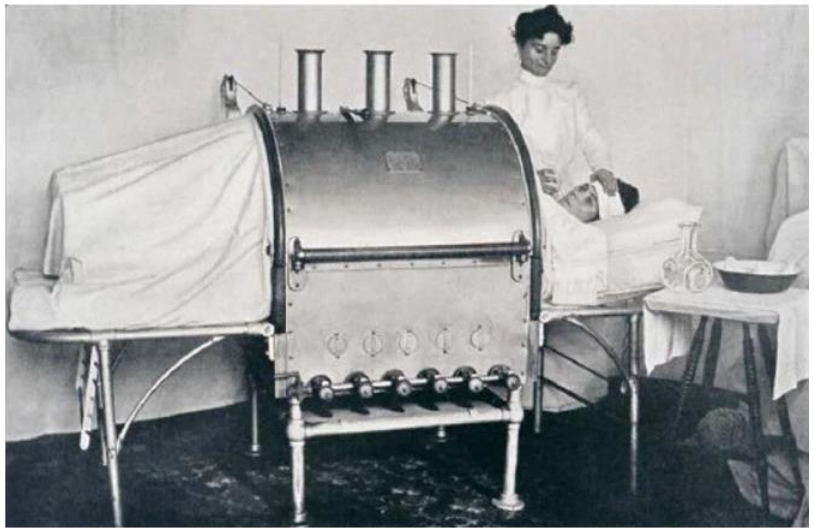
“STIs and antibiotic resistance”

