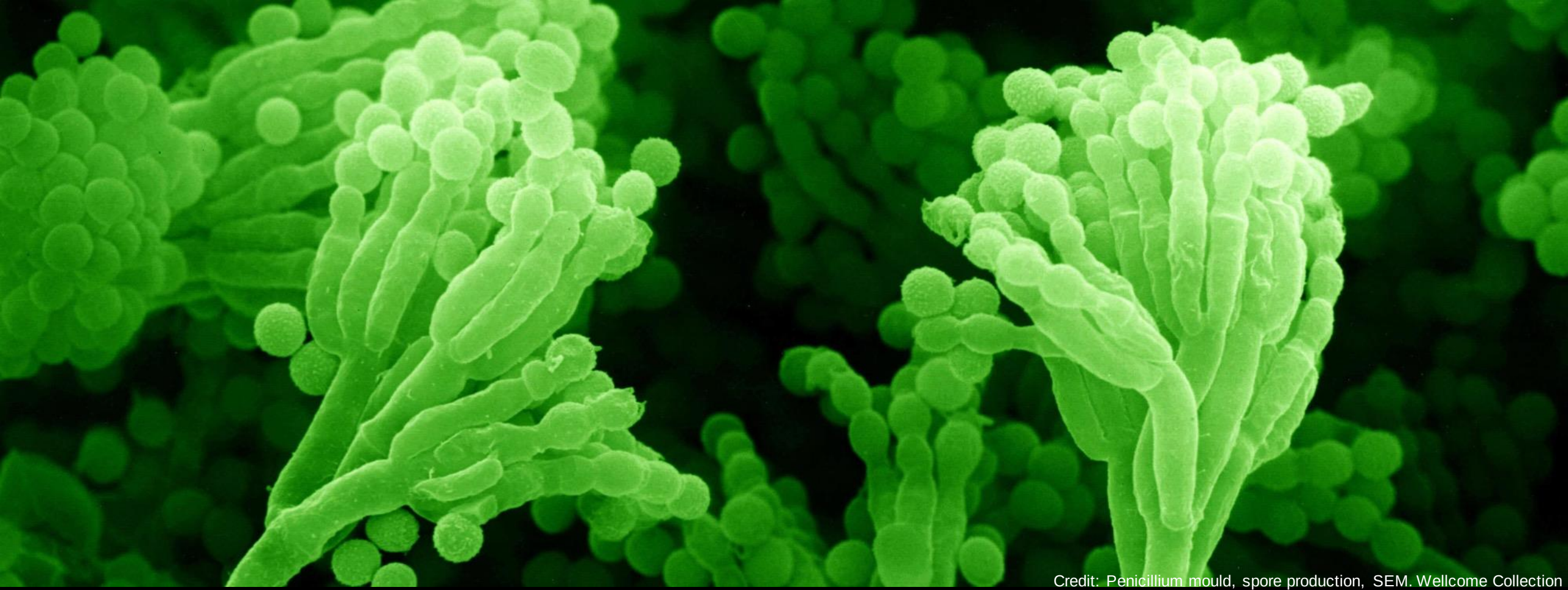
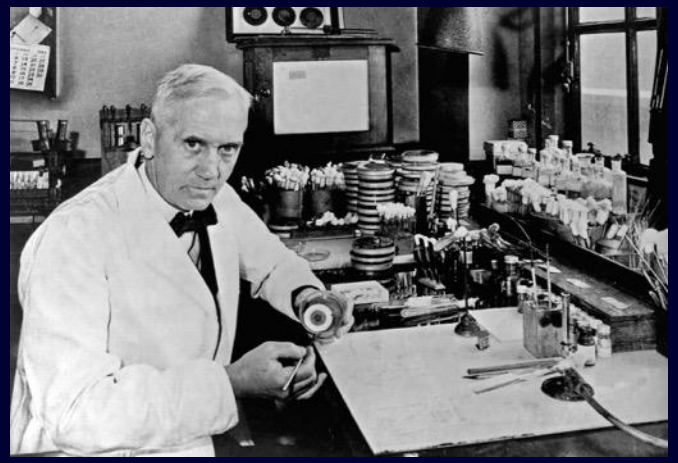


Credit: Penicillium mould, spore production, SEM. Wellcome Collection

The End of Antibiotics: Evaluating antimicrobial resistance in *Neisseria gonorrhoeae* among HIV PrEP users in Vietnam

Paul Adamson, MD, MPH (he/him/his)
Assistant Clinical Professor
Division of Infectious Diseases, UCLA

Penicillin



1928: London, UK
Discovered by Sir Alexander Flemming

1942: New Haven, CT
First US patient receives penicillin for septicemia

1942-45: World War 2
Penicillin mass produced in US during war effort

Penicillin for gonorrhea

CDC 1944: How it started

CDC 2022: How it's going

Overview

- Antimicrobial resistance (AMR) - how it develops and why it's important
- Epidemiology of AMR in *N. gonorrhoeae*
- Gonorrhea in Vietnam: AMR and key populations
- Preliminary findings from ongoing research
- Questions and Discussion

Case

- February 2018, a heterosexual male in the U.K. presented to a sexual health clinic with 4-day history of urethral discharge and dysuria

- Three days prior, he had sexual intercourse with a female in the UK. He recently returned from Thailand, where he reported having sexual intercourse with a female.

Eyre, DW, et al., *Eurosurveillance*, 2018

Exam, Lab Results, and Treatment

- Exam notable for purulent urethral discharge
- 3+ inflammatory cells and Gram-negative diplococci on microscopy
- Treated with ceftriaxone 1g IM once and doxycycline 100mg BID for 7 days

- NAAT positive for NG in urine
- Culture from urethral swab grew *N. gonorrhoeae* resistant to azithromycin, ceftriaxone, cefixime, tetracycline, and ciprofloxacin; susceptible to spectinomycin

Eyre, DW, et al., *Eurosurveillance*, 2018

Follow-up

- Day 13: recalled to clinic, symptoms resolved, received spectinomycin 2g IM, urine NG NAAT (-)
- Day 33: Pharyngeal swab culture positive for NG, same antibiotic susceptibility profile
  - Denied sexual contact after treatment
  - Received ertapenem 1g IV for 3 days
- Day 54: NAAT and culture of urethral and pharyngeal swabs were negative
  - Unable to contact Thai partner

Eyre, DW, et al., *Eurosurveillance*, 2018

The Clap Heard ‘Round the World

Sections

The Washington Post
Democracy Dies in Darkness

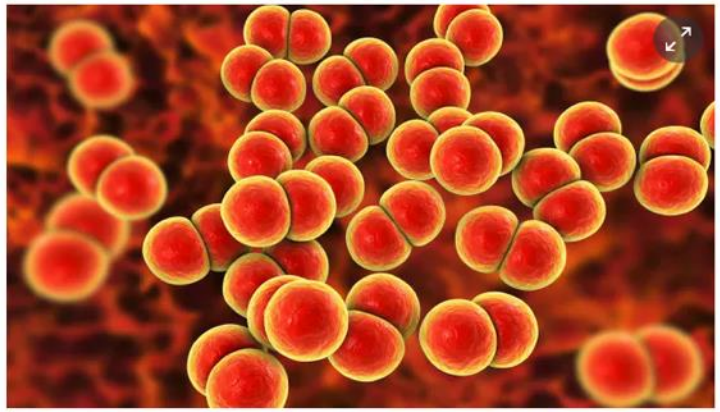
Sign

‘Our greatest fear’: Highly drug-resistant gonorrhea confirmed by health officials

theguardian

UK man has world-first case of super-strength gonorrhoea

Public Health England say case is first global report of strand resilient to main antibiotic care



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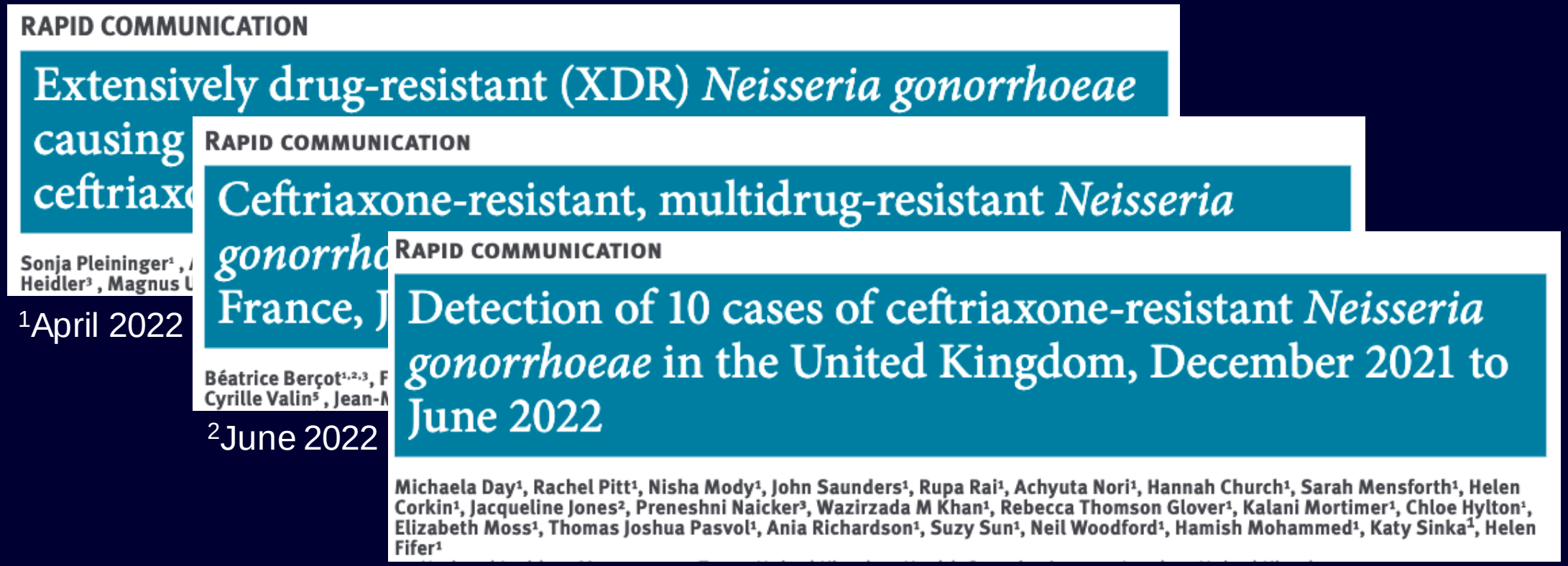
Health

Man has 'world's worst' super-gonorrhoea

By James Gallagher
Health and science correspondent, BBC News

28 March 2018 Share

Detection of ceftriaxone-resistant strains



[1]April 2022

[2]June 2022

[3]Dec 2021 - June 2022

[1]Pleininger et al, Eurosurveillance, 2022; [2] Bercot et al, Eurosurveillance, 2022;
[3]Day et al, Eurosurveillance, 2022;

Detection of ceftriaxone-resistant strains

January 2023

CNN health | Life, But Better | Fitness | Food | Sleep | Mindfulness | Relationships

First cases of gonorrhea resistant to several classes of antibiotics identified in the U.S.

by Brenda Goodman, CNN

Published 6:27 PM EST, Thu January 19, 2023

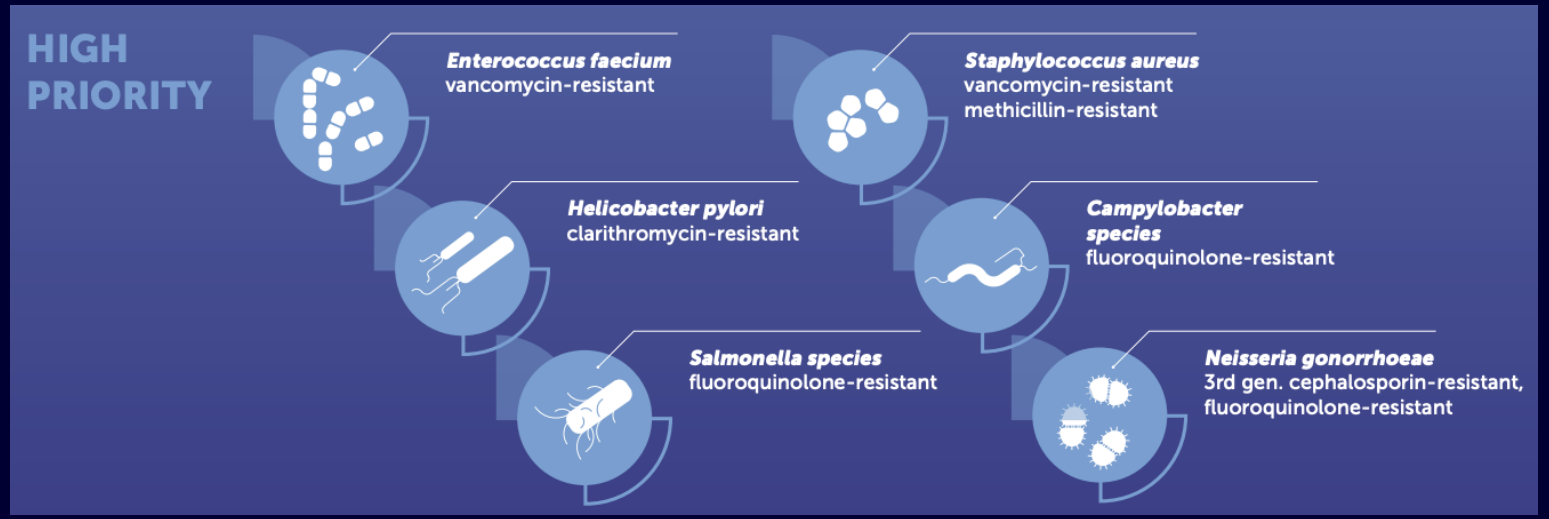
Drug-resistant *N. gonorrhoeae* is a global health threat

