# Tracking transmission of antimicrobial-resistant

# *Neisseria gonorrhoeae*

–

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**Deputy Director, Microbiological Diagnostic Unit Public Health Laboratory**
**NHMRC Early Career Fellow**

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Doherty Institute
The University of Melbourne
The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

# Overview

- Linking epidemiology and laboratory data
- Incorporating genomics into gonorrhoea epidemiology
  - Understanding transmission of gonorrhoea
  - Using genomics to understand ‘incursions’ of resistant gonorrhoea
- What does the future hold?

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## Microbiological Diagnostic Unit Public Health Laboratory

- Located within the Doherty Institute at the University of Melbourne
- Established in 1897
- Provides state, national and international public health microbiology services
- Receives all isolates of notifiable pathogens, including *Neisseria gonorrhoeae*

# Microbiology Laboratory at Melbourne Sexual Health Centre

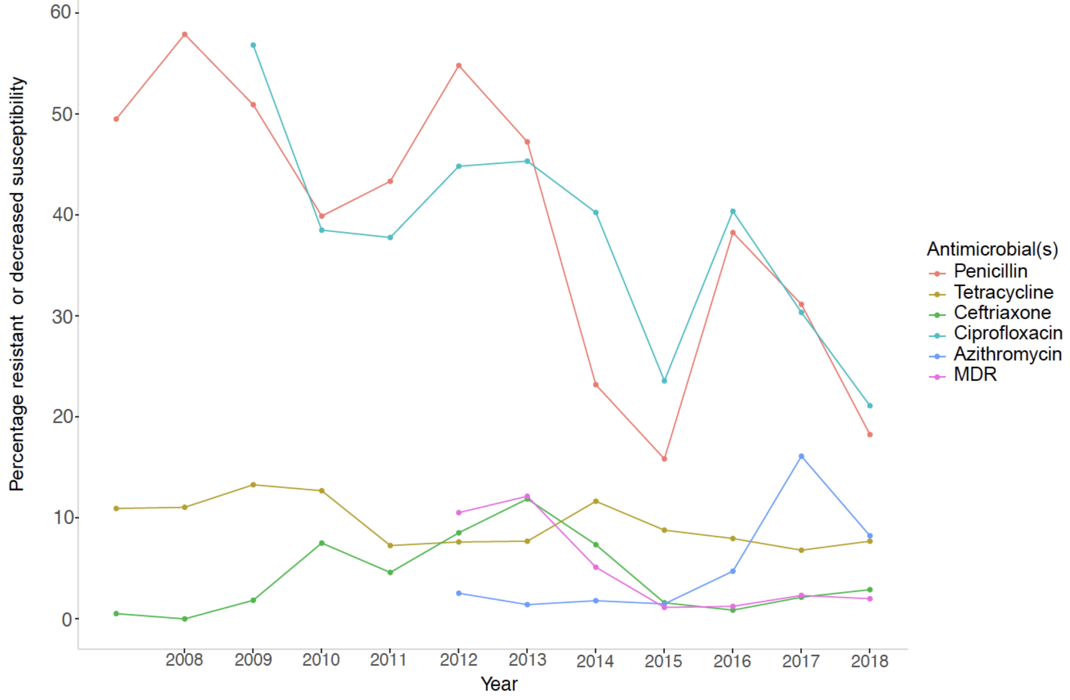
- On-site laboratory within MSHC
- Range of diagnostic bacteriology services
- On-site molecular testing (100,000+ specimens / year)
  - *Neisseria gonorrhoeae*
  - *Chlamydia trachomatis*
  - *Trichomonas vaginalis*
  - *Mycoplasma genitalium*

# Trends in AMR in *Neisseria gonorrhoeae*

- Few surveillance programmes combine AMR data with epidemiological and individual-level behavioural risk factors.
- Such information can provide insights into factors promoting the acquisition of resistant *N. gonorrhoeae*, such as sexual orientation, international travel or sexual behaviours
- Identification of specific risk groups may enable targeted public health action:
  - Intensified screening
  - Contact tracing
  - Monitoring for failure of empiric therapy

# AMR in Victoria, 2007 - 2018

7,588 isolates from 5,593 individuals



*Williamson et al, AAC, 2019*

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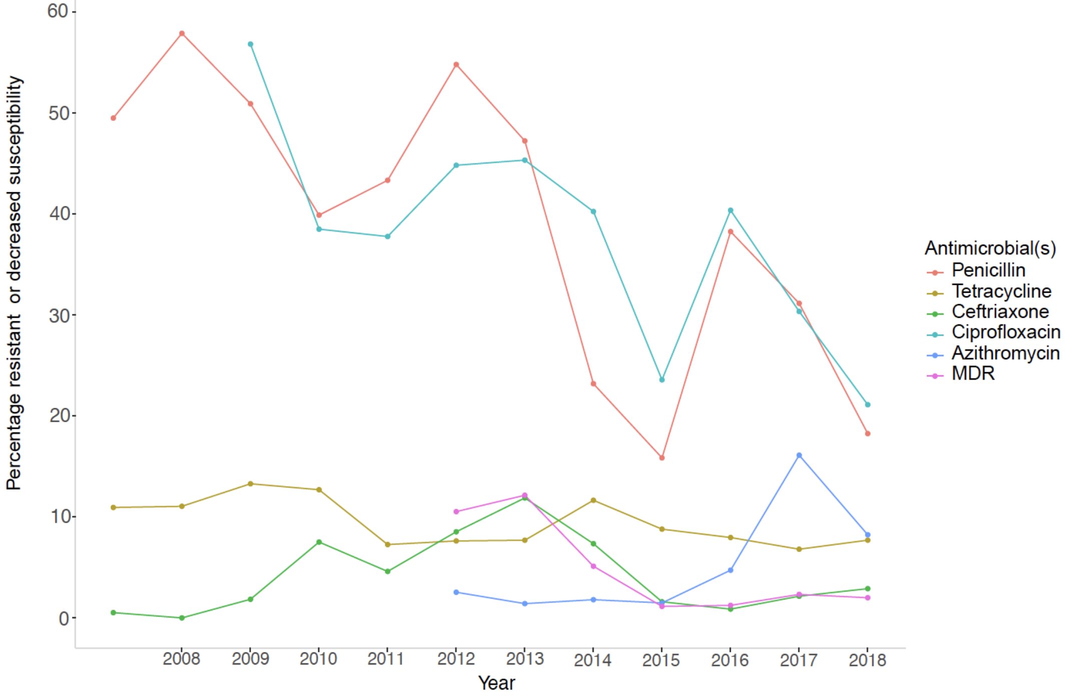
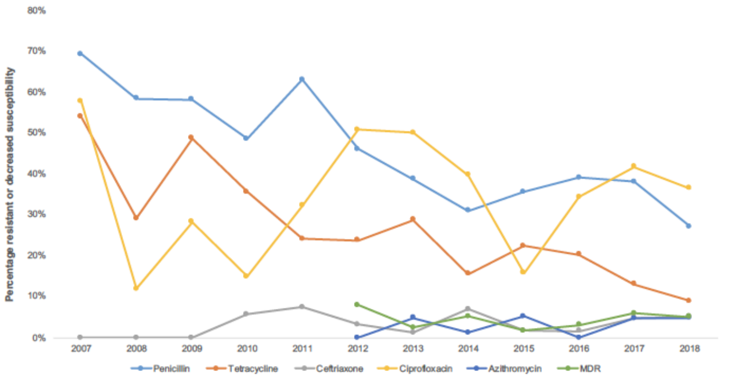
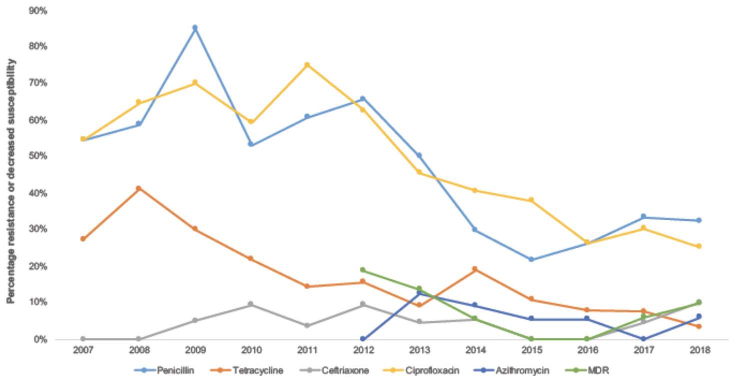


