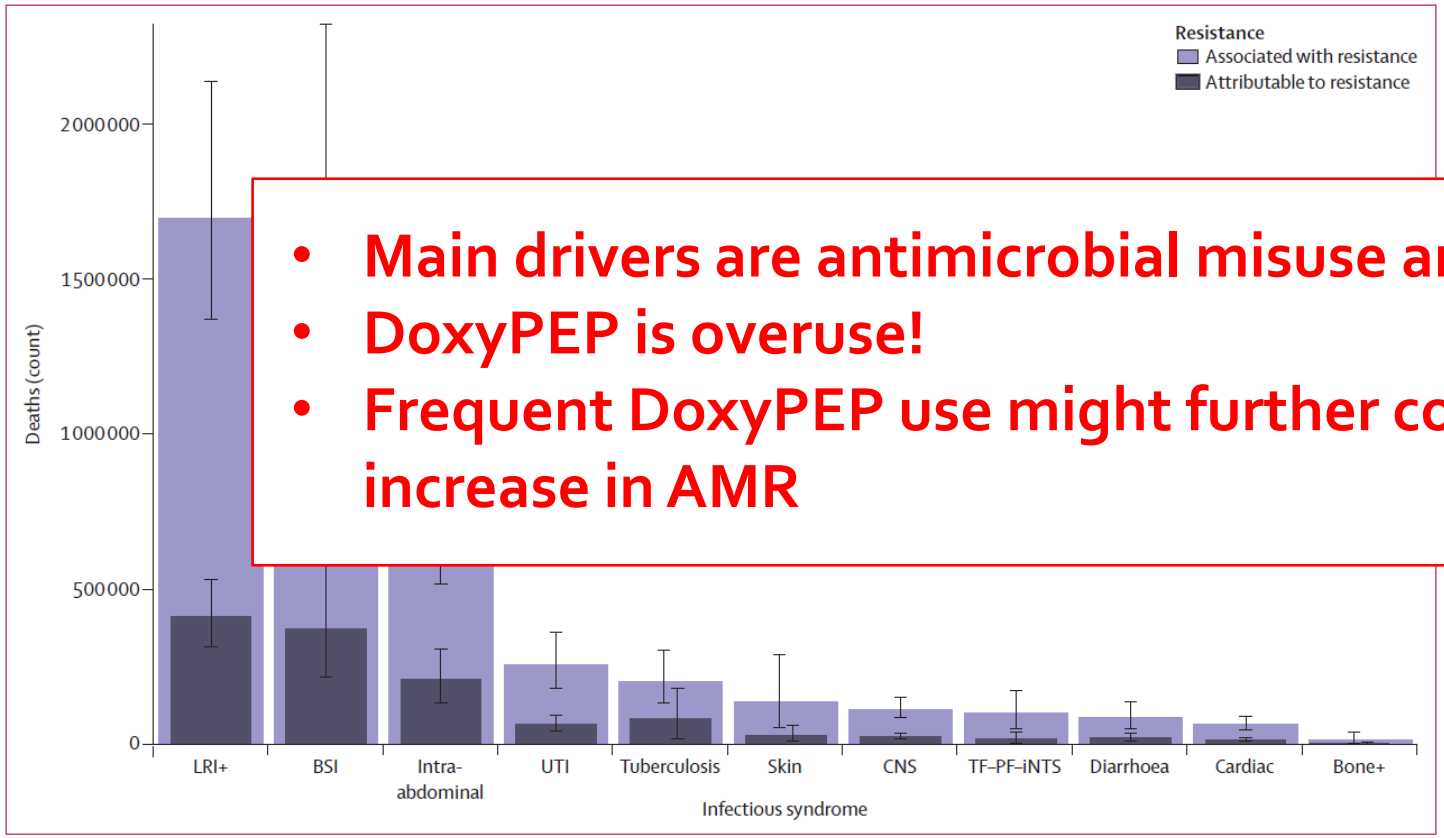


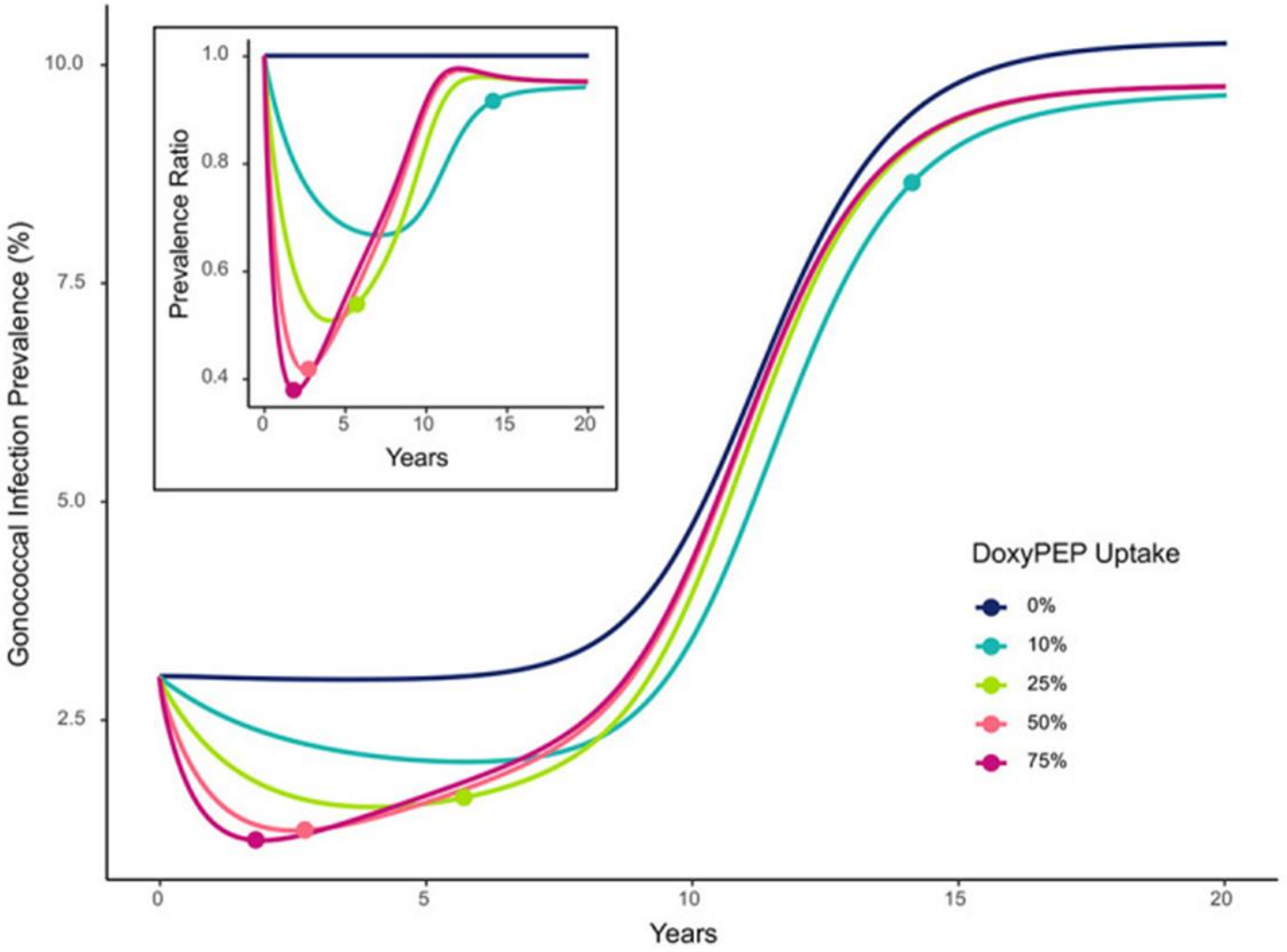
Figure 3: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019