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

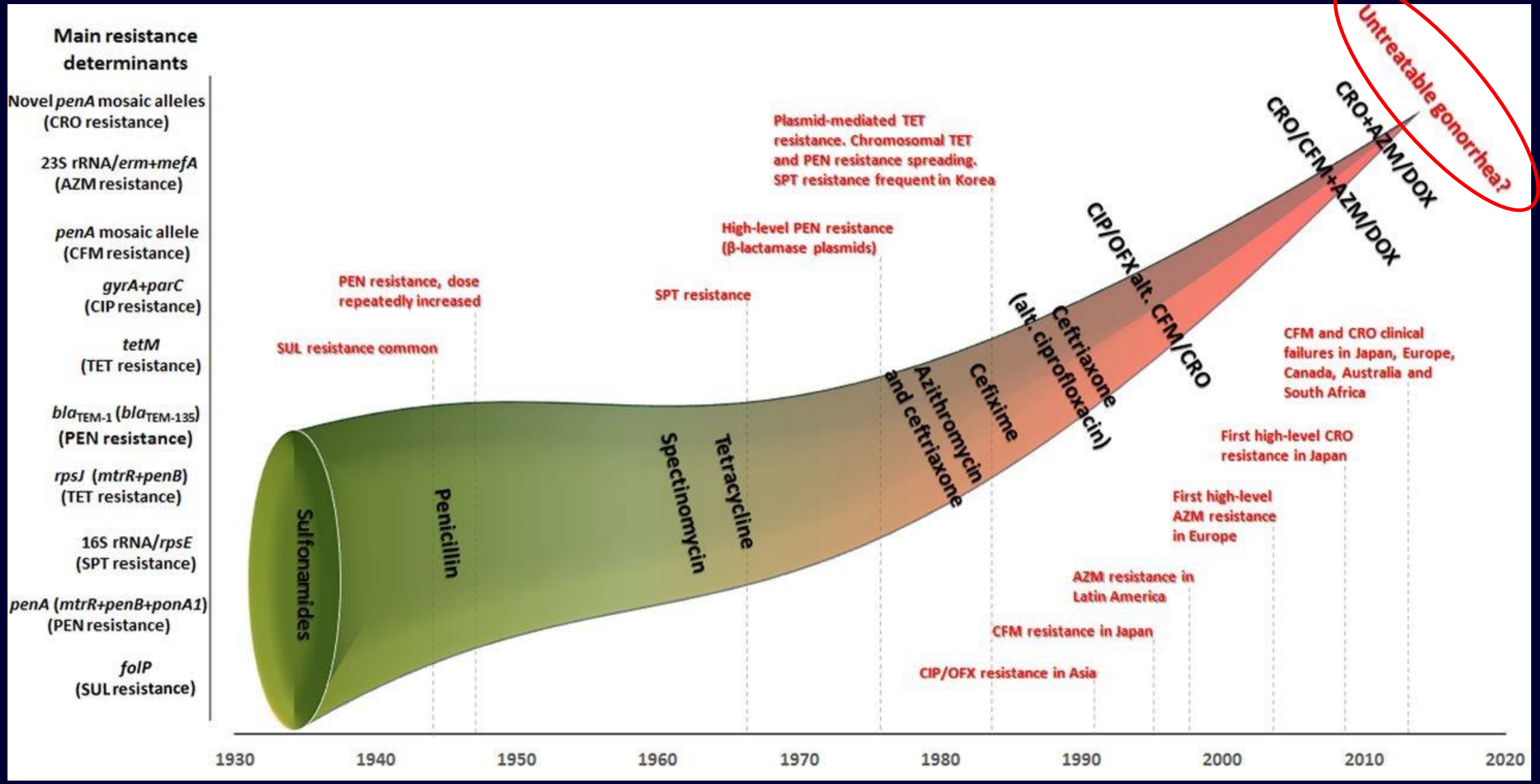
Threat Level: URGENT

World Health Organization

High Priority Pathogen List



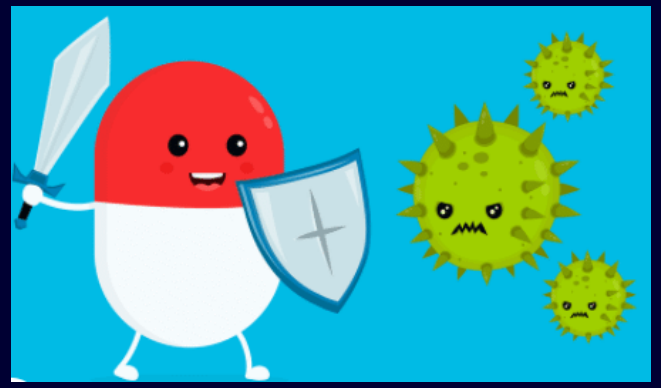
How did we get here?



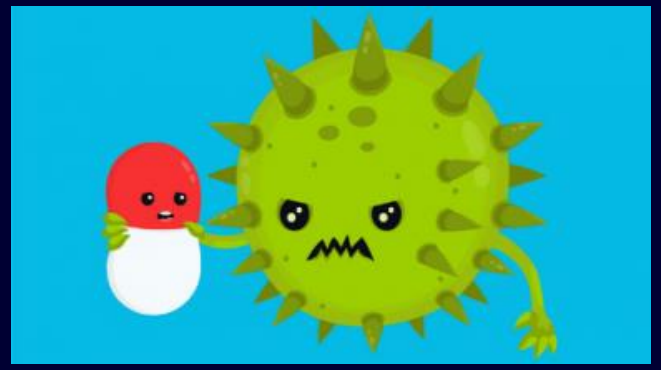
Unemo and Shafer, Clin. Microbiol. Rev. 2014

What causes antibiotic resistance?

- Evolutionary struggle between microbes
- Mutation/adaptation → Resistance → Selection
- Exposure to antibiotics increases selection pressure
  - Agriculture: ~75% of all tetracycline use worldwide
  - Medicine: Overuse/Misuse of antibiotics