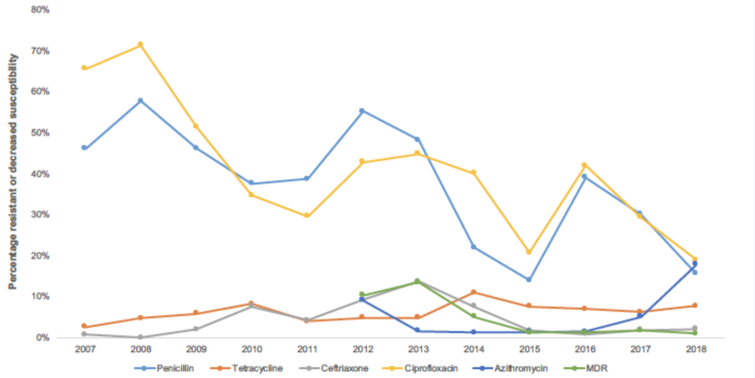
**Heterosexual males**



**Females**



**MSM**



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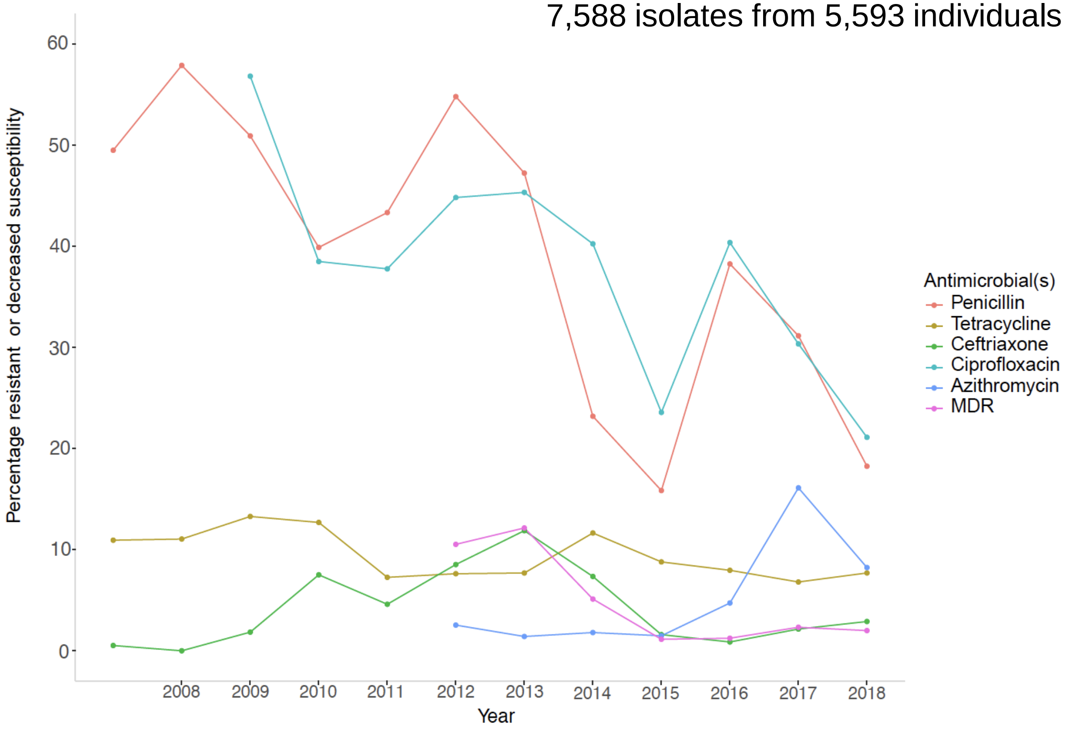
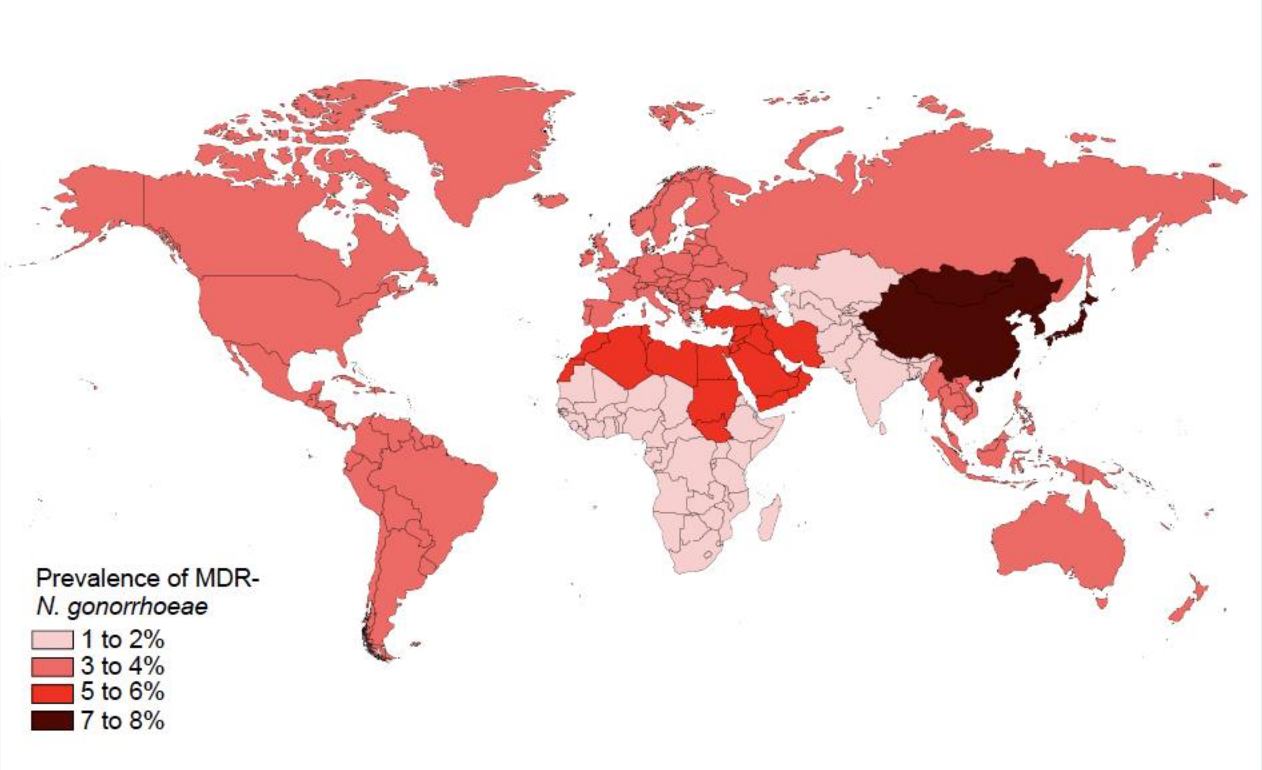
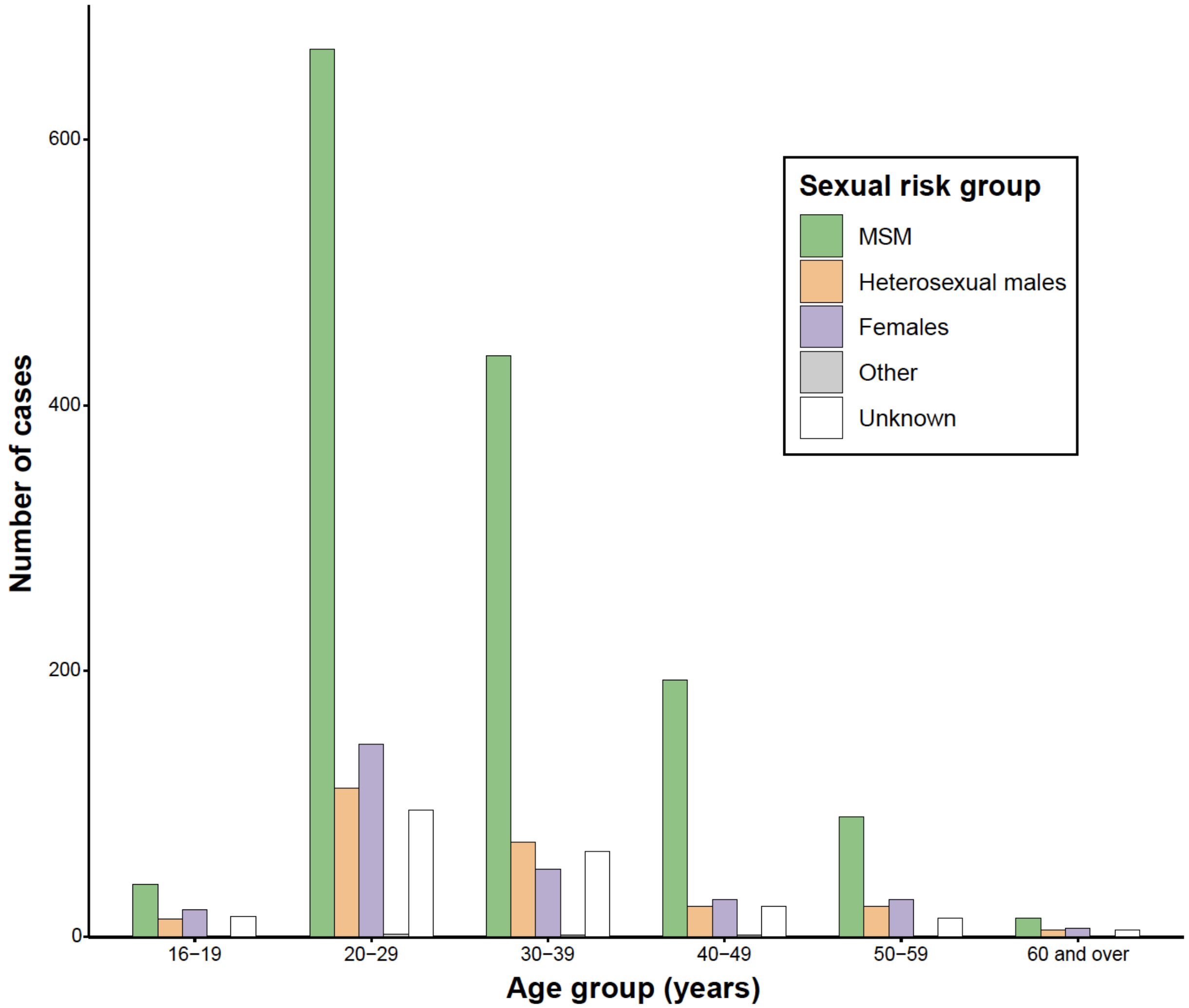


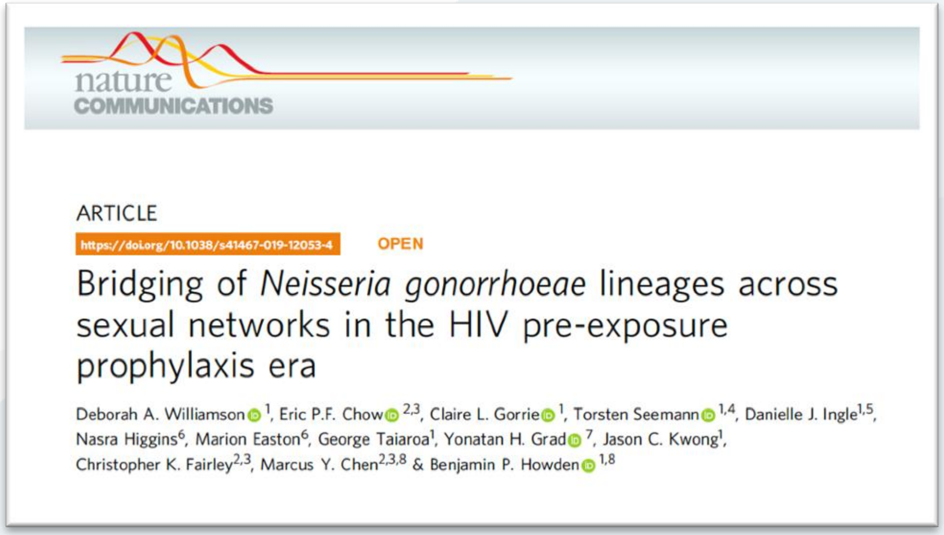


*Williamson et al, AAC, 2019*

# Transmission of *N. gonorrhoeae* in Victoria

- **Aim**: To determine the extent and duration of transmission (including AMR) within and across sexual networks in a dense urban area
- Sequenced 2,186 isolates from January 2017 – December 2017
- Epidemiological metadata from MSHC and Victorian DHHS
- Used 10 SNP cut-off to identify ‘transmission clusters’ based on hierarchical single-linkage clustering
    - Derived from maximum pairwise SNP distance between pairs of individuals




