CHU Poitiers
CENTRE HOSPITALIER UNIVERSITAIRE

gérico
GROUPE D'ÉPIDÉMIOLOGIE ET RECHERCHE EN INFECTIOLOGIE CLINIQUE CENTRE OUEST

DOXY-PEP contre

Gwenaël Le Moal, Poitiers

Liens d’intérêt

Aucun

Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré
- Efficace
  - Sur toutes les IST (Gono, CT, Syphilis)
  - Quelque soit le genre/patient
  - Sans modification des comportements si possible
- Peu cher voire coût efficace
- Pas de sélection de résistances
  - IST
  - Autres bactéries
- Peu ou pas d’action sur le microbiote

Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré?
- Efficace
  - Sur toutes les IST (Gono, CT, Syphilis)
  - Quelque soit le genre/patient
  - Sans modification des comportements si possible
- Peu cher voire coût efficace
- Pas de sélection de résistances
  - IST
  - Autres bactéries
- Peu ou pas d'action sur le microbiote

Possible effets indésirables de la DOXYCYCLINE

- Céphalées
- Troubles gastrointestinaux, perforation intestinale
- Photosensibilité
- Ulcération œsophagienne (prise debout, avant le coucher)
- Coloration noire des ongles

Clinical Therapeutics/Volume 27, Number 9, 2005

Safety of Doxycycline and Minocycline: A Systematic Review

Kelly Smith, MD[1]; and James J. Leyden, MD[2]

[1]Warner Chilcott Laboratories, Rockaway, New Jersey; and [2]Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania

Table I. Case reports of adverse events with doxycycline, 1966 through August 2003 (N = 130 patients).[9-38]

	No. (%) of Adverse Events		
Body System	Total	US	Non-US
Whole body	130 (100)	13 (10)	117 (90)
Digestive system			
Esophageal erosion	72 (55)	9 (7)	63 (48)
Skin			
Photosensitivity	47 (36)	–	47 (36)
Photo-onycholysis	5 (4)	2 (2)	3 (2)
Rash	1 (<1)	–	1 (<1)
Central nervous system			
Intracranial hypertension	2 (2)	–	2 (2)
Other			
Hypoglycemia	2 (2)	2 (2)	–
Anosmia	1 (<1)	–	1 (<1)

US = United States.

- 24 essais cliniques avec DOXY (n=3833)
- Incidence effets II : 0 à 61%
- Gastro-intestinal +++
- CDC (1998-2003) : 13/millions de dose de DOXY (2,3/millions/années)

Longer term doxycycline use is safe

Systematic review from 1987-2022

10,106 people using doxycycline doses from 20-200 mg/day ranging from 8 weeks to >3 yrs

- Moderate AE (0-88%) and severe AE (0-14%) not always attributed to doxycycline
- GI effects common (n/v, abd. pain): 0-50%
- Derm. effects (rash): 0-38%
- Metabolic effects: no comprehensive studies, results vary. Weight gain paper *retracted* for ethical misconduct
- Microbiome effect: small, descriptive studies with limited data

TABLE 2. Relative Risk of Adverse Events Between Doxycycline and Placebo Arms of Randomized Controlled Trials

Outcome	κ	Relative Risk (95% CI)	I^2%	*P*
Included RCT studies				
Any AE	9	1.03 (0.89–1.21)	59.6	0.66
Severe AE	12	0.83 (0.59–1.16)	2.20	0.28
Neurological AE	11	0.88 (0.73–1.05)	0.90	0.15
Gastrointestinal AE	12	1.68 (1.19–2.38)	72.2	<0.01
Dermatological AE	9	3.55 (1.39–9.01)	45.9	0.01
Dropped due to AE	18	1.62 (1.12–2.34)	7.50	0.01
100- to 200-mg dosages				
Any AE	3	1.35 (0.69–2.64)	74.7	0.38
Severe AE	6	0.94 (0.65–1.34)	0.00	0.73
Neurological AE	5	0.99 (0.97–1.02)	0.17	0.68
Gastrointestinal AE	6	1.78 (1.16–2.74)	81.9	0.01
Dermatological AE	4	5.52 (1.75–17.42)	68.3	<0.01
Dropped due to AE	10	1.82 (1.06–3.11)	20.9	0.03

I^2 variation across studies because of heterogeneity rather than chance.

AE indicates adverse event; κ, number of studies; RCT, randomized controlled trial.

CROI 2024

Chan, et al. *Sex Transm Dis* 2023

Characteristics of studies identified by the systematic literature review that assess longer-term1 doxycycline use and adverse events

First Author	Publication Year	Study	Population	Study Site	Drug	Duration (Days)	Doxycycline (N)	Mild* (n)	Moderate* (n)	Severe* (n)	Stopped (adverse events)
Akhyani (27)	2008	Rosacea Treatment	27-72 years old	Iran	Doxycycline 100mg once daily	91	30	NR	NR	NR	0
Alexis (28)	2012	Rosacea Treatment	18+ years old	United States	Doxycycline 40mg once daily (30 mg immediate release and 10 mg delayed release beads) once daily	84	1196	NR	NR	NR	NR
Andersen (29)**	1998	Malaria Prophylaxis	18-55 years old	Kenya	Doxycycline 100mg once daily	70	55	NR	NR	NR	1
Angelakis (30)	2014	Q Fever Endocarditis Treatment	18+ years old	France	Doxycycline 100mg twice a day (and hydroxychloroquine)	540+	48	NR	NR	NR	NR
Arman (31)	2015	Rosacea Treatment	Adults	Turkey	Doxycycline 100mg BID for one month then once daily for two months	90	19	NR	NR	NR	NR
Babaeinejad (32)	2011	Acne Treatment	13+ years old	Iran	Doxycycline 100mg once daily	90	50	4	0	0	0
Baudon (33)	1999	Malaria Prophylaxis	Adult soldiers	Gabon and the Central African Republic	Doxycycline 100mg once daily	120+	171	NR	NR	NR	11
Baxter (34)	2002	Abdominal Aortic Aneurysm Treatment	54-84 years old	United States (Multiple States)	Doxycycline 100mg twice per day	90+	36	NR	NR	NR	3

Berende (35)	2016	Lyme Disease Treatment	Adults	Netherlands	Doxycycline 100mg twice a day	84	86	39 (Mild or Moderate)	39 (Mild or Moderate)	3	3
Brandt (36)**	2005	Osteoarthritis Treatment	45-64 years old	United States (Indiana)	Doxycycline 100mg twice a day	900	218	NR	NR	31	25
Brill (37)	2015	COPD Treatment	45+ years old	United Kingdom	Doxycycline 100mg once daily	91	25	2 (Mild or Moderate)	2 (Mild or Moderate)	0	0
Caton (38)**	2000	Chronic Periodontitis	30-75 years old	United States (Multiple)	Doxycycline 20mg twice a day	274	93	NR	NR	1	1
Del Rosso (39)**	2007	Rosacea Treatment	18+ years old	United States and Puerto Rico	Doxycycline monohydrate 40mg once daily (formulation: 30-mg immediate-release and 10-mg delayed-release beads)	112	269	133 (Mild or Moderate)	133 (Mild or Moderate)	16	19
Del Rosso (40)**	2022	Acne Treatment	12+ years old	United States (Multiple Sites)	Doxycycline 120mg once daily (with trifarotene cream)	84	133	3 (Mild or Moderate)	3 (Mild or Moderate)	0	0
Del Rosso (41)**	2022	Rosacea Treatment	18-80 years old	United States (Multiple Sites)	Doxycycline 40mg modified-release capsules once daily	84+	300	12 (Mild or Moderate)	12 (Mild or Moderate)	0	0
Del Rosso (42)	2012	Rosacea Treatment	Adults	United States	Doxycycline modified-release 40mg once daily (30mg immediate-release and 10 mg delayed-release)	84	1196	NR	NR	NR	NR
Del Rosso (43)	2018	Acne Treatment	12+ years old	United States	Doxycycline hyclate delayed-release 100mg twice daily	84	175	26 (Mild or moderate)	26 (Mild or moderate)	1	4
Del Rosso (44)	2008	Rosacea Treatment	18+ years old	United States	Doxycycline 100mg daily or 40mg delayed-release daily (with topical metronidazole 1% gel)	112	91	16	18	6	9
Donta (45)**	2004	Gulf War Illness Treatment	Adult veterans	United States (Multiple sites)	Doxycycline 200mg once daily	365	245	NR	NR	12	7
Frenzel (46)	2008	Treatment of Brain Vascular Malformations	15-78 years old	United States (California)	Doxycycline 100mg twice a day	730	13	NR	NR	1	2
Gollnick (47)	2010	Rosacea Treatment	19-91 years old	Germany	Doxycycline 100mg once daily for 14 days then 50mg once daily	84	143	NR	NR	NR	NR
Golub (48)	2001	Chronic periodontitis treatment	18-75 years old	United States	Doxycycline 20mg once or twice daily	84	75	NR	NR	NR	3
Kaneshiro (49)**	2012	Prevention of Menstrual Bleeding	18-45 years old females	United States	Doxycycline 40mg once daily	84	32	NR	NR	NR	0
Kitchener (50)	2005	Malaria Prophylaxis	Adult soldiers	Australian soldiers settled in East Timor at risk for malaria	Doxycycline (Dose not reported)	180+	388	245*	78*	7*	1
Kus (51)	2005	Acne Treatment	18-30 years old	Turkey	Doxycycline 100mg BID for one month and then once daily for the next two months	90	26	NR	NR	NR	NR
Layton (18)	1993	Acne Treatment	13-49 years old	United Kingdom	Doxycycline 150 or 200 mg/day	183	106	NR	NR	NR	37
Lee (52)**	2004	Chronic periodontitis treatment	Adults	South Korea	Doxycycline hyclate 20mg twice daily	274	24	NR	NR	NR	NR
Leijtens (53)	2019	Suppression of Prosthetic Joint Infection	40-88 years old	Netherlands	Doxycycline 100-200mg once daily	1157	14	NR	NR	NR	1
Leyden (54)**	2013	Acne Treatment	12-45 years old	United States	Doxycycline calcium 40-160mg (weight based)	84	190	NR	NR	NR	1
Lin (55)	2015	Graves Disease Treatment	18-60 years old	China	Doxycycline 50mg once daily	84	16	2	0	0	0
Makunde (56)	2006	Wuchereria Bancrofti Treatment	14-68 years old	Tanzania	Doxycycline 200mg once daily	60	19	7	0	0	0
Maleszka (57)	2011	Acne Treatment	14+ years old	Poland and Croatia	Doxycycline 100mg once daily	84	120	NR	NR	NR	0
Molina (3)	2017	STI Prophylaxis	Adult Males	France	Single dose doxycycline 200mg within 24 hrs after sex and no later then 72 hrs	261+	116	102 (Mild or Moderate)	102 (Mild or Moderate)	4	8
Moore (58)**	2015	Acne Treatment	12-59 years old	United States	Doxycycline 40-100mg once daily	112	440	NR	NR	2	2
Naini (59)	2007	Diabetic Proteinuria Treatment	49-77 years old	Iran	Doxycycline 100mg once daily	61	35	NR	NR	0	3
Novak (60)	2002	Chronic periodontitis treatment	29-45 years old	United States	Doxycycline hyclate 20mg twice daily	183	10	NR	NR	NR	NR
Ohrt (61)**	1997	Malaria Prophylaxis	Adult soldiers	Indonesia	Doxycycline 100mg once daily	91	67	NR	NR	NR	0
Pagès (62)	2002	Malaria Prophylaxis	Adult soldiers	French soldiers deployed in Gabon and Chad	Doxycycline monohydrate 100mg once daily	120	275	NR	NR	NR	15
Pan (63)**	2022	Thyroid Disease	Adults	China	Doxycycline 50mg once daily	84	50	1	0	0	0
Pang (64)**	1998	Malaria Prophylaxis	10-16 years old	Thailand	Doxycycline 25-100mg daily depending on weight	105	144	NR	NR	NR	0
Pang (65)	1987	Malaria Prophylaxis	10-15 years old	Thailand	Doxycycline 100mg once daily for those over 40kg; Doxycycline 50mg once daily for those less than 40kg	63	95	NR	0	0	0
Parish (66)	2005	Acne Treatment	14-36 years old	United States	Doxycycline hyclate 100mg twice a day	56	12	NR	NR	NR	NR
Park (67)	2015	Rosacea Treatment	18+ years old	South Korea	Doxycycline 100mg twice a day	770	15	NR	NR	NR	0
Pfeffer (68)	2011	Rosacea Treatment	Adults	Germany	Doxycycline 40mg once daily (slow-release form)	60+	7	0	0	0	0

