

Syphilis, Doxy-PEP, and mpox

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01. **SYPHILIS**

01,1 *EPIDEMIOLOGY AND
DIAGNOSIS*

01,2 *CONGENITAL SYPHILIS
AND NEUROSYPHILIS*

01,3 *ALTERNATIVE ANTIBIOTICS*

02. **DOXY-PEP**

02,1 RANDOMIZED CLINICAL
TRIALS

02,2 REAL LIFE EXPERIENCE

02,3 ANTIMICROBIAL RESISTANCE
AND IMPACT ON MICROBIOME

03. **MPOX**

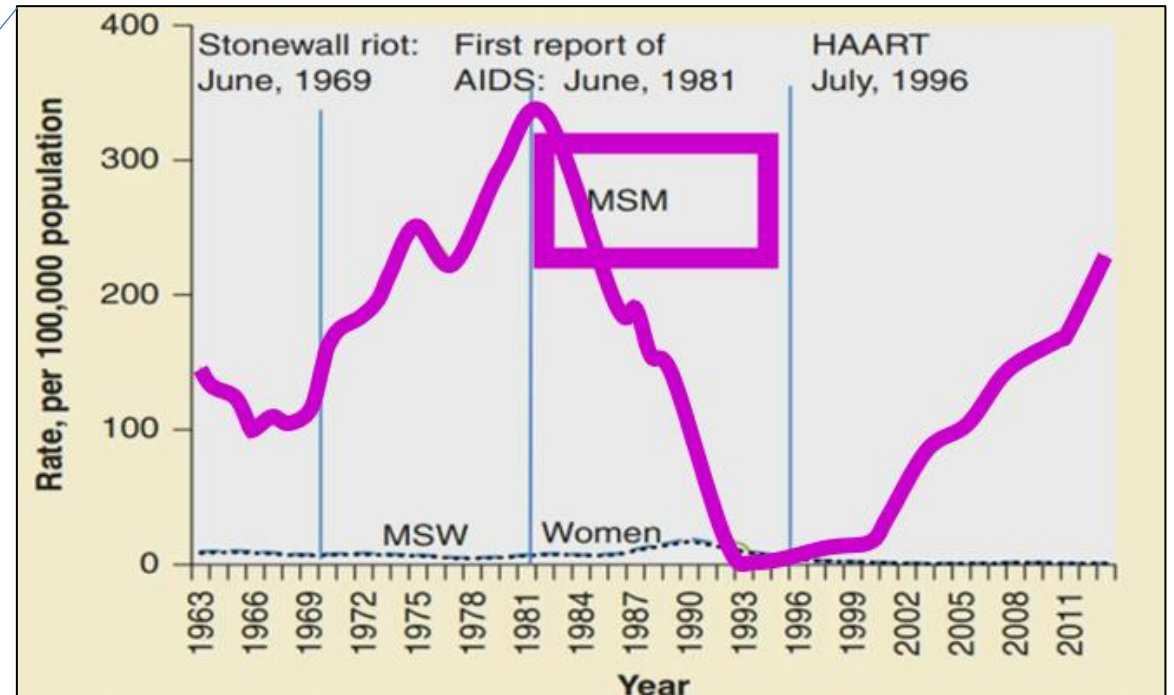
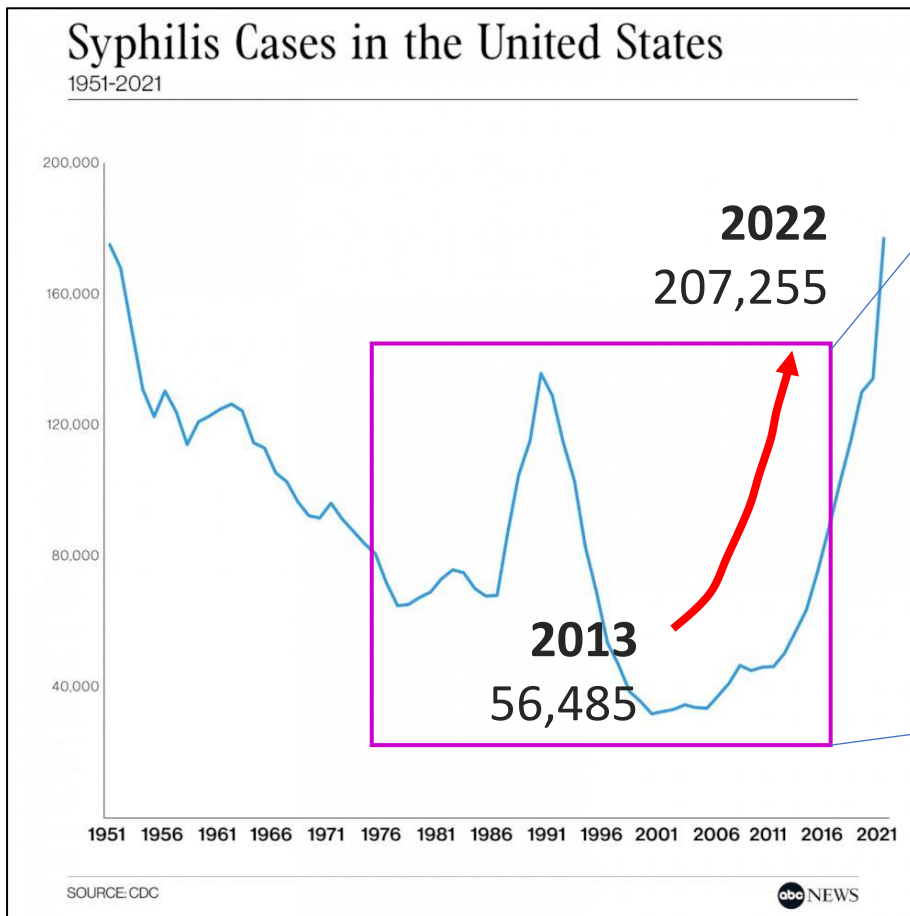
03,1 TRANSMISSION

03,2 THERAPY

03,3 IMMUNITY

 Syphilis is reaching **highest levels** in the US since the 1950s

MSM are most affected



Seroprevalence of syphilis in the general pop. (for example, blood donors) is <0.1%

	Active infection	Sample size, location, year
#1156: Emergency department	1%	1,951 users, <u>Baltimore</u> 2022
#1161:		
• HIV PrEP	5%	20,033 clients, <u>Canada</u> 2018-22
• HIV PrEP & STI/HIV <12mo	11-15%	
• PLWH	4%	
#1158: MSM	7%	10,000 people, <u>India</u> , 2012-2016