ARTICLE

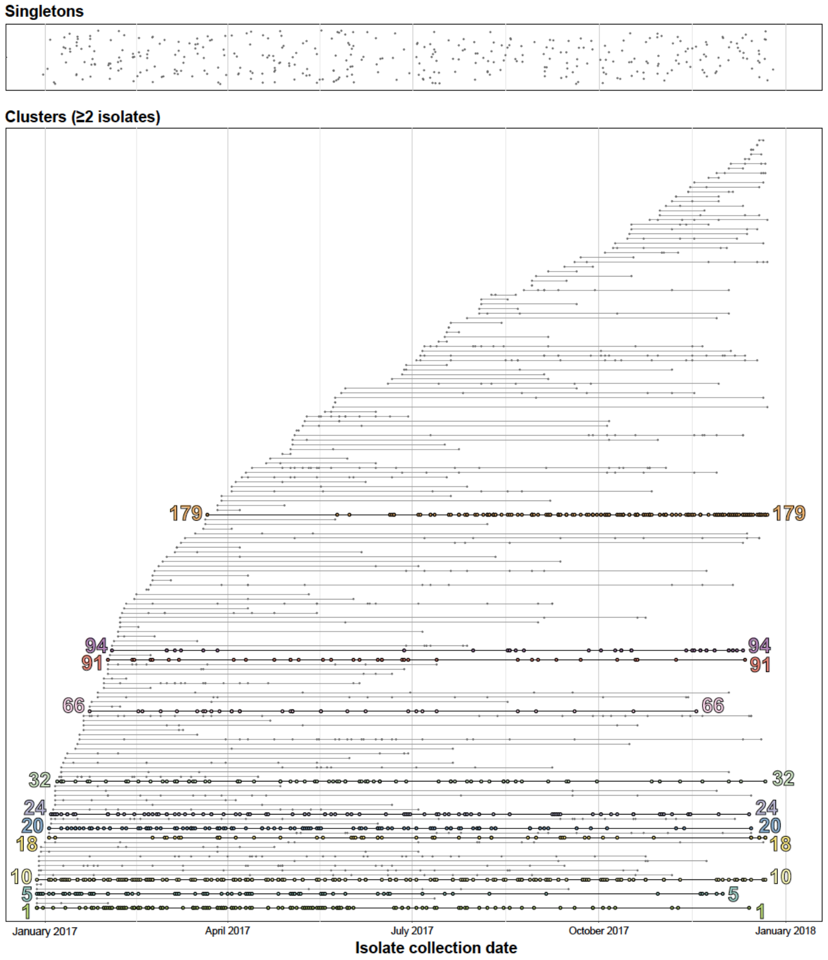
https://doi.org/10.1038/s41467-019-12053-4 OPEN

Bridging of *Neisseria gonorrhoeae* lineages across sexual networks in the HIV pre-exposure prophylaxis era

Deborah A. Williamson[1], Eric P.F. Chow[2,3], Claire L. Gorrie[1], Torsten Seemann[1,4], Danielle J. Ingle[1,5], Nasra Higgins[6], Marion Easton[6], George Taiaroa[1], Yonatan H. Grad[7], Jason C. Kwong[1], Christopher K. Fairley[2,3], Marcus Y. Chen[2,3,8] & Benjamin P. Howden[1,8]

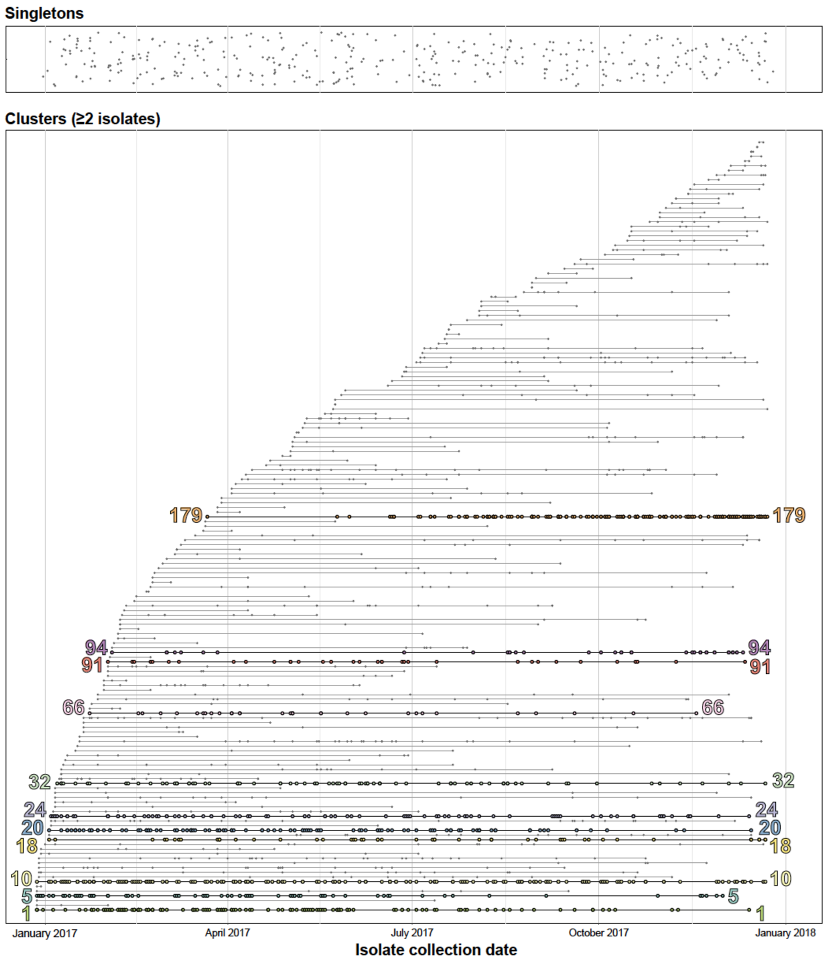
- 7,309 gonorrhoea notifications in 2017
  - 2,055 (28.1%) associated with culture
- 86.3% males
  - Of these, 84.6% were MSM

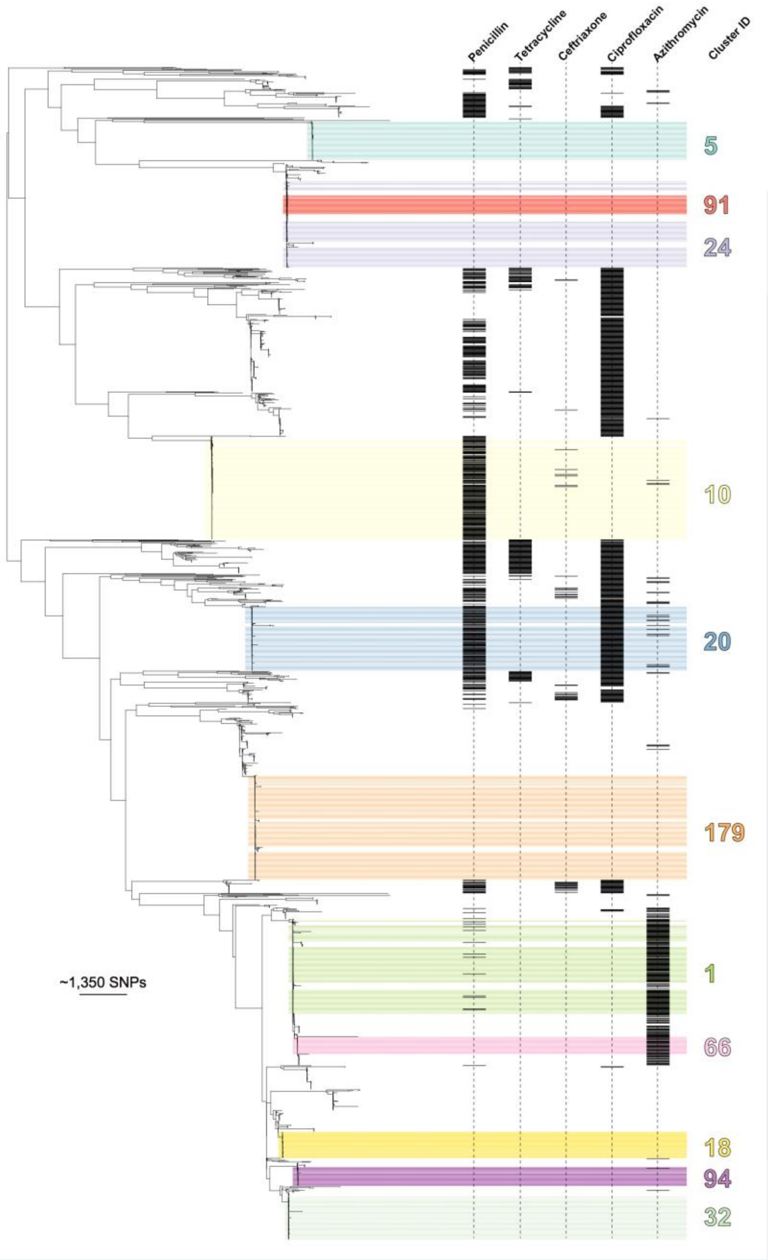
*Williamson DA, Chow EPF et al. Nature Comms, 2019*



- **161 clusters** of two or more related isolates (83% of the dataset)
- Median size: **3 cases** (range 2 to 181 patients)
- Median time from first to last case: **102 days** (range 0 to 362 days).