Low rate of adverse events in doxy-PEP trials

Randomized clinical trial	Laboratory abnormalities	Adverse events	Discontinuations	Other outcomes
IPERGAY	Grade 4 transaminitis due to acute hepatitis C infection (n = 3)	Drug-related gastrointestinal adverse events (n = 29); more common in PEP group (*P* = .03)	29 (26%) for all reasons; 8 (7%) due to drug-related adverse events	No difference between groups in serious adverse events
DoxyPEP	Grade 2 transaminitis (n = 1)	Grade 3 diarrhea or headache (n = 5)	2%	No weight gain compared to standard of care
DOXYVAC	None as of July 2023	Gastrointestinal adverse events (n = 2)	3 (0.9%) due to gastro-intestinal adverse events or fear of adverse events	Further data pending final review
dPEP Kenya	Not collected	7% (gastrointestinal side effects)	5%	Social harms related to PEP use among 3 participants

No serious AEs related to doxycycline in DoxyPEP, DOXYVAC, dPEP or DuDHS trials

Cannon & Celum, *Top Antivir Med* 2023
Hazra, et al. *Clin Infect Dis* 2024

CROI 2024

Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré
- Efficace ?
  - Sur toutes les IST (Gono, CT, Syphilis)
  - Quelque soit le genre/patient
  - Sans modification des comportements si possible
- Peu cher voire coût efficace
- Pas de sélection de résistances
  - IST
  - Autres bactéries
- Peu ou pas d’action sur le microbiote

Efficace ?

- OK chez les HSH dans les essais randomisés
- Mais chez des sujets asymptomatiques pour la plupart!
- Quid en vraie vie?

Et pour les femmes?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women

Jenell Stewart, D.O., M.P.H., Kevin Oware, M.A., Deborah Donnell, Ph.D., Lauren R. Violette, M.P.H., Josephine Odoyo, R.N., M.P.H., Olusegun O. Soge, Ph.D., Caitlin W. Scoville, M.P.H., Victor Omollo, M.B., Ch.B., M.P.H., Felix O. Mogaka, M.B., Ch.B., Fredericka A. Sesay, M.B., Ch.B., M.P.H., R. Scott McClelland, M.D., M.P.H., Matthew Spinelli, M.D., M.P.H., Monica Gandhi, M.D., M.P.H., Elizabeth A. Bukusi, M.B., Ch.B., M.Med., M.P.H., Ph.D., and Jared M. Baeten, M.D., Ph.D., for the dPEP Kenya Study Team*

- Essai randomisé en ouvert (1:1)
  - DOXY 200mg pris dans les 72h après RS comparé au SC
  - Kenya 2020-2022
  - Objectif principal : incidence IST/3mois pendant 1 an

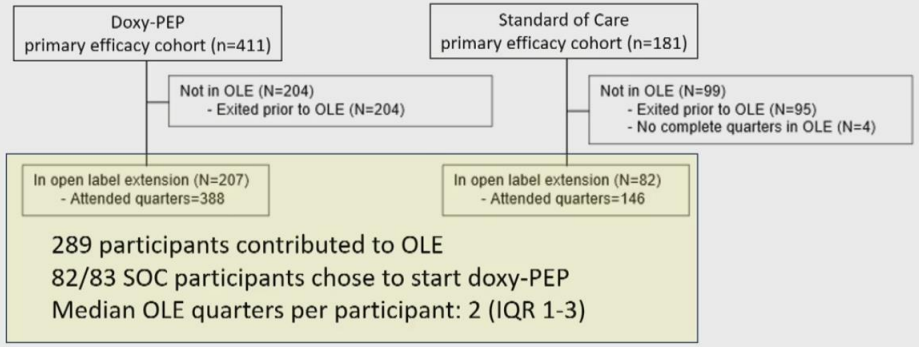
- Résultats
  - 449 femmes cis (18-30ans) avec PrEP (224 PEP vs 225 SC)
  - 109 IST (50 (25,1 pour 100 personnes.années) vs 59 (29 pour 100 personnes.années)
  - Faible observance (prélèvements dans les cheveux + pour 44% des femmes dans le bras DOXY)

Table 2. Intention-to-Treat and Subgroup Analyses of Incident STIs.

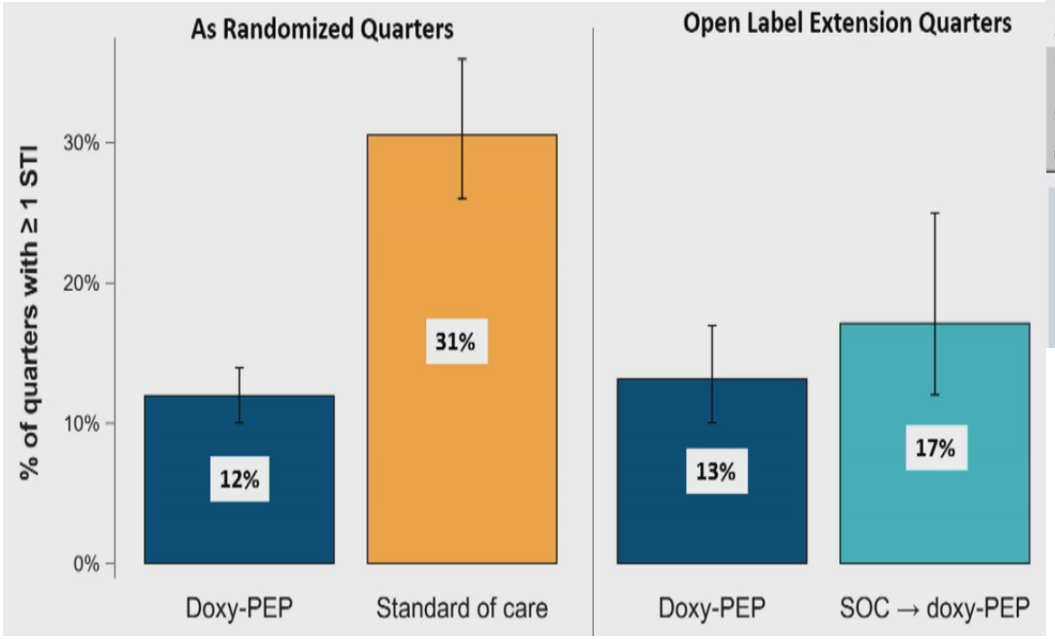
Analysis and End Point	Doxycycline PEP (N = 224)	Standard Care (N = 225)	Relative Risk (95% CI)*
	no. of events/no. of trial visits		
Intention to treat			
Any STI (primary end point)	50/854	59/886	0.88 (0.60–1.29)†
Chlamydia	35/854	50/886	0.73 (0.47–1.13)
Gonorrhea	19/854	12/886	1.64 (0.78–3.47)