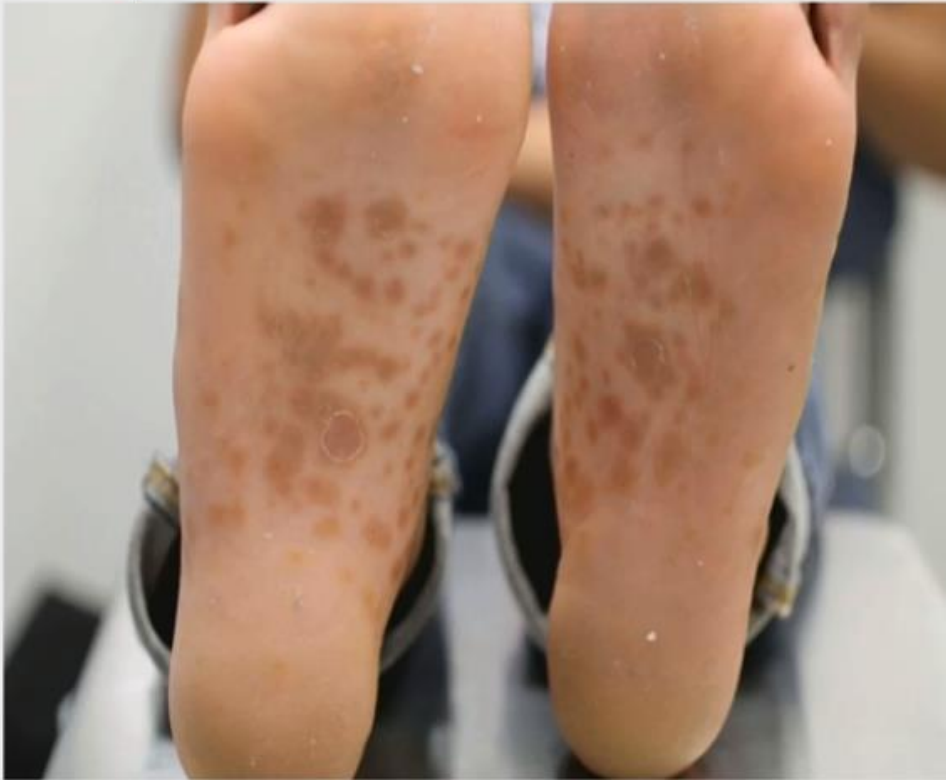
#1159: Opt-out screening in pregnancy (Chicago)

- Before the intervention = 296 tested / 4,764 encounters **(6.2%) (1% positive)**
- After the intervention, 8-fold increase to 2,307 / 4,401 **(52.4%) (1% positive)**

#24: Why can't we do better at diagnosing syphilis?

Because syphilis can look like almost anything

This is syphilis...



And so is this.



This is syphilis...



SFDPH

And so is this.

This is also syphilis...



#24: Why can't we do better at diagnosing syphilis?

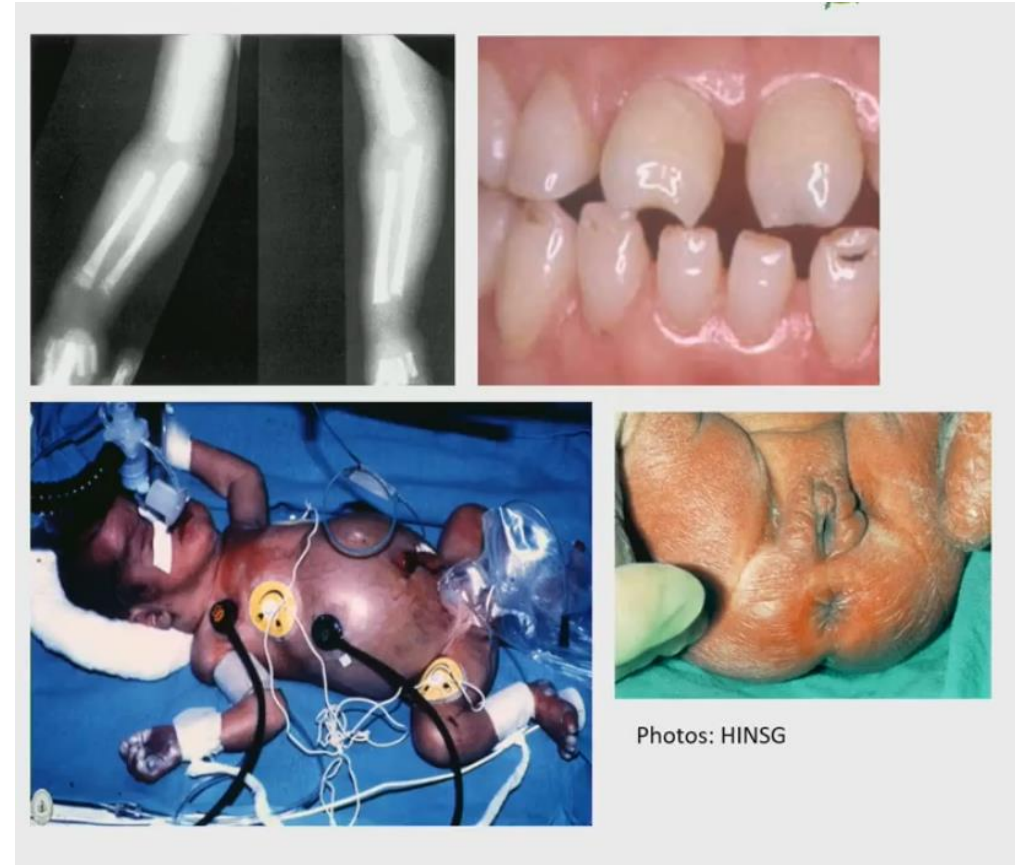
Take home message

TEST, TEST, TEST for syphilis all the time:

rash, anogenital ulcer/lesions, red eye, visual/hearing changes, hair loss, anogenital warts, lymphadenopathy, flu-like symptoms