*Williamson DA, Chow EPF et al. Nature Comms, 2019*





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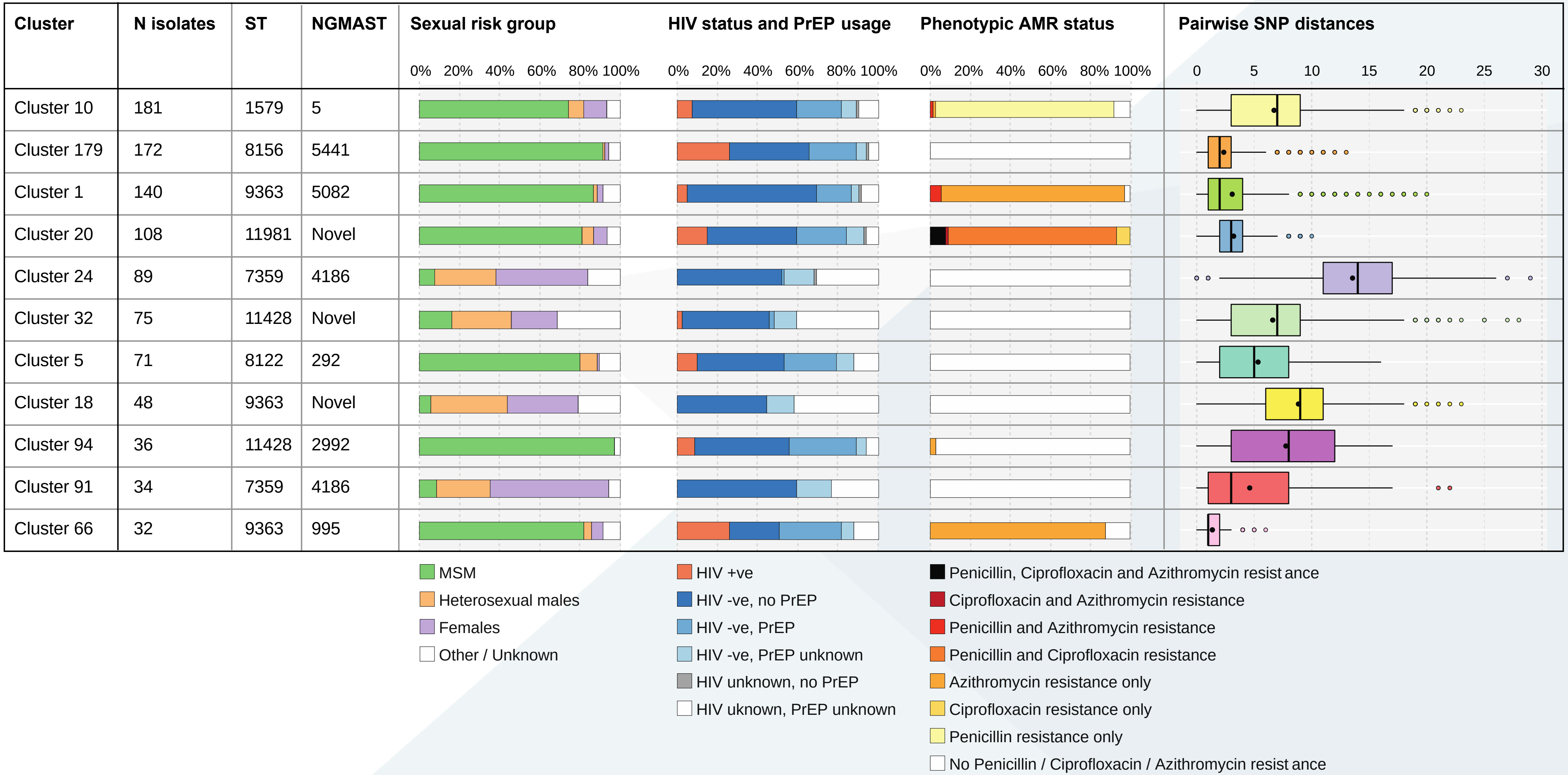
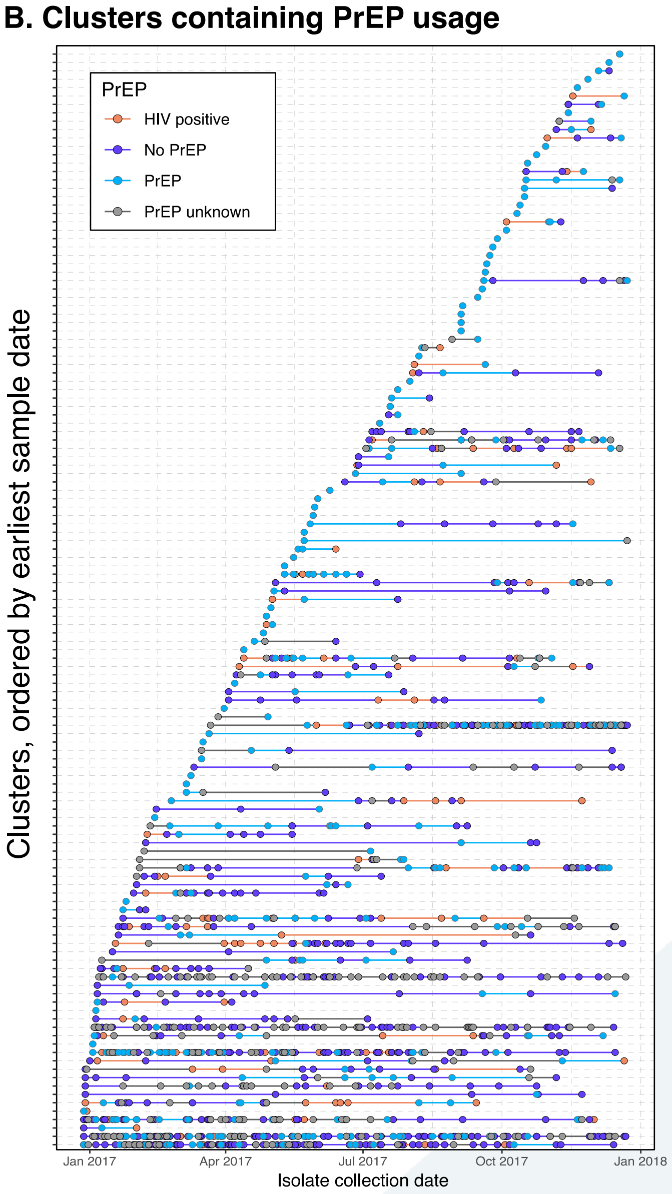
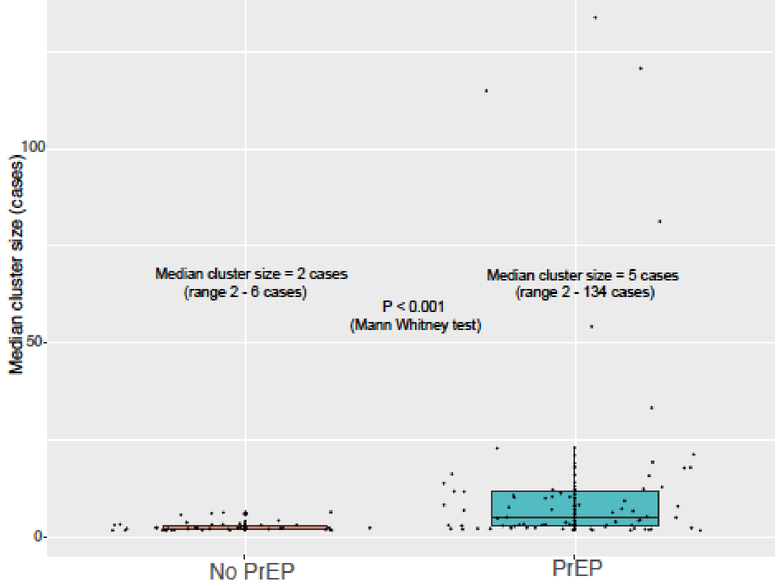


| Cluster | N isolates | ST | NGMAST |
|---|---|---|---|
| Cluster 10 | 181 | 1579 | 5 |
| Cluster 179 | 172 | 8156 | 5441 |
| Cluster 1 | 140 | 9363 | 5082 |
| Cluster 20 | 108 | 11981 | Novel |
| Cluster 24 | 89 | 7359 | 4186 |
| Cluster 32 | 75 | 11428 | Novel |
| Cluster 5 | 71 | 8122 | 292 |
| Cluster 18 | 48 | 9363 | Novel |
| Cluster 94 | 36 | 11428 | 2992 |
| Cluster 91 | 34 | 7359 | 4186 |
| Cluster 66 | 32 | 9363 | 995 |

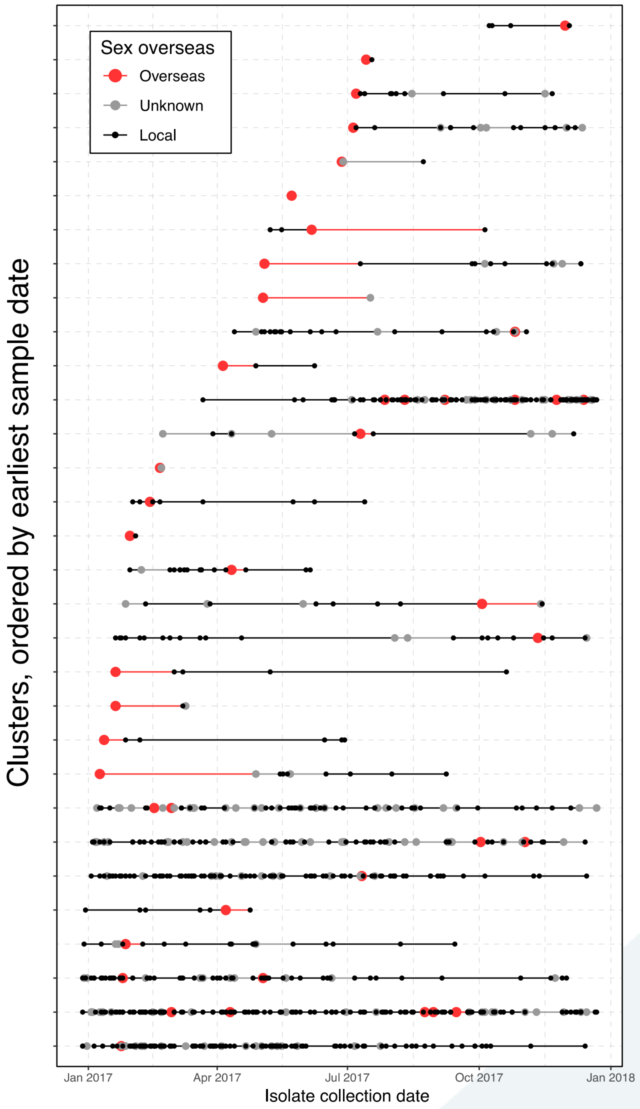
*Williamson DA, Chow EPF et al. Nature Comms, 2019*



- Clusters containing both HIV-positive and HIV-negative MSM indicating disassortative sexual mixing and gonorrhoea transmission

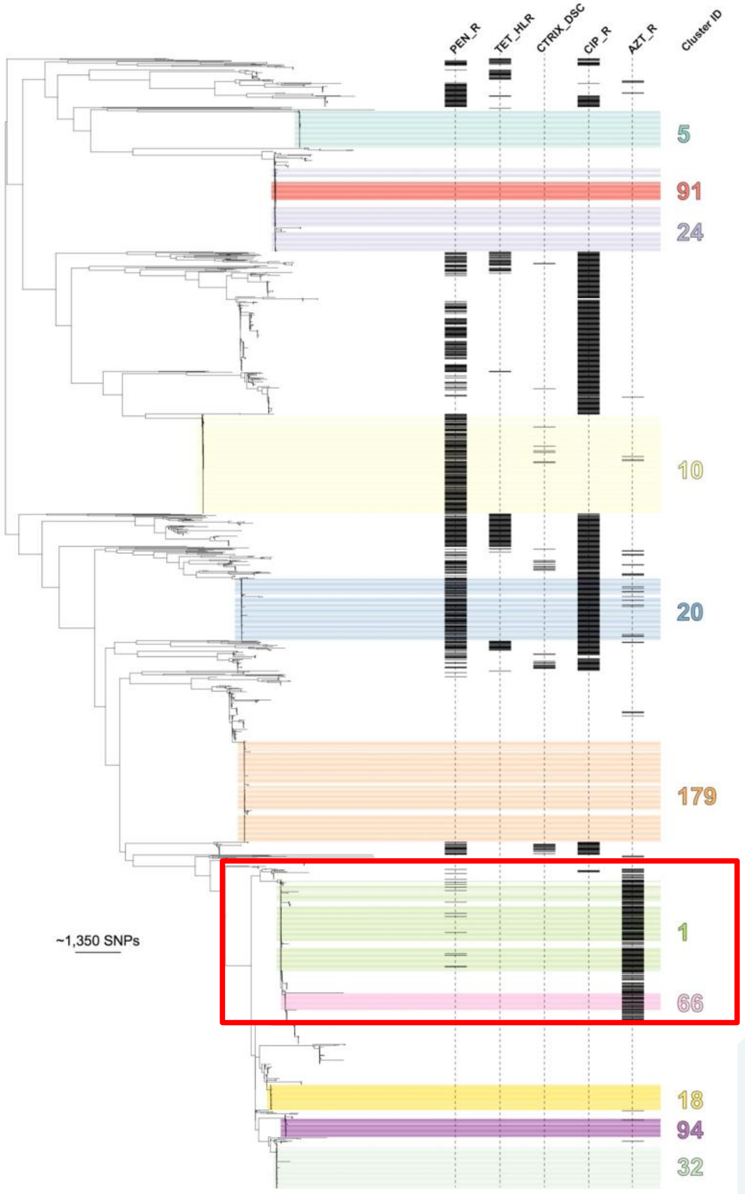


*Williamson DA, Chow EPF et al. Nature Comms, 2019*



- Travel related infections more likely to be sporadic
  - 18.5% sporadic infection vs. 3.1% in a cluster (P <0.001)
- 31 clusters containing patients who reported recent sex overseas
  - First isolate in 13 (42%) of these clusters was from a travel-associated case