Stewart J et al, CROI 2024 P1148

Open Label Extension



DOXYPEP



CROI
Conference on Retroviruses and Opportunistic Infections

Sexual behavior during OLE

median (IQR)	As-randomized: doxy-PEP N quarters = 1077	As-randomized: SOC N quarters = 455	AR→OLE: doxy-PEP N quarters = 388	AR→OLE: SOC → doxy-PEP N quarters = 146
Doxy doses/quarter	15 (4-30)	—	17 (7-32)	17 (5-30)
Sex partners/quarter	10 (4-25)	8 (4-15)	12 (6-25)	16.5 (5-31)
Condomless insertive sex acts/quarter	5 (1-20)	4 (2-12)	8 (2-20)	8 (3-25)
Condomless receptive sex acts/quarter	8 (2-20)	5 (1-15)	10 (2-23.5)	10 (2-25)
% of condomless sex acts covered by doxy-PEP per quarter	82.4%	—	77.3%	81.3%

- **Sexual partners & condomless sex:** ↑ during OLE in both groups; doubled in SOC → doxy-PEP
- **Reported doxy-PEP coverage of condomless sex:** High (> 75%) during OLE; comparable to doxy-PEP AR

Luetkemeyer A et al, CROI 2024 A125

Utilisation en vraie vie

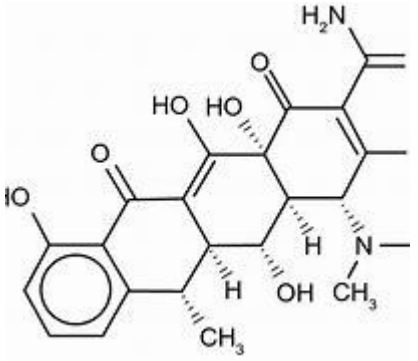
- Méthodes
  - Surveillance questionnaire online en septembre 2023
  - Utilisation des atb pour la prévention des IST
- Résultats
  - 649 répondants, 50 états
  - 89% HSH, 42% sous PreP, 19% PVVIH
  - 95% intéressés par l'utilisation d'une prophylaxie IST, 49% en avait entendu parlé
  - 143 utilisateurs
    - 45% avant le sexe
    - 72% après le sexe dont 45% pris dans les 24H
    - Molécules utilisées : doxy 78%, amox 19%, azythro 16%
    - DoxyPEP : 36% en ont entendu parler et 13% en ont pris dans les 12 derniers mois parmi lesquels 24% à une autre dose que 200mg

CROI 2024 Denver P 1153

Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré
- Efficace
  - Sur toutes les IST (Gono, CT, Syphilis)
  - Quelque soit le genre/patient
  - Sans modification des comportements si possible
- Peu cher voire coût efficace?
- Pas de sélection de résistances
  - IST
  - Autres bactéries
- Peu ou pas d’action sur le microbiote

Coût efficace?



DOXYCYCLINE ARROW 100 mg, cp

Claude Bernard

INFORMER LE MÉDECIN en cas de maux de tête ou de troubles visuels (risque d'augmentation de la pression à l'intérieur du crâne).
EVITER de s'exposer directement au soleil et aux UV en raison des risques de sensibilisation à la lumière.

Données technico-réglementaires

Code UCD7	9250632
Code UCD13	3400892506326
Code CIS	67164569
Médicament T2A	Non
Laboratoire titulaire AMM	ARROW GENERIQUES
Laboratoire exploitant	ARROW GENERIQUES 26, Avenue TONY GARNIER 69007 LYON Tel : 04 72 72 60 72 Fax : 04 72 72 60 70 Mail : arrow@arrow-generiques.com Site Web : http://www.arrow-generiques.com
Prix de vente TTC	DOXYCYCLINE 100MG ARROW CPR 15 : 3.26 € (Prix hors honoraire de dispensation - pharmacie) DOXYCYCLINE 100MG ARROW CPR 30 : 6.11 € (Prix hors honoraire de dispensation - pharmacie) DOXYCYCLINE 100MG ARROW CPR 5 : 1.80 € (Prix hors honoraire de dispensation - pharmacie)
Taux de TVA	DOXYCYCLINE 100MG ARROW CPR 15 : 2.1 % DOXYCYCLINE 100MG ARROW CPR 30 : 2.1 % DOXYCYCLINE 100MG ARROW CPR 5 : 2.1 %
Base de remboursement SS	DOXYCYCLINE 100MG ARROW CPR 15 : 3.26 € (Prix hors honoraire de dispensation - pharmacie) DOXYCYCLINE 100MG ARROW CPR 30 : 6.11 € (Prix hors honoraire de dispensation - pharmacie) DOXYCYCLINE 100MG ARROW CPR 5 : 1.80 € (Prix hors honoraire de dispensation - pharmacie)
Taux SS	DOXYCYCLINE 100MG ARROW CPR 15 : 65 % DOXYCYCLINE 100MG ARROW CPR 30 : 65 % DOXYCYCLINE 100MG ARROW CPR 5 : 65 %
	DOXYCYCLINE 100MG ARROW CPR 15 : Oui

A quand une étude de coût ?

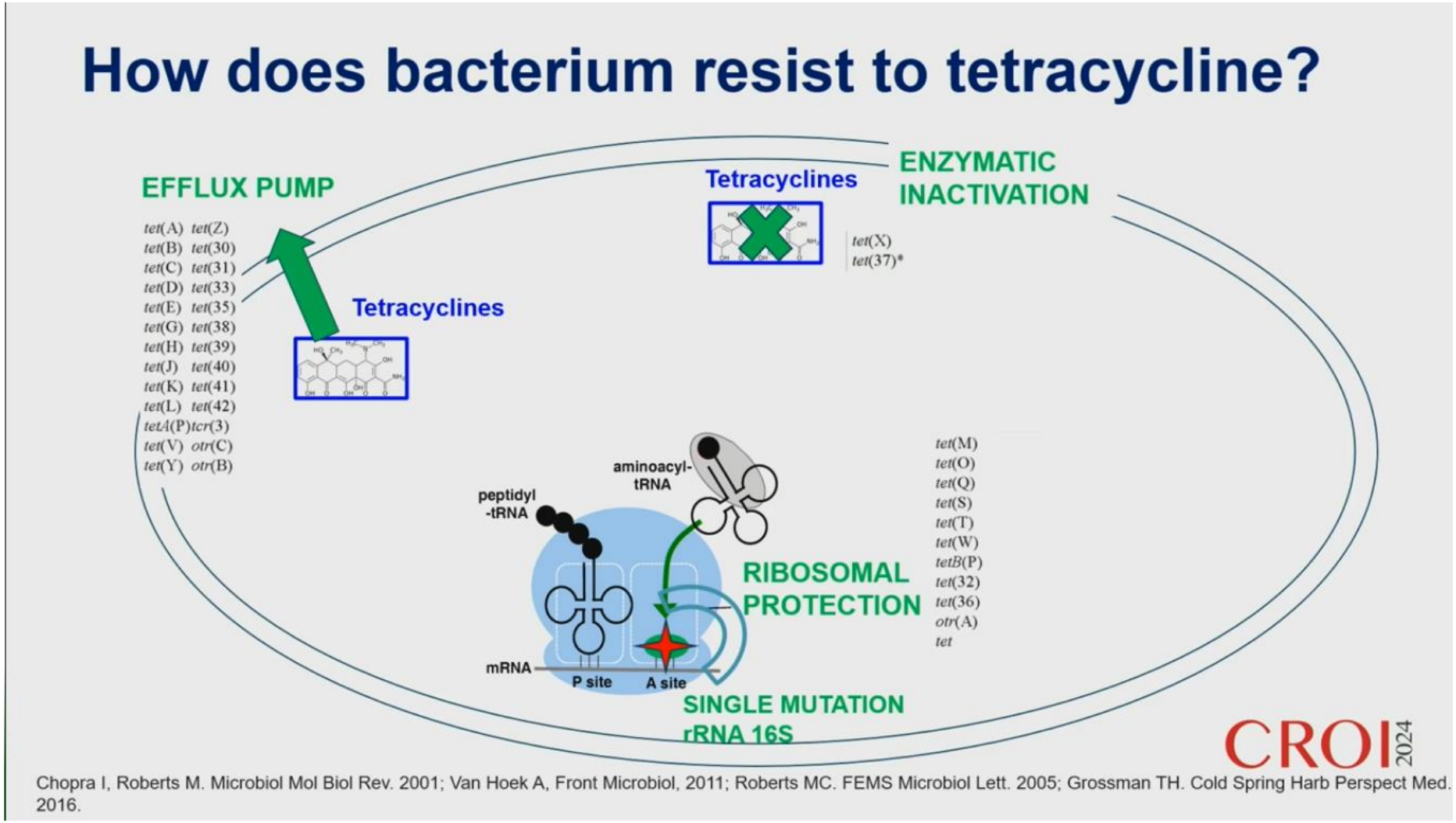
Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré
- Efficace
  - Sur toutes les IST (Gono, CT, Syphilis)
  - Quelque soit le genre/patient
  - Sans modification des comportements si possible
- Peu cher voire coût efficace
- Pas de sélection de résistances?
  - IST
  - Autres bactéries
- Peu ou pas d'action sur le microbiote

Doxycycline et résistance

Cyclines

- Large spectre d'activité : CocciG+, BGN, anaérobies, Rickettsiose, bartonelle, spirochète, paludisme, etc….
- Mécanisme d'action : bloque synthèse protéique et transcription ARN au niveau du ribosome



Chopra I, Roberts M. Microbiol Mol Biol Rev. 2001; Van Hoek A, Front Microbiol, 2011; Roberts MC. FEMS Microbiol Lett. 2005; Grossman TH. Cold Spring Harb Perspect Med. 2016.