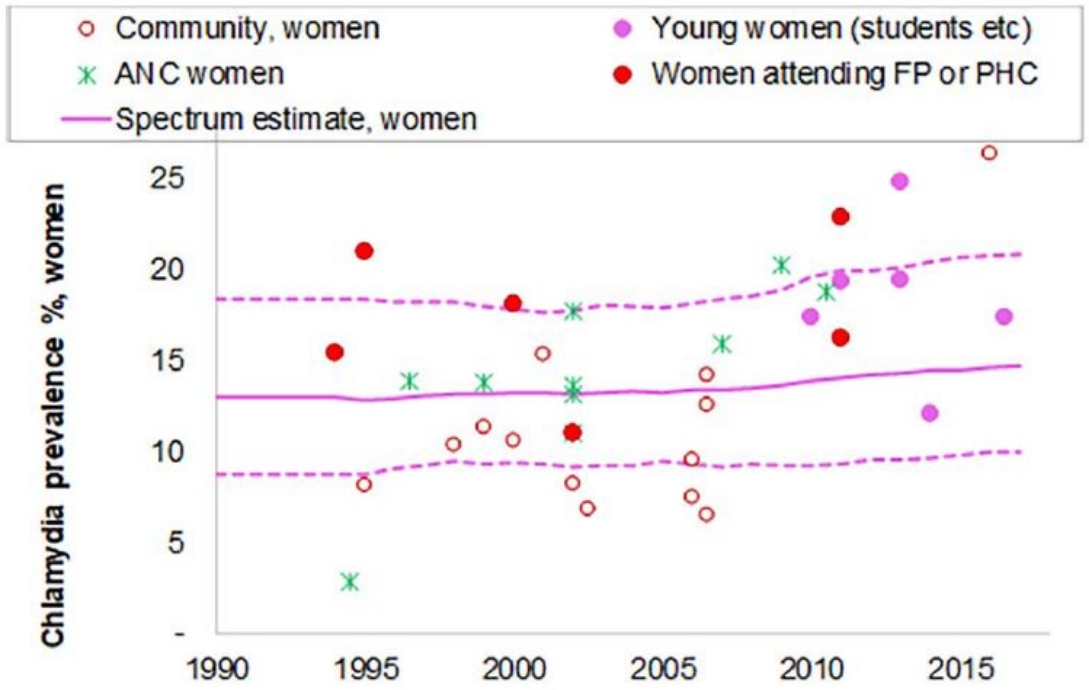


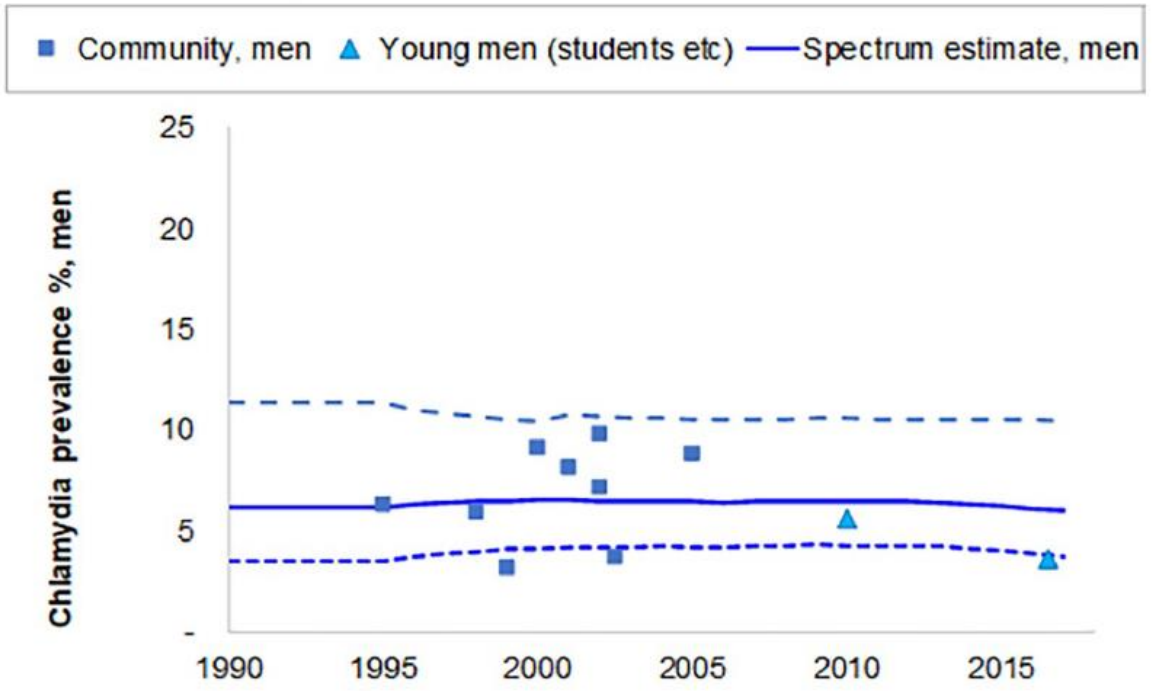
Prof Remco Peters

21 November 2023

Source: https://www.thestar.com/news/world/the-rise-of-the-super-gonorrhea/article_1db8b24a-bea2-588e-93d5-a5c12f3d7ddf.html?

STI prevalence: high and unchanged for 30 years





Women
Chlamydia trachomatis: 14.7%
Neisseria gonorrhoea: 6.6%

Men
Chlamydia trachomatis: 6.0%
Neisseria gonorrhoea: 3.5%

Kularatne R et al. PLoS One 2018

STI burden in South Africa

- **Majority of the 6 million cases remain untreated**
  - Patient and provider-related barriers and stigma
  - Limitations of syndromic management approach

	Neisseria gonorrhoeae	*Chlamydia trachomatis*
Estimated incident cases	2.21 million	3.87 million
Estimated symptomatic cases	1.42 million	1.28 million
Estimated cases treated	850 000 (38%)	765 000 (20%)

Hoffman CM et al. Trop Med Int Health 2019
Kularatne RS et al. PLoS One 2019

Syndromic management approach

- **Combination of empirical antimicrobial that covers the most likely treatment aetiology for each syndrome**
  - Male urethral discharge syndrome and vaginal discharge syndrome
  - Genital ulcer syndrome

Advantages	Disadvantages
• Relatively cheap • Easy to implement	• Asymptomatic infections untreated • Poor antimicrobial stewardship • Management of treatment failure • Antimicrobial resistance