#25: Congenital syphilis

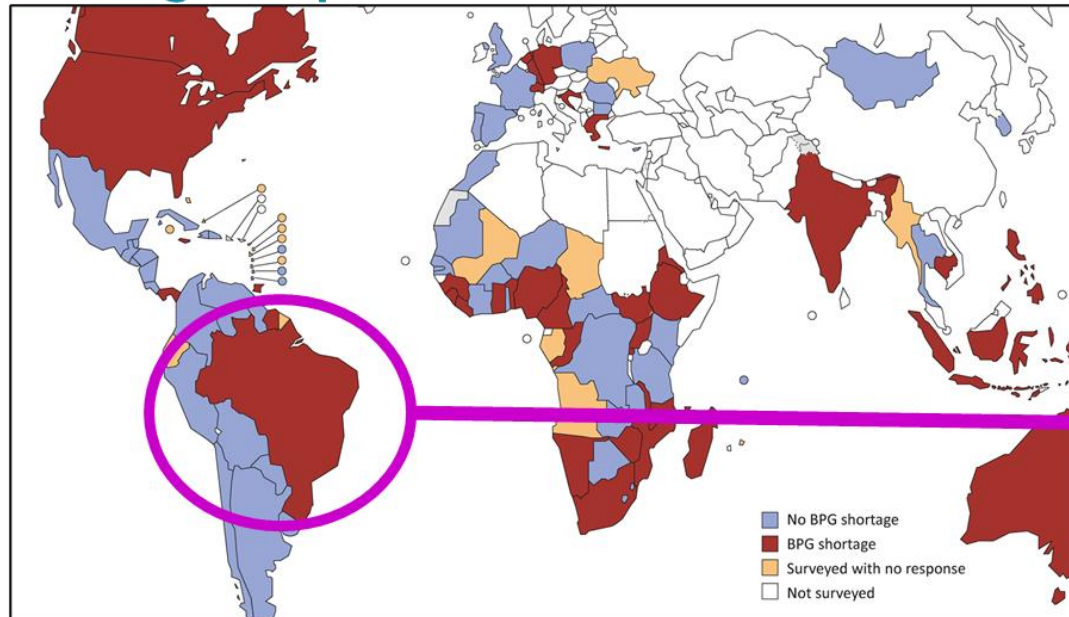
- Congenital syphilis leads to stillbirth, infant death and morbidity.
- Globally (WHO, 2020): **200,000 stillbirths**
- US (2022): **300 stillbirths among 3,800 cases of Congenital Syphilis**, compared to 362 in 2013



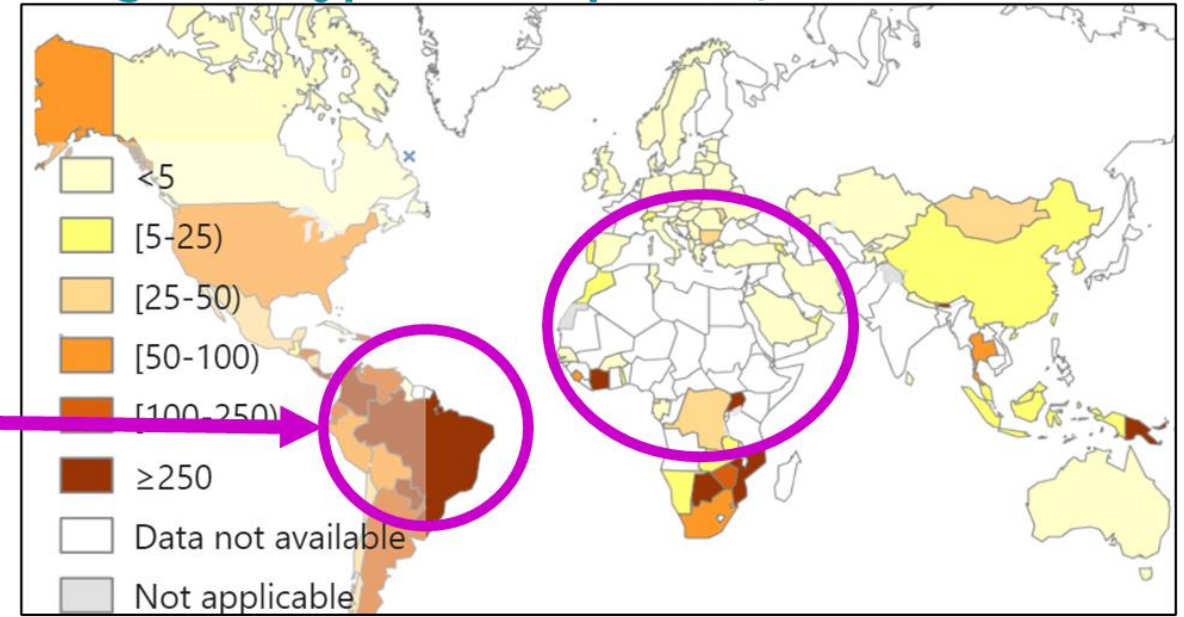
#1159: Congenital Syphilis (experience from South Africa)

343 cases of CS		
Not tested during ANC	10%	✗
Tested but not treated	30%	✗
Treated but too late	25%	✗
Treated ≥ 28 days before delivery	35%	✓

Shortages of penicillin



Congenital syphilis rate per 100,000 live births



25: In vitro studies on *T. pallidum* susceptibility

	Range tested (mg/L)	Primary MIC (mg/L) [†]	Secondary MIC (mg/L) [†]	MBC (mg/L)	Drug plasma C _{min} (mg/L)
Natural penicillins					
Benzathine penicillin G	0.0001–0.06‡	Not tested in this study	0.003‡	0.003‡	0.012§
Aminopenicillins					
Amoxicillin	0.0025–0.16	0.02	0.01	0.01	>0.2¶
Cephalosporins					
Ceftriaxone	0.00063–1	0.0025	0.0025	0.0025	29.7
Cephalexin	0.0625–8	0.25	0.25	0.25	0.30¶
Cefetamet	0.0039–0.25	0.0313	0.0625	0.0625	>0.3
Cefuroxime	0.0039–0.25	0.0156	0.0156	0.0156	0.20¶
Cefixime	0.0039–0.25	0.0313	0.0313	0.0313	0.08
Oxazolidinones					
Linezolid	0.0156–2	0.5	0.125	0.125	6.2
Tedizolid	0.0078–0.5	0.0625	0.313	0.0156–0.0313	0.41
Lipoglycopeptides					
Dalbavancin	0.0039–0.25	0.125	0.125	0.125	19.5††
Aminoglycosides					
Spectinomycin	0.02–2	0.1	0.1	0.25	15¶
Tetracyclines					
Doxycycline	0.004–2.5	0.1	Not determined in this study	0.1	>1

THE LANCET
Microbe

ARTICLES | VOLUME 4, ISSUE 12, E994–E1004, DECEMBER 2023

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Antimicrobial susceptibility of *Treponema pallidum* subspecies *pallidum*: an in-vitro study



Carbapenems					
✗ Ertapenem	0.00375–2	>2	>2	>2	0.8
Fluoroquinolones					
✗ Moxifloxacin	0.06–2‡	Not determined in this study	2‡	>2‡	0.4–0.6
Balofloxacin	0.25–16	2	2	>2	0.23
Antimycobacterials					
Isoniazid	0.0078–0.5	>0.5	>0.5	>0.5	Undetectable
✗ Pyrazinamide	1.0–64	>64	>64	>64	7
✗ Clofazimine	0.06–2‡	Not determined in this study	1‡	1‡	0.02§§
Antiparasitics					
✗ Ivermectin	0.125–40	MIC threshold unattained‡‡	MIC threshold unattained‡‡	MIC threshold unattained‡‡	0.01§§
Nitroimidazoles					
✗ Metronidazole	0.0313–2	>2	>2	>2	11.8

25: Pilot RCTs on cefixime and linezolid

JOURNAL ARTICLE

Clinical Efficacy of Cefixime for the Treatment of Early Syphilis

Chrysovalantis Stafylis, Kori Keith, Shivani Mehta, David Tellalian, Pamela Burian, Carl Millner, Jeffrey D Klausner 

Clinical Infectious Diseases, Volume 73, Issue 5, 1 September 2021, Pages 907–910,

THE LANCET
Infectious Diseases

Oral linezolid compared with benzathine penicillin G for treatment of early syphilis in adults (Trep-AB Study) in Spain: a prospective, open-label, non-inferiority, randomised controlled trial

Intervention	Sample size	Clinical and serological cure	
		Experimental group	Control group
Cefixime (Stafylis)	N=30	87%	93%
Linezolid 600mg/24h for 5 days	N=59	70%	100%
Linezolid 600mg/12h for 10 days	N=31 (interim)	100%	100%



- Highlighted **linezolid** as an alternative in neurosyphilis and congenital syphilis.
Urgent need to complete the adult syphilis trial in Barcelona (under ERC funding).