- Gène tet ou mutation ARNr 16S
- Possibilité de transférer le gène tet par plasmide ou transposon horizontalement à d'autres espèces bactériennes

Doxycycline et antibiorésistance

- Quel est l’impact de la DOXY sur la R aux IST
- Quel est l’impact de la DOXY sur la R aux autres bactéries
  - La Résistance à la DOXY est elle transférable aux autres bactéries?

Impact de la DOXY sur la R aux IST

- Quel risque pour CT alors que c'est TT de référence?

Volume 56, Issue 5
October 2010

RESEARCH ARTICLES | OCTOBER 12 2010

Decreased Susceptibility to Azithromycin and Doxycycline in Clinical Isolates of *Chlamydia trachomatis* Obtained from Recurrently Infected Female Patients in India

Subject Area: Further Areas , Oncology , Pharmacology

Apurb Rashmi Bhengraj; Harsh Vardhan; Pragya Srivastava; Sudha Salhan; Aruna Mittal

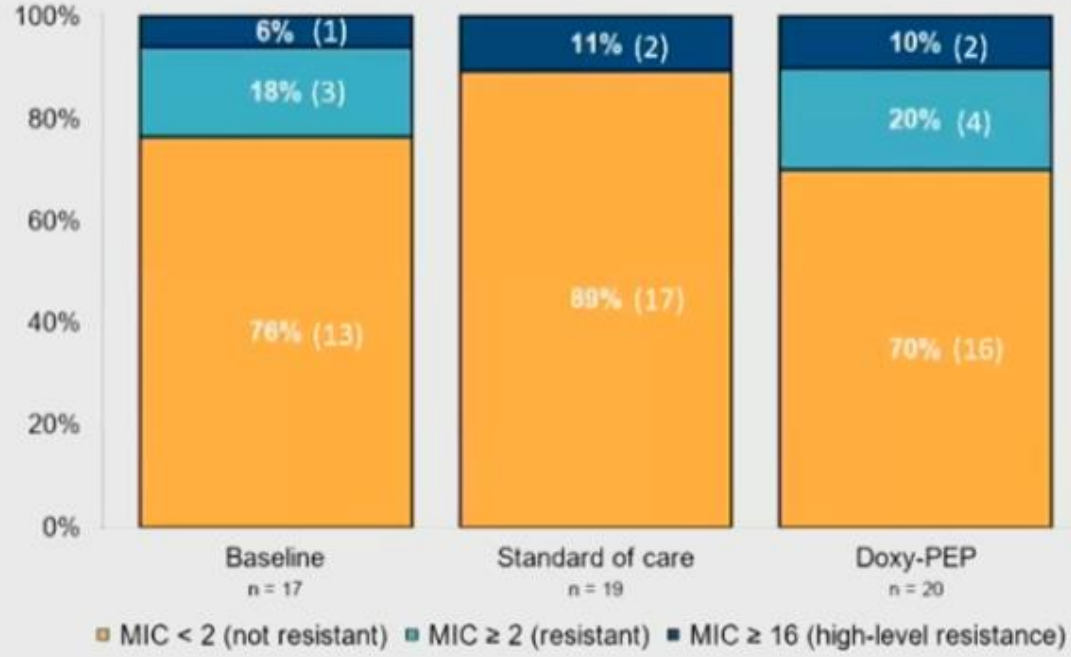
- Analyse in vitro de le sensibilité à la Doxycycline et Azithromycine
- 21 souches de CT de femmes avec infections récurrentes symptomatiques
- Résultats :
  - 8 souches (38%) avec diminution de sensibilité
  - 2/8 avec CMI > 8 µg/ml

- Quel risque pour Syphilis alors que c'est le seul TT en cas d'allergie?
- Et MG?

GC: Impact in Doxyvac/DoxyPEP trials (2020-22)

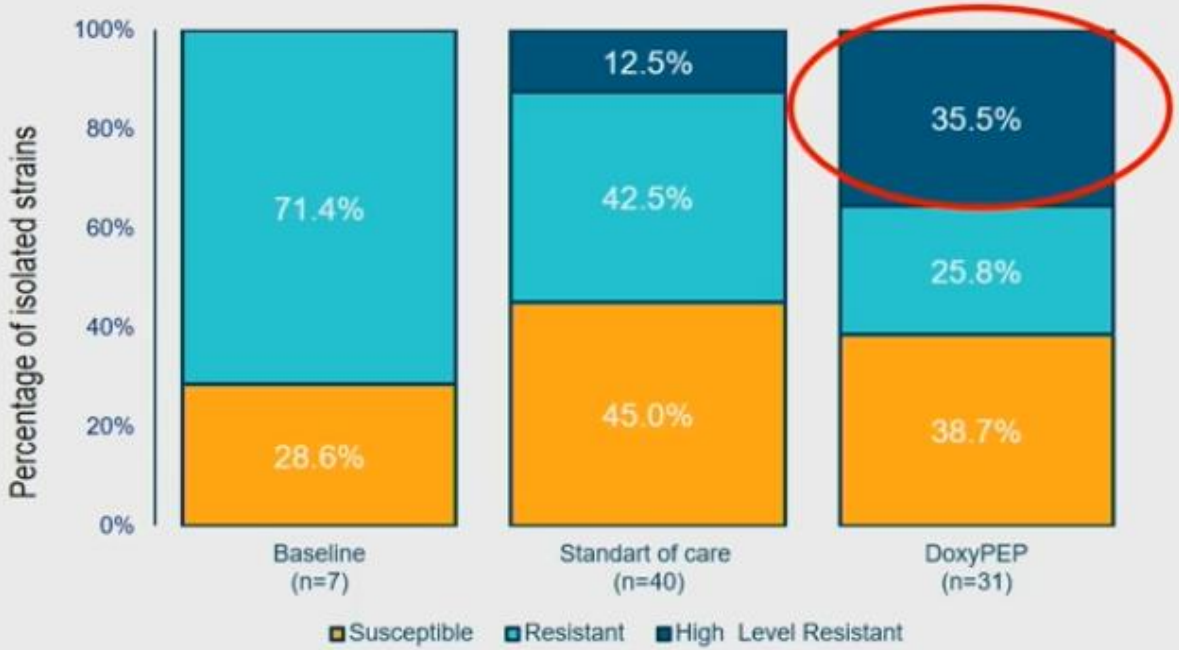
DOXYPEP

- **GC**: 56 cultures



Doxyvac

- **GC:** 78 cultures



Resistance defined by MIC ≥ 2 mg/L

Increased TCN-R in doxy-PEP vs. standard of care suggests doxy-PEP may be less protective against GC strains with existing TCN-R.

More high-level tetracycline-resistant isolates in the PEP group (*p= 0.04*)

Luetkemeyer A et al, New Engl J Med 2023; Molina et al, CROI 2024

Clinical Infectious Diseases

BRIEF REPORT

A Genomic Perspective on the Near-term Impact of Doxycycline Post-exposure Prophylaxis on *Neisseria gonorrhoeae* Antimicrobial Resistance

Tatum D. Mortimer and Yonatan H. Grad

Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Pre-existing tetracycline resistance in *Neisseria gonorrhoeae* limits the effectiveness of post-exposure prophylaxis (PEP) with doxycycline against gonorrhea, and selection for tetracycline resistance may influence prevalence of multi-drug resistant strains. Using genomic and antimicrobial susceptibility data from *N. gonorrhoeae*, we assessed the near-term impact of doxycycline PEP on *N. gonorrhoeae* resistance.

- R Tetracycline médiée par mutations plasmidiques *tetM* et mutations chromosomiques