Impact of (untreated) STIs

- Genital tract morbidity and psychological burden
- Adverse pregnancy outcomes
- Reproductive tract complications
- Facilitate HIV transmission and acquisition

Antimicrobial resistant gonorrhoea

Drug-resistant gonorrhoea is a growing threat: a South African case study

Published: October 27, 2020 4.23pm SAST

Illustration of Neisseria gonorrhoeae bacteria. GettyImages

Email
Twitter 20
Facebook 412
LinkedIn
Print

Gonorrhoea is a sexually transmitted infection caused by a bacterium called *Neisseria gonorrhoeae*. This infection affects 87 million people every year across the world. It can lead to genital discharge, pregnancy complications and infertility. Gonorrhoea can be treated successfully with antibiotics.

Current first-line treatment is a ceftriaxone injection combined with azithromycin given as oral tablet. But in recent years, alarming reports emerged of these drugs failing to treat gonorrhoea patients. Drug-resistance has been reported in Asia, Europe and Australia.

Authors

Remco Peters
Extraordinary Professor in the Department of Medical Microbiology, University of Pretoria

Liteboho Daniel Maduna
Post doctoral researcher, University of Pretoria

Disclosure statement

Remco Peters is affiliated with the Research Unit of the Foundation for Professional Development in East London, South

Gonorrhea is about to become impossible to treat

Antibiotic resistance means the STD might soon spread more aggressively than ever

by Arielle Duhaime-Ross | Mar 12, 2014, 12:00pm EDT

HEALTHLINE NEWS

Concerns Over 'Super Gonorrhea' Spreading to the United States

Written by Nicole Makris on 04 May 2016

The virulent, antibiotic-resistant strain of the venereal disease has hit England, Japan, and Canada, highlighting the disease's historic ability to mutate.

BBC Sign in Home News Sport Reel Worklife

NEWS

Home | War in Ukraine | Climate | Video | World | US & Canada | UK | Business | Tech | Science

Health

Man has 'world's worst' super-gonorrhoea

28 March 2018

News InFact Politics Voices Indy/Life Business Sport Tech Culture Subscribe

INDY/PULSE

'SEX SUPERBUG': CONCERNS OVER SPREAD OF HIGHLY RESISTANT GONORRHOEA STRAIN FOUND IN AUSTRALIA

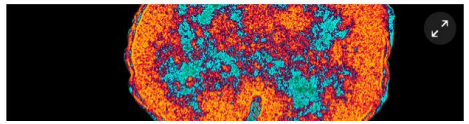
theguardian

all opinion culture business lifestyle fashion environment tech travel browse all sections

scotland wales northern ireland education media

Doctors fear spread of 'super-gonorrhoea' across Britain

Drug-resistant strain of sexually transmitted superbug at risk of becoming untreatable, say health experts