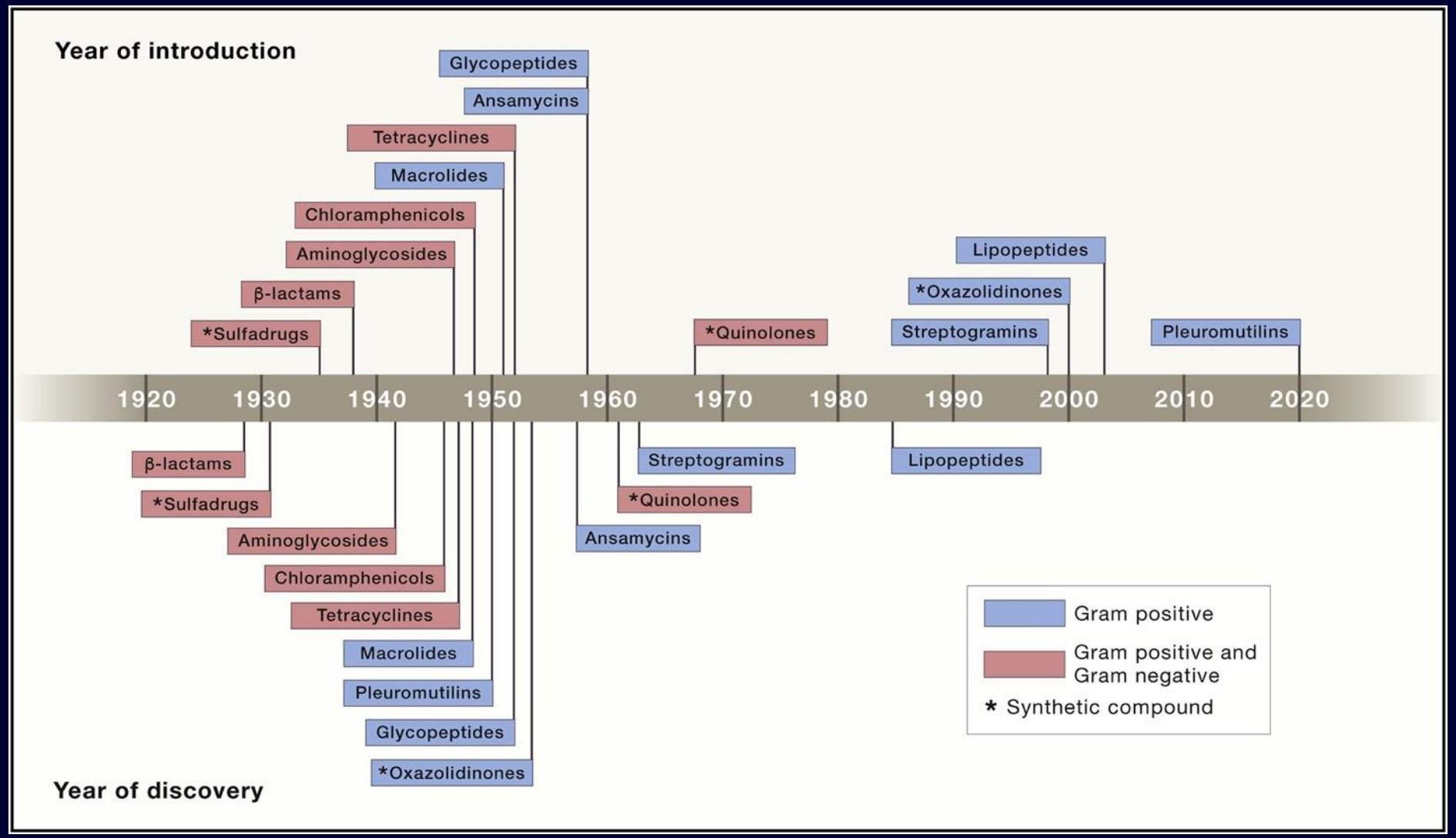


How it started



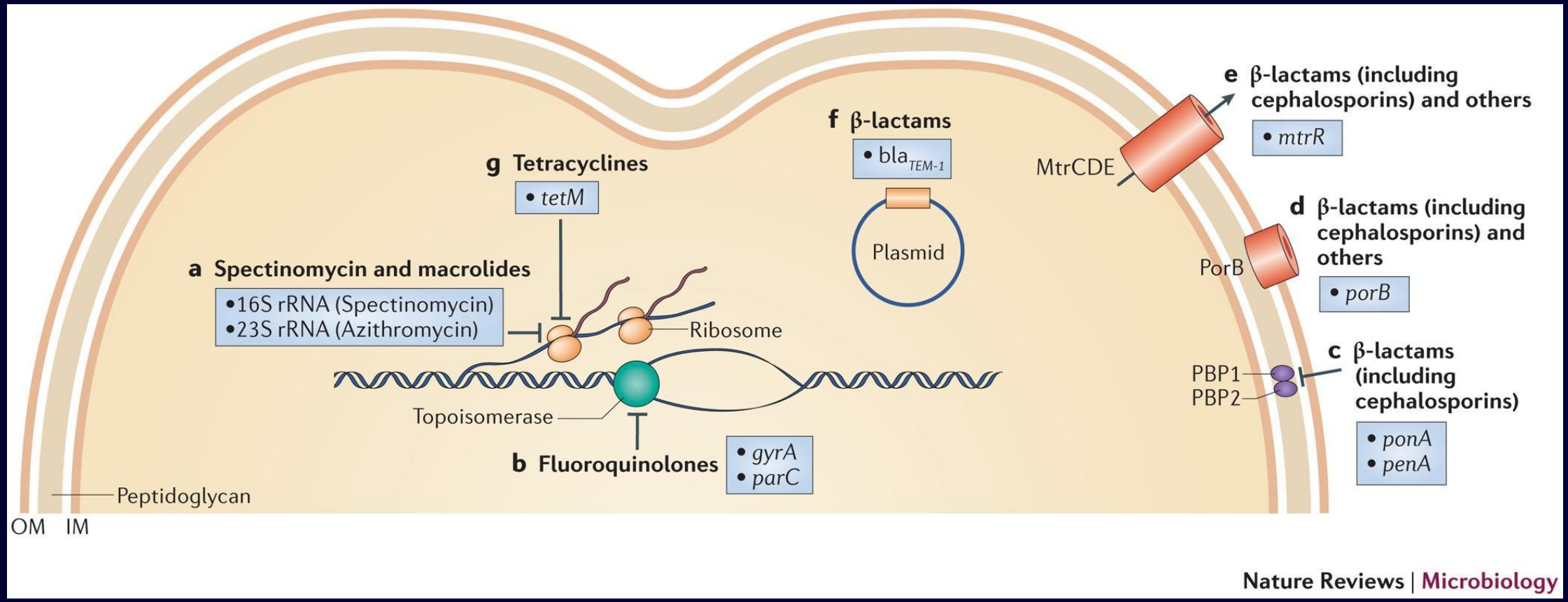
How it's going

Antibiotic Development Timeline



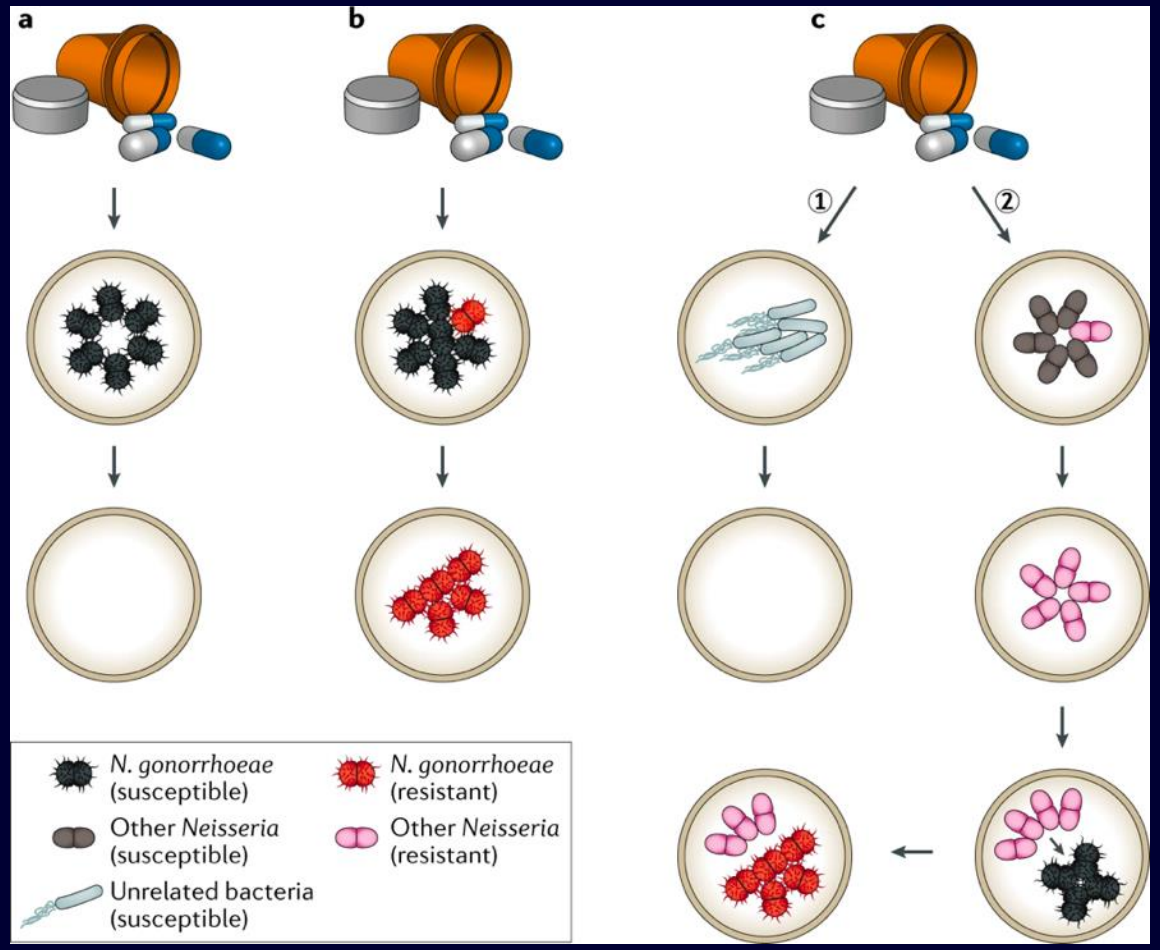
Lewis, Cell, 2020

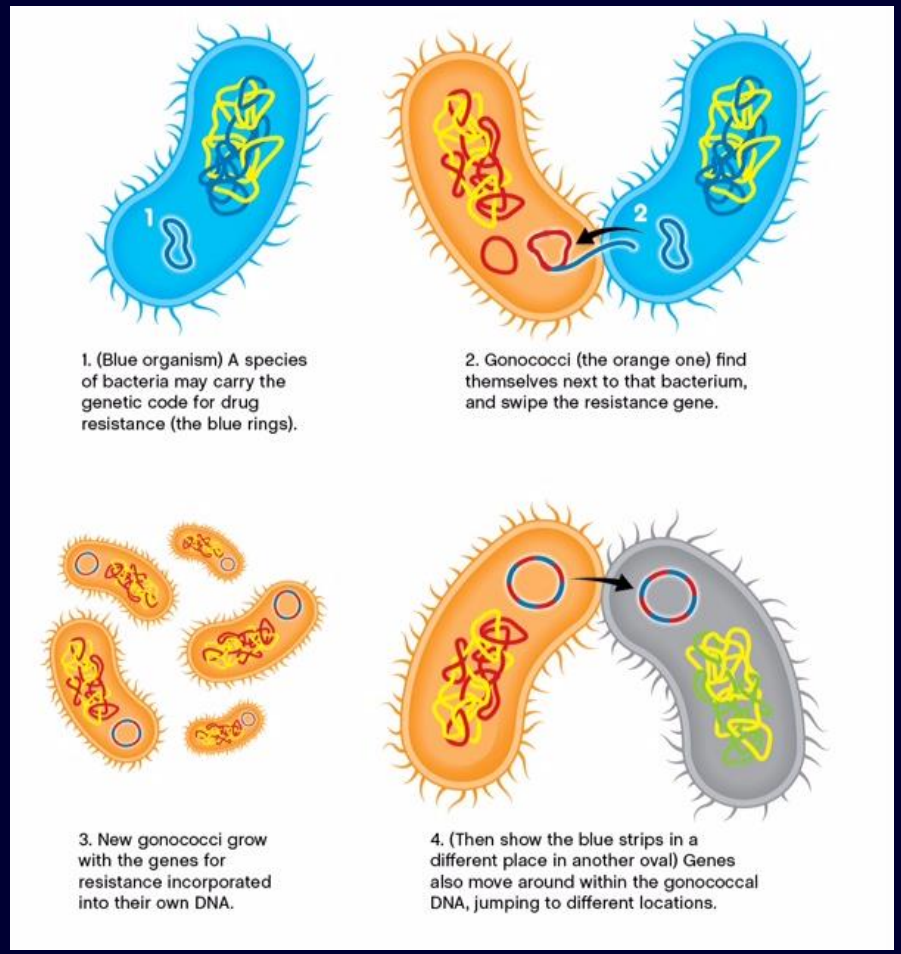
Many mechanisms for AMR



Goire et al, Nat Rev Micro, 2014

Antibiotic use exerts selective pressure for drug resistance





Dong HV and Klausner JD, *Nat Rev Urol*, 2019

Clinical Infectious Diseases

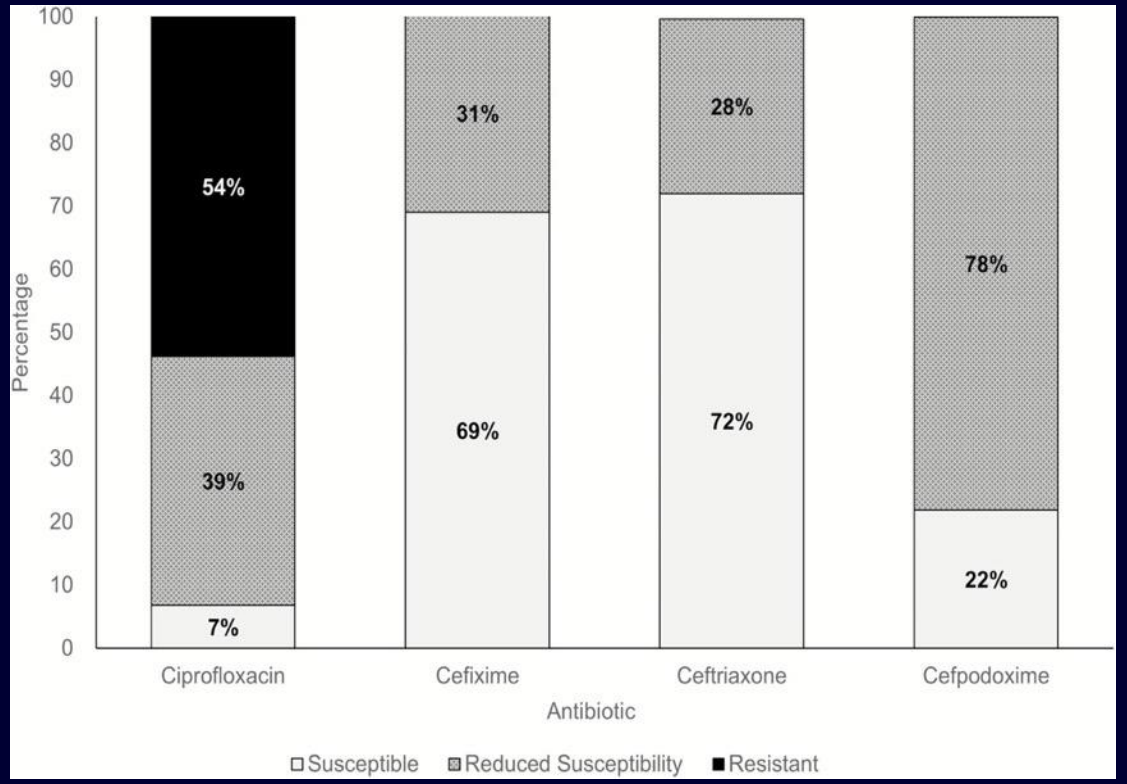
MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Decreased Cephalosporin Susceptibility of Oropharyngeal *Neisseria* Species in Antibiotic-using Men Who Have Sex With Men in Hanoi, Vietnam

Huan V. Dong,[1,2] Loc Q. Pham,[3,4] Hoa T. Nguyen,[5] Minh X. B. Nguyen,[4,6] Trung V. Nguyen,[5,7] Folasade May,[2] Giang M. Le,[4] and Jeffrey D. Klausner[2,3]

