Potential impacts of doxycycline post-exposure prophylaxis on gonorrhoea AMR and novel molecular strategies for AMR surveillance and resistance-guided management

Dr Emma Sweeney

Senior Research Fellow & Co-lead: Molecular

Diagnostics and Characterisation Laboratory

The University of Queensland Centre for Clinical Research

Acknowledgement of Country

The University of Queensland (UQ) acknowledges the Traditional Owners and their custodianship of the lands on which we meet.

We pay our respects to their Ancestors and their descendants, who continue cultural and spiritual connections to Country.

We recognise their valuable contributions to Australian and global society.

The Brisbane River pattern from *A Guidance Through Time* by Casey Coolwell and Kyra Mancktelow.

Disclaimers

We report research funding from SpeeDx Pty Ltd. SpeeDx Pty Ltd did not have any role in the conception or drafting of work presented.

We wish to clarify that we do not advise against the use of doxy-PEP but simply want to highlight important considerations pertaining to its use, particularly in relation to AMR

Take a single 200 mg dose on Monday morning to cover all sex within the previous 72 hours

Friday | Saturday | Sunday | Monday

Doxycycline to prevent STIs– syphilis, chlamydia, gonorrhoea, *M. genitalium*

Focuses on high-risk patients

Well tolerated, could be effective at reducing incidence of STIs (esp. syphilis)

Limitations of doxy-PEP for gonorrhoea

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Author Manuscript
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Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men who have Sex with Men who Continue to Engage in High Risk Sex: A Randomized, Controlled Pilot Study

Robert K. Bolan, MD*, Matthew R. Beymer, MPH*,†, Robert E. Weiss, PhD††, Risa P. Flynn*, Arleen A. Leibowitz, PhD**, and Jeffrey D. Klausner, MD, MPH‡

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Articles

Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

*Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Eric Cua, Constance Delaugerre, Catherine Capitant, Daniela Rojas-Castro, Julien Fonsart, Béatrice Barcat, Cécile Bébéar, Laurent Cotte, Olivier Robineau, François Raffi, Pierre Charbonneau, Alexandre Aslan, Julie Chas, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

The NEW ENGLAND JOURNAL of MEDICINE

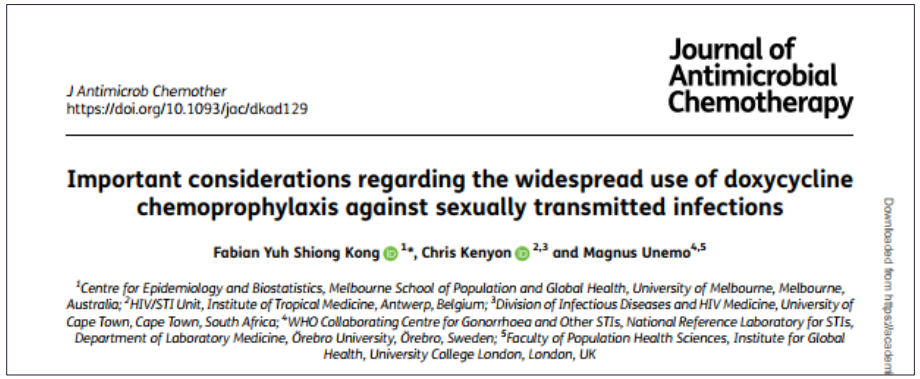
ORIGINAL ARTICLE

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections

Anne F. Luetkemeyer, M.D., Deborah Donnell, Ph.D., Julia C. Dombrowski, M.D., M.P.H., Stephanie Cohen, M.D., M.P.H., Cole Grabow, M.P.H., Clare E. Brown, Ph.D., Cheryl Malinski, B.S., Rodney Perkins, R.N., M.P.H., Melody Nasser, B.A., Carolina Lopez, B.A., Eric Vittinghoff, Ph.D., Susan P. Buchbinder, M.D., Hyman Scott, M.D., M.P.H., Edwin D. Charlebois, Ph.D., M.P.H., Diane V. Havlir, M.D., Olusegun O. Soge, Ph.D., and Connie Celum, M.D., M.P.H., for the DoxyPEP Study Team*

- **Very few isolates tested, potential overrepresentation of oropharyngeal isolates, short follow-up time → challenging to confirm selection of tetracycline resistance.**
- **Only 17% of infections had tetracycline MIC testing performed, with resistance increasing in doxy-PEP arm**
- **Differences in decreases of gonorrhoea incidence ?doxycycline resistance rates in the US (20%) and France (60%)**