Advertisement

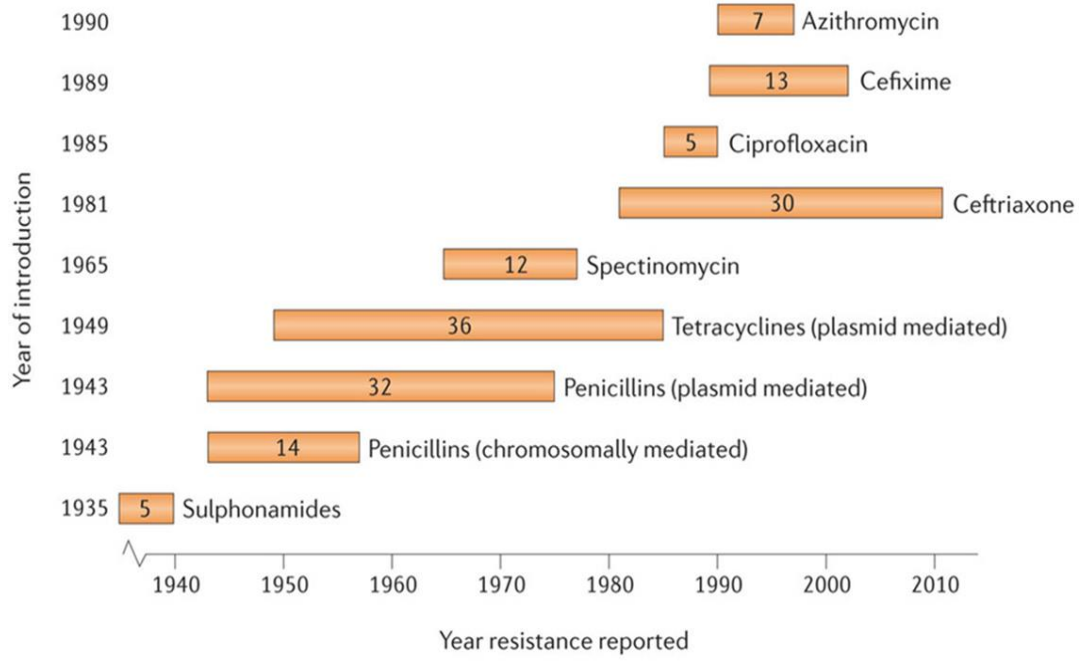
nowCompare.com

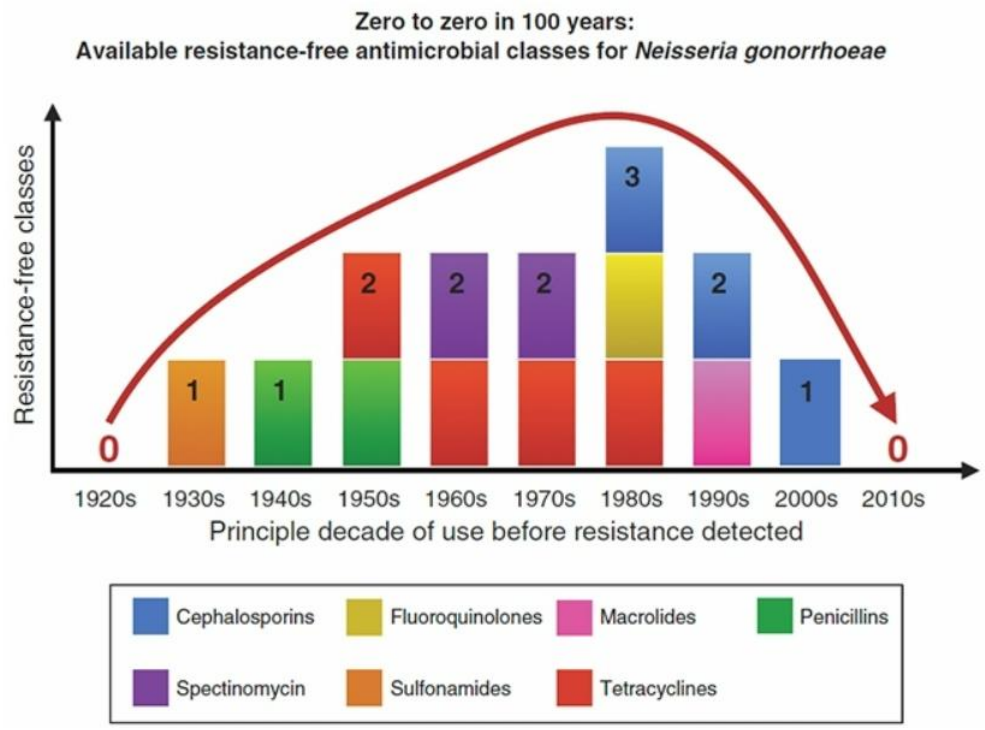
78%

https://theconversation.com/drug-resistant-gonorrhoea-is-a-growing-threat-a-south-african-case-study-148012

Lessons from history

- Antimicrobial resistance develops quickly and outcompetes drug development effort