- **Main drivers are antimicrobial misuse and overuse**
- **DoxyPEP is overuse!**
- **Frequent DoxyPEP use might further contribute to the increase in AMR**

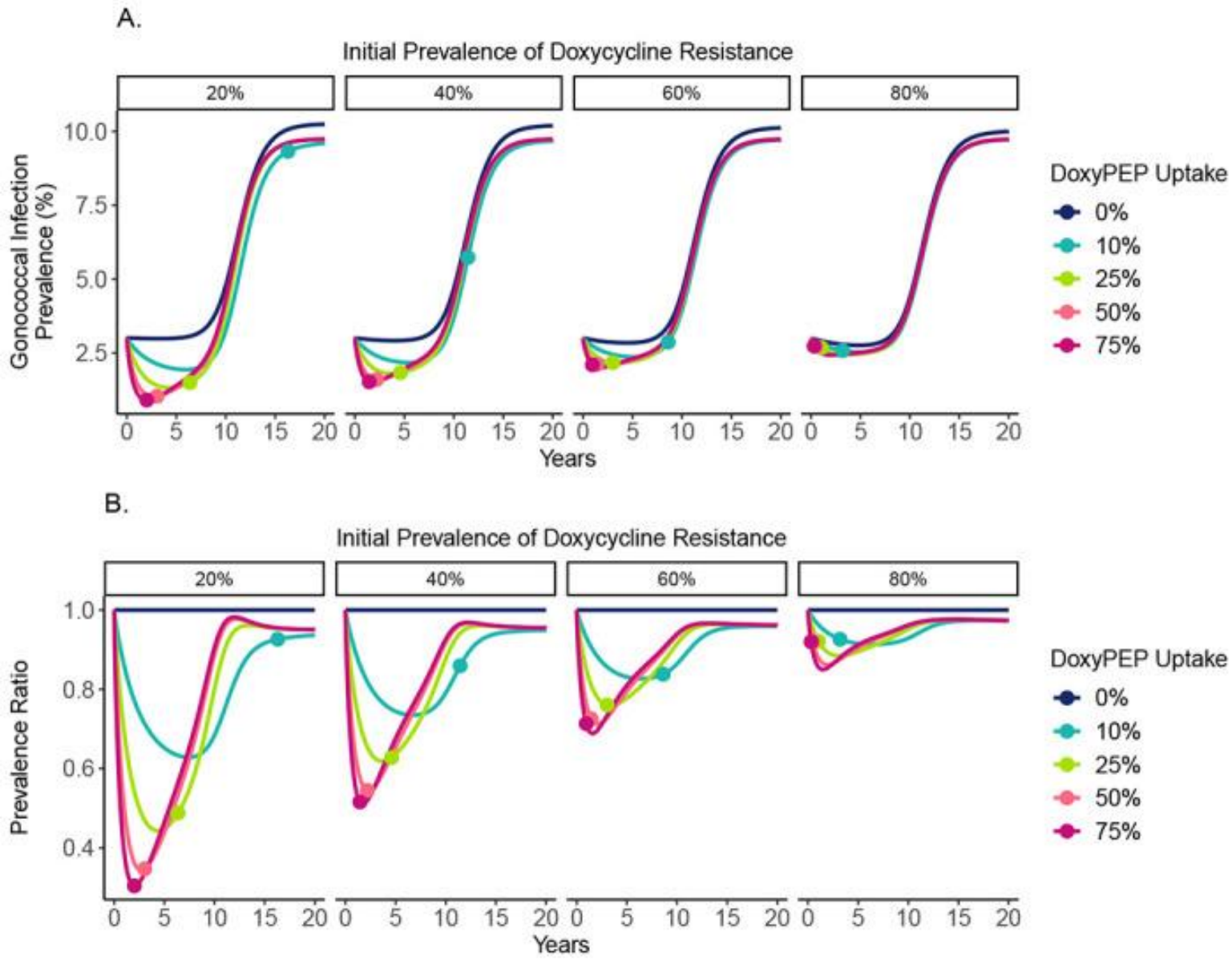
Antimicrobial resistance (who.int), accessed 4 September 2024;
Antimicrobial Resistance Collaborators, Lancet 2022