*Williamson DA, Chow EPF et al. Nature Comms, 2019*



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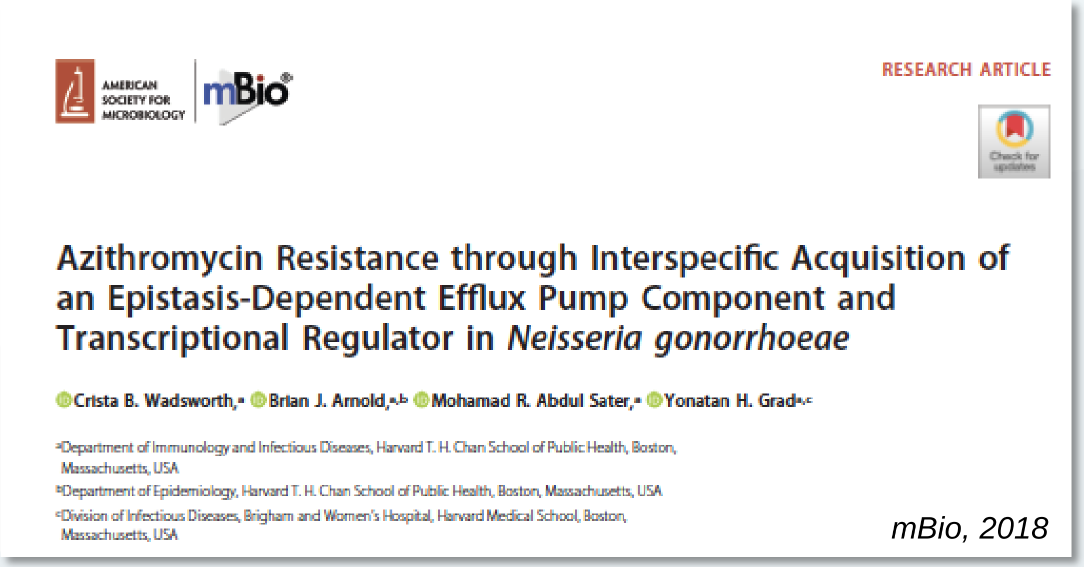
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RESEARCH ARTICLE

## Azithromycin Resistance through Interspecific Acquisition of an Epistasis-Dependent Efflux Pump Component and Transcriptional Regulator in *Neisseria gonorrhoeae*

Crista B. Wadsworth,[a] Brian J. Arnold,[a,b] Mohamad R. Abdul Sater,[a] Yonatan H. Grad[a,c]

[a]Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA
[b]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA
[c]Division of Infectious Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

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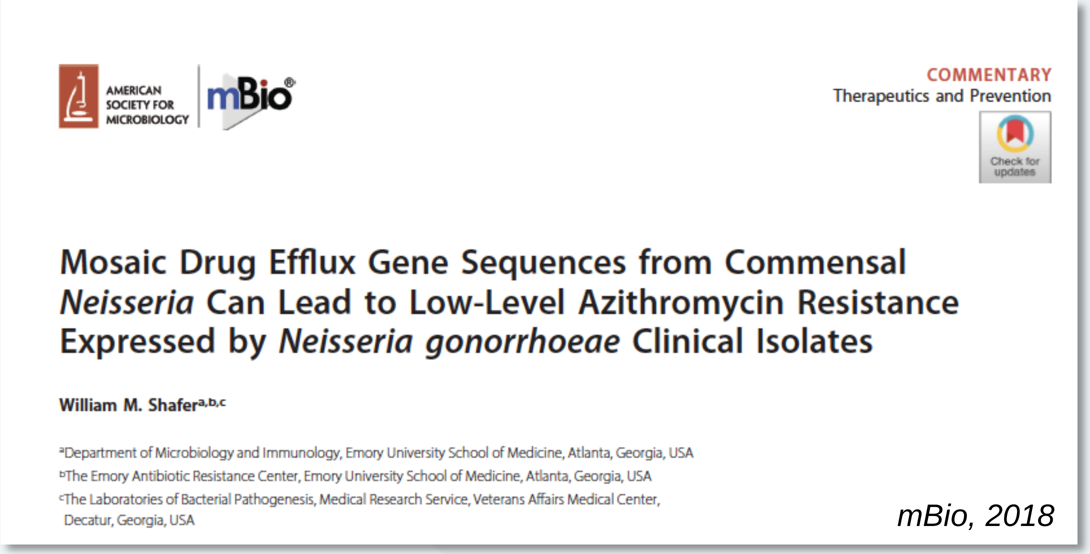
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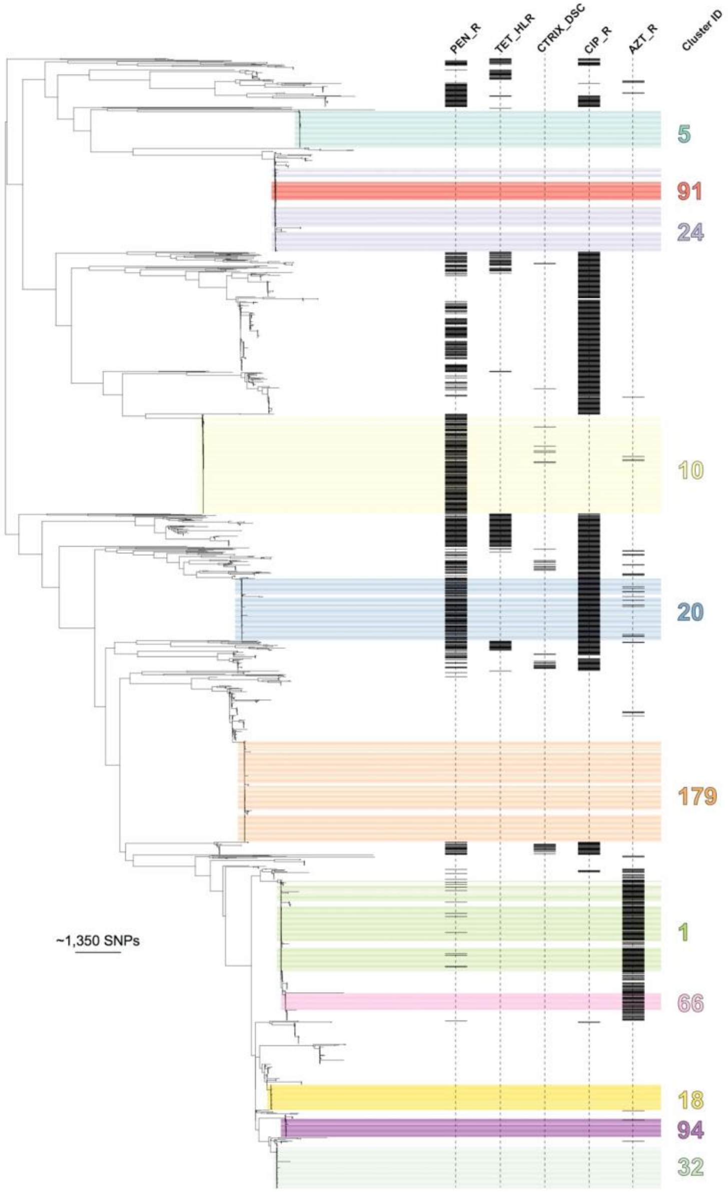
COMMENTARY
Therapeutics and Prevention

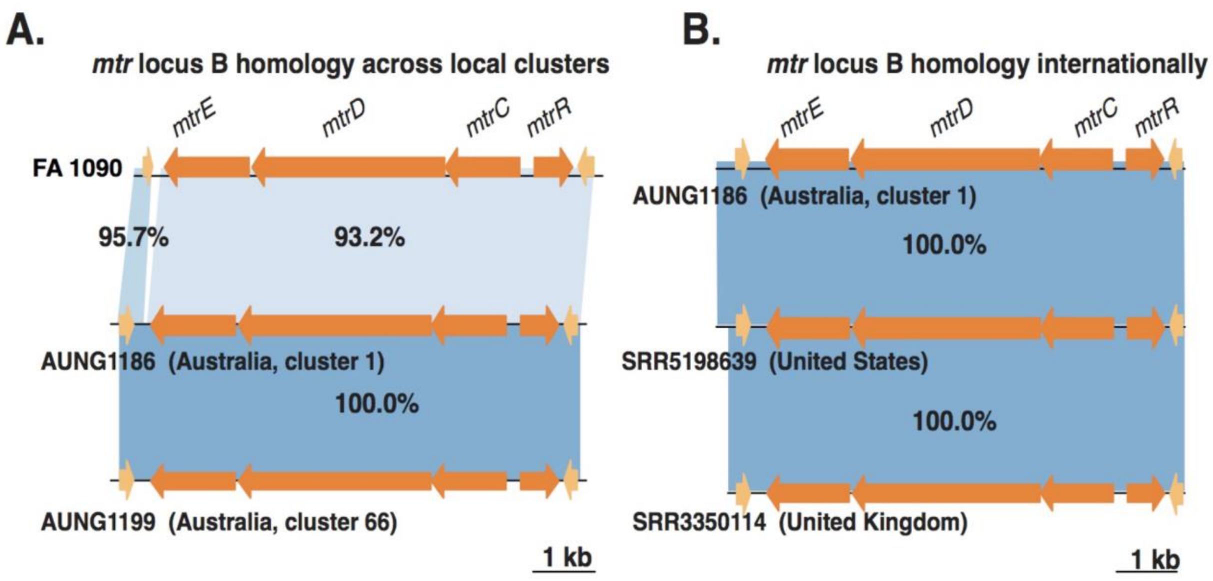
## Mosaic Drug Efflux Gene Sequences from Commensal *Neisseria* Can Lead to Low-Level Azithromycin Resistance Expressed by *Neisseria gonorrhoeae* Clinical Isolates

William M. Shafer[a,b,c]

[a]Department of Microbiology and Immunology, Emory University School of Medicine, Atlanta, Georgia, USA
[b]The Emory Antibiotic Resistance Center, Emory University School of Medicine, Atlanta, Georgia, USA
[c]The Laboratories of Bacterial Pathogenesis, Medical Research Service, Veterans Affairs Medical Center, Decatur, Georgia, USA

mBio, 2018

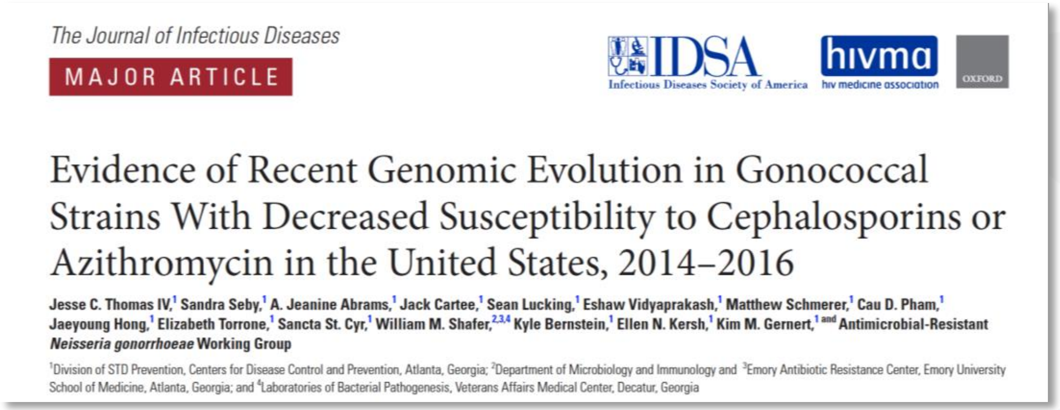




- Interspecies recombination at *mtr locus* major mechanism of azithromycin resistance