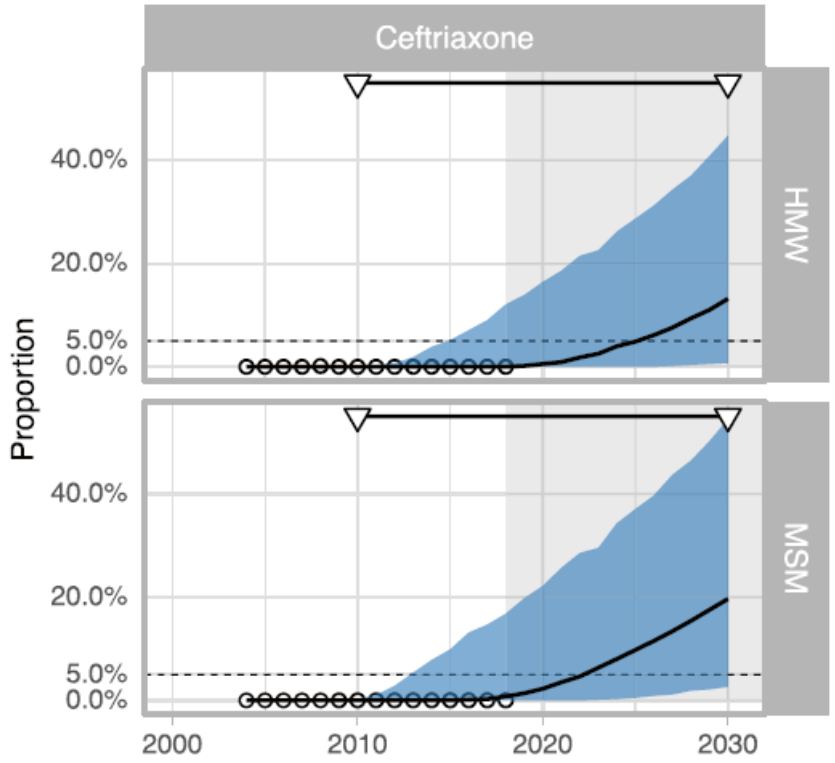




Goire N, et al. Nat Rev Microbiol 2014
Lahra MM, et al. Microbiology Today 2016

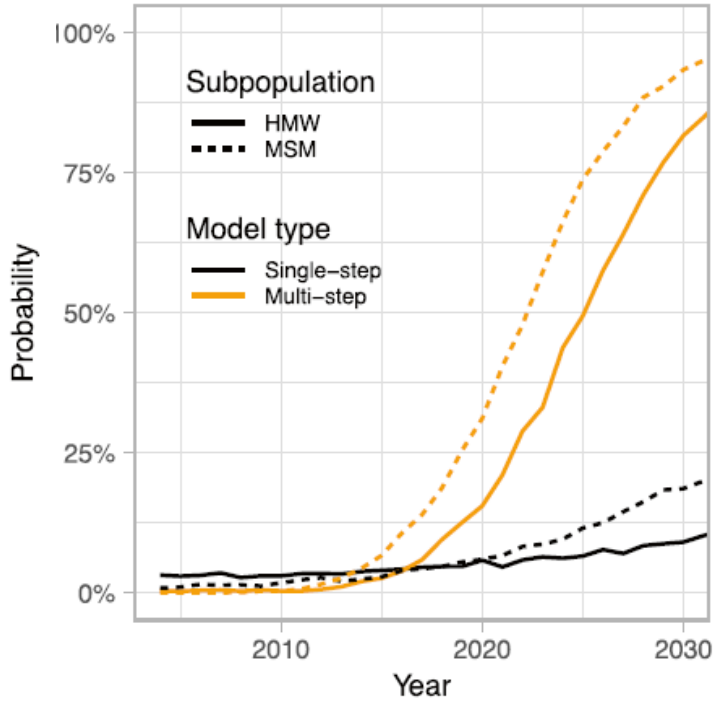
Will ceftriaxone resistance emerge?

- Mechanistic multi-step model based on MIC values from GRASP database



By 2030: 13.2%
(CrI: 0.7 – 44.8%)

By 2030: 19.6%
(CrI: 2.6 – 54.5%)



97%

92%

Riou J, et al. BMC Infect Dis 2023

Will ceftriaxone resistance spread?