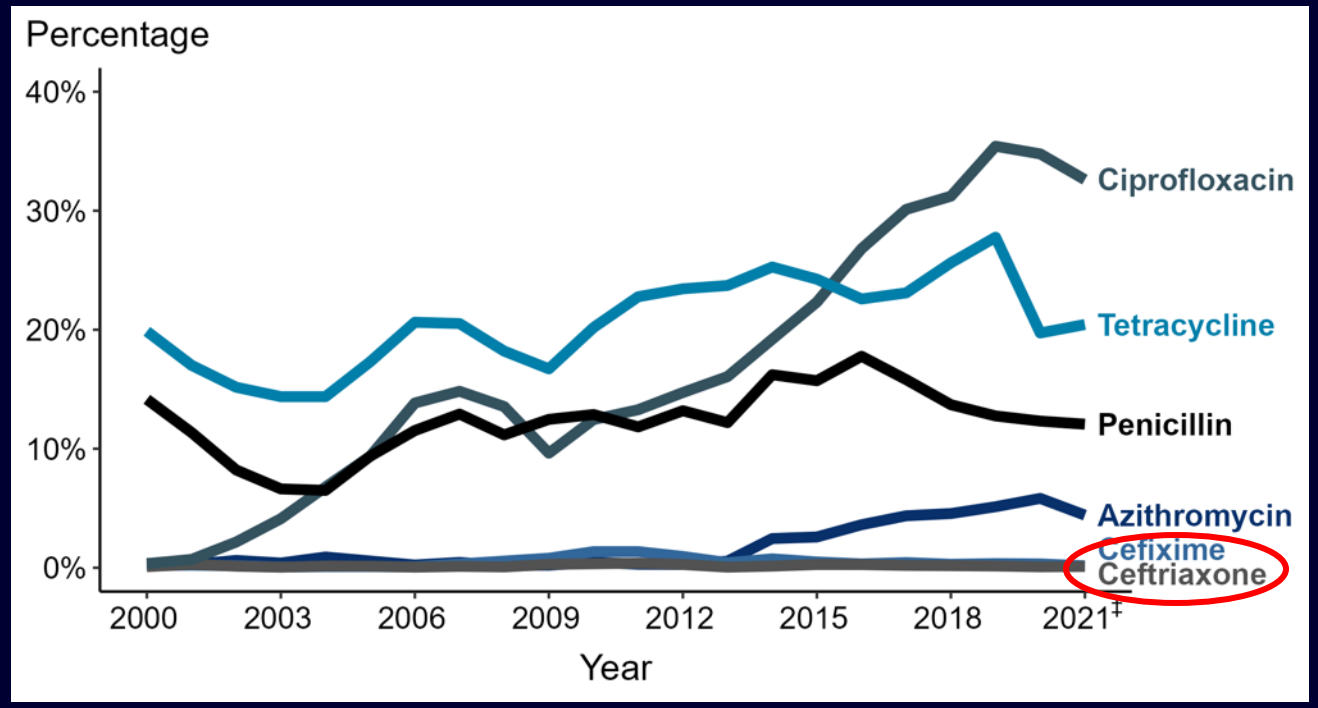
- 207 pharyngeal swabs collected from MSM in 2016-2017
- 100% grew ≥ 1 *Neisseria sp.*
  - *N. flavescens* – 47.2%
  - *N. subflava* – 21.5%
  - *N. perflava* – 11.3%
  - *N. gonorrhoeae* – 3.4%
- Any antibiotic use in prior month was associated with increased resistance



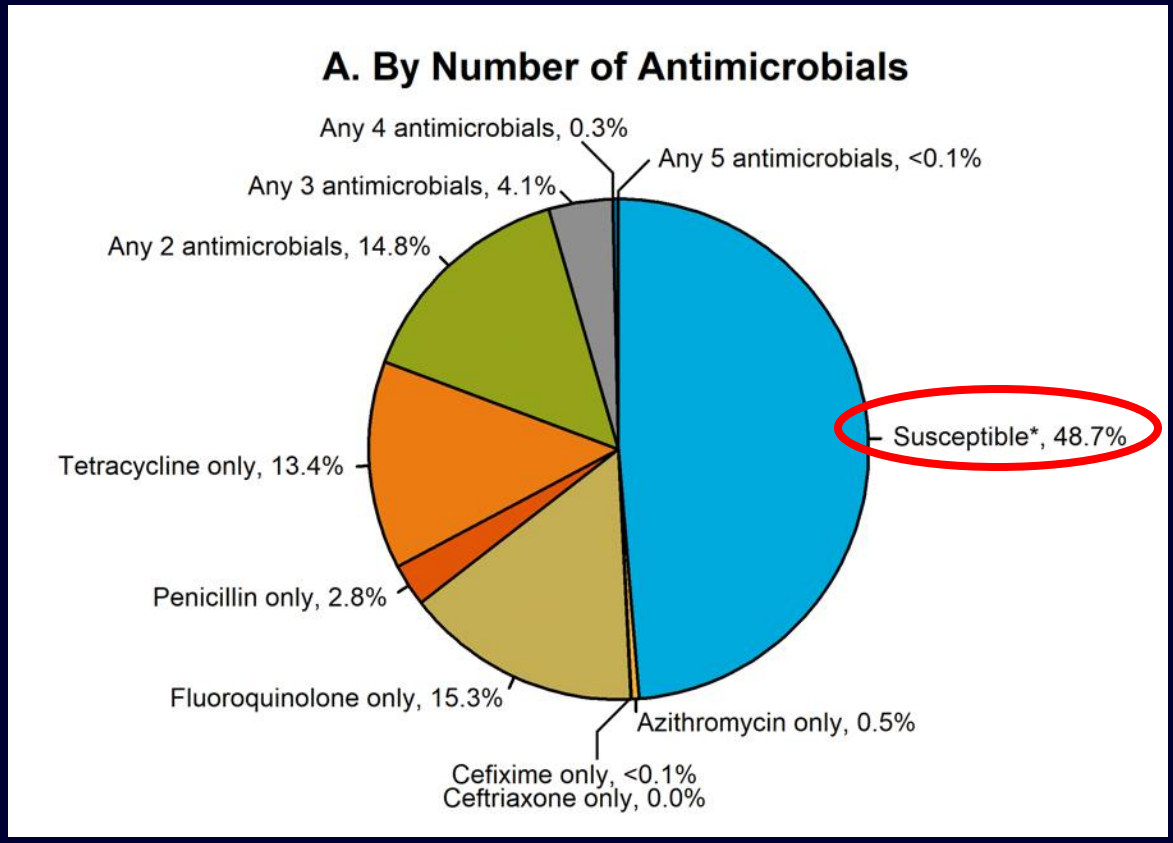
Dong HV et al, *CID*, 2019

AMR of *N. gonorrhoeae* in US

Prevalence of Tetracycline, Penicillin, or Ciprofloxacin Resistance* or Elevated Cefixime, Ceftriaxone, or Azithromycin MICs by Year — Gonococcal Isolate Surveillance Project (GISP), 2000–2021



STD Surveillance 2021, CDC



STD Surveillance 2018, CDC

Resistance-Guided Treatment of Gonorrhea: A Prospective Clinical Study

Jeffrey D. Klausner,[1] Claire C. Bristow,[2] Olusegun O. Soge,[3] Akbar Shahkolahi,[4] Toni Waymer,[4] Robert K. Bolan,[5] Susan S. Philip,[6] Lenore E. Asbel,[7] Stephanie N. Taylor,[8] Leandro A. Mena,[9] Deborah A. Goldstein,[10] Jonathan A. Powell,[11] Michael R. Wierzbicki,[11] and Sheldon R. Morris[2]

- Used gyrA PCR test (Ser-91) in a multi-site, prospective study to evaluate the efficacy of ciprofloxacin 500mg PO once to treat *N. gonorrhoeae*
- Follow-up microbiological cure 5-10 days post-treatment
- Enrolled 211 participants
- Microbiologic cure:
  - Intent-to-treat arm: 91.7%
  - Per-protocol arm: 100%

[1]Klausner, JD et al., CID, 2020

Clinical Infectious Diseases
VIEWPOINTS
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Resistance-Guided Therapy for *Neisseria gonorrhoeae*

Lao-Tzu Allan-Blitz,[1,2] Paul C. Adamson,[3] and Jeffrey D. Klausner[4]

- **Ciprofloxacin**: Assays available
  - No commercial assays in US
  - British STI guidelines incorporate
- **Cefixime**
- **Ceftriaxone**

} Assays under development: must detect multiple mutations

- **Zoliflodacin?** ← Future Therapy

SpeeDx

Addressing AMR in *N. gonorrhoeae* is an urgent global health issue

- **Surveillance**
  - Limited data in many parts of the world with high AMR[1]

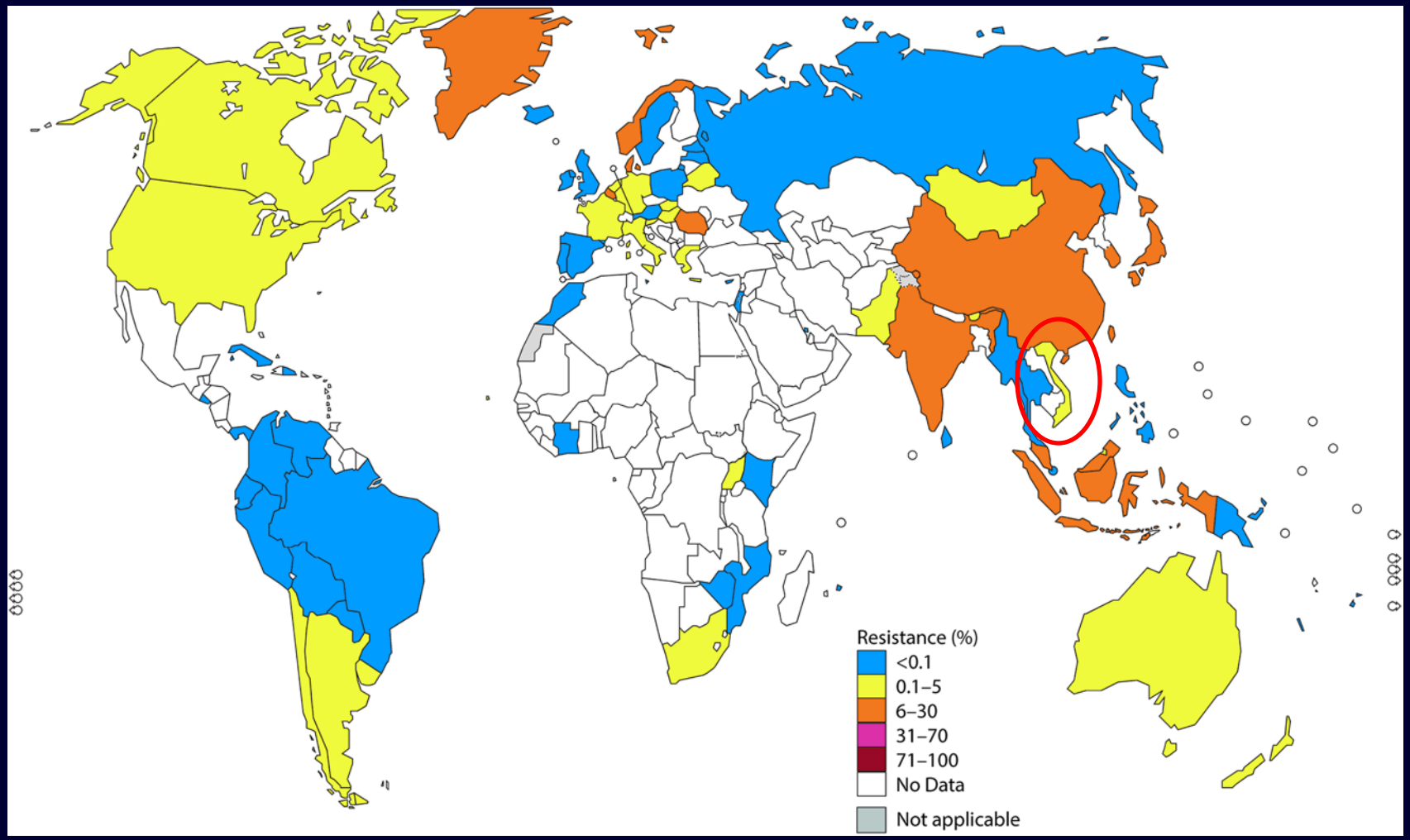
- **Diagnosis**
  - Syndromic management in many low-resource settings[2]
  - Lack of detection of AMR at diagnosis[2]

- **Treatment**
  - Empiric in most settings
  - Limited therapeutic options remain