Doxy-PEP for gonorrhoea raises concerns



J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad129

Journal of Antimicrobial Chemotherapy

Important considerations regarding the widespread use of doxycycline chemoprophylaxis against sexually transmitted infections

Fabian Yuh Shiong Kong [1]*, Chris Kenyon [2,3] and Magnus Unemo [4,5]

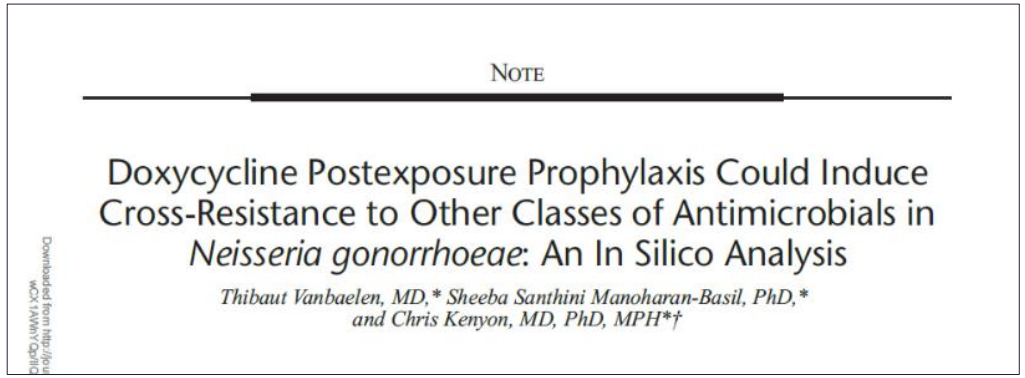
[1]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia; [2]HIV/STI Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Division of Infectious Diseases and HIV Medicine, University of Cape Town, Cape Town, South Africa; [4]WHO Collaborating Centre for Gonorrhoea and Other STIs, National Reference Laboratory for STIs, Department of Laboratory Medicine, Örebro University, Örebro, Sweden; [5]Faculty of Population Health Sciences, Institute for Global Health, University College London, London, UK

News & views

Sexual medicine

https://doi.org/10.1038/s41585-023-00788-1

Doxycycline-PEP – novel and promising but needs monitoring



NOTE

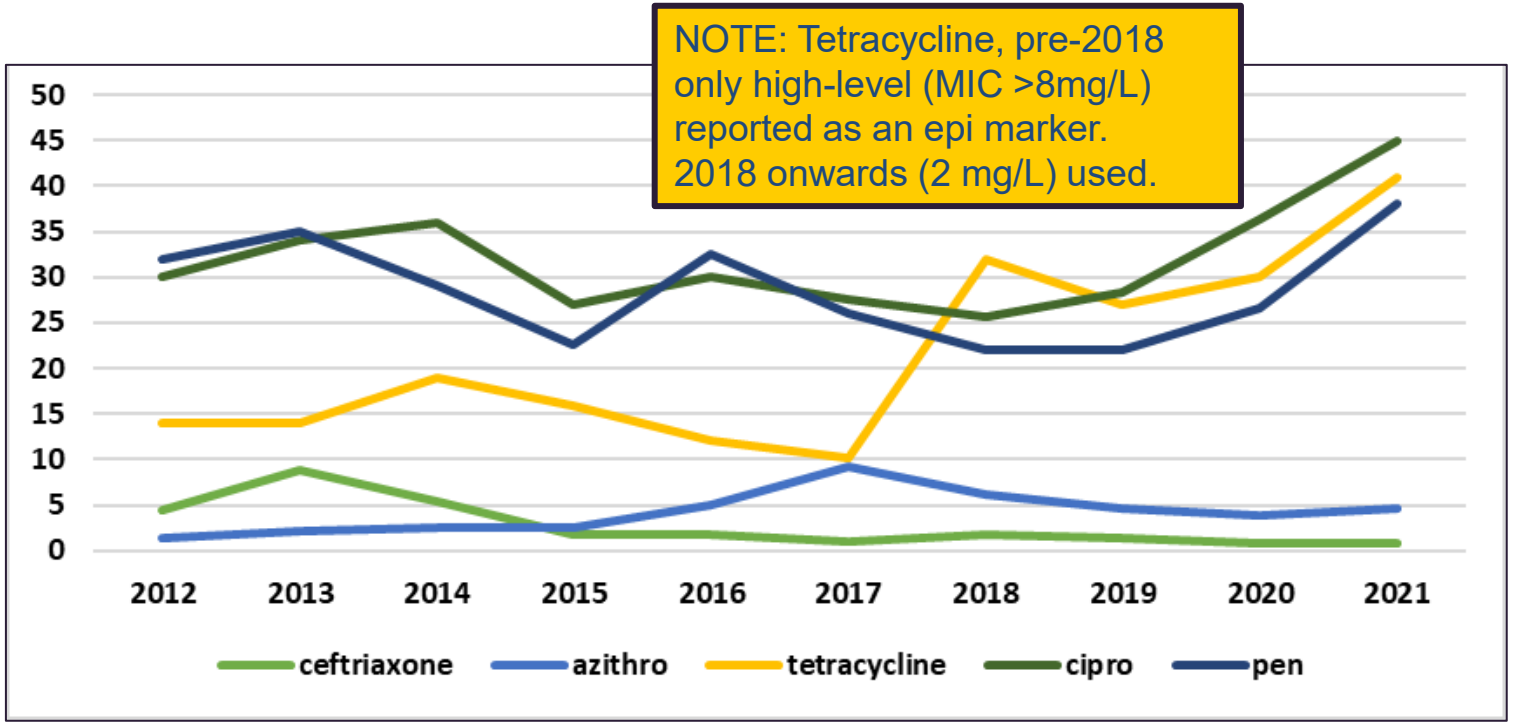
Doxycycline Postexposure Prophylaxis Could Induce Cross-Resistance to Other Classes of Antimicrobials in *Neisseria gonorrhoeae*: An In Silico Analysis