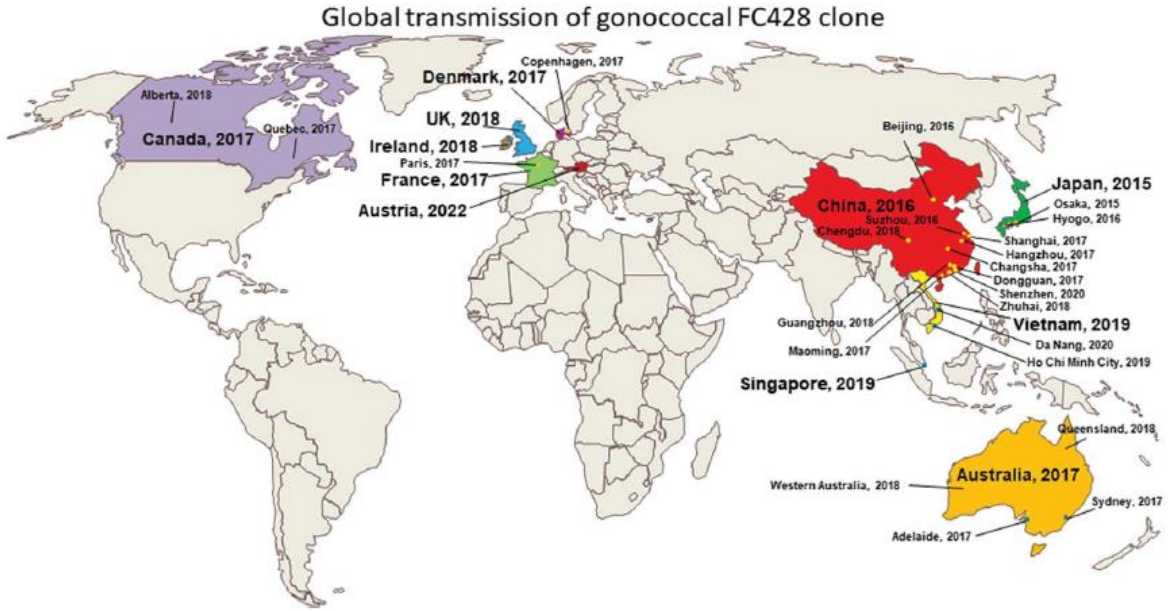


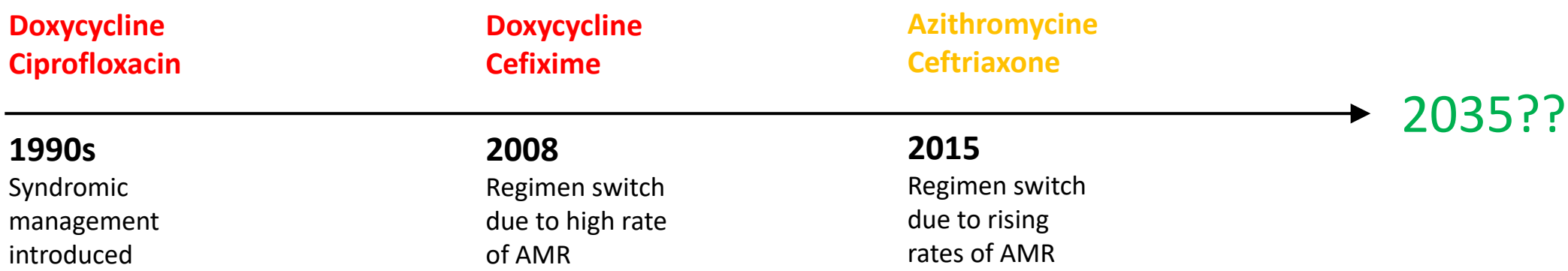
Figure 1. Global transmission of gonococcal strains associated with the FC428 clone or containing *penA* allele 60.001. The map displays countries, cities, and provinces/states where strains and/or clinical cases associated with the gonococcal FC428 clone or containing *penA* allele 60.001 have been reported. The year in which the first incidence has been reported is included.