→  Please refer patients to the **Barcelona Checkpoint for recruitment**

93 318 2056 or amendoza@lluaita.org

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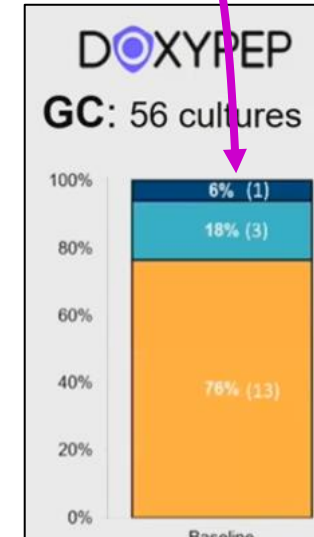
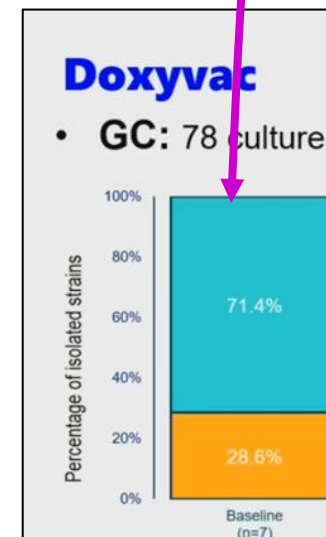
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#5: Introduction to DoxyPEP

		Overall	CT	NG	TP
IPEGAY (France n=232) [Molina; 2023 Lancet Inf Dis]	Difference (HR)	47%	70%	17% !!	73%
	Incident cases in DoxyPEP vs SOC	22% vs 42%	6% vs 19%	16% vs 23%	3% vs 11%
Doxy-PEP (Seattle n=501) [Luetkemeyer; 2023 NEJM]	Difference (HR)	65%	74-88%	55-57%	77-87%
	Incident cases in DoxyPEP vs SOC	12% vs 32%	4% vs 14%	9% vs 20%	0.4% vs 3%



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#125: DoxyPEP Seattle : Sustained reduction in STIs during

- Open label extension (OLE) after RCT discontinuation; almost all SOC patients accepted Doxy-PEP.

	RCT DoxyPEP	RCT SOC	OLE DoxyPEP	OLE SOC → DoxyPEP
≥1STI endpoint	12%	32%	13%	18%

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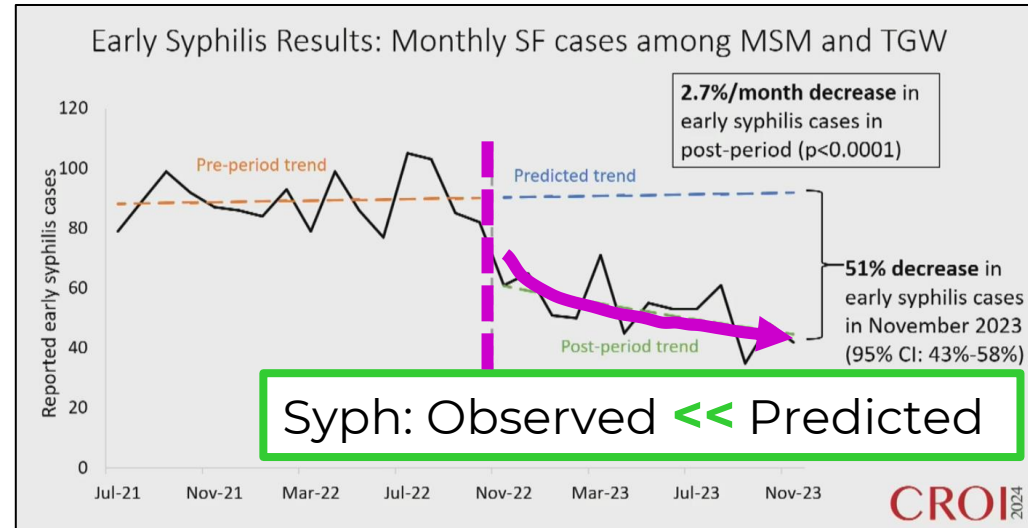
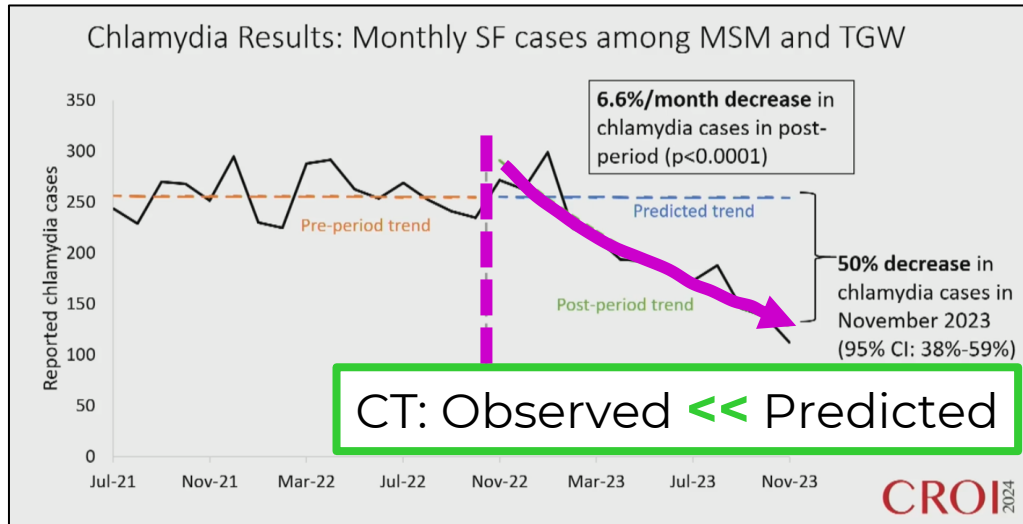
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Doxy-PEP (Kenya n=449) [Stewart; 2023; NEJM]	Difference (HR)	12% !!	27%	-64%	
	Incident cases in DoxyPEP vs SOC	25% vs 29%	15% vs 18%		