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

More evidence for efficacy needed and greater understanding of contribution to gonococcal AMR

Gonococcal AMR

- Gonorrhoea has developed resistance to all recommended treatments.
- Ciprofloxacin resistance means should only be used in resistance-guided treatment.
- Azithromycin resistance looking bad in many countries.
- Ceftriaxone resistance now a very real problem.
- How rapidly are we heading towards XDR (or largely untreatable) gonorrhoea?



Data from the Australian Gonococcal Surveillance Program .

Selection of *Neisseria gonorrhoeae* ceftriaxone resistance using doxycycline post-exposure prophylaxis

There is increasing evidence that doxycycline post-exposure prophylaxis (doxy-PEP) is effective for preventing sexually transmitted infections among high-risk patients, particularly in patients using HIV pre-exposure prophylaxis.[1–3] However, case, 32 more penA60 (and the more recently emerged and closely related penA237) reports have been published. Combined, this entails 96 isolates or strains from 14 countries, with tetracycline susceptibility data available for 75 (78·1%) of 96 reported strains. Of strains with tetracycline resistance data reported, only eight (10·7%) of 75 showed susceptibility to tetracyclines, with eight (10·7%) showing intermediate susceptibility, and 59 (78·7%) resistant to tetracyclines (using EUCAST and CLSI breakpoints for tetracycline). Secondly, is unknown. It is likely that this will depend on many factors, including how widespread the doxy-PEP use is, the populations in which it is used (including associated circulating gonococcal antimicrobial resistance profiles), and whether additional measures are put in place, such as complementing doxy-PEP with enhanced *N gonorrhoeae* antimicrobial resistance surveillance. Furthermore, the net effects that antimicrobial selection pressure will have on the circulating *N gonorrhoeae* clones, especially if doxy-PEP strategies are