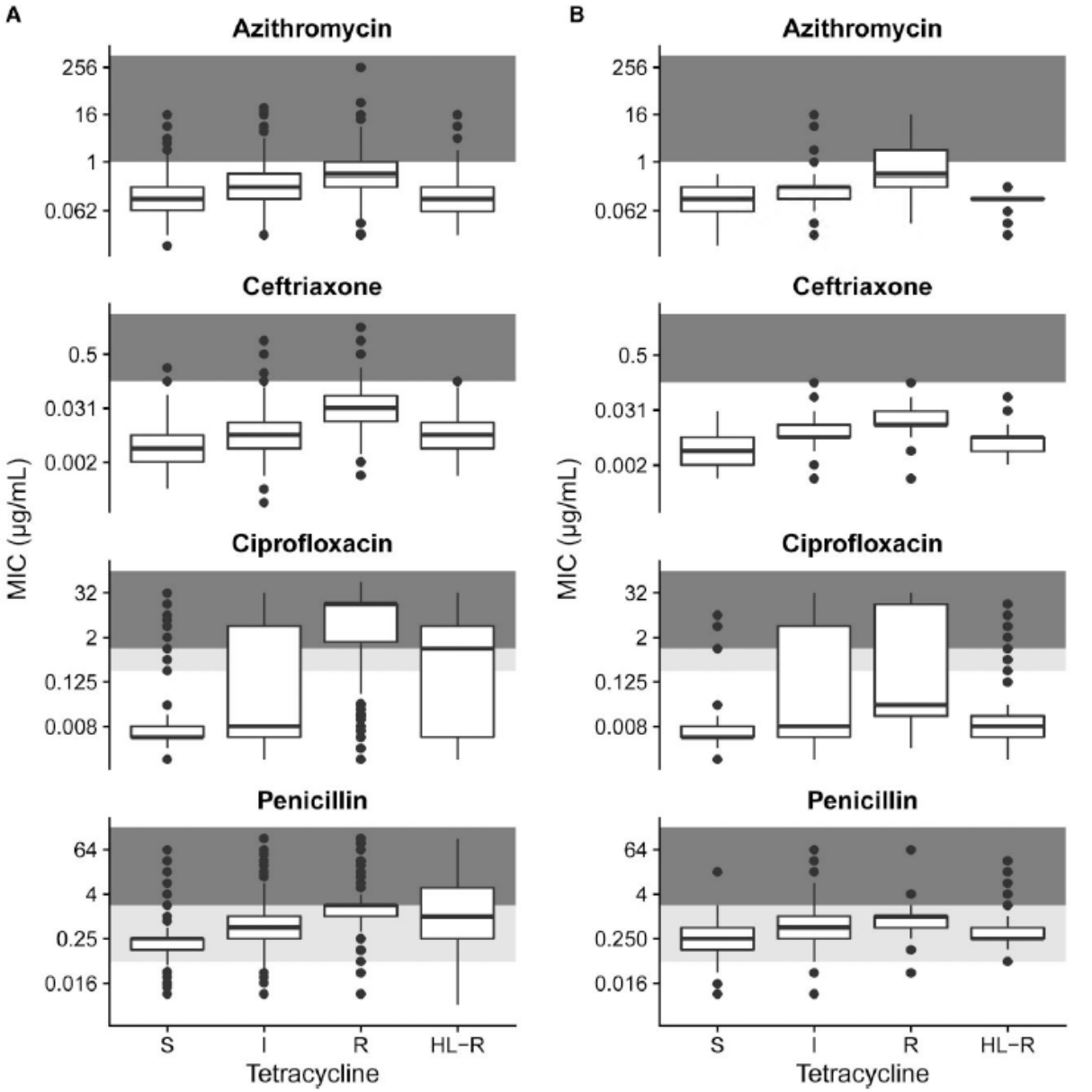


Figure 1. Co-resistance with other antimicrobials is highest among isolates with chromosomally encoded resistance to tetracyclines. Isolates were classified as susceptible (MIC ≤ 0.25 µg/mL), intermediate (0.25 < MIC < 2 µg/mL), resistant (2 ≤ MIC ≤ 8 µg/mL), or high-level resistant (MIC > 8 µg/mL) in 5644 global *Neisseria gonorrhoeae* isolates (*A*) and 1041 isolates collected in the United States in 2018 (*B*). Background shading corresponds to susceptible (white), intermediate (light gray), and resistant/non-susceptible (dark gray) MICs for each antimicrobial. Abbreviation: MIC, minimum inhibitory concentration.

SEXUALLY TRANSMITTED DISEASES
Journal of the American Sexually Transmitted Diseases Association (ASTDA)
www.stdjournal.com

NOTES

Doxycycline Postexposure Prophylaxis Could Induce Cross-Resistance to Other Classes of Antimicrobials in *Neisseria gonorrhoeae*: An In Silico Analysis

Vanbaelen, Thibaut MD*; Manoharan-Basil, Sheeba Santhini PhD*; Kenyon, Chris MD, PhD, MPH*,†

- Analyse de 2375 isolats de gonocoque du 2018 Euro-GASP survey Samples
  - Individus qui avaient un episode infectieux avec culture + à gono dans 26 pays européens
  - Séquençage de tout le génome, et mutations de RAM

- Forte association entre mutation rpsJ V57M et gyrA, penA, porB1a, mtrR promoter/mtrD, et folP RAMs
- Risque potentiel d'acquérir R aux autres classes

NOTE

Doxycycline Postexposure Prophylaxis Could Induce Cross-Resistance to Other Classes of Antimicrobials in *Neisseria gonorrhoeae*: An In Silico Analysis

Thibaut Vanbaelen, MD, Sheeba Santhini Manoharan-Basil, PhD,* and Chris Kenyon, MD, PhD, MPH*†*

MATERIALS AND METHODS

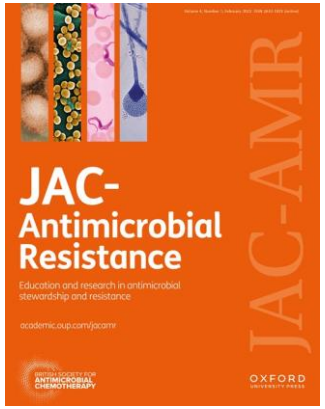
DATA ANALYSIS

RESULTS

Clonality by Genogroup

490 Sexually Transmitted Diseases • Volume 50, Number 8, August 2023

Impact de la DOXY sur la R aux autres bactéries



JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac009

JAC-
Antimicrobial
Resistance

A systematic review of the impacts of oral tetracycline class antibiotics on antimicrobial resistance in normal human flora

Robinson Truong[1,2], Vincent Tang[1], Troy Grennan[3,4] and Darrell H. S. Tan[1,2,5,6]*

- Augmentation R dans la flore de la cavité orale, digestive et respi après 2-18 semaines de TT
- Effet modeste et transitoire

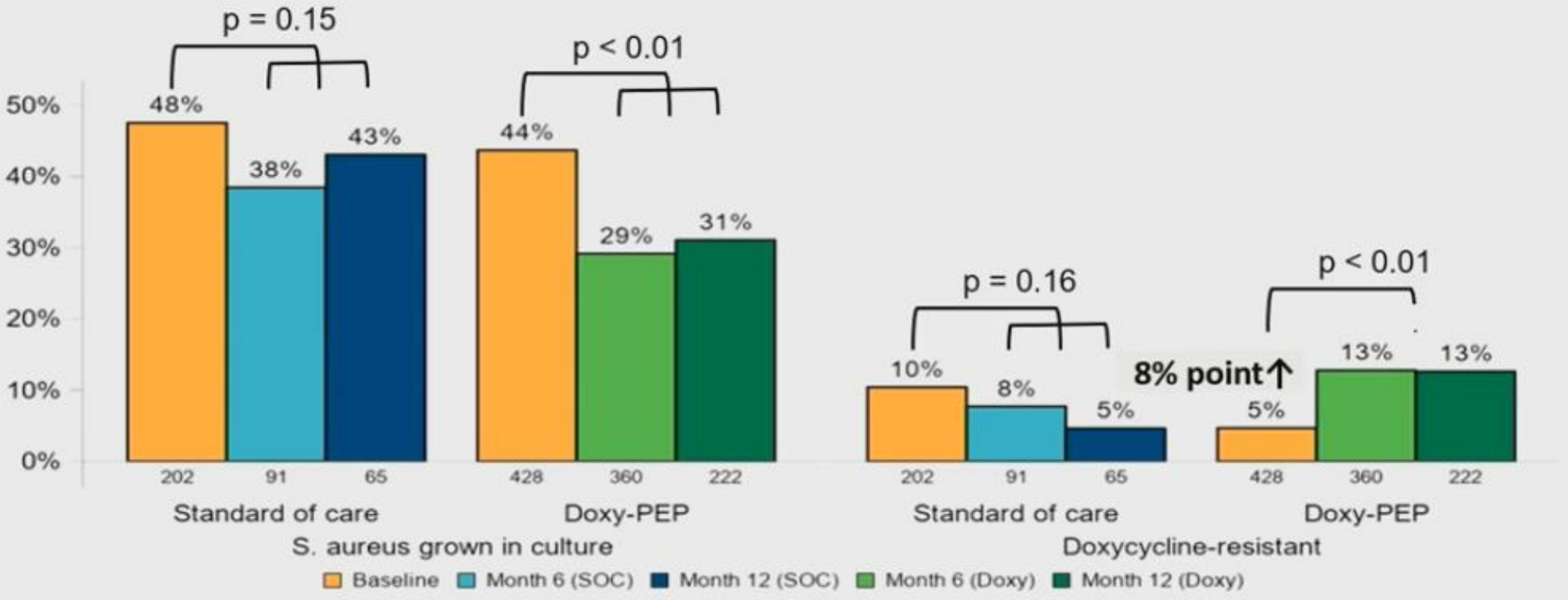
Results: Our search yielded 6265 abstracts of which 7 articles fulfilled inclusion criteria. Most were at moderate/high risk of bias, generally due to inadequate methodologic reporting. Studies used doxycycline, tetracycline, oxytetracycline or minocycline for 2–18 weeks. Most observed an increased burden of tetracycline resistance, including in subgingival ($n=3$ studies), gastrointestinal ($n=2$) and upper respiratory tract ($n=1$) flora; one study of skin flora found no change in tetracycline-resistant *Propionibacterium* species after 18 weeks of oxytetracycline/minocycline. Four studies reassessed AMR at 2–50 weeks post-intervention and reported varying degrees of resistance. Three articles reported on the prevalence of non-tetracycline AMR after doxycycline prophylaxis, of which one found a transient increase among gastrointestinal *Escherichia coli*; the other two showed no difference from control.

5. Impact of tetracycline on *S. aureus* colonization

S aureus colonization

DOXYPEP

- 14% absolute decrease in doxy-PEP arm
- 8% absolute increase in doxycycline resistance (doxy-R) in doxy-PEP arm.