#1148: Cisgender women in Kenya

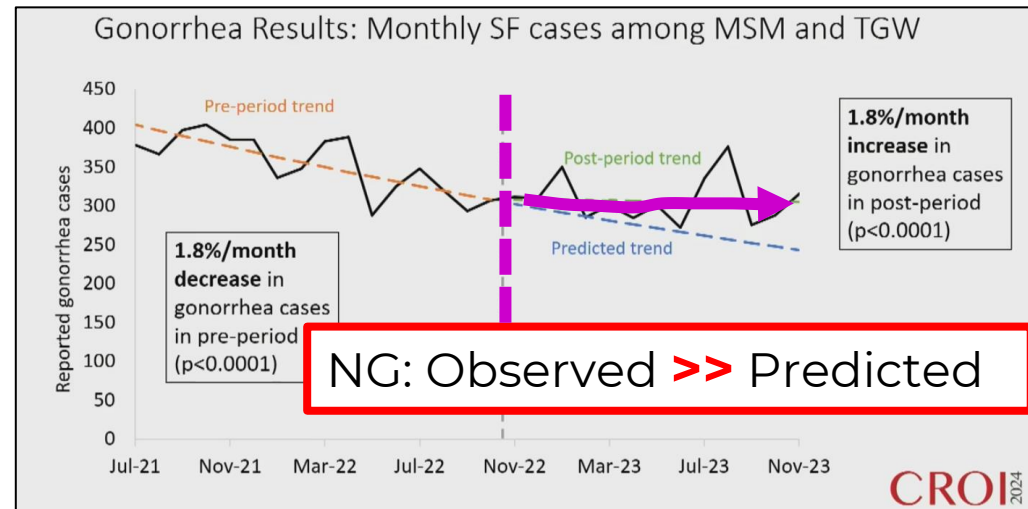
- Subset of 50x4 visits participants assigned to Doxy-PEP – 1 cm hair assessed for doxy >0.020ng/ml)
- **Doxycycline was detected in only 29.0%** (58/200) of hair samples.
- Higher compliance associated with older age and no primary partner.



#127: NEW In San Francisco, a policy 2022 recommending doxy-PEP to MSM and Trans Women was associated with declines in Chlamydia and Syphilis.

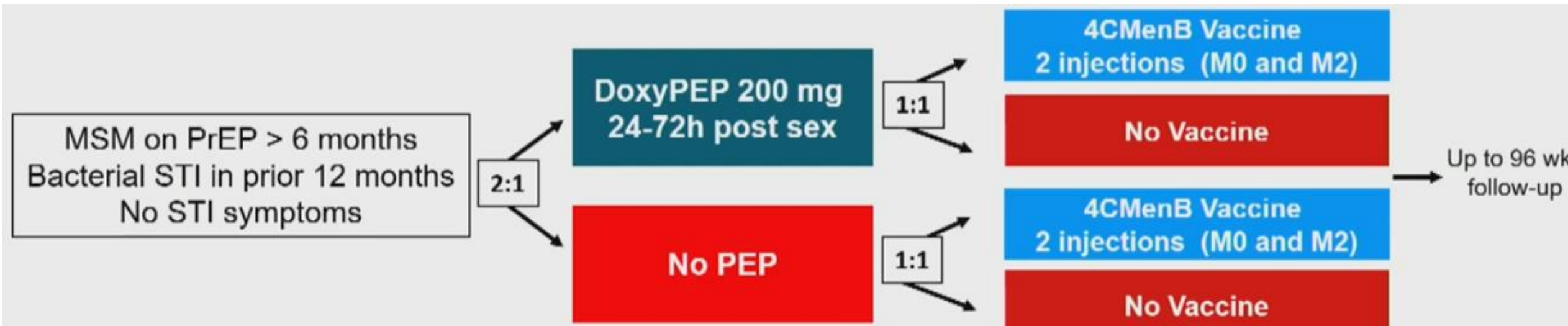


But no significant change observed for gonorrhoea



#124: **NEW** Final Results of ANRS 174 DOXYVAC (France)

- Multicenter. 2x2 factorial RCT
- Two primary endpoints:
 - Impact of Doxy-PEP on time to a first episode of syph, CT, NG
 - Impact of 4cNemB vaccine on time to a first episode of NG

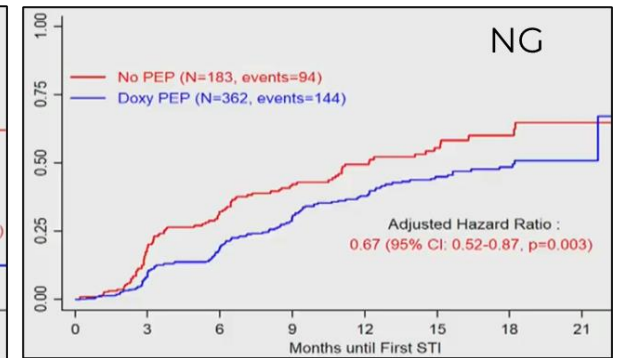
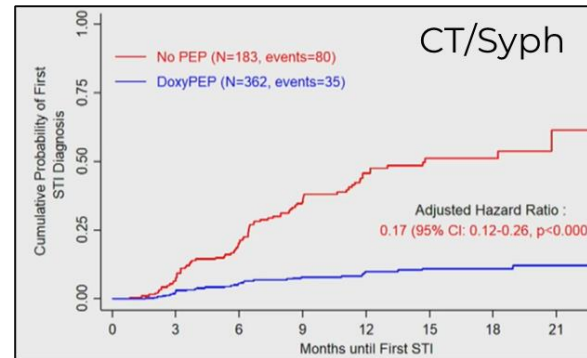
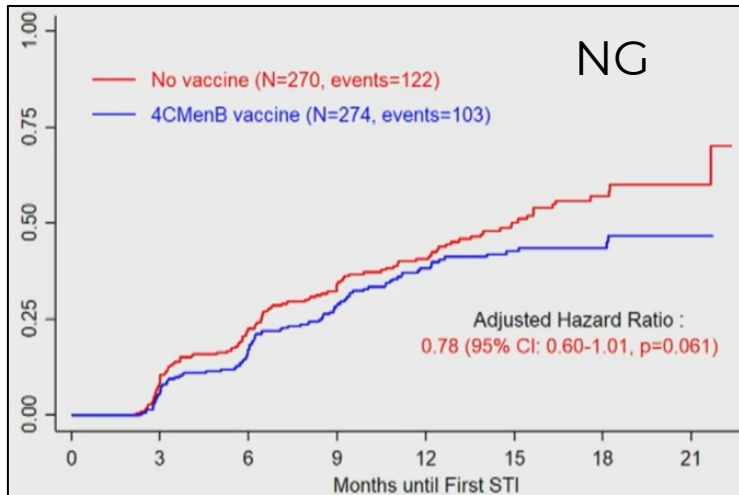




#124: NEW Final Results of ANRS 174 DOXYVAC (France): The vaccine provides almost no benefit. Better vaccines are needed.