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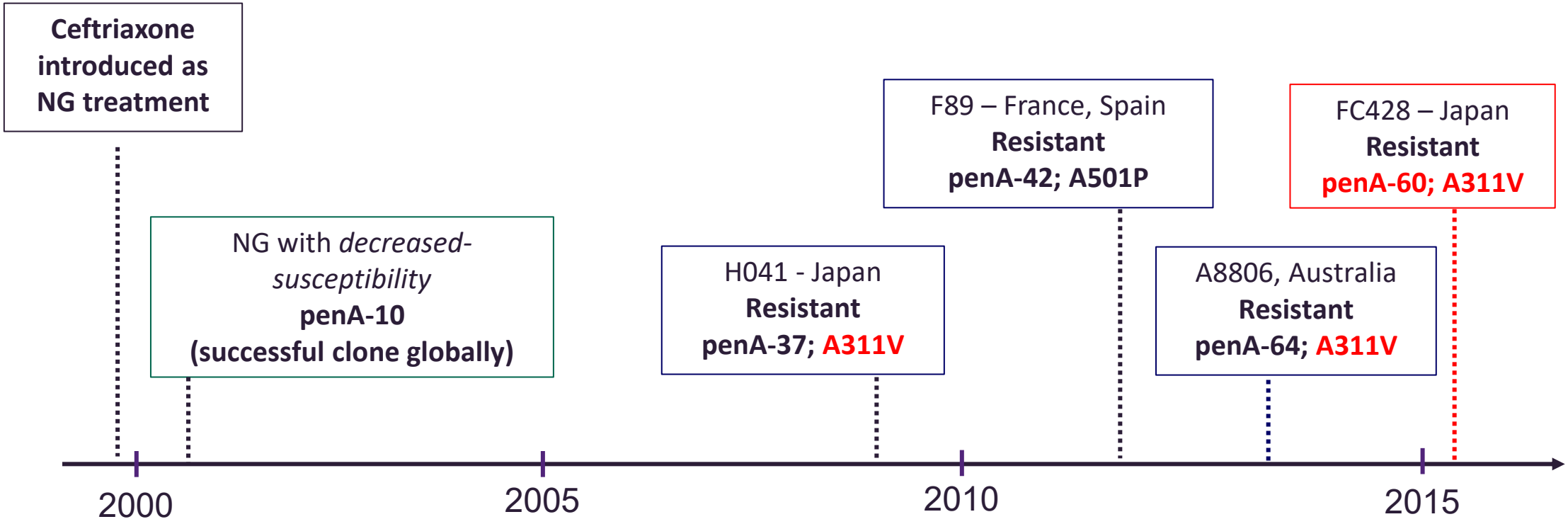
S1473-3099(23)00359-6

David Whiley, Jacob Tickner, Ratan Kundu, Tiffany Hogan, Sebastiaan van Hal, Monica Lahra. The Lancet Infectious Diseases 2023