[1]Wi T, et al. *PLOS Medicine*, 2017; [2]Wi T, et al. *J Int AIDS Soc*. 2019

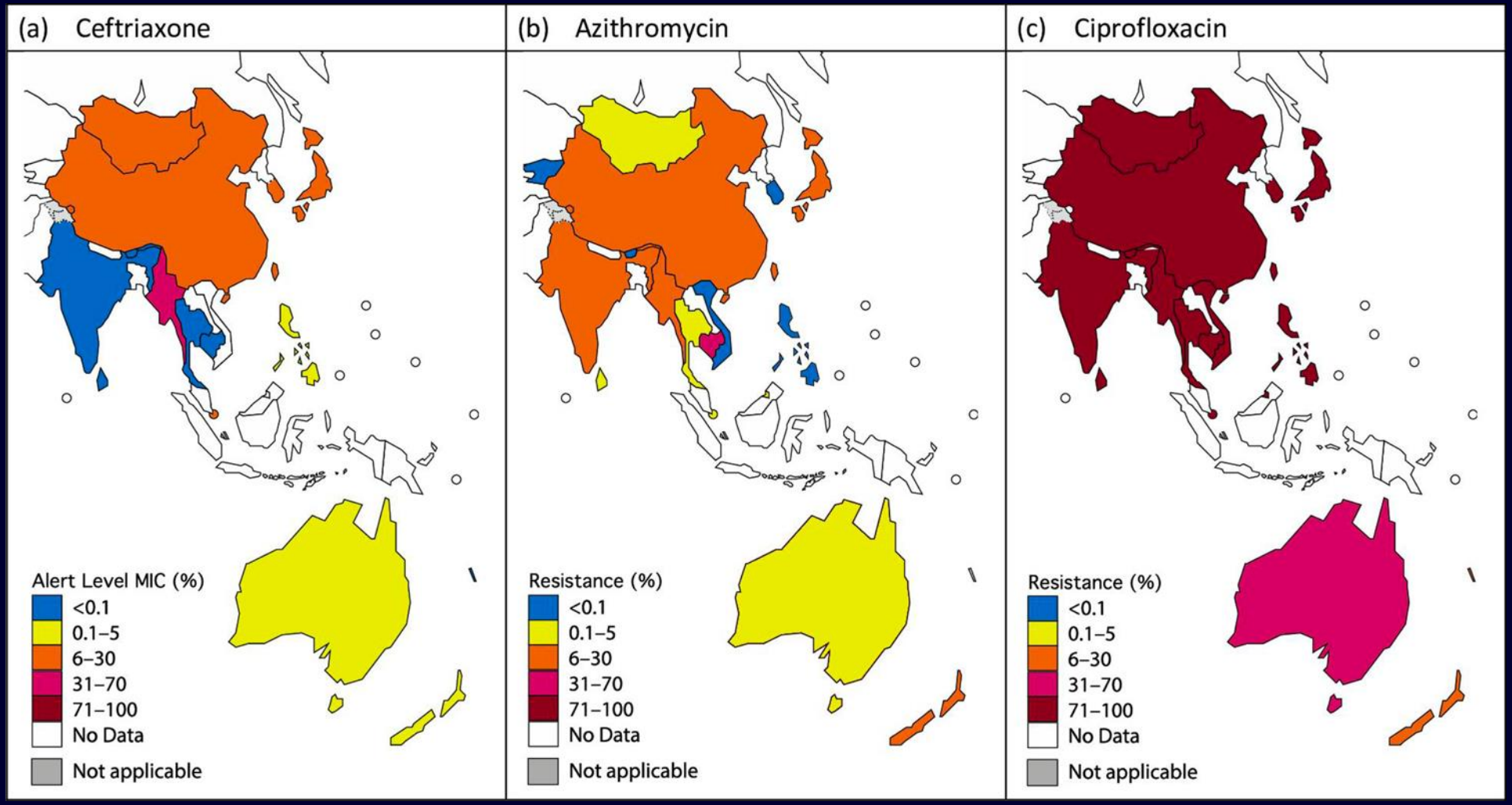
WHO Global Gonococcal Antimicrobial Surveillance Programme

Extended Spectrum Cephalosporins



Wi T, et al. PLOS Medicine, 2017

AMR in *N. gonorrhoeae*: Western Pacific Region



George, CRR et al. PLOS One, 2017

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Trends in antimicrobial resistance in *Neisseria gonorrhoeae* in Hanoi, Vietnam, 2017–2019

Paul C. Adamson[1*†], Hung Van Le[2,3†], Hai Ha Long Le[2,3], Giang Minh Le[3], Trung Vu Nguyen[3,4] and Jeffrey D. Klausner[1,5]

409 clinical isolates from Hanoi, 2017 - 2019

→ 0% susceptible to penicillin

→ 98.5% resistant to ciprofloxacin

→ 30% azithromycin resistance

→ Very few ceftriaxone resistant isolates

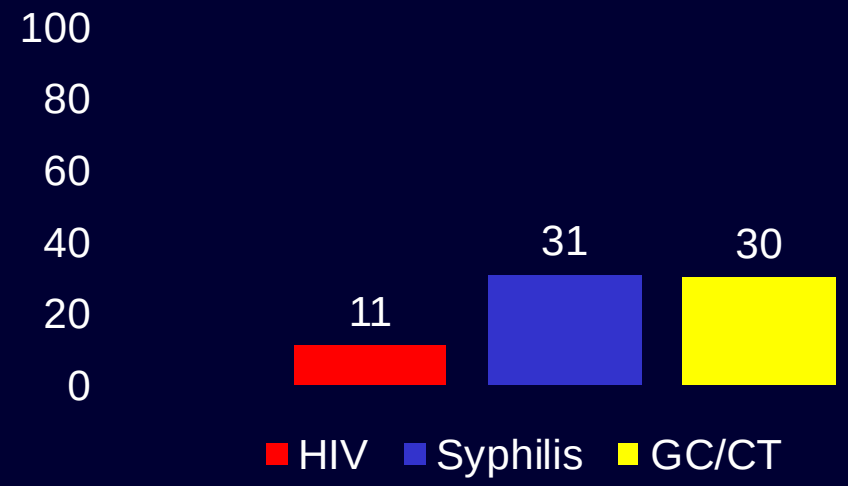
→ All isolates susceptible to spectinomycin

	Interpretive Categories, n (%)		
	2017	**2018**	**2019**
Azithromycin (n = 407)			
Resistant	17 (15.3%)	63 (46.7%)	42 (26.1%)
Cefixime (n = 406)			
Non-susceptible	2 (1.8%)	7 (5.7%)	4 (2.5%)
Ceftriaxone (n = 408)			
Non-susceptible	0 (0%)	1 (0.7%)	2 (1.2%)

Prevalence of STIs among MSM in Hanoi

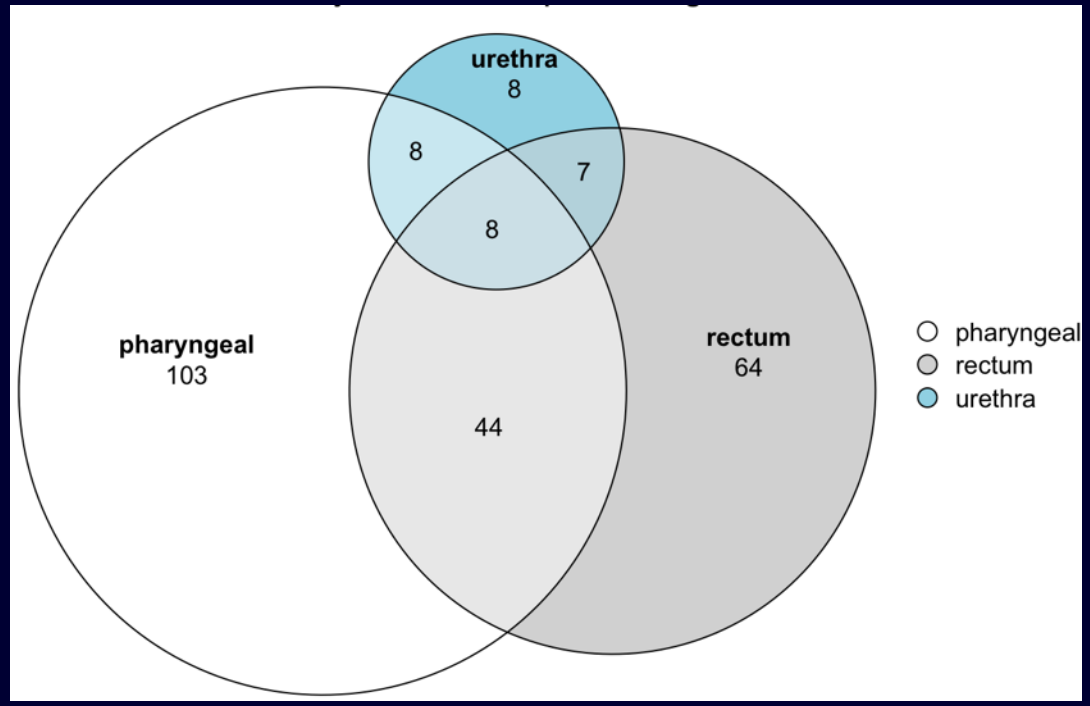
- Prospective cohort study among men who have sex with men in Hanoi, 2017 – 2019
- Baseline screening for HIV, syphilis, gonorrhea and chlamydia (urethral, rectal, and pharyngeal)
- Recruited 1893 participants
- First HIV PrEP program in Vietnam

Baseline Prevalence

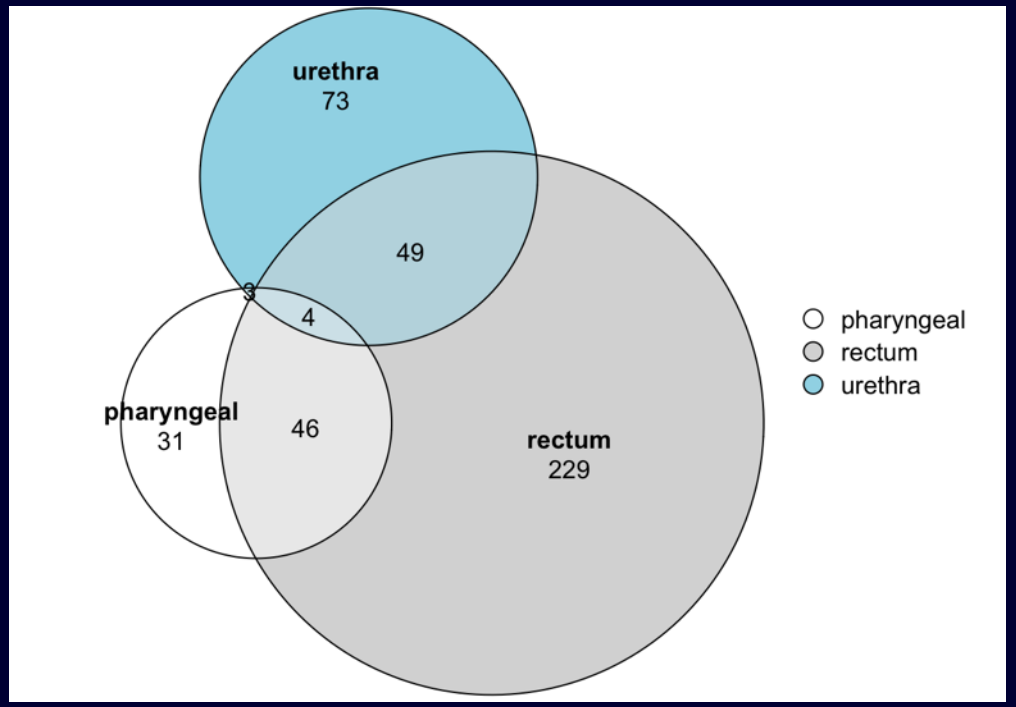


Gonorrhea is often extragenital and asymptomatic

Prevalence of gonorrhea: 13% (n=242)



Prevalence of chlamydia: 23% (n=435)