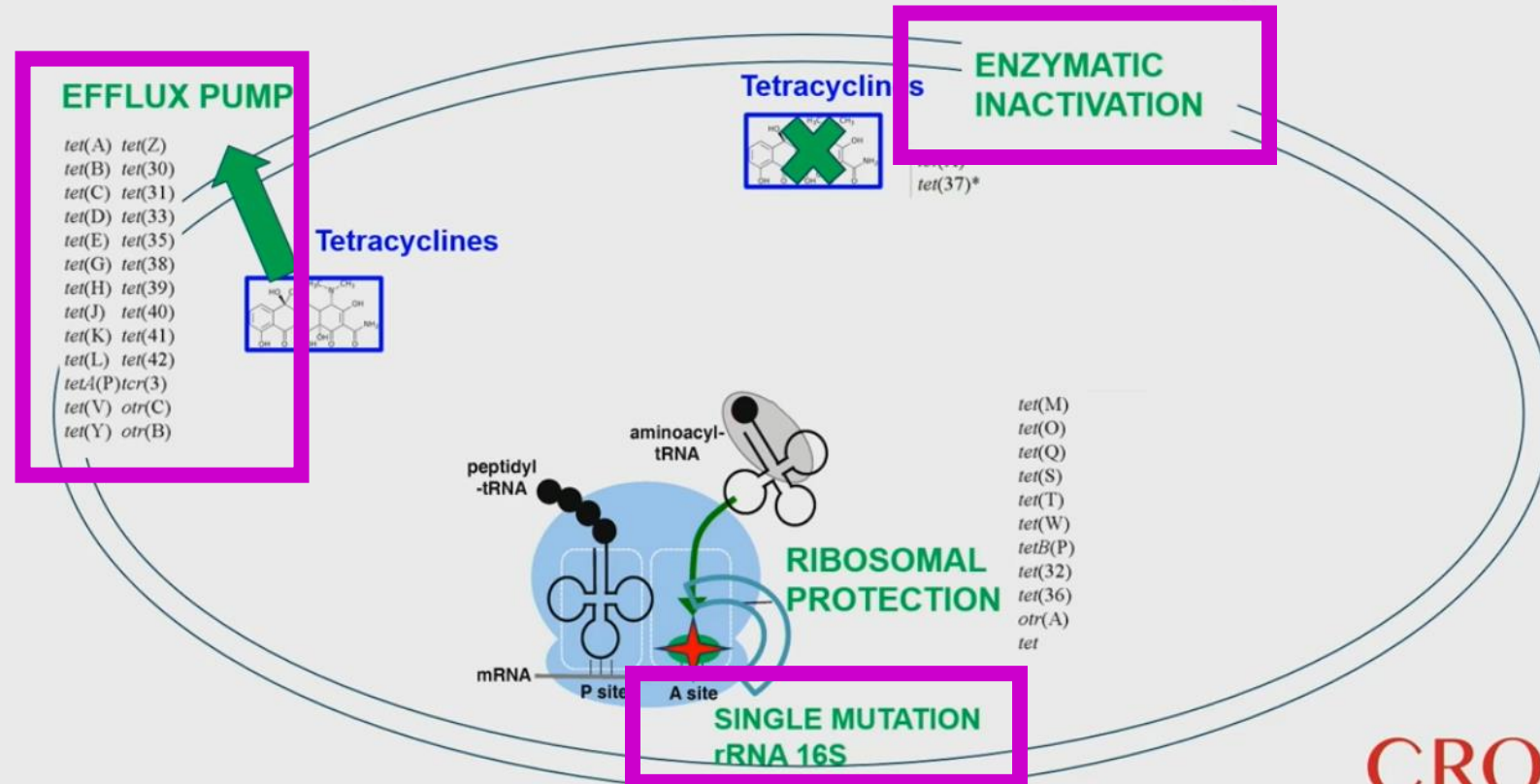
4CMenB Vaccine	
	NG
No Vaccine	122/270 (45%)
4CMenB	103/274 (37%)
Hazard ratio	0.78 (0.60 - 1.01) ❌

Time to First infection with Doxy-PEP		
	CT/Syph	NG
No PEP	80/183 (44%)	94/183 (51%)
Doxy PEP	35/362 (10%)	144/362 (40%)
Hazard ratio	0.17 (0.12-0.26) ✅	0.67 (0.52-0.87) ❌



#36: DoxyPEP: Should We Worry About Antimicrobial Resistance?

How does bacterium resist to tetracycline?