History of gonococcal ceftriaxone resistance



Global dissemination of penA-60

Global dissemination of penA-60

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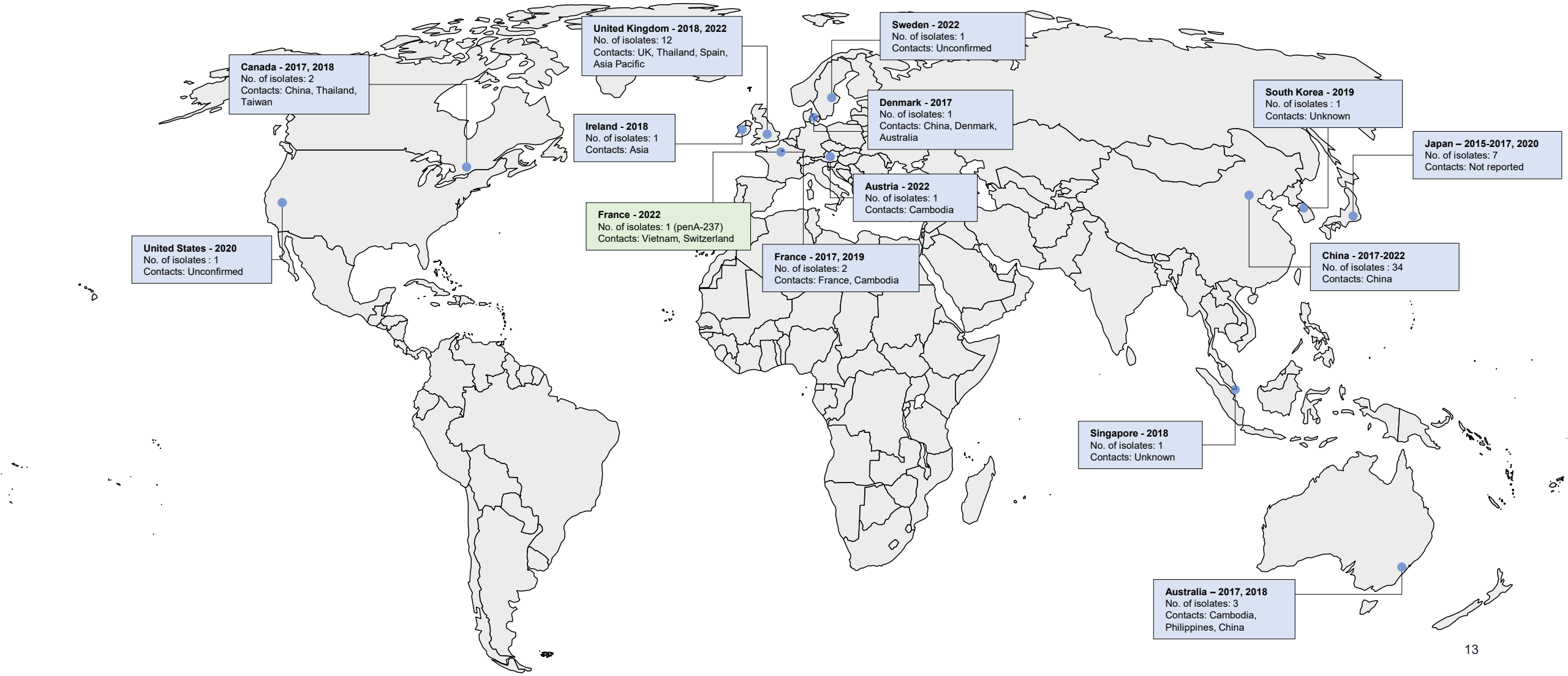
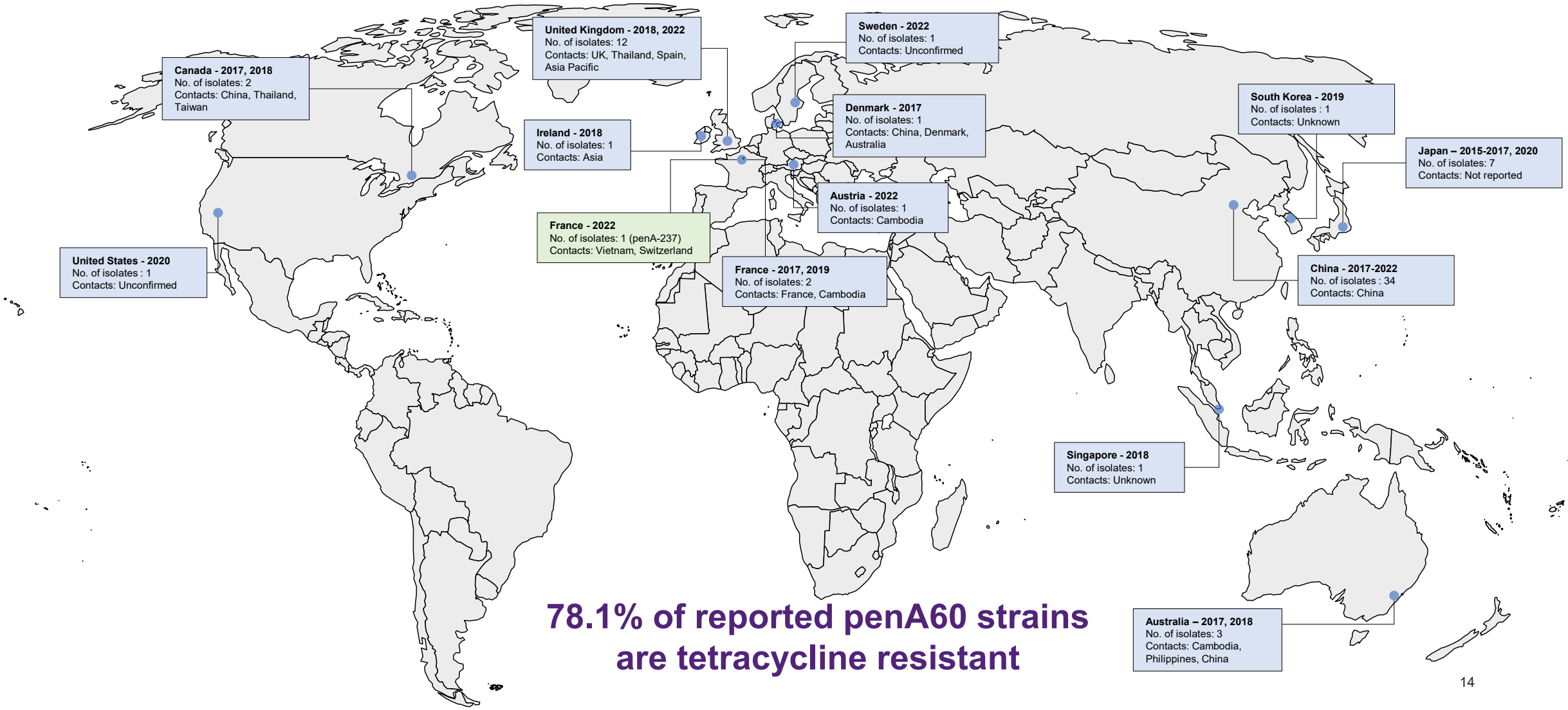
Global dissemination of penA-60