*Williamson DA, Chow EPF et al. Nature Comms, 2019*

# International dissemination of an azithromycin-resistant lineage



The Journal of Infectious Diseases

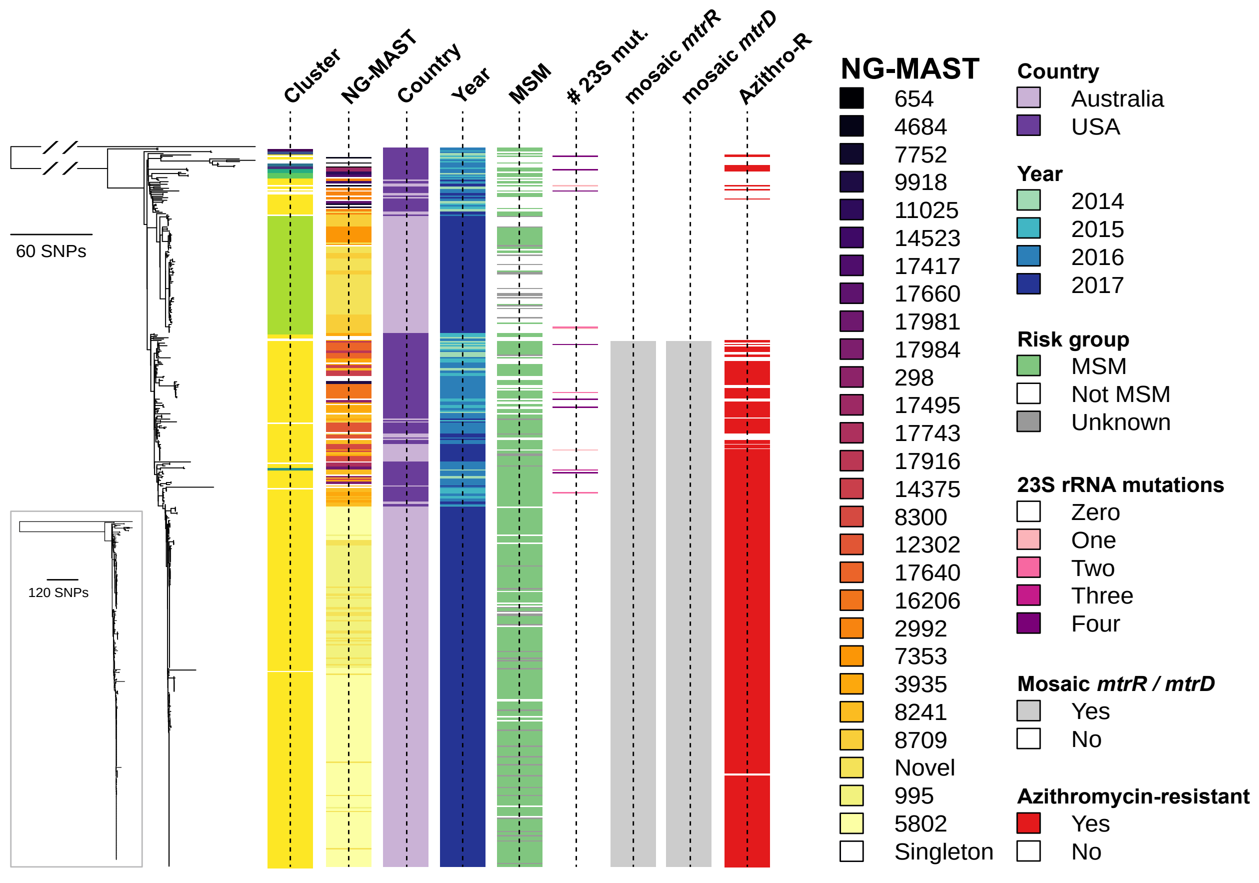
**MAJOR ARTICLE**

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

## Evidence of Recent Genomic Evolution in Gonococcal Strains With Decreased Susceptibility to Cephalosporins or Azithromycin in the United States, 2014–2016

**Jesse C. Thomas IV,[1] Sandra Seby,[1] A. Jeanine Abrams,[1] Jack Cartee,[1] Sean Lucking,[1] Eshaw Vidyaprakash,[1] Matthew Schmerer,[1] Cau D. Pham,[1] Jaeyoung Hong,[1] Elizabeth Torrone,[1] Sancta St. Cyr,[1] William M. Shafer,[2,3,4] Kyle Bernstein,[1] Ellen N. Kersh,[1] Kim M. Gernert,[1] and Antimicrobial-Resistant *Neisseria gonorrhoeae* Working Group**

[1]Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Department of Microbiology and Immunology and [3]Emory Antibiotic Resistance Center, Emory University School of Medicine, Atlanta, Georgia; and [4]Laboratories of Bacterial Pathogenesis, Veterans Affairs Medical Center, Decatur, Georgia



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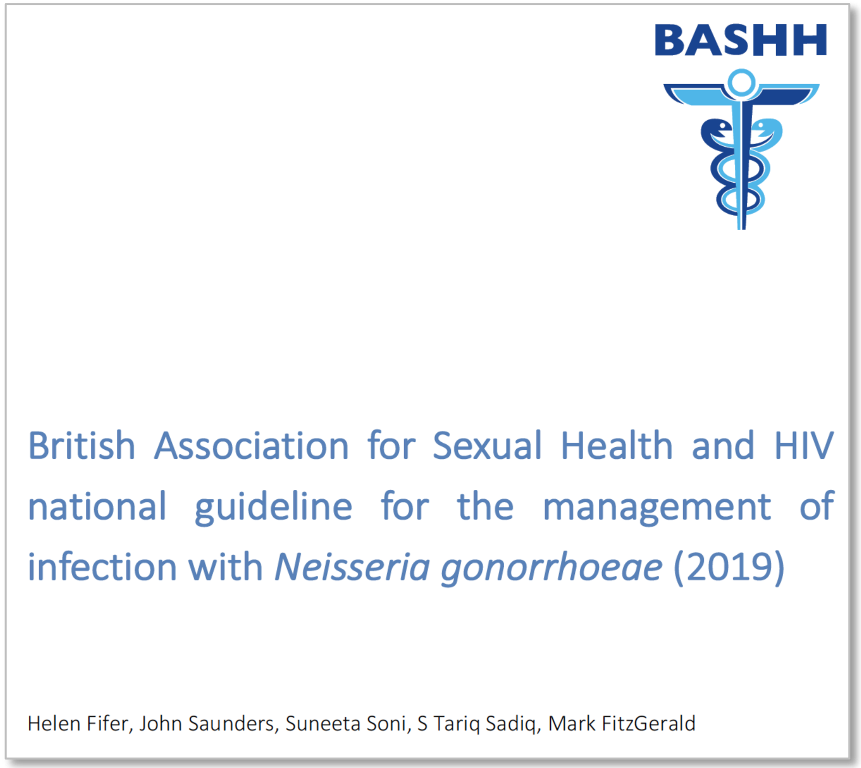
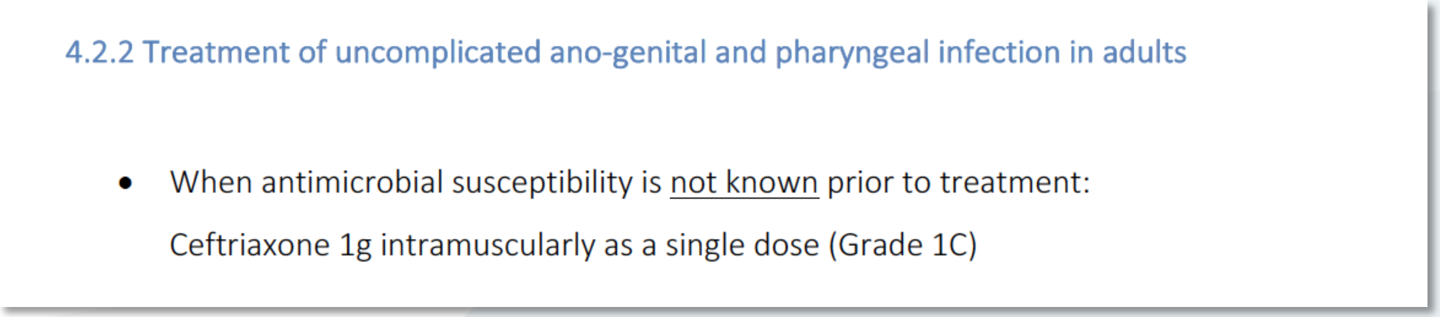


BASHH

British Association for Sexual Health and HIV national guideline for the management of infection with *Neisseria gonorrhoeae* (2019)

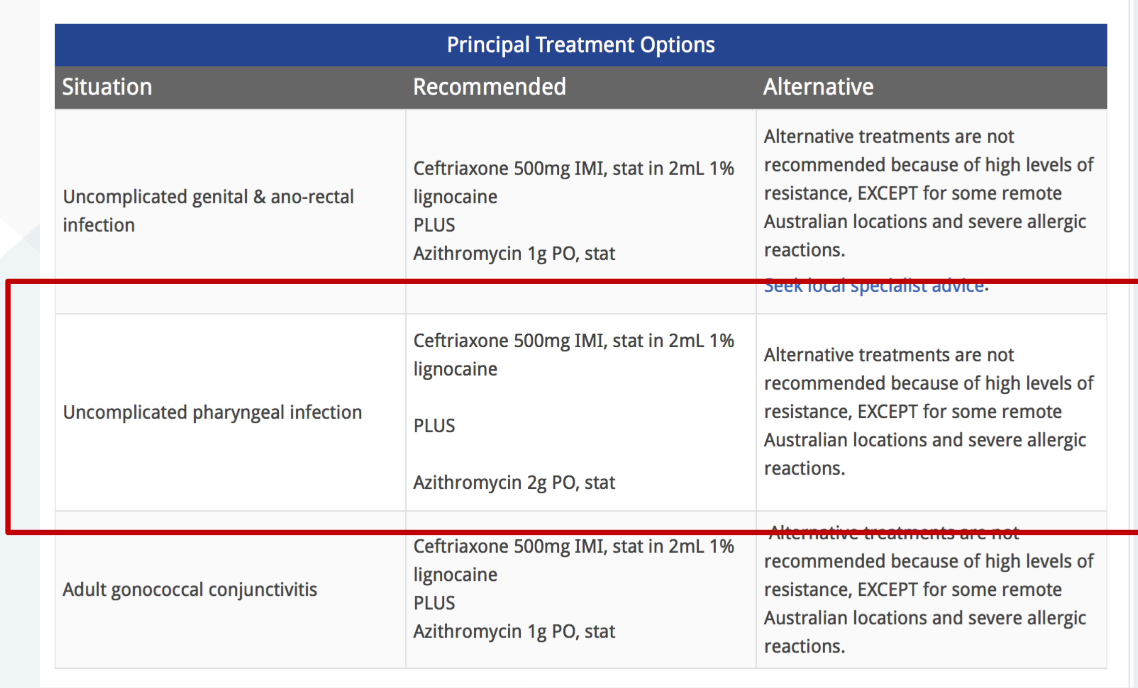
Helen Fifer, John Saunders, Suneeta Soni, S Tariq Sadiq, Mark FitzGerald