- Infectious diseases are never restricted by borders
- Weak surveillance systems may under-estimate true burden

Van der Veen S. Infect Microb Dis 2023

Gonorrhoea treatment in South Africa

Syndromic treatment regimens over time in South Africa



Gonorrhoea treatment in South Africa

Syndromic treatment regimens over time in South Africa

Doxycycline
Ciprofloxacin

1990s
Syndromic management introduced

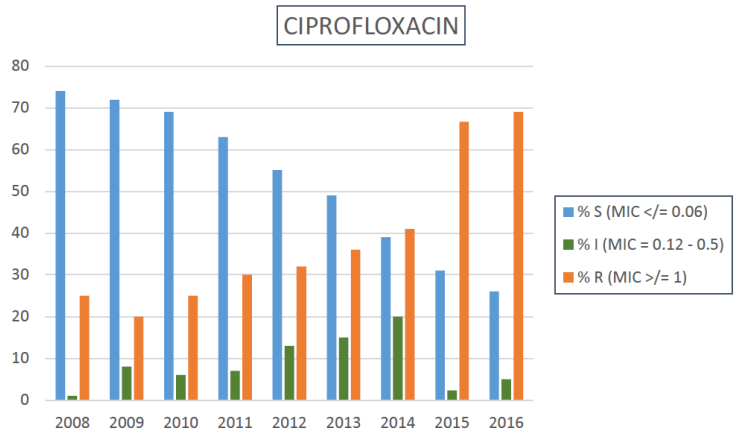
Doxycycline
Cefixime

2008
Regimen switch due to high rate of AMR

Azithromycine
Ceftriaxone

2015
Regimen switch due to rising rates of AMR

2035??



Gonorrhoea treatment in South Africa

Syndromic treatment regimens over time in South Africa

Doxycycline
Ciprofloxacin

1990s
Syndromic management introduced

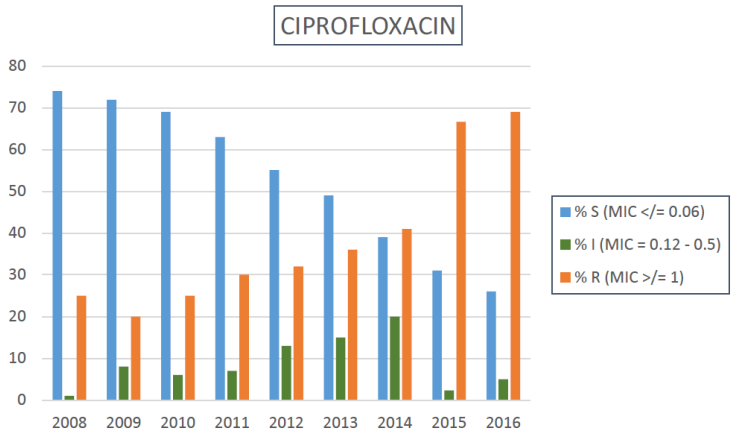
Doxycycline
Cefixime

2008
Regimen switch due to high rate of AMR

Azithromycine
Ceftriaxone

2015
Regimen switch due to rising rates of AMR

2035??



J Antimicrob Chemother
doi:10.1093/jac/dkt034

Journal of Antimicrobial Chemotherapy

Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant *Neisseria gonorrhoeae* infection in South Africa and association with cefixime treatment failure

David A. Lewis[1–3]*, Charlotte Sriruttan[4], Etienne E. Müller[1], Daniel Golparian[5], Lindy Gumede[1], Donald Fick[6], Johan de Wet[7], Venessa Maseko[1], Jennifer Coetzee[4] and Magnus Unemo[5]

Neisseria gonorrhoeae AMR in South Africa

- Antimicrobial resistance surveillance at sentinel sites
- Research data

antibiotics

MDPI

Article

Trends in *Neisseria gonorrhoeae* Antimicrobial Resistance over a Ten-Year Surveillance Period, Johannesburg, South Africa, 2008–2017

Ranmini Kularatne [1,2,*], Venessa Maseko [1], Lindy Gumede [1] and Tendesayi Kufa [1,3]