AMR and DoxyPEP: evidence from modelling studies

Gonorrhoea infections prevalence over time by DoxyPEP uptake levels in MSM



Reichert, MedRxiv 2023



Reichert, MedRxiv 2023

AMR and DoxyPEP: Evidence from in vivo and in vitro models

DoxyPEP might have an impact on resistance development on a broader range of bacterial species

In vitro study: Simulation of DoxyPEP in a *Galleria mellonella* infection model

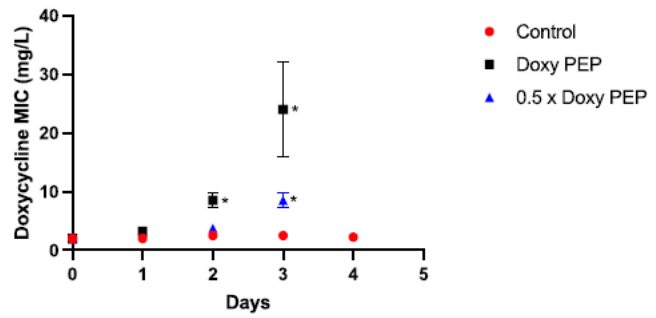


FIGURE 2
Individual-level selection. Increase in doxycycline MICs in *K. pneumoniae* during individual-level selection following PEP equivalent doses of doxycycline (200 mg/day, Doxy PEP) or 50% of this dose (0.5 x Doxy PEP) in a *Galleria mellonella* model of *K. pneumoniae* infection. Symbols represent the mean MIC at each timepoint, and the error bars show the standard deviation of the mean. Unpaired t-tests were done to compare the MICs between controls and doxycycline exposed strains at each timepoint. *$p < 0.01$.

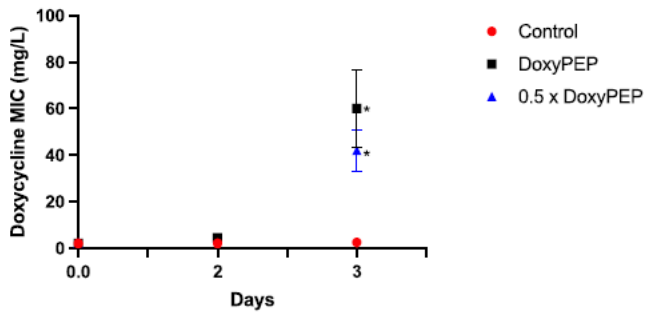


FIGURE 3
Network-level selection. Increase in doxycycline MICs in *K. pneumoniae* during network-level selection following doxycycline PEP equivalent doses of doxycycline in a *Galleria mellonella* model of *K. pneumoniae* infection. Symbols represent the mean MIC at each timepoint, and the error bars show the standard deviation of the mean. Unpaired *t*- tests were done to compare the MICs between controls and doxycycline exposed strains at each timepoint. *$p < 0.05$.

DoxyPEP can select for doxycycline, ceftriaxone and ciprofloxacin resistance in *Klebsiella pneumoniae*

Kenyon et al , Frontiers Micobiol 2023

DoxyPEP and microbiome

Impact of DoxyPEP on Microbiome composition and associated antimicrobial resistance genes is unknown/poorly understood