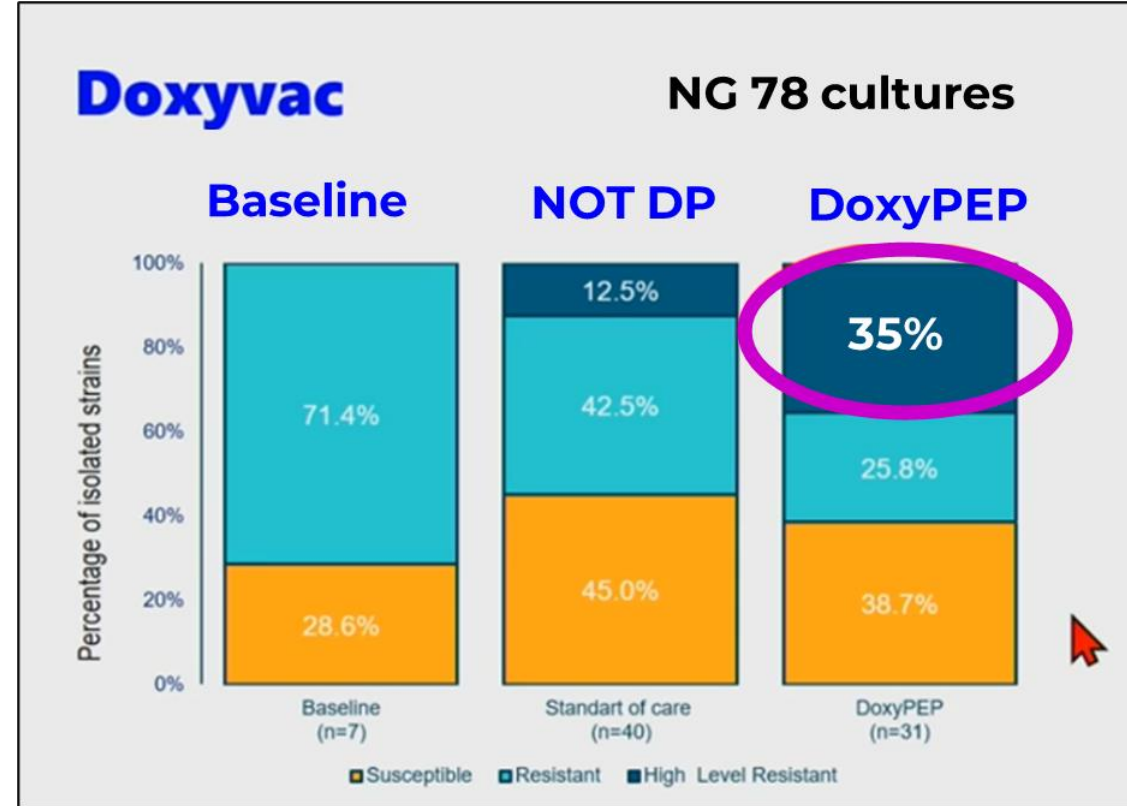
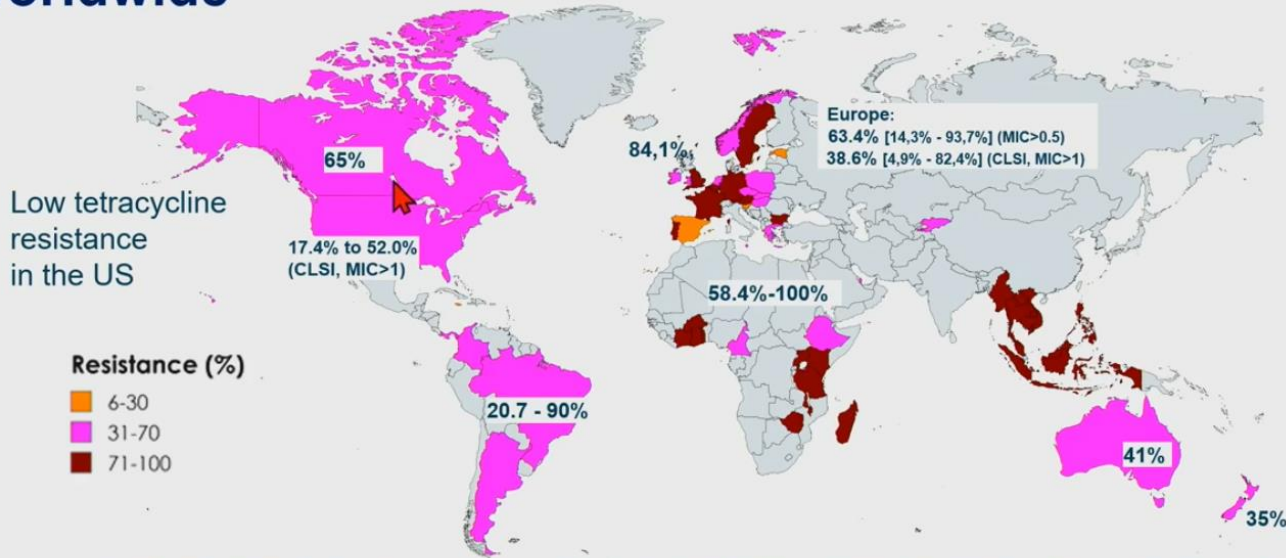


Chopra I, Roberts M. Microbiol Mol Biol Rev. 2001; Van Hoek A, Front Microbiol, 2011; Roberts MC. FEMS Microbiol Lett. 2005; Grossman TH. Cold Spring Harb Perspect Med. 2016.

(1/5) DoxyPEP and resistance in Gonorrhoea

- Widespread resistance to Doxy among NG, and
- Doxy-PEP can select for high-level resistance.

A large reservoir of tetracycline-resistant GC isolates worldwide



Unemo, Lancet Reg Health Eur, 2024. <https://www-cdc-gov.proxy.insermbiblio.inist.fr/std/GISP/>; Mortimer, Clin Infect Dis, 2023; Congo-Ouedraogo M, J Eur Acad Dermatol, 22; Naiki Attram, PLoS One, 2019; Alain Yéo A, 2019 Sex Transm Dis; Crucitti T, Int J STD AIDS 2020; Nireshni Mitchev, AAC 2021; Machado H de M, JAC Antimicrob Resi 2022; Thakur, Sexual Trans Dis, 2017; Golparian D, J Antimicrob Chemother, 2022; Cornelisse VJ, Sex Health, 2023; Sawatzky, RMTc, 2023; Rivillas-García JC, Rev Pana Salud Publica, 2020; Kahsay AG, Infection and Drug Resistance 2023; Cameron-McDermott SM, J Antimicrob Chemother 2022; Matoga M, Sexually Transmitted Diseases, 22; Núñez-Samudio V, Microorganisms, 2023; Aboud S, Trop. Med. Infect. Dis. 2022; Hamill MM, BMC Infectious Diseases 2022.

(2/5) DoxyPEP and resistance in Syphilis

- Phenotypic susceptibility testing (only performed in 3 labs worldwide)
- After multiple exposures to sub-therapeutic doxycycline, bacterial growth is not inhibited in the presence of the antibiotic.