CROI 2024

frontiers | Frontiers in Microbiology

TYPE Original Research
PUBLISHED 30 August 2023
DOI 10.3389/fmicb.2023.1208014

OPEN ACCESS

EDITED BY
Axel Cloeckaert,
Institut National de recherche pour l'agriculture, l'alimentation et l'environnement (INRAE), France

REVIEWED BY
William William Shafer,
Emory University, United States
Prasanth Manohar,
Texas A&M University, United States

*CORRESPONDENCE
Chris Kenyon
ckenyon@itg.be

†These authors have contributed equally to this work

Doxycycline PEP can induce doxycycline resistance in *Klebsiella pneumoniae* in a *Galleria mellonella* model of PEP

Chris Kenyon[1,2]*, Zina Gestels[1], Thibaut Vanbaelen[1], Said Abdellati[3], Dorien Van Den Bossche[3], Irith De Baetselier[3], Basil Britto Xavier[1,4†] and Sheeba Santhini Manoharan-Basil[1†]

[1]STI Unit, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, [2]Division of Infectious Diseases and HIV Medicine, University of Cape Town, Cape Town, South Africa, [3]Clinical Reference Laboratory, Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, [4]Hospital Outbreak Support Team-HOST, Ziekenhuis Netwerk Antwerpen Middelheim, Antwerp, Belgium

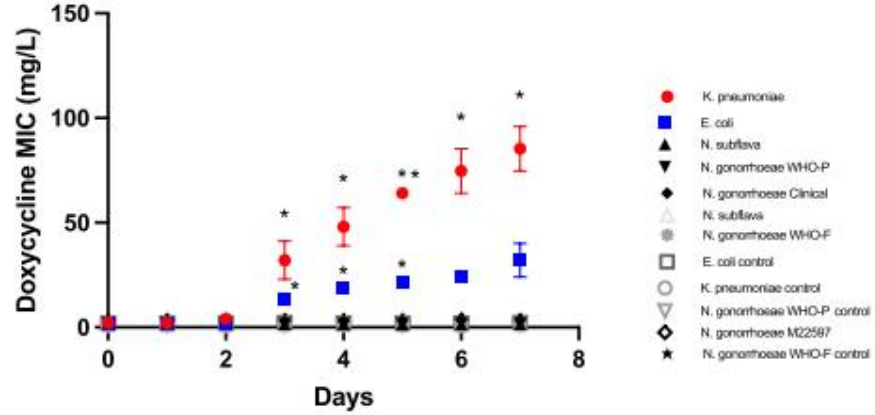


FIGURE 1
Increase in doxycycline MICs in *Klebsiella pneumoniae*, *E coli*, *N. subflava* and two strains of *Neisseria gonorrhoeae* during passage on chocolate agar plates containing a gradient of doxycycline (0.016 μg/mL to 256 μg/mL). Symbols represent the mean MIC at each timepoint, and the error bars show the standard deviation of the mean. Unpaired *t*-test was done to compare the MICs between controls and doxycycline exposed strain at each timepoint. $*p < 0.01$; $**p < 0.001$.

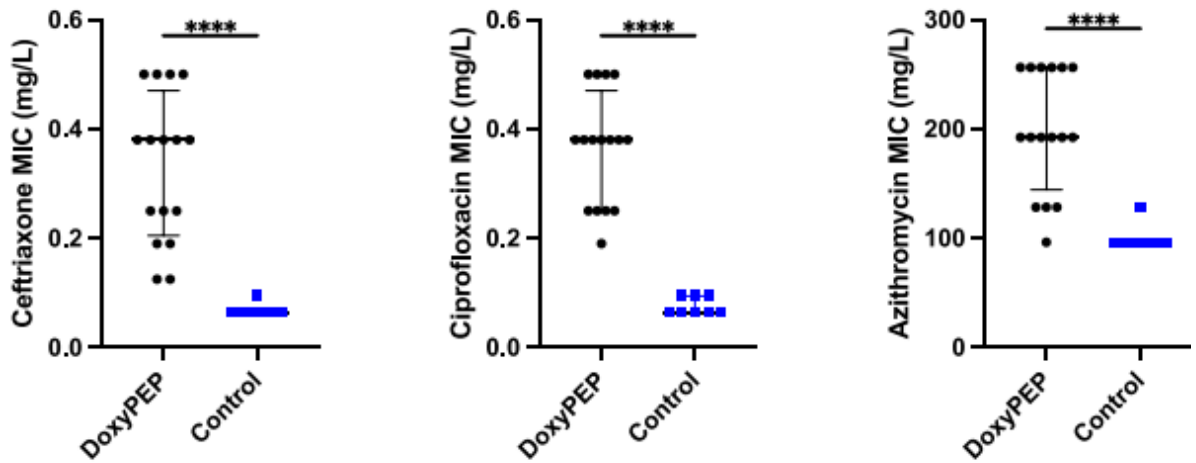


FIGURE 4
Selection of resistance to ceftriaxone, ciprofloxacin, and azithromycin in *Klebsiella pneumoniae* in *Galleria mellonella* exposed to doxycycline PEP (combined individual– and network-level experiments).

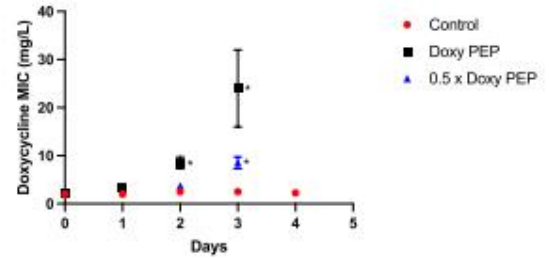


FIGURE 2
Individual-level selection. Increase in doxycycline MICs in *K. pneumoniae* during individual-level selection following PEP equivalent doses of doxycycline (200 mg/day, Doxy PEP) or 50% of this dose (0.5 x Doxy PEP) in a *Galleria mellonella* model of *K. pneumoniae* infection. Symbols represent 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. $*p < 0.01$.

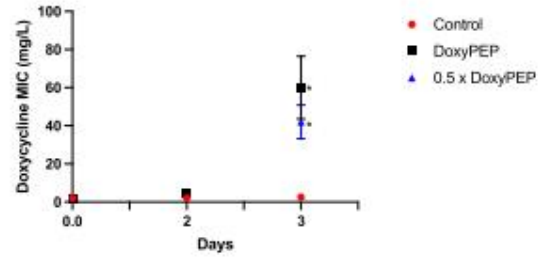


FIGURE 3
Network-level selection. Increase in doxycycline MICs in *K. pneumoniae* during network-level selection following doxycycline PEP equivalent doses of doxycycline in a *Galleria mellonella* model of *K. pneumoniae* infection. Symbols represent the mean MIC at each timepoint, and the error bars 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. $*p < 0.05$.

- Mutations acquises dans le géne ramR qui régule l'expression de la pompe à efflux (AcrAB-TolC)

Et en vraie vie?

Military studies on travelers diarrhea

Citation	Summary of Findings	Number of Participants	Quality of Evidence
Arthur JD, Echeverria P, Shanks GD, Karwacki J, Bodhidatta L, Brown JE. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria prophylaxis. Am J Trop Med Hyg. 1990 Dec;43(6):608-13. doi: 10.4269/ajtmh.1990.43.608.	People in doxy group were no more likely to have tet-R Campylobacter, ETEC than the mefloquine group. Tet-R non ETEC Ecoli was more common in those on doxy at the end of the training tour (p=0.01) but thought related to location. Military on deployment in Thailand. Doxy vs mefloquine and GI illness. No diff in non-ETEC bacteria resistance. Most of Campy was resistant. No diff in ETEC resistance. Training in Thailand meant participants may have acquired new GI flora that was resistant to Abx NOT taking doxy v mefloquine DOSE: 100 mg doxy qday.	253 soldiers on doxy or mefloquine for malaria prophylaxis for 3 months 12 weeks of doxy 21 Campylobacter isolates 200 non ETEC 34 ETECs	Medium
Buchek G, Mende K, Telu K, Kaiser S, Fraser J, Mitra I, Stam J, Lalani T, Tribble D, Yun HC. Travel-associated multidrug-resistant organism acquisition and risk factors among US military personnel. J Travel Med. 2021 Apr 14;28(3):taab028. doi: 10.1093/jtm/taab028.	Study examined 110 military travelers and 11 took doxy. MDRO collected and examined. No diff in ESBL Enterobacteraciae, no relationship with doxy in the 2-7 isolates.	Small sample size	Low

Military Studies of S aureus

Citation	Summary of Findings	Number of Participants	Quality of Evidence
Lesens O, Haus-Cheymol R, Dubrous P, Verret C, Spiegel A, Bonnet R, Bes M, Laurichesse H, Beytout J, Etienne J, Migliani R, Koeck JL; Working Group on Cutaneous Infections in the Army. Methicillin-susceptible, doxycycline-resistant Staphylococcus aureus, Côte d'Ivoire. Emerg Infect Dis. 2007 Mar;13(3):488-90. doi: 10.3201/eid1303.060729.	Two outbreaks of doxy-R MSSA skin disease in French soldiers with some on doxy prophy, 100 mg a day. Nasal carriage of PVL + MSSA in soldiers being deployed was associated with a history of doxy use but not doxy-R MSSA. All soldiers with PVL+ doxy R MSSA had been on doxy prophy (n=8) Some impact/ relationship with PVL+ MSSA but sample size is slow.	4 months of doxy	Medium
Mende K, Beckius ML, Zera WC, Yu X, Li P, Tribble DR, Murray CK; Infectious Disease Clinical Research Program Trauma Infectious Disease Outcomes Study Investigative Team. Lack of doxycycline antimalarial prophylaxis impact on Staphylococcus aureus tetracycline resistance. Diagn Microbiol Infect Dis. 2016 Oct;86(2):211-20. doi: 10.1016/j.diagmicrobio.2016.07.014. Epub 2016 Jul 15.	160 patients with a history of military trauma injuries were + for S aureus and isolates were cultured. 23% were tet-R. 25/38 were doxy-R and 68% were from people on antimalarial prophy with doxy. "There was no significant difference regarding methicillin and tetracycline resistance and PFT profiles between the groups of isolates from doxycycline-exposed and unexposed patients. Although the profile of tet genes was not significantly different between the groups, a statistically higher proportion of tet(M) genes were found in doxycycline-exposed patients (p=0.031). Although there was no statistically significant difference related to the overall profile of resistance to other antimicrobials between the two groups, there was a significantly greater proportion of isolates from patients exposed to doxycycline that were resistant to levofloxacin (25% versus 10%; p=0.016), and moxifloxacin (25% versus 10%; p=0.016). In a logistic regression multivariate model, sustaining an injury in Afghanistan was significantly associated with doxycycline exposure (odds ratio: 29.9; 95% Wald confidence interval: 6.3-141.2). Isolate type (e.g., infecting) and occurrence of tet(M) gene were not significantly associated with doxycycline antimalarial prophylaxis."	N= 92 No duration given	Medium