Global dissemination of penA-60



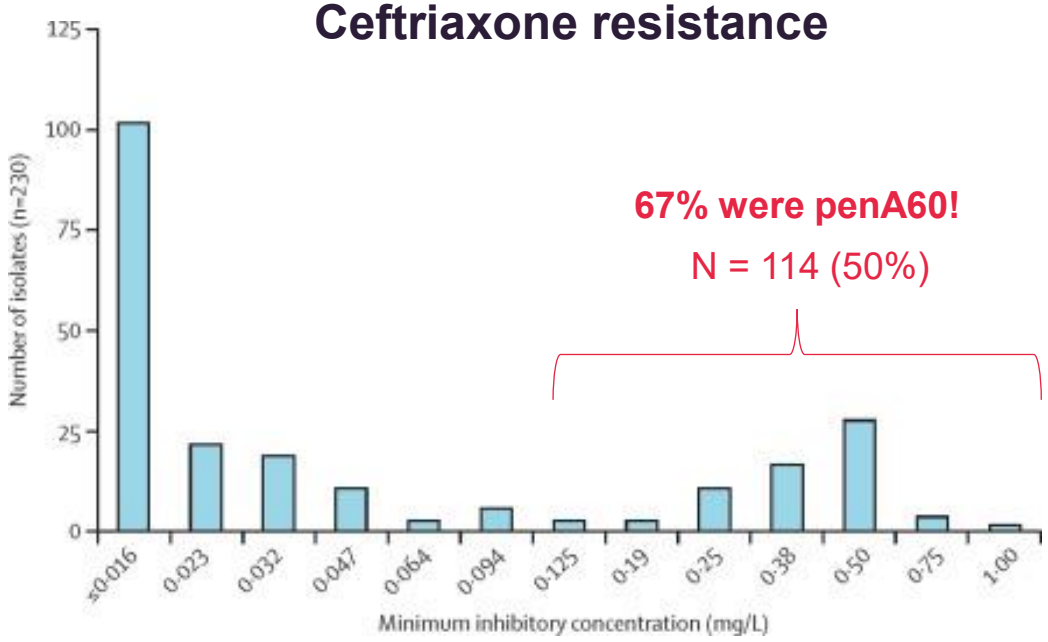
78.1% of reported penA60 strains are tetracycline resistant

Gonococcal AMR trends close to home

Ceftriaxone resistance in *Neisseria gonorrhoeae associated with the penA-60.001* allele in Hanoi, Viet Nam

Paul C Adamson [a] ✉, Vu N Hieu [b], Pham H Nhung [b], DM Whiley [c], TM Chau [b] ✉

Ceftriaxone resistance



67% were penA60!

N = 114 (50%)