### 4.2.2 Treatment of uncomplicated ano-genital and pharyngeal infection in adults

- When antimicrobial susceptibility is not known prior to treatment:

  Ceftriaxone 1g intramuscularly as a single dose (Grade 1C)

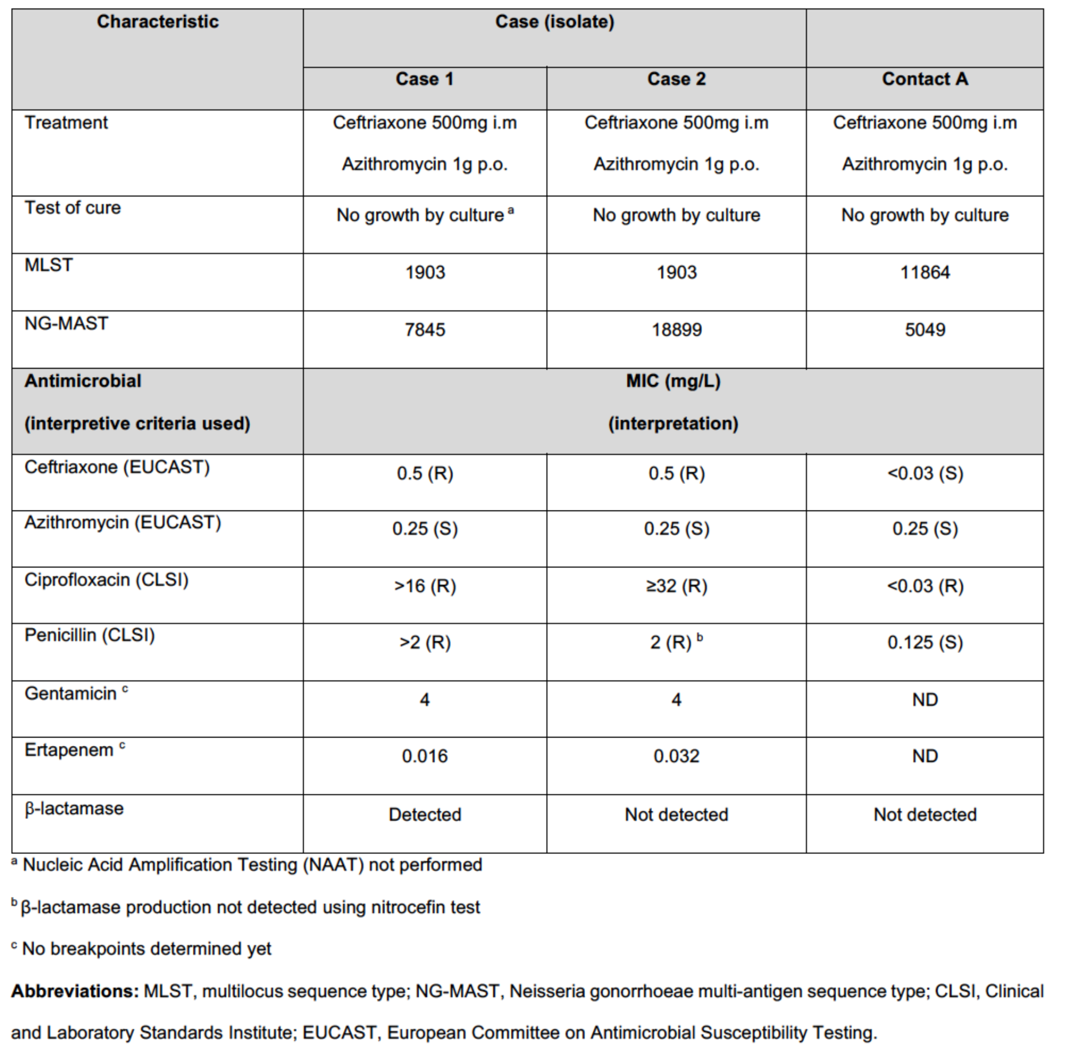


**Principal Treatment Options**

| Situation | Recommended | Alternative |
|---|---|---|
| Uncomplicated genital & ano-rectal infection | Ceftriaxone 500mg IMI, stat in 2mL 1% lignocaine<br>PLUS<br>Azithromycin 1g PO, stat | Alternative treatments are not recommended because of high levels of resistance, EXCEPT for some remote Australian locations and severe allergic reactions.<br>Seek local specialist advice. |
| Uncomplicated pharyngeal infection | Ceftriaxone 500mg IMI, stat in 2mL 1% lignocaine<br>PLUS<br>Azithromycin 2g PO, stat | Alternative treatments are not recommended because of high levels of resistance, EXCEPT for some remote Australian locations and severe allergic reactions. |
| Adult gonococcal conjunctivitis | Ceftriaxone 500mg IMI, stat in 2mL 1% lignocaine<br>PLUS<br>Azithromycin 1g PO, stat | Alternative treatments are not recommended because of high levels of resistance, EXCEPT for some remote Australian locations and severe allergic reactions. |

# Ceftriaxone-resistant *Neisseria gonorrhoeae* in Australia

- Since 2017, there have been sporadic reports of an internationally-disseminated ceftriaxone-resistant *N. gonorrhoeae* clone (‘**FC428 clone**’),
- Initially reported from Japan, and subsequently from Australia, Canada, Denmark, France, Ireland, China, South Korea, Singapore and the United Kingdom
- Reported from heterosexuals, including small cluster of local transmission in the UK
- At least five cases in Australia this year, including first report from MSM



| Characteristic | Case (isolate) | | |
|---|---|---|---|
| | Case 1 | Case 2 | Contact A |
| Treatment | Ceftriaxone 500mg i.m<br>Azithromycin 1g p.o. | Ceftriaxone 500mg i.m<br>Azithromycin 1g p.o. | Ceftriaxone 500mg i.m<br>Azithromycin 1g p.o. |
| Test of cure | No growth by culture [a] | No growth by culture | No growth by culture |
| MLST | 1903 | 1903 | 11864 |
| NG-MAST | 7845 | 18899 | 5049 |
| **Antimicrobial (interpretive criteria used)** | **MIC (mg/L) (interpretation)** | | |
| Ceftriaxone (EUCAST) | 0.5 (R) | 0.5 (R) | <0.03 (S) |
| Azithromycin (EUCAST) | 0.25 (S) | 0.25 (S) | 0.25 (S) |
| Ciprofloxacin (CLSI) | >16 (R) | ≥32 (R) | <0.03 (R) |
| Penicillin (CLSI) | >2 (R) | 2 (R) [b] | 0.125 (S) |
| Gentamicin [c] | 4 | 4 | ND |
| Ertapenem [c] | 0.016 | 0.032 | ND |
| β-lactamase | Detected | Not detected | Not detected |

[a] Nucleic Acid Amplification Testing (NAAT) not performed

[b] β-lactamase production not detected using nitrocefin test

[c] No breakpoints determined yet

**Abbreviations:** MLST, multilocus sequence type; NG-MAST, Neisseria gonorrhoeae multi-antigen sequence type; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

*Under review*

| Characteristic | Case (isolate) | | |
|---|---|---|---|
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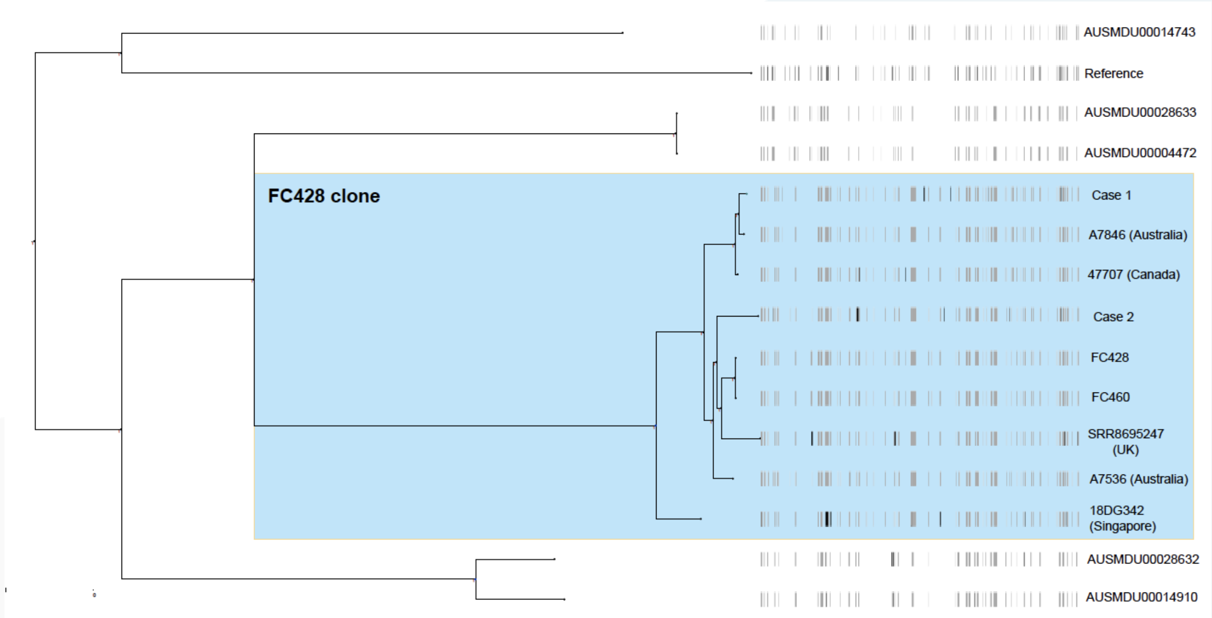

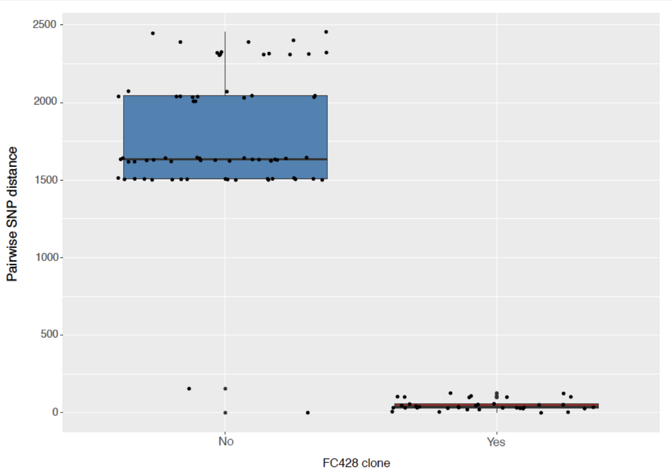

*Under review*

# Summary

- Combining laboratory and epidemiological data provides far greater insights into the spread of AMR *N. gonorrhoeae* than either alone
- Optimal combination:
  - Genomics
  - Phenotypic susceptibility data
  - Behavioural and risk factor data
- Next step is how to combine and translate into policy and practice