(3/5) DoxyPEP and resistance in C. trachomatis

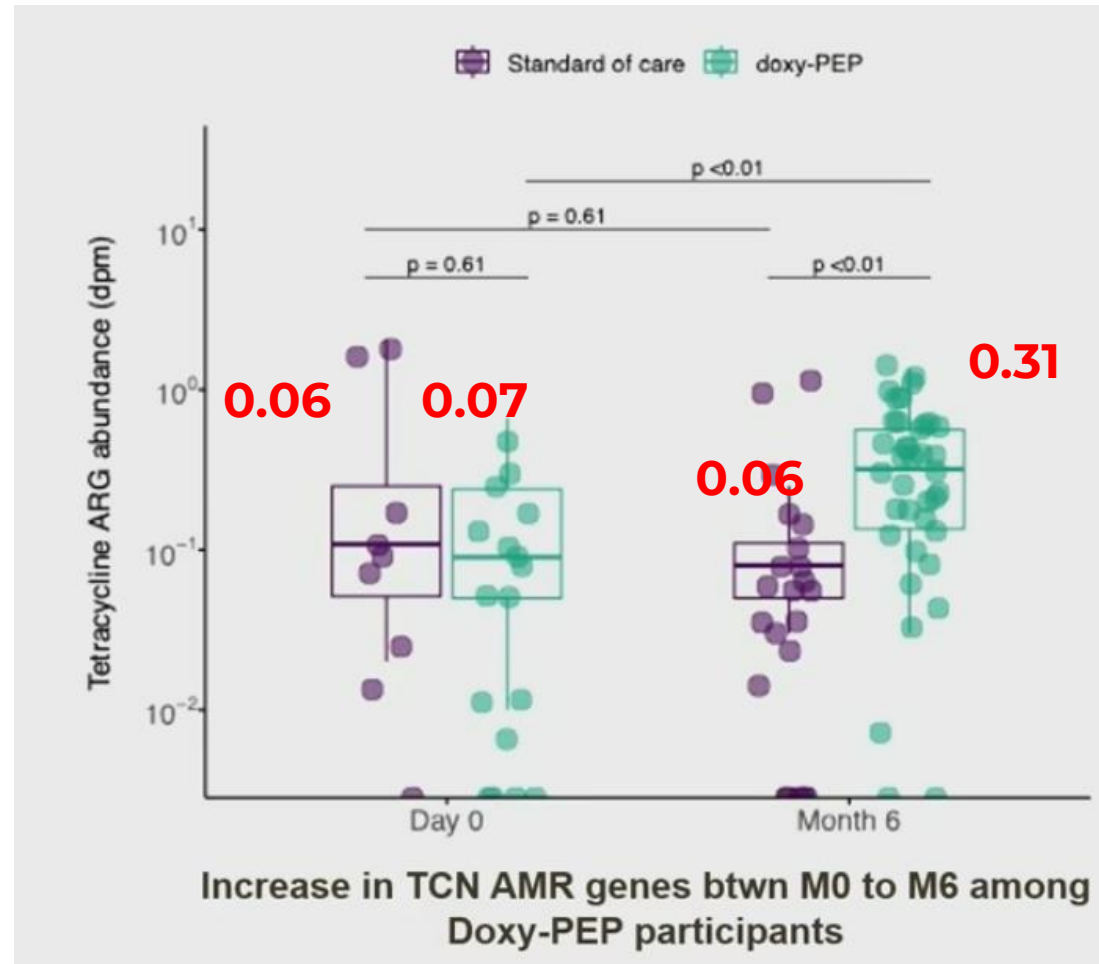
- *Chlamydia suis* strains in pigs
- Transfer to TCN resistance genes between Chlamydia species
- 3 human *C. trachomatis* isolates high level resistance

(4/5) DoxyPEP and resistance in M. genitalium

- Phenotypic susceptibility testing not commonly done. Genotypic for macrolides and quinolones.
- TCN mutations would impact sequential tx and minocycline efficacy.
- Substudy of IPERGAY: 12.5 % **(2/16)** of MG 16S rRNA associated to TCN resistance (increase MICs from 0,06 to 1,0 ug/ml).
- Other potential mutations tet(M) efflux pump.

(5/5) DoxyPEP and resistance in gut bacterial microbiome (#1154)

- 501 MSM/TW
- 4,4-fold higher abundance of the region of interest (depth per million, dpm)
- Clinical impact should be further studied



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#426 Unlikelihood of behavioral change in contributing to mpox decline

Classical STIs had a constant presence throughout the year (Milan 2022)



#1079 Herd immunity level = 7.1% (6/84) Seroprevalence of IgG in unvaccinated PLWH (Rome, 2022)

#419 Mpox progression with**Early Tecovirimat (<7 days) 3/56 (5.4%) vs Late/No TPOX 13/56 (23.2%)**

[matched cohort study, OR 11.0 (95% CI 1.4, 85.1)]

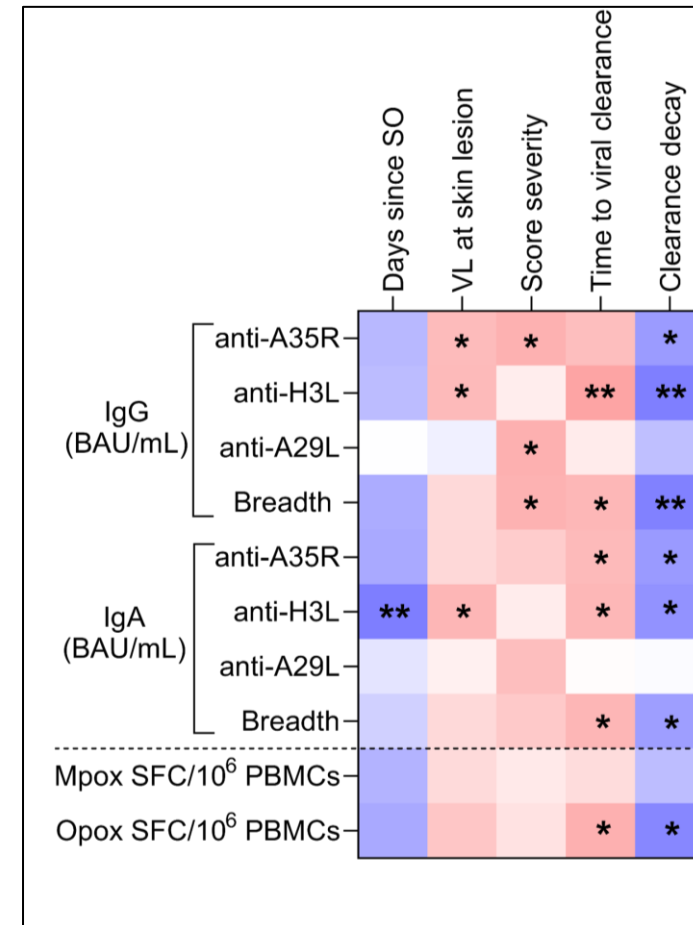
(Nguyen, Suñer et al) Early Tecovirimat modelling

	Time to peak VL	Peak VL	Time to undetectable VL
Without treatment	D9	8.0 log	D29
Early treatment	D7	7.2 log	D23
Post-exposure	D7	6.4 log	D21

#416 Natural infection: Titers of antibodies at baseline associated with (Moraes-Cardoso et al)

- **Faster mpox Viral Clearance and**
- **Faster lesion resolution**

- In-vitro neutralization was not fully observed until 91 days after infection



#417 MVA-BN vaccination

- **Protection 2 doses (66-90%) 1 dose (35-86%).** Variability related to control populations, but consistency of findings is reassuring.
- Low MPXV specific IgG and nAb after MVA-BN.
- Duration of the protection is unclear.

#427, 430 Mpox Vaccination Uptake (Los Angeles)

- PrEP users (72%),
- PLWH (33%),
- **Inequities with** less coverage in younger, black, and underserved neighbourhoods

TAKE HOME MESSAGES

- There is an urgent need for **alternative antibiotics to treat syphilis**, with linezolid highlighted.
- The final results of the DOXYVAC showed that the **meningitis B vaccine did not have significant protection against gonorrhea**.
- **In San Francisco, doxy-PEP was strongly associated with a decline in the incidence of chlamydia and syphilis**. Additional supportive data from the open-label extension of the DOXYPEP study. Guidelines are expected soon; they're already in draft form.
- **Concerns about Doxy-PEP and AMR**: Will it fail to prevent gonorrhea? Syphilis risk? Chlamydia suis? Empirical management of MG?
- **MPXV infection** halted by humoral immunity. But the correlation between MVA-BN vaccine effectiveness and immunogenicity remains unclear.