Gonococcal surveillance in 2021 – 2022

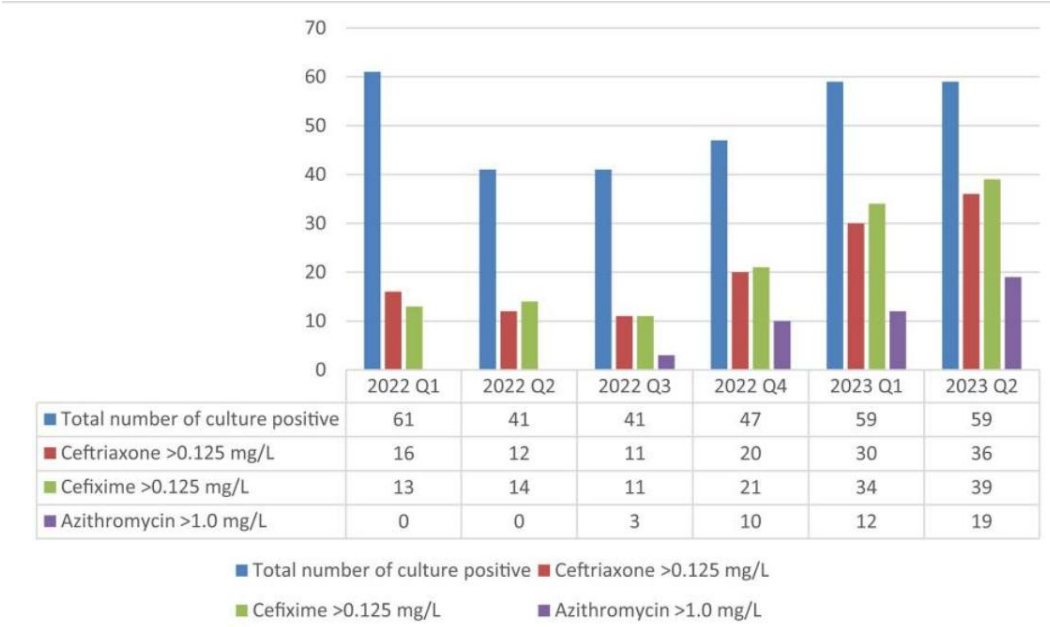
- 243 isolates tested, 230 tested for ceftriaxone MICs
- Ceftriaxone resistance present in half of all samples tested.
- penA60 represented 67% of all resistant isolates.
- All penA60 isolates had:
  - **Ceftriaxone MICs > 0.125 mg/L and were RESISTANT TO CEFIXIME**

Gonococcal AMR trends close to home

High prevalence of ceftriaxone-resistant and XDR *Neisseria gonorrhoeae* in several cities of Cambodia, 2022–23: WHO Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP)

V. Ouk[1], L. Say Heng[1], M. Virak[2], S. Deng[3], M. M. Lahra[4], R. Frankson[5], K. Kreisel[5], R. McDonald[5], M. Escher[6], M. Unemo[7,8], T. Wi[9] and I. Maatouk [9]* on behalf of the EGASP Cambodia Working Group†

- 15.4% resistant to ceftriaxone
  - **40% also resistant to azithromycin**
- 43.1% resistant to cefixime
- 14.4% resistant to azithromycin
- 97.1% resistant to ciprofloxacin



	2022 Q1	2022 Q2	2022 Q3	2022 Q4	2023 Q1	2023 Q2
Total number of culture positive	61	41	41	47	59	59
Ceftriaxone >0.125 mg/L	16	12	11	20	30	36
Cefixime >0.125 mg/L	13	14	11	21	34	39
Azithromycin >1.0 mg/L	0	0	3	10	12	19

- **19 isolates were resistant to all antibiotics tested and classified as XDR strains**

AGSP gonococcal AMR data (2023)

~10k isolates tested

- 22 isolates with ceftriaxone resistance

  NSW (8), VIC (8), QLD (3), WA (2), SA (1)

  4/8 isolates from VIC had an XDR profile

~64% of isolates (14/22) confirmed penA60

Many patients had travel history within the Asia-Pacific

Communicable Diseases Intelligence

Australian Gonococcal Surveillance Programme, 1 January to 31 March 2024

Monica M Lahra, Sebastiaan Van Hal, Sonya Natasha Hutabarat, Tiffany R Hogan

Table 2: The national number of gonococcal isolates and proportion of *N. gonorrhoeae* with ceftriaxone MIC values 0.064 and ≥ 0.125 mg/L and resistance to azithromycin, Australia, 2010 to 2023 and 1 January to 31 March 2024

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024 Q1
Number of isolates tested nationally	4,100	4,230	4,718	4,897	4,804	5,411	6,378	7,835	9,006	9,668	7,222	6,254	8,199	10,105	2,920
Ceftriaxone MIC 0.064 mg/L	4.80%	3.20%	4.10%	8.20%	4.80%	1.70%	1.65%	1.02%	1.67%	1.19%	0.87%	0.83%	5.05%	3.29%	2.88%
Ceftriaxone MIC ≥ 0.125 mg/L	0.10%	0.10%	0.30%	0.60%	0.60%	0.10%	0.05%	0.04%	0.06%	0.11%	0.07%	0.03%	0.51%	0.22%	0.31%
Total proportion of isolates with ceftriaxone MIC values ≥ 0.064 mg/L	**4.90%**	**3.30%**	**4.40%**	**8.80%**	**5.40%**	**1.80%**	**1.70%**	**1.06%**	**1.73%**	**1.30%**	**0.94%**	**0.86%**	**5.56%**	**3.51%**	**3.19%**
Azithromycin resistance	n/a	1.1%	1.3%	2.1%	2.5%	2.6%	5.0%	9.3%	6.2%	4.6%	3.9%	4.7%	3.9%	4.5%	3.3%

So what can we do?....

ashm

2023 Consensus Statement on doxycycline prophylaxis (Doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual, and other men who have sex with men in Australia.