<u>Asymptomatic infections:</u>

→ 47.9% rectal

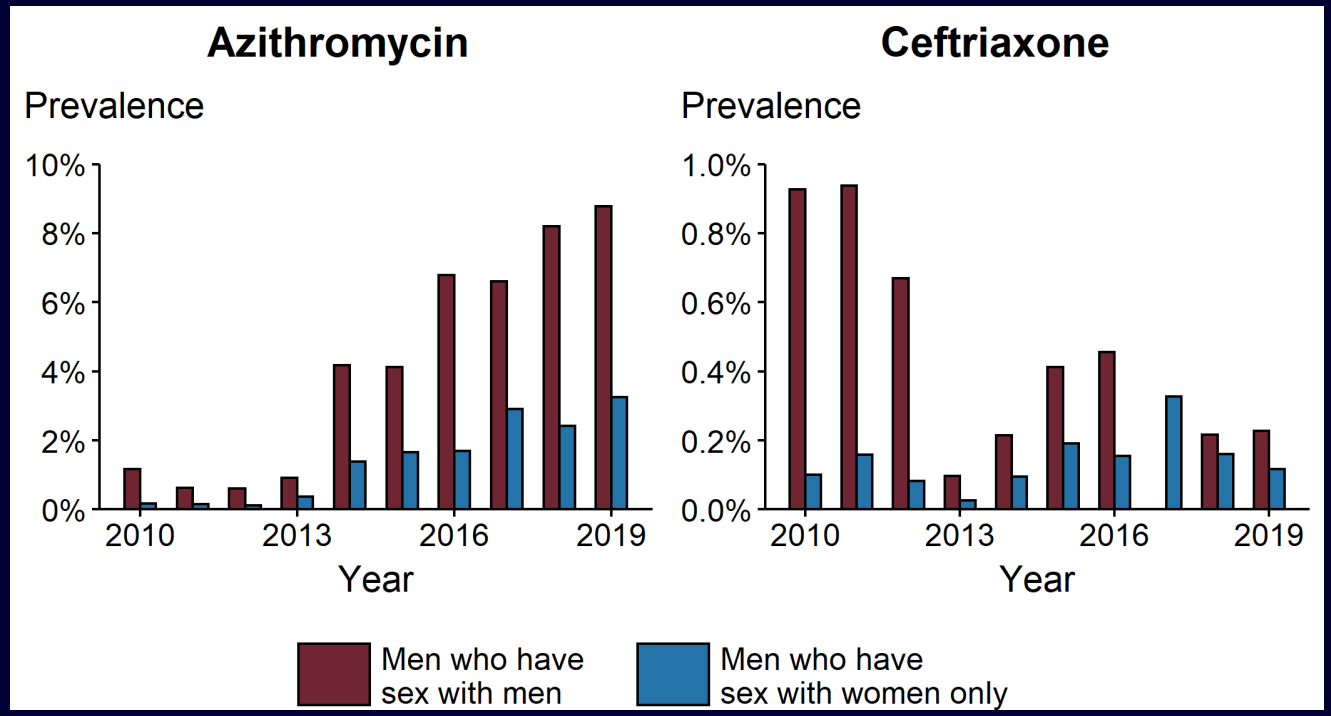
→ 42.8% urethral

→ 46.4% pharyngeal*

→ Routine Screening for CT/NG

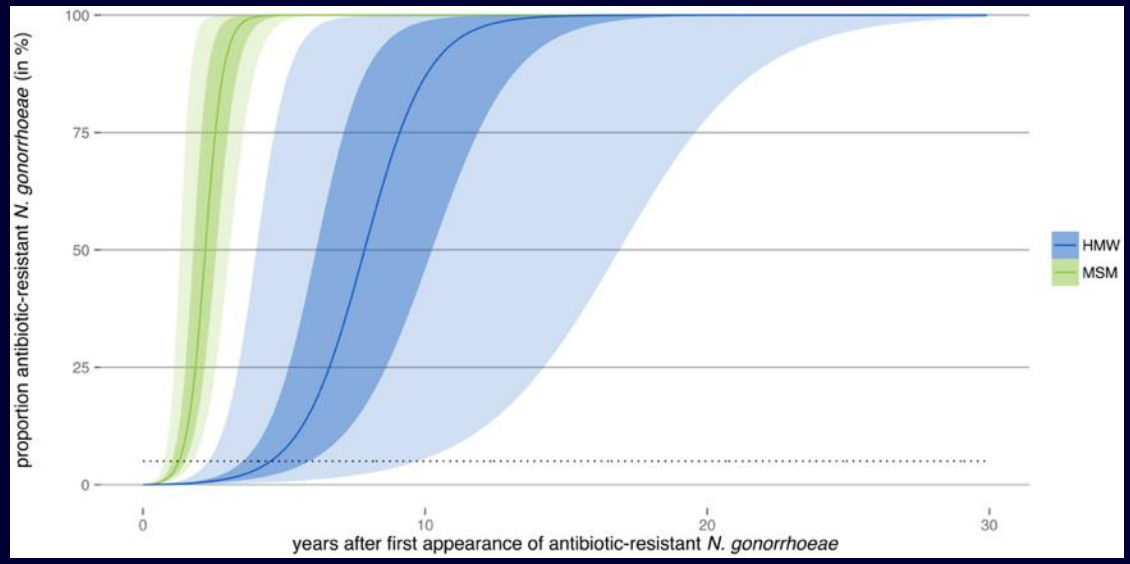
Adamson et al, STD, 2021

AMR in *N. gonorrhoeae* in key populations



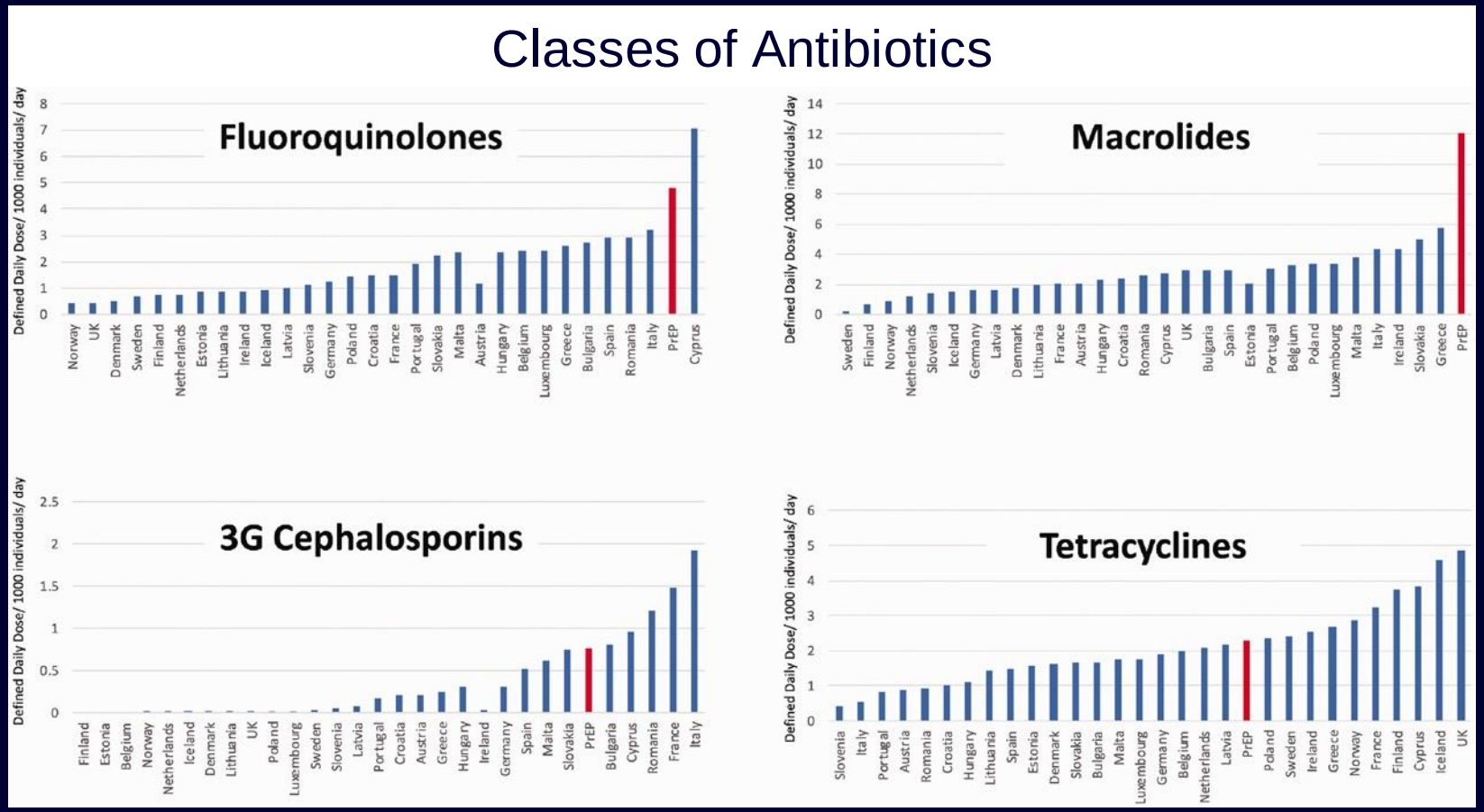
CDC, 2019 STD Surveillance

Resistance spreads faster with more treatment, not more sexual partners

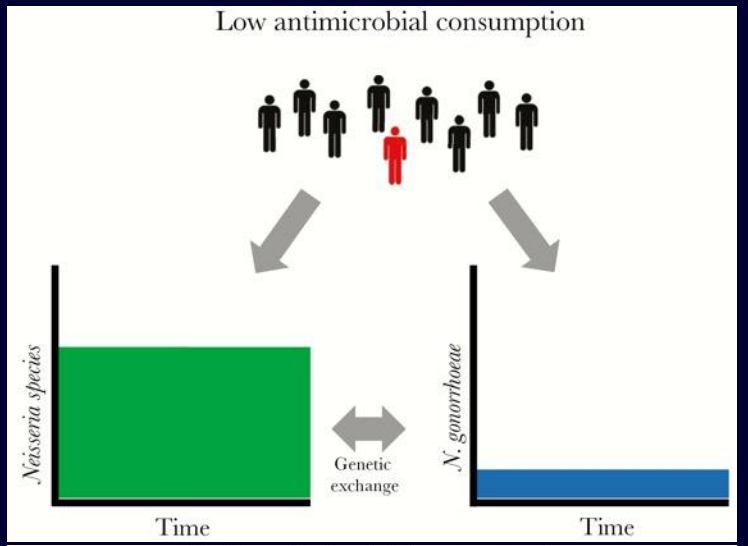


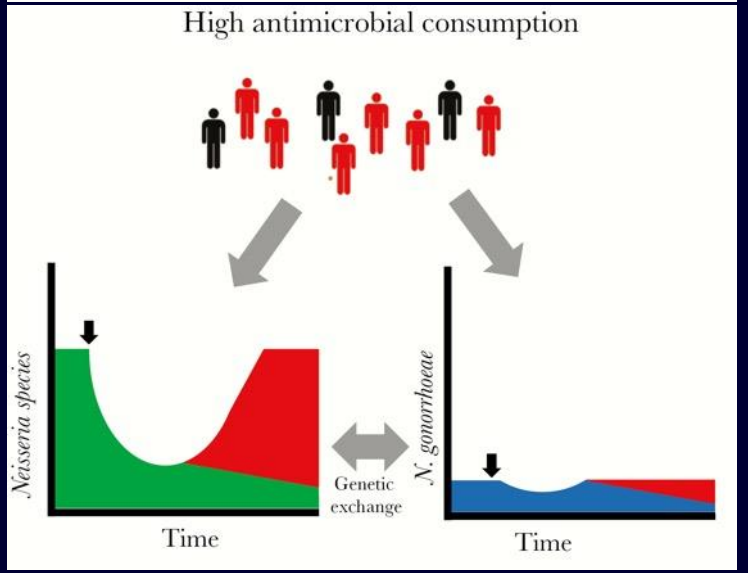
Fingerhuth et al, PLOS Pathogens, 2016

Antibiotic consumption in PrEP programs



Kenyon et al, Int J STD & AIDS, 2020





Kenyon et al, JID, 2020

Are PrEP participants in Vietnam at increased risk for AMR?

- STIs are common among people in HIV PrEP programs
- Undergo routine testing for STIs
- Increased antibiotic consumption
- Setting with high prevalence of AMR
- Will this select for resistance?

3-6 months

Sexual Health and Promotion Clinic

Testing for STIs and AMR within a PrEP program

Study Objectives:

- Prevalence of CT/NG at 3 anatomic sites
- Routine culture of *N. gonorrhoeae* and testing for AMR
- Piloting a test-of-cure program for pharyngeal infections
- Genomic epidemiology of gonococcal infections
- Commensal *Neisseria* – prevalence of AMR and perform whole-genome sequencing

Study Overview

- Design: Observational study
- Population: PrEP program participants
  - Exclusion criteria: testing for STIs in the prior < 3 months (asymptomatic)
- Sample Size: Approximately 1500 PrEP participants

Study Overview - Procedures

- Enroll participants within SHP Clinic PrEP program
  - *C. trachomatis* and *N. gonorrhoeae* testing by NAAT at rectal, urogenital, pharyngeal sites and testing for commensal *Neisseria*
  - Questionnaire to assess antibiotic education and practices

- Participants with infection return to clinic for treatment

- Participants with NG infection:
  - Collect swabs for culture and antibiotic susceptibility testing
  - Return for test-of-cure 10-14 days following treatment
  - Additional swabs taken at TOC visit for culture and AST