# Acknowledgements

**Melbourne Sexual Heath Centre**

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Nasra Higgins

Nicola Stephens

**MDU PHL**

Ben Howden

Susan Ballard

Michelle Sait

Claire Gorrie

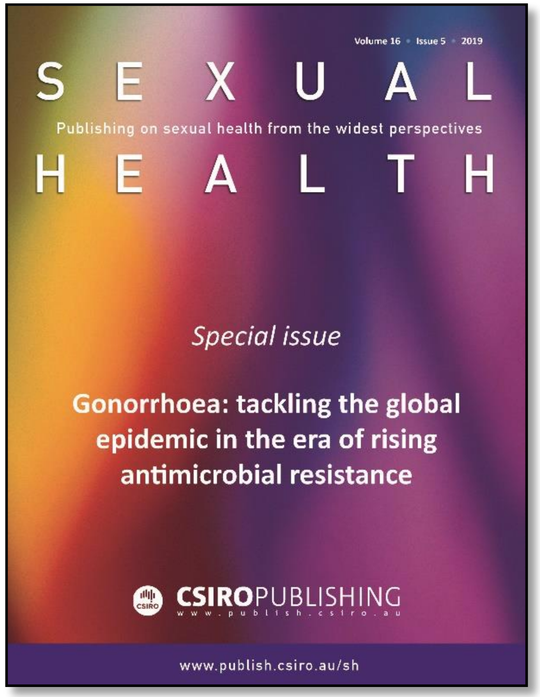
Sarah Baines

Torsten Seemann

Anders Gonçalves Da Silva

Andre Mu

Jason Kwong



# With thanks

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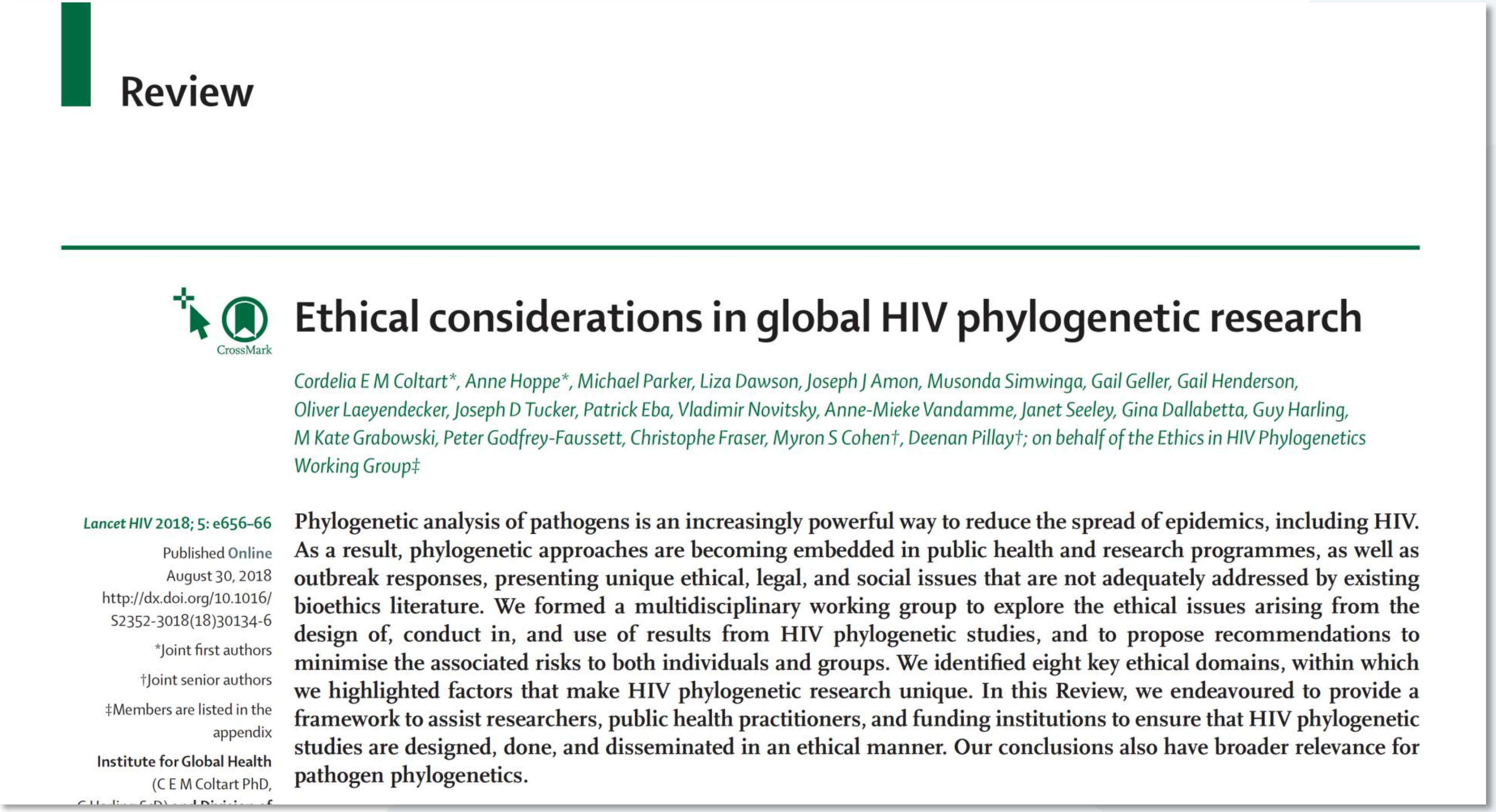


Review

# Ethical considerations in global HIV phylogenetic research

*Cordelia E M Coltart*, Anne Hoppe*, Michael Parker, Liza Dawson, Joseph J Amon, Musonda Simwinga, Gail Geller, Gail Henderson, Oliver Laeyendecker, Joseph D Tucker, Patrick Eba, Vladimir Novitsky, Anne-Mieke Vandamme, Janet Seeley, Gina Dallabetta, Guy Harling, M Kate Grabowski, Peter Godfrey-Faussett, Christophe Fraser, Myron S Cohen†, Deenan Pillay†; on behalf of the Ethics in HIV Phylogenetics Working Group‡*

**Lancet HIV 2018; 5: e656–66**

http://dx.doi.org/10.1016/S2352-3018(18)30134-6

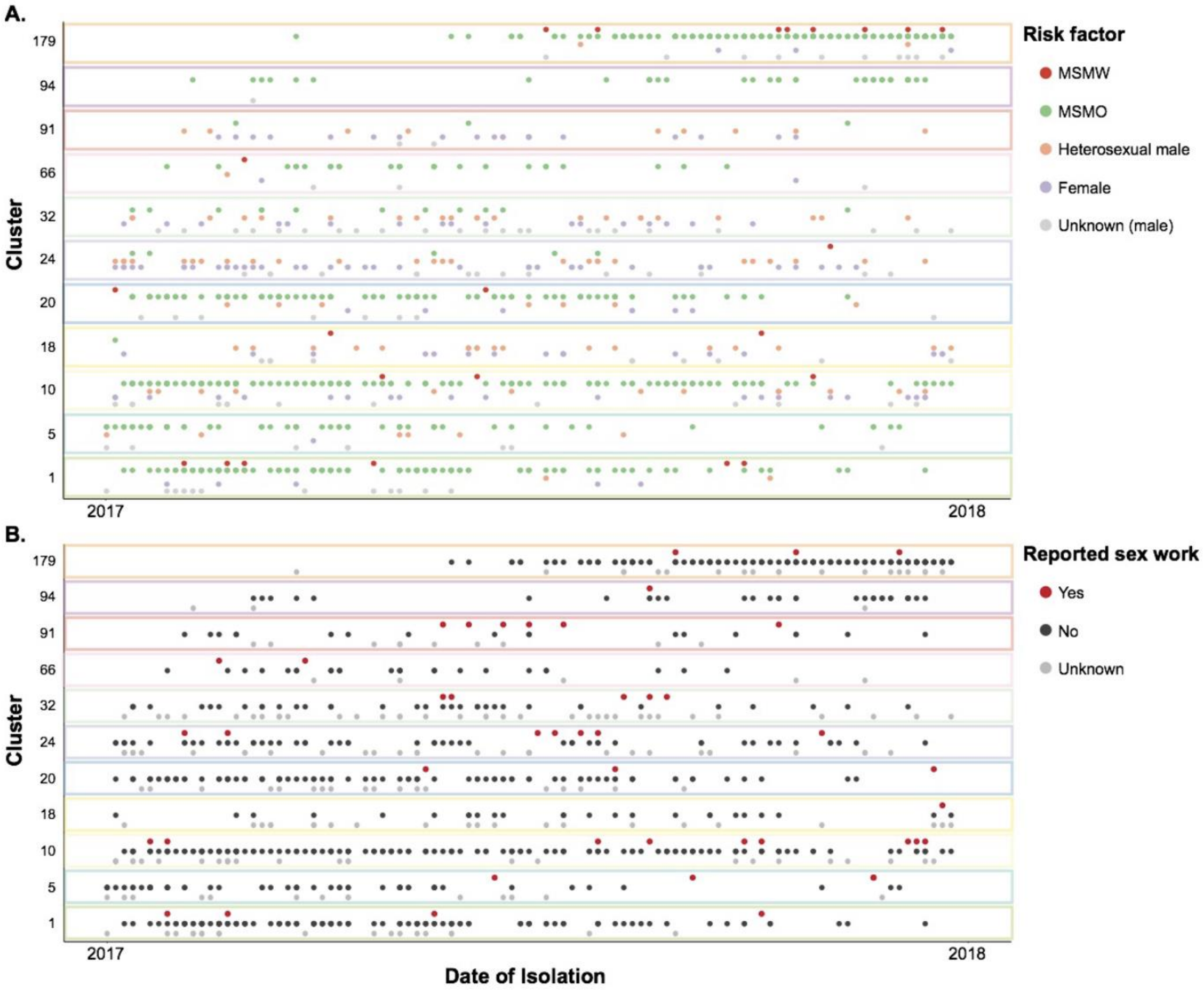
*Joint first authors

†Joint senior authors

‡Members are listed in the appendix

**Institute for Global Health**
(C E M Coltart PhD,

Phylogenetic analysis of pathogens is an increasingly powerful way to reduce the spread of epidemics, including HIV. As a result, phylogenetic approaches are becoming embedded in public health and research programmes, as well as outbreak responses, presenting unique ethical, legal, and social issues that are not adequately addressed by existing bioethics literature. We formed a multidisciplinary working group to explore the ethical issues arising from the design of, conduct in, and use of results from HIV phylogenetic studies, and to propose recommendations to minimise the associated risks to both individuals and groups. We identified eight key ethical domains, within which we highlighted factors that make HIV phylogenetic research unique. In this Review, we endeavoured to provide a framework to assist researchers, public health practitioners, and funding institutions to ensure that HIV phylogenetic studies are designed, done, and disseminated in an ethical manner. Our conclusions also have broader relevance for pathogen phylogenetics.



*Nature Comms, 2019*