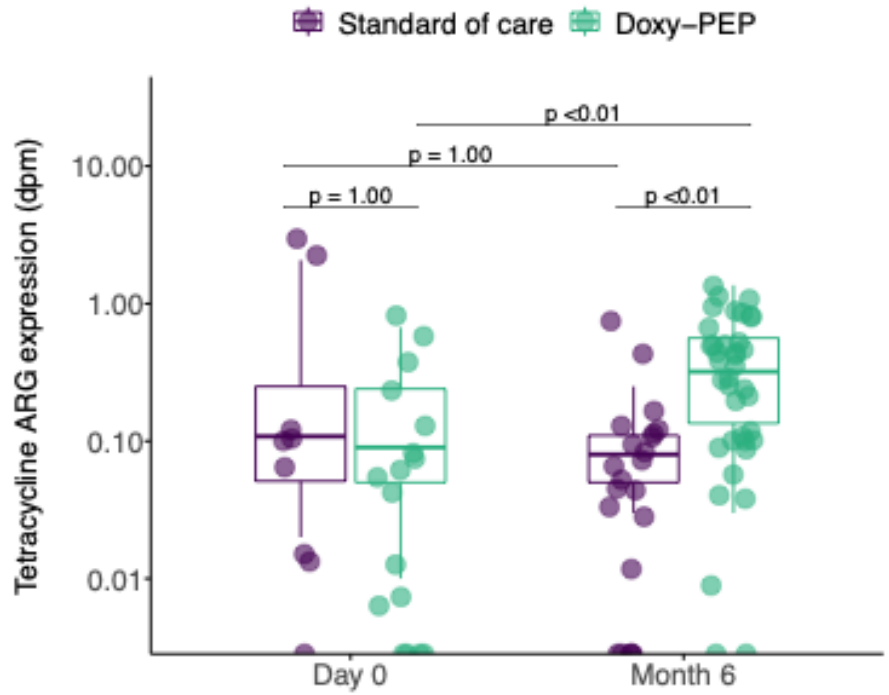


Figure. Tetracycline antimicrobial resistance gene (ARG) normalized expression, measured in average ARG sequencing depth per million reads sequenced (dpm), between the Month 0 and Month 6 samples in the doxy-PEP and SOC arms.

DoxyPrEP is associated with an increase in tetracycline (TCN) antimicrobial resistance gene (ARG) expression, without affecting non-TCN ARG classes

Chu et al , CROI 2024

More about DoxyPEP use

Prescribing DoxyPeP use in key populations at high risk of STI acquisition might result in

- an increase in sexual risk behaviour (impact not yet evaluated), as demonstrated for HIV PrEP
- less testing and hence delayed diagnoses and ongoing spread of severe sexually transmitted infections including HIV and viral hepatitis B and C (not yet evaluated)
- delayed syphilis diagnoses and masked neurosyphilis infections

DoxyPEP use in the larger population at lower risk of STI and maybe less compliant will increase if Doxy-PrEP is endorsed for specific populations at high risk of bacterial STI

- might not be (cost-)effective and increase the risk of AMR development

Fact

- Off-label use of antibiotics from other classes as 'DoxyPEP'
  e.g. ciprofloxacin, azithromycin, and cefixime

Summary: do not prescribe DoxyPEP for bacterial STIs

Except for syphilis, no strong evidence that DoxyPEP reduces STI acquisition in the short term
Many uncertainties and lack of data

- Long term effect on STI incidence questionable
- Rise in AMR and negative impact op microbiome likely

Continue the STI test-and-treat strategy* as part of comprehensive sexual health services

* In absence of symptoms, do not test for *C trachomatis* infection

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Henry the Vries
Authors of the papers presented
Participants of the studies included

Audience

What is your position now?

- In favour of Doxy-PEP
- Against Doxy-PEP

1. Are you a Doxy PEP prescriber?

No

Yes

2. Is evidence on the long term effect of DoxyPEP on STI incidence needed?

No

Yes

3. Do we need more data on the effect of DoxyPEP on antimicrobial resistance?

No

Yes

4. To whom will you prescribe DoxyPEP?

1. Everybody
2. Individuals who ask for DoxyPEP
3. Individuals with a syphilis reinfection
4. Nobody

5. If DoxyPEP is implemented in routine care, do we need to continue screening for secondary resistance?

No

Yes

6. If an individual is on DoxyPEP, do we need to continue STI screening at the same frequency?

No

Yes