Acne patient studies

Citation	Summary of Findings	Number of Particpants (Studies)	Quality of evidence
Moon SH(1), Roh HS, Kim YH, Kim JE, Ko JY, Ro YS. J Dermatol. 2012 Oct;39(10):833-7. doi: 10.1111/j.1346-8138.2012.01626.x. Epub 2012 Jul 11. Antibiotic resistance of microbial strains isolated from Korean acne patients. Antibiotic resistance of microbial strains isolated from Korean acne patients.	Bacteria were isolated from 20-28% of the patients. Only the bacteria from patients in the treatment group were resistant to antibiotics, whereas none of the bacteria were resistant to antibiotics in the non-treatment group. The untreated group (doxy) was small, n=4 (Proprionibacterium acnes) and n=7 (Staphylococcus epidermis). Staphylococcus epidermis: Resistance not related to treatment history p= 0.23 Doxycycline DOSE taken by patients: no details on mg or length of treatment aside from "long-term" treatment being of interest	100 patients with acne yielded: 30 P acnes strains, 36 S epi colonies, 8 S aureus colonies.	Low
Tan HH(1), Goh CL, Yeo MG, Tan MLAntibiotic sensitivity of Propionibacterium acnes isolates from patients with acne vulgaris in a tertiary dermatological referral centre in Singapore. . Ann Acad Med Singap. 2001 Jan;30(1):22-5.	In patients who had never been on antibiotics, there were no resistant isolates of Proprionibacterium acnes. In patients who had been on short-term antibiotics (between 6 to 18 weeks), there were 2 resistant strains among the 34 isolates (6.25%); in patients who had been on antibiotics for longer periods, there were 11 resistant strains among the 51 isolates (21.6%). [0-6-22% across the 3 groups was significant] The differences in the rates of isolation of resistant strains between patients who had not been on antibiotics to those that had been on long-term antibiotics were statistically significant (P = 0.015). There was also a significant difference in isolation of resistant strains from those on short-term antibiotics compared to those who had been on long-term antibiotics (P = 0.036). Resistance to erythromycin was most commonly encountered. Most of the erythromycin-resistant strains also showed cross-resistance to clindamycin. The average MICs to antibiotics such as minocycline, erythromycin and clindamycin in those on long-term antibiotics were significantly higher when compared to patients who had not been on antibiotics. FOR DOXY: they looked at MICs which followed the same pattern of MIC increasing from Group A to B to C but was not significant. DOSE: no standard regimen reported	150 patients; results indicate 85 isolates; 6-18 weeks duration vs 24 to 52 weeks of Abx	Low
Legiawati L, Halim PA, Fitriani M, Hikmahrachim HG, Lim HW. Microbiomes in Acne Vulgaris and Their Susceptibility to Antibiotics in Indonesia: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2023 Jan 11;12(1):145. doi: 10.3390/antibiotics12010145.	Limited to Indonesia. C. acnes and S. epidermidis was most common from acne vulgaris lesions. 11/16 included studies examined AMR in isolates: 24-28% of isolates were TET-R. No causal relationship can be drawn. DOSE: not standardized across the studies	16 included studies	Low
Nakase K, Koizumi J, Fukumoto S, Hayashi N, Noguchi N, Nakaminami H. Increased Prevalence of Minocycline-Resistant Staphylococcus epidermidis with tet(M) by Tetracycline Use for Acne Treatment. Microb Drug Resist. 2022 Aug;28(8):861-866. doi: 10.1089/mdr.2021.0319. Epub 2022 Jun 20. PMID: 35723664	179 strains of S epi: Similarly, strains isolated from patients who had used tetracyclines and quinolones showed significantly higher resistance rates to minocycline (hospital, 23.5%; clinics, 39.4%) and levofloxacin (hospital, 81.3%; clinics, 51.4%), respectively, than those of strains isolated from patients who had not used antimicrobials ($p < 0.05$). In contrast, no difference in doxycycline resistance rate was observed between strains isolated from patients who had and had not been on treatment. *the predominance of TetM S epidermitis strains were minocycline resistant but doxycycline sensitive Dose: 100 mg of doxy qday but not validated that patients were taking that.	179 strains 84 patients on tetracyclines but not did not list exact number of people taking doxy Can't draw conclusions on doxy acne treatment as was lumped together	Low

DOXYCYCLINE et antibiorésistance – au total

- Utilisation de la DOXY dans différentes indications (acne, IST, diarrhées du voyageur, S, aureus) avec posologies différentes et durée différentes
- Impact de la résistance sur différentes espèces bactériennes démontrées
- faible niveau de preuve

Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré
- Efficace
  - Sur toutes les IST (Gono, CT, Syphilis)
  - Quelque soit le genre/patient
  - Sans modification des comportements si possible
- Peu cher voire coût efficace
- Pas de sélection de résistances
  - IST
  - Autres bactéries
- Peu ou pas d’action sur le microbiote?

frontiers | Frontiers in Microbiology

ORIGINAL RESEARCH
published: 31 May 2022
doi: 10.3389/fmicb.2022.901911

Microbiote

Profiling the Effects of Systemic Antibiotics for Acne, Including the Narrow-Spectrum Antibiotic Sarecycline, on the Human Gut Microbiota

OPEN ACCESS

*Ines B. Moura[1], Ayman Grada[2], William Spittal[1], Emma Clark[1], Duncan Ewin[1], James Altringham[1], Emilio Fumero[2], Mark H. Wilcox[1,3] and Anthony M. Buckley[1,4]**

- 3 modèles in vitro de colon humain
  - Instillation avec minocycline, doxycycline ou sarecycline
  - Mesure du microbiote et du changement
  - Perte de la diversité du microbiote intestinal
    - DOXY :
      - 7% decline in Lactobacillaceae and Bacteroidaceae
      - Augmentation >10% des enterobactéries
      - Retour au niveau antérieur après l'exposition

- Pas de données encore chez les Prepeurs

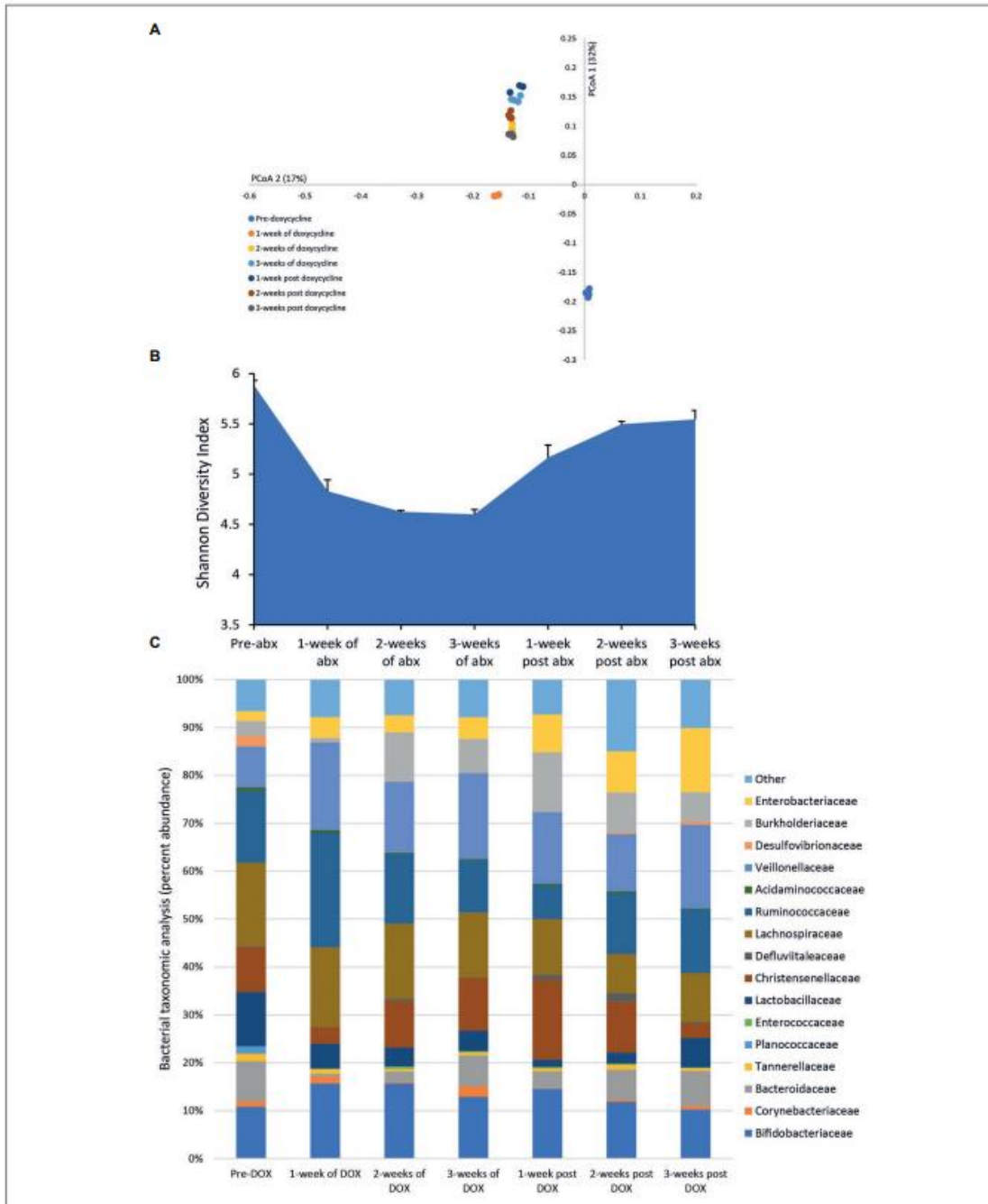


FIGURE 4 | Effect of doxycycline on the human microbiota. Changes to the microbiota profile during each week of doxycycline instillation and the recovery phase shown as a Principal Coordinate Analysis plot **(A)**. Results shown are four technical replicates. Changes in the microbial diversity after exposure to doxycycline and the recovery phase, as measured by the Shannon diversity index from four technical replicates **(B)**. Bacterial taxonomic abundance changes in response to doxycycline instillation **(C)**. Stacked bar graphs are mean percent abundance, from four technical replicates, analyzed from 16S rRNA sequencing.