Study Overview – Participant Timeline

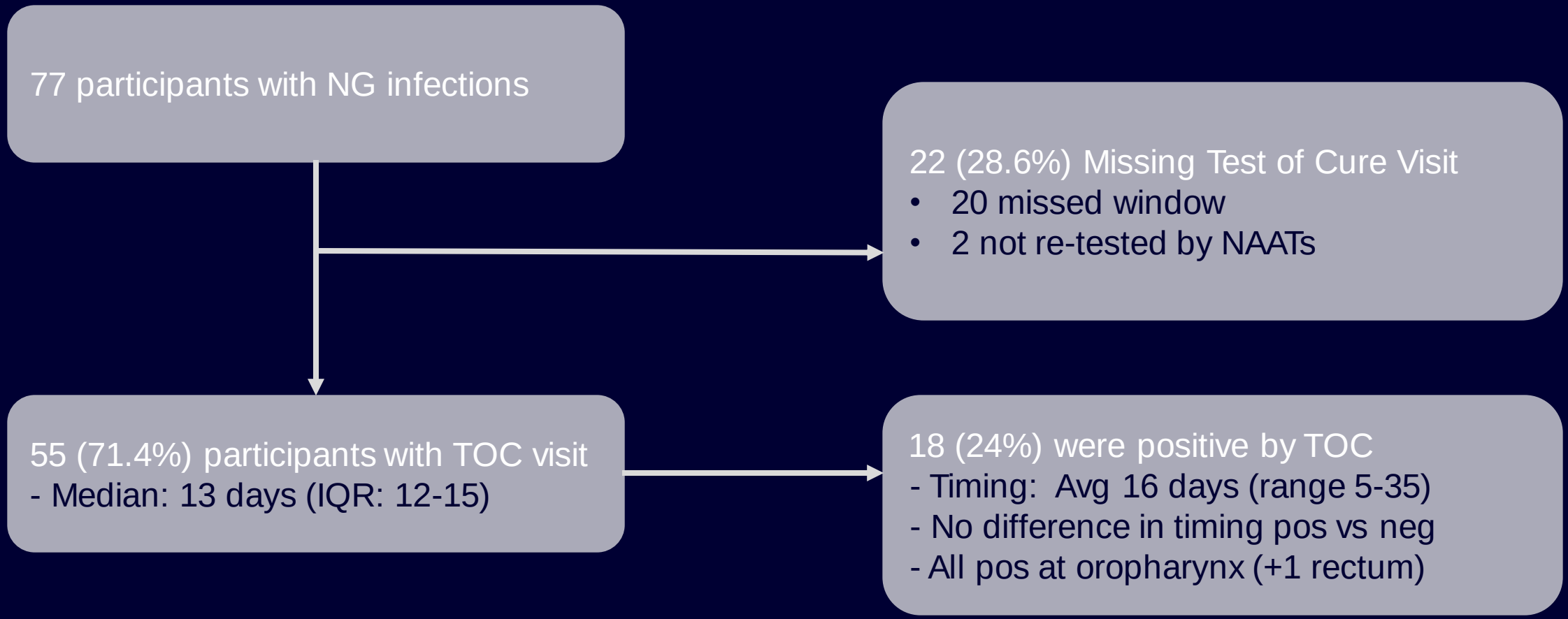
Preliminary Study Results

- Enrolled 601 participants (Jan 2022 - Jan 2023)
- Prevalence of *Chlamydia trachomatis*: 20.4% (n=108)
  - 67.6% were rectal infections
- Prevalence of *N. gonorrhoeae*: 14.6% (n=77)
  - 80.5% were pharyngeal infections

Infections more common among those reporting symptoms

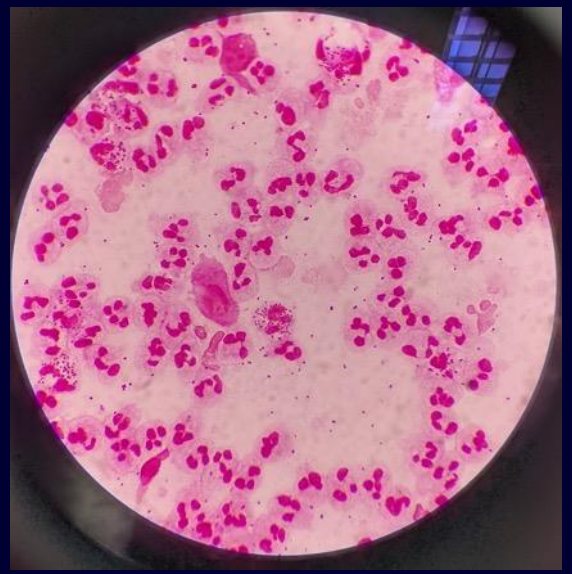
	Overall N=529	Symptoms in prior week		No symptoms		P-value
NG infection		n	%	n	%	P-value
Urethral	16 (3.0%)	14	6.5	2	0.6	<0.001
Rectal	38 (7.2%)	21	9.8	17	5.4	0.06
Oropharyngeal	62 (11.7%)	33	15.3	29	9.2	0.03
Any site	77 (14.6%)	40	18.6	37	11.8	0.03
CT infection						
Urethral	23 (4.3%)	11	5.1	12	3.8	0.47
Rectal	73 (13.8 %)	30	14.0	43	13.7	0.93
Oropharyngeal	30 (5.7%)	15	7.0	15	4.8	0.28
Any site	108 (20.4%)	47	21.9	61	19.4	0.50
CT or NG infection						
Urethral	34 (6.4%)	21	9.8	13	4.1	0.009
Rectal	95 (18.0%)	40	18.6	55	17.5	0.75
Oropharyngeal	83 (15.7%)	42	19.5	41	13.1	0.04
Any site	155 (29.3%)	68	31.6	87	27.7	0.33

Results: Test of Cure



Results: Culturing *N. gonorrhoeae*

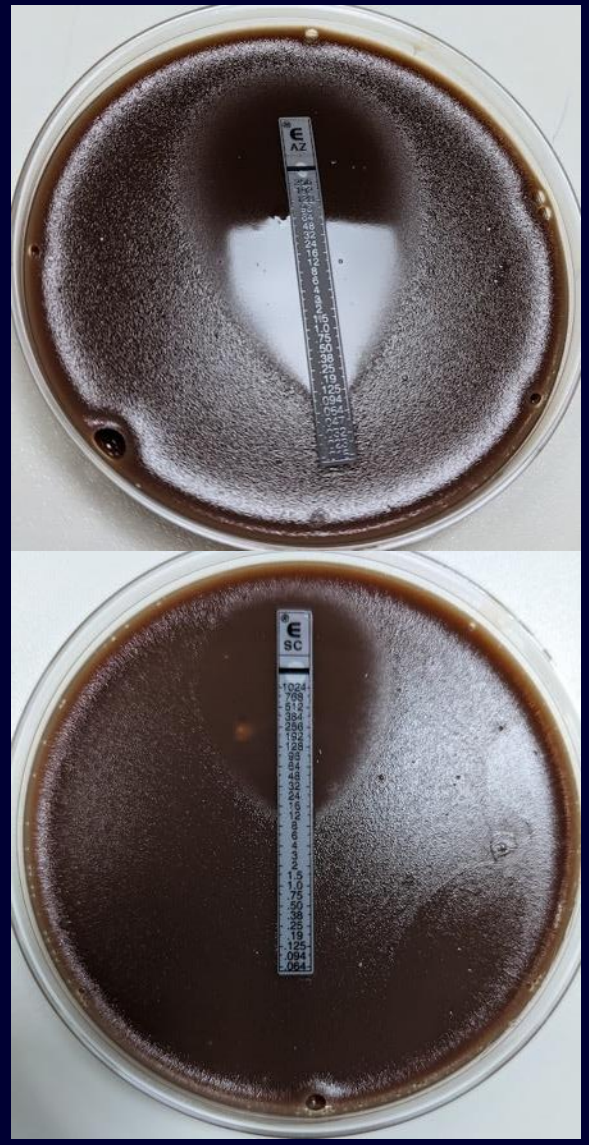
- Overall, 13 isolates cultured, recovery varies by anatomic site and symptom status
  - Urethral – 35.7% (5/14) → all 5 reported symptoms
  - Rectal – 10% (4/40) → 3/4 reported symptoms
  - Pharyngeal – 6.2% (4/65) → 2 w/ symptoms + 2 without



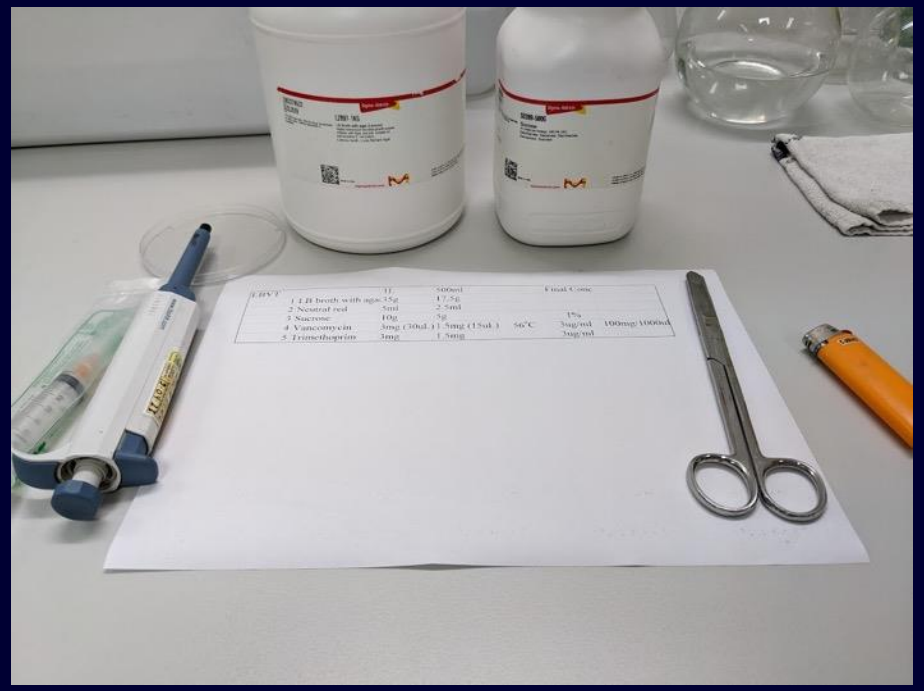
Results: Resistance in *N. gonorrhoeae*

13 isolates for antibiotic susceptibility testing

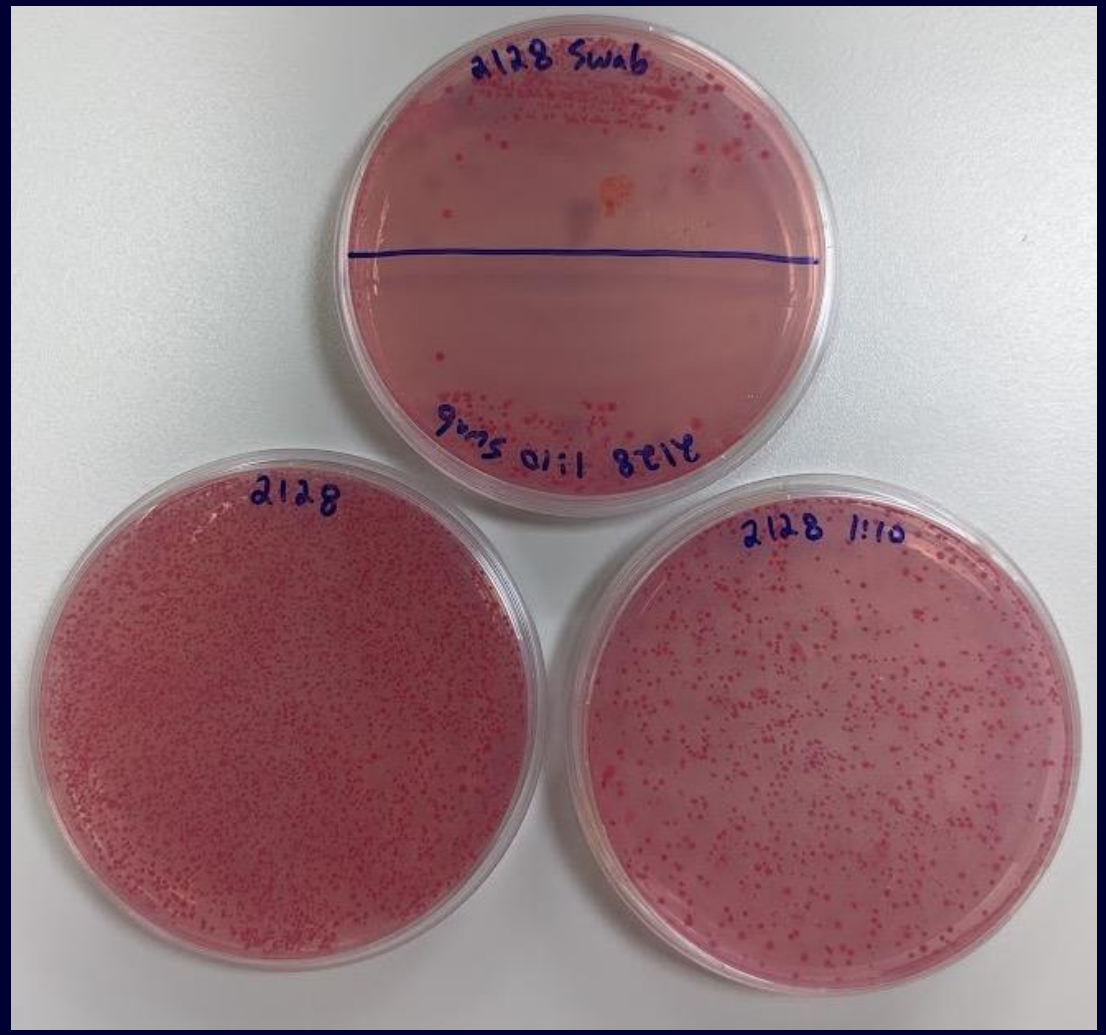
- Spectinomycin – all susceptible
- Azithromycin – 4 (31%) resistant
- Cefixime – 1 (7.7%) decreased susceptible
- Ceftriaxone – 2 (15.4%) decreased susceptible