Recommendations for community and clinicians

8 Culture samples must be collected for all gonorrhoea diagnoses prior to administration of antibiotics, to enable AMR surveillance for this organism.

Recommendations for research, guidelines, and policy

6 Molecular tests to monitor AMR should be developed, which could be deployed as reflex tests on all samples positive for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (and swabs positive for *Treponema pallidum* PCR), to comprehensively monitor for the emergence of AMR in STIs and other organisms.

7 Pathology and public health bodies should be appropriately funded to monitor AMR.

› Med J Aust. 2024 Apr 15;220(7):356-360. doi: 10.5694/mja2.52255. Epub 2024 Mar 13.

Response to the ASHM 2023 statement on the use of doxy–PEP in Australia: considerations and recommendations

Sara F E Bell [1], Emma L Sweeney [1], Fabian Y S Kong [2], David M Whiley [1 3], Catriona S Bradshaw [4], Jacob A Tickner [1]

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Molecular tests for gonococcal AMR

Molecular tests have replaced culture for majority of gonorrhoea diagnoses.

WHO strategy: development of rapid molecular assays for detection of AMR, to enhance surveillance and directly inform individual patient treatment.

- ResistancePlus GC (gonorrhoea detection + ciprofloxacin SUSC + RES)

ResistancePlus® GC

Detect *Neisseria gonorrhoeae* and ciprofloxacin susceptibility markers
Dual *N. gonorrhoeae* targets (*opa* & *porA*), *gyrA* S91F mutant, & *gyrA* S91 wildtype
in a single-well multiplex qPCR test

Smarter diagnostics. Simplified patient care

Conclusions. Resistance-guided treatment of *N. gonorrhoeae* infections with single-dose oral ciprofloxacin was highly efficacious. The widespread introduction and scale-up of *gyrA* serine 91 genotyping in *N. gonorrhoeae* infections could have substantial medical and public health benefits in settings where the majority of gonococcal infections are ciprofloxacin susceptible.

Molecular tests for gonococcal AMR

….. However, there have been challenges:

Azithromycin resistance: multiple markers, difficult from a commercial design perspective to target all mediators of resistance

Tetracycline resistance: *tetM* confers high-level resistance; however, existing primers have poor specificity for gonorrhoea

Ceftriaxone resistance: historical lack of certainty regarding suitable molecular targets → **But penA60 has emerged as target with high utility!**

Molecular tests for gonococcal AMR

The need for a commercial test using the *penA*60 allele to identify ceftriaxone-resistant *Neisseria gonorrhoeae*

*Jacob A Tickner, Monica M Lahra, *David M Whiley*
d.whiley@uq.edu.au

- penA60 molecular target is appealing – **single representative mutation with high predictive value**
- Enables simple, affordable and rapid detection of ceftriaxone resistance
  - **Molecular assays to monitor this resistance are important – more NAAT samples vs isolates → molecular tests have potential to enhance AMR surveillance**
  - **Cost-effective means to enact individualised treatment of gonorrhoea**

Molecular tests for gonococcal AMR

Future of molecular AMR detection: amplicon sequencing?

- Targets regions of the genome relevant to AMR (+/- gonococcal sequence typing markers)
- Cost-effective vs whole genome and multiple PCR tests
- **More powerful AMR surveillance ☺**

Take home messages

Benefits of doxyPEP should be carefully weighed against risks and potential harm in selecting for multi-drug/XDR gonococcal strains

At the very least, we need to enhance AMR surveillance among populations using doxyPEP

…But also useful for other populations (incursion of strains from GBMSM to hetero populations reported)

Molecular tools have the potential to meet these needs, now more urgent considering doxyPEP being used in Australia

Thank you!

Dr Emma Sweeney

Senior Research Fellow, UQ Centre for Clinical Research

e.l.sweeney@uq.edu.au

@MicroDx_UQ @theamrhub

@ScienceNerdEmma

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