Impact of Doxycycline as STI Postexposure Prophylaxis on the Gut Microbiome and Antimicrobial Resistance Gene Expression

1154

Victoria T. Chu[1,2], Abigail Glascock[2], Deborah Donnell[3], Cole Grabow[4], Clare E. Brown[4], Ryan Ward[1], Christina Love[1], Stephanie Cohen[1,5], Julia C. Dombrowski[4], Chase Cannon[4], Michael Woodworth[6], Colleen Kelley[6], Connie Celum[4], Anne F. Luetkemeyer[1], Charles Langelier[1,2]

[1]University of California, San Francisco, CA, US, [2]Chan Zuckerberg Biohub, San Francisco, CA, US, [3]Fred Hutchinson Cancer Center, Seattle, WA, US, [4]University of Washington, Seattle, WA, US, [5]San Francisco Department of Public Health, San Francisco, CA, US, [6]Emory School of Medicine, Atlanta, GA, US

- 50 SOC et 100 DoxyPEP
  - Écouvillon rectal M0 et M6
  - Analyse microbiote (diversité et abondance) et du resistome (expression gène de R)
- Résultats : DOXYPEP
  - Pas d'altération du microbiote
  - Augmentation de l'expression du gène de R
  - Dépend de la durée d'utilisation

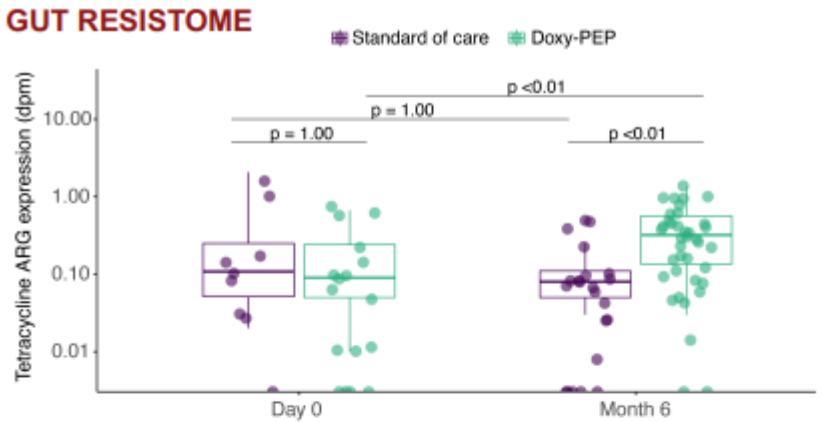


Figure 3. Tetracycline ARG expression by study arm and visit in the RNA-seq samples (n=86). Tetracycline ARG expression increased in the doxy-PEP Month 6 group compared with the SOC Month 6 and the doxy-PEP Day 0 groups.

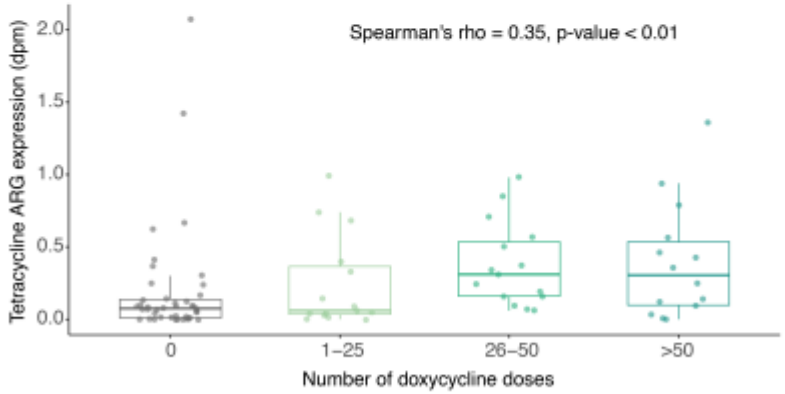


Figure 4. Tetracycline ARG expression increased with number of doxycycline doses since enrollment in the RNA-seq samples (n=86).

Un traitement contre les IST en PEP efficace/idéal ça serait quoi?

- Simple à prendre, bien toléré : oui mais attention
- Efficace
  - Sur les IST : oui
  - Quelque soit le genre/patient : bof
  - Sans modification des comportements si possible ?
- Peu cher voire coût efficace : plutôt oui
- Pas de sélection de résistantes
  - IST : à surveiller
  - Autres bactéries : à surveiller
- Peu ou pas d'action sur le microbiote : non?

Alors vraiment contre?

Que ations ?

- USA
- Aust
- UK
- EAC
- Fran

Title: Position Statement on Doxycycline as Prophylaxis for Sexually Transmitted Infections 2021 Update

Authors: John Saunders [1,2], Manik Kohli [2,3], Nicholas Medland [4,5], Helen Fifer [1]

Affiliations:

1. Blood Safety, Hepatitis, STIs and HIV Division, UK Health Security Agency, London, UK
2. Institute for Global Health, University College London, London, UK
3. Central and North West London NHS Foundation Trust, London, UK
4. The Kirby Institute, University of NSW, Sydney, Australia
5. Monash University Central Clinical School, Melbourne Sexual Health Centre, Australia

Key points:

- Doxycycline taken as Pre- or Post- endorsed by BASHH or the UK He
- The use of other antibiotics as pr sexually transmitted infections (S
- Recognising that many patients a the UKHSA recommend that clini benefit. Clinical monitoring for ad are using doxycycline as prophyla
- Several clinical studies are curren doxycycline on antimicrobial resis

1. Background

In 2017, the British Association for Sexual published a position statement on the us 'extreme caution in the use of doxycycline restricted to the research setting.'(1)

Since that time, although little new evide many individuals at higher risk of acquirin accessed through several routes.

To support a person-centred approach to

ycline

est for

rol and Health

riod.

e the n

Recommendations for community and clinicians

1 Doxy-PEP should be considered primarily for the prevention of syphilis in GBMSM who are at risk of this STI, although for some individuals the reduction in chlamydia, and the lesser reduction of gonorrhoea might be important. Some stakeholders held the view that Doxy-PEP should be considered *only* for the prevention of syphilis in GBMSM, for the reasons listed above.

KEY MESSAGES FROM THE PRESENTATION

Doxy-PEP is promising, but there is a need for additional data on potential emergence and spread of antimicrobial resistance to tetracyclines and other classes among bacteria causing STIs, but also other pathogens and commensals. More data are also needed on other potential adverse events linked to the effect on the microbiome. Such data would be useful before the use of doxy-PEP is recommended outside of study settings.

indicated that minocycline prophylaxis would probably have limited effectiveness as a public health measure because of selection of resistant gonococci [10]. Findings from a systematic review suggest that oral tetracycline use for 2–18 weeks may result in increased resistance in subgingival, gastrointestinal, and upper respiratory tract flora [11]. Another concern was the development of cross-resistance to other antimicrobial classes, through selection of genetic elements carrying resistance to multiple antimicrobial classes or through induction of efflux pumps [9]. In addition, there could be a negative impact on gastrointestinal tract microbiome diversity, potentially linked to an increased risk of inflammatory bowel disease [12].

Potential benefits and harms at individual and public health level of doxycycline prophylaxis

Points raised by meeting participants during the discussion

short-term use, however, further research is needed on the potential metabolic impact of longer-term use [13]. Results for efficacy in preventing gonorrhoea were mixed in studies conducted in Europe, possibly related to differences in resistance of *N. gonorrhoeae* between Europe and the US.

Since the meeting reported here was held, clinical guidelines were issued for consultation by the US Centers for Disease Control and Prevention advising healthcare practitioners to consider doxy-PEP in individuals at high risk for STIs (e.g. people using PrEP for HIV) as one element of a comprehensive sexual health package, accompanied by regular screening, treatment of infections, vaccinations, risk reduction counselling, awareness on benefits and known and unknown harms [14]. The European AIDS Clinical Society indicates in its 2023 guidelines update that doxy-PEP can be proposed to persons with repeated STIs living with HIV or taking

Oui si

- Absence de guidelines et d'accompagnement des médecins et des patients
  - DOXY-PEP utile pour les patients avec multiples IST bactériennes (Nb?)
- Absence de surveillance de la résistance
  - Reste des inconnus si implémenté dans la population en vraie vie
    - Préjudices microbiotes
    - Préjudices bactériologiques avec de la résistance à l'échelon individuel et collectif