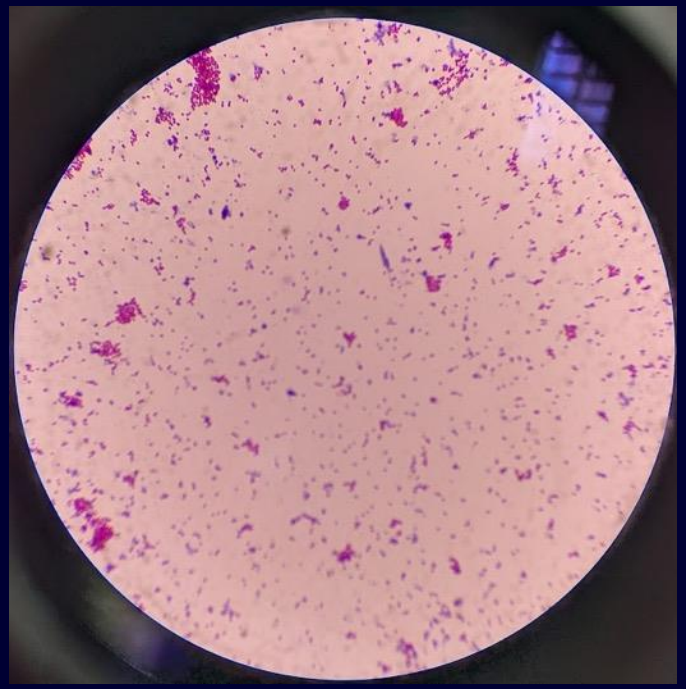


Commensal *Neisseria* study



Commensal *Neisseria* study





Commensal *Neisseria* study

Study summary and next steps

- High prevalence of CT/NG infections
- Routine culturing of NG has low positivity but can increase isolates for AST/surveillance
- High positivity of tests-of-cure
- Next steps:
  - Whole genome sequencing of *N. gonorrhoeae*
  - Analysis of test-of-cure specimens
  - Commensal *Neisseria* sequencing

Addressing AMR in *N. gonorrhoeae* is an urgent global health issue

- **Surveillance**
  - Limited data in many parts of the world with high AMR[1]

- **Diagnosis**
  - Syndromic management in many low-resource settings[2]
  - Lack of detection of AMR at diagnosis[2]

- **Treatment**
  - Empiric in most settings
  - Limited therapeutic options remain

[1]Wi T, et al. *PLOS Medicine*, 2017; [2]Wi T, et al. *J Int AIDS Soc*. 2019

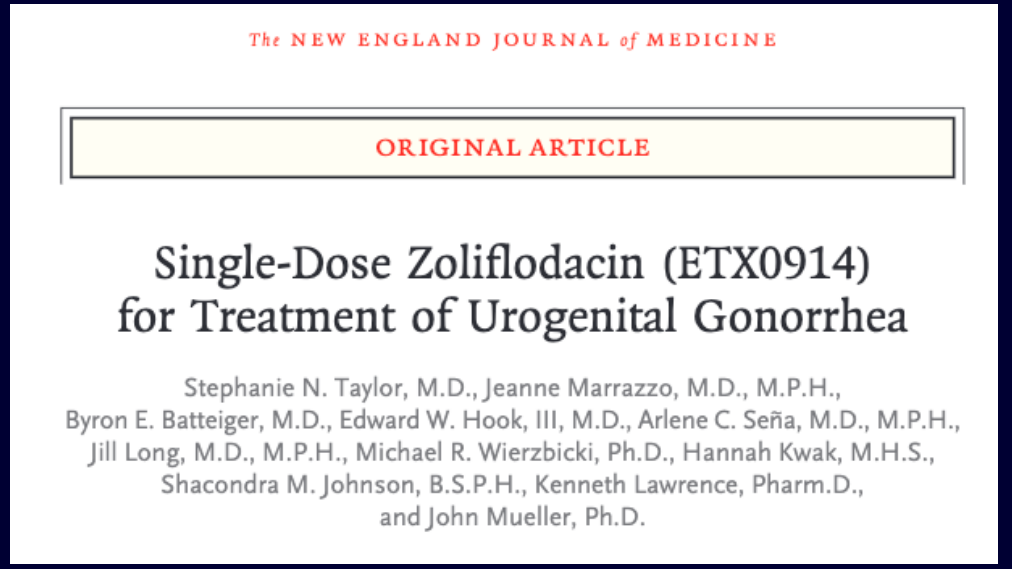
resistance
New ~~treatment~~ for gonorrhea!?

Zoliflodacin - novel antibiotic of the spiropyrimidinetrione class that targets the B subunit of DNA gyrase (GyrB)

Promising Phase 2 results for urogenital and rectal gonorrhea; Phase 3 trial underway

Zoliflodacin resistance - D429N, K450T or K450N mutations in GyrB

These were selected experimentally, but do they occur naturally?

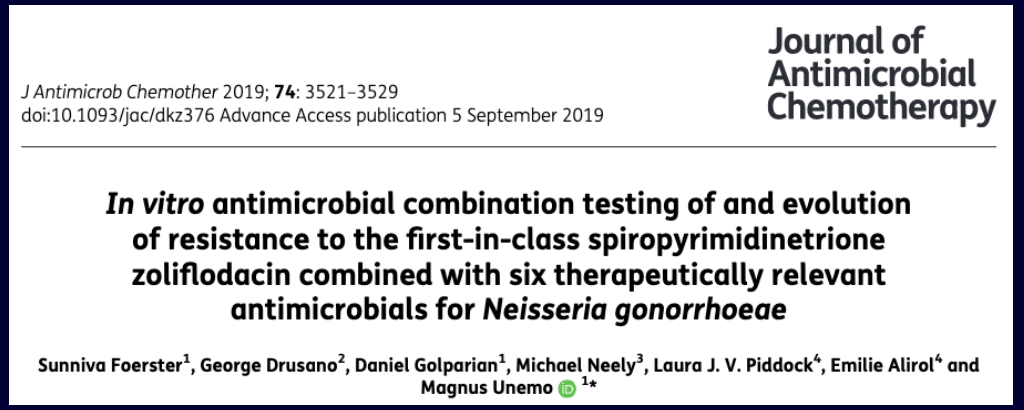


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea

Stephanie N. Taylor, M.D., Jeanne Marrazzo, M.D., M.P.H., Byron E. Batteiger, M.D., Edward W. Hook, III, M.D., Arlene C. Seña, M.D., M.P.H., Jill Long, M.D., M.P.H., Michael R. Wierzbicki, Ph.D., Hannah Kwak, M.H.S., Shacondra M. Johnson, B.S.P.H., Kenneth Lawrence, Pharm.D., and John Mueller, Ph.D.



J Antimicrob Chemother 2019; **74**: 3521–3529
doi:10.1093/jac/dkz376 Advance Access publication 5 September 2019

Journal of Antimicrobial Chemotherapy

In vitro* antimicrobial combination testing of and evolution of resistance to the first-in-class spiropyrimidinetrione zoliflodacin combined with six therapeutically relevant antimicrobials for *Neisseria gonorrhoeae

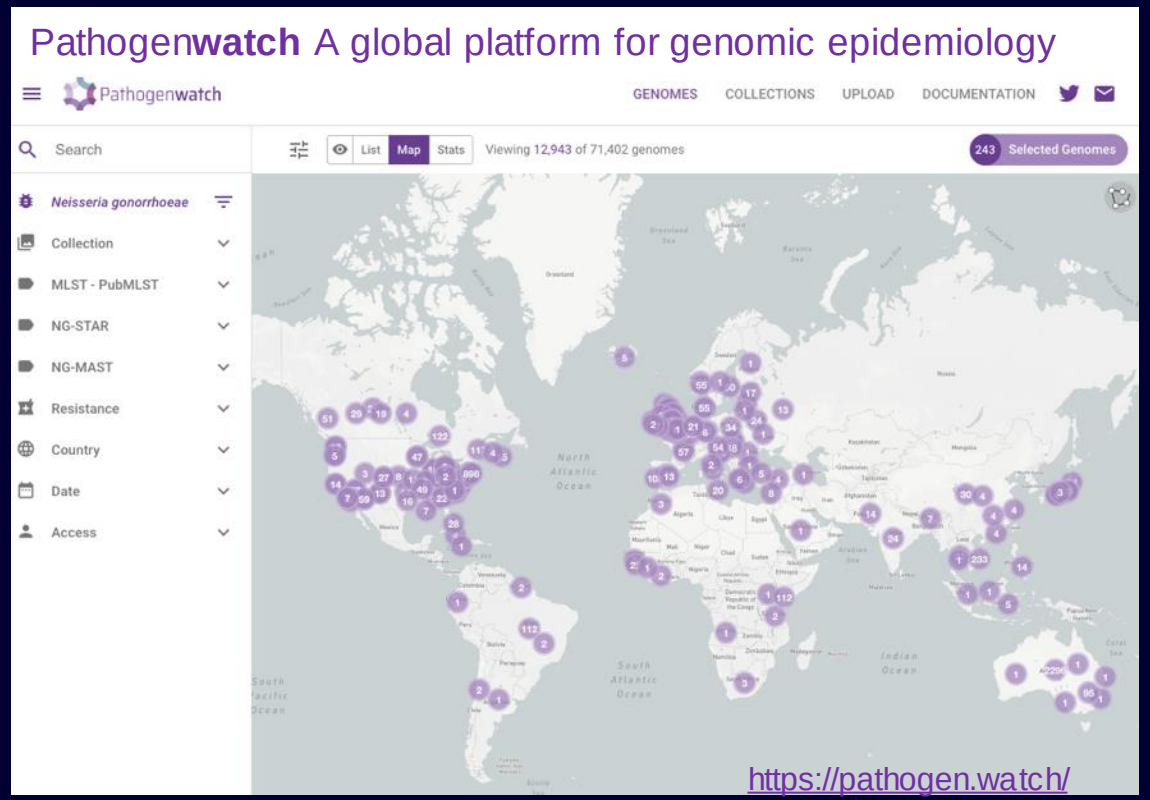
Sunniva Foerster[1], George Drusano[2], Daniel Golparian[1], Michael Neely[3], Laura J. V. Piddock[4], Emilie Alirol[4] and Magnus Unemo [1]*

J Antimicrob Chemother 2021; **76**: 2847–2849
doi:10.1093/jac/dkab262 Advance Access publication 29 July 2021

Journal of Antimicrobial Chemotherapy

Using a public database of *Neisseria gonorrhoeae* genomes to detect mutations associated with zoliflodacin resistance

Paul C. Adamson [1]*, Eric Y. Lin [2], Sung-Min Ha [3] and Jeffrey D. Klausner [4]



A global collection of nearly 13,000 *N. gonorrhoeae* genomes

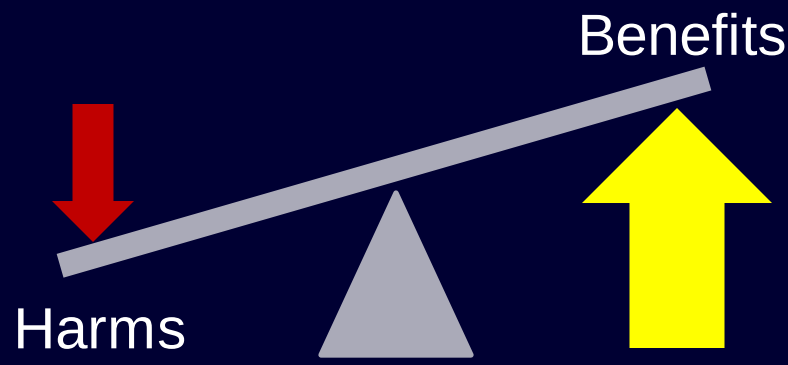
Includes tools that enable detection of AMR

No GyrB mutation analysis tools

Adamson PC, et al., https://doi.org/10.1093/jac/dkab262

Summary

- AMR in *N. gonorrhoeae* is an urgent global health threat
- Prevalence is higher in Western Pacific Region
- Antibiotic consumption might lead to resistance in *N. gonorrhoeae*
- Increased vulnerability to AMR among key populations
- Research to optimize STI screening, treatment, and monitoring for AMR



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Thank you!

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