[1] Centre for HIV & Sexually Transmitted Infections, National Institute for Communicable Diseases, Johannesburg 2131, South Africa; venessam@nicd.ac.za (V.M.); lindyg@nicd.ac.za (L.G.);

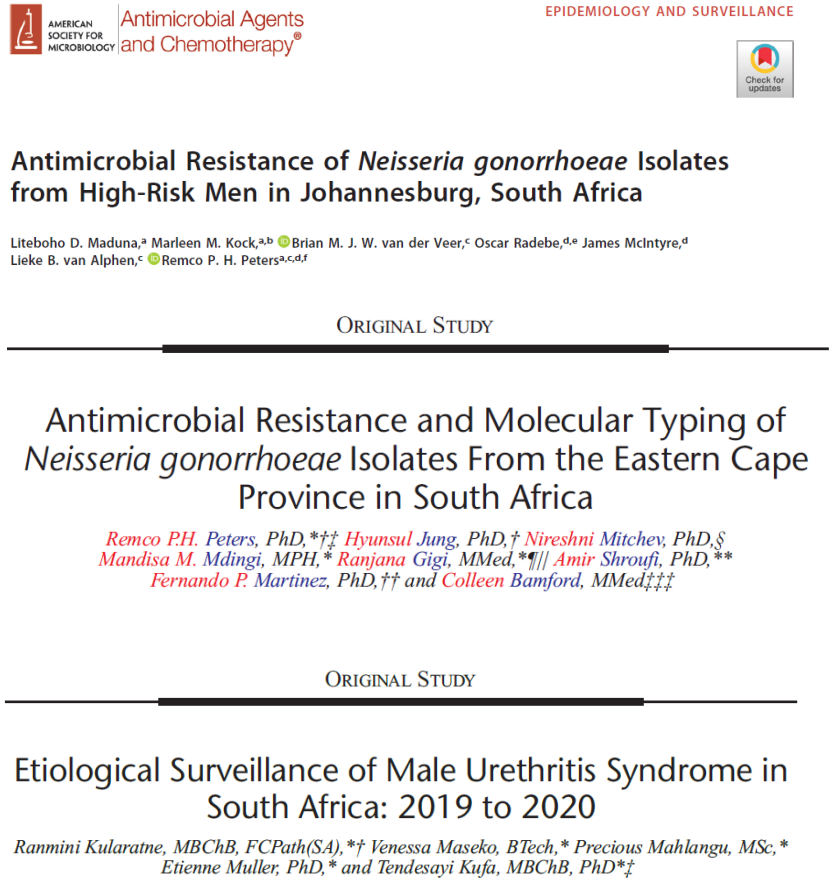
AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

Check for updates

Antimicrobial Resistance Mechanisms, Multilocus Sequence Typing, and NG-STAR Sequence Types of Diverse *Neisseria gonorrhoeae* Isolates in KwaZulu-Natal, South Africa

Nireshni Mitchev,[a] Ravesh Singh,[a,b] Mushal Allam,[c] Stanford Kwenda,[c] Arshad Ismail,[c] Nigel Garrett,[d,e] Veron Ramsuran,[a] Abraham J. Niehaus,[a] Koleka P. Mlisana[a,d,f]



AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

Check for updates

Antimicrobial Resistance of *Neisseria gonorrhoeae* Isolates from High-Risk Men in Johannesburg, South Africa

Liteboho D. Maduna,[a] Marleen M. Kock,[a,b] Brian M. J. W. van der Veer,[c] Oscar Radebe,[d,e] James McIntyre,[d] Lieke B. van Alphen,[c] Remco P. H. Peters[a,c,d,f]

ORIGINAL STUDY

Antimicrobial Resistance and Molecular Typing of *Neisseria gonorrhoeae* Isolates From the Eastern Cape Province in South Africa

Remco P.H. Peters, PhD,†‡ Hyunsul Jung, PhD,† Nireshni Mitchev, PhD,§ Mandisa M. Mdingi, MPH,* Ranjana Gigi, MMed,*¶‖ Amir Shroufi, PhD,** Fernando P. Martinez, PhD,†† and Colleen Bamford, MMed‡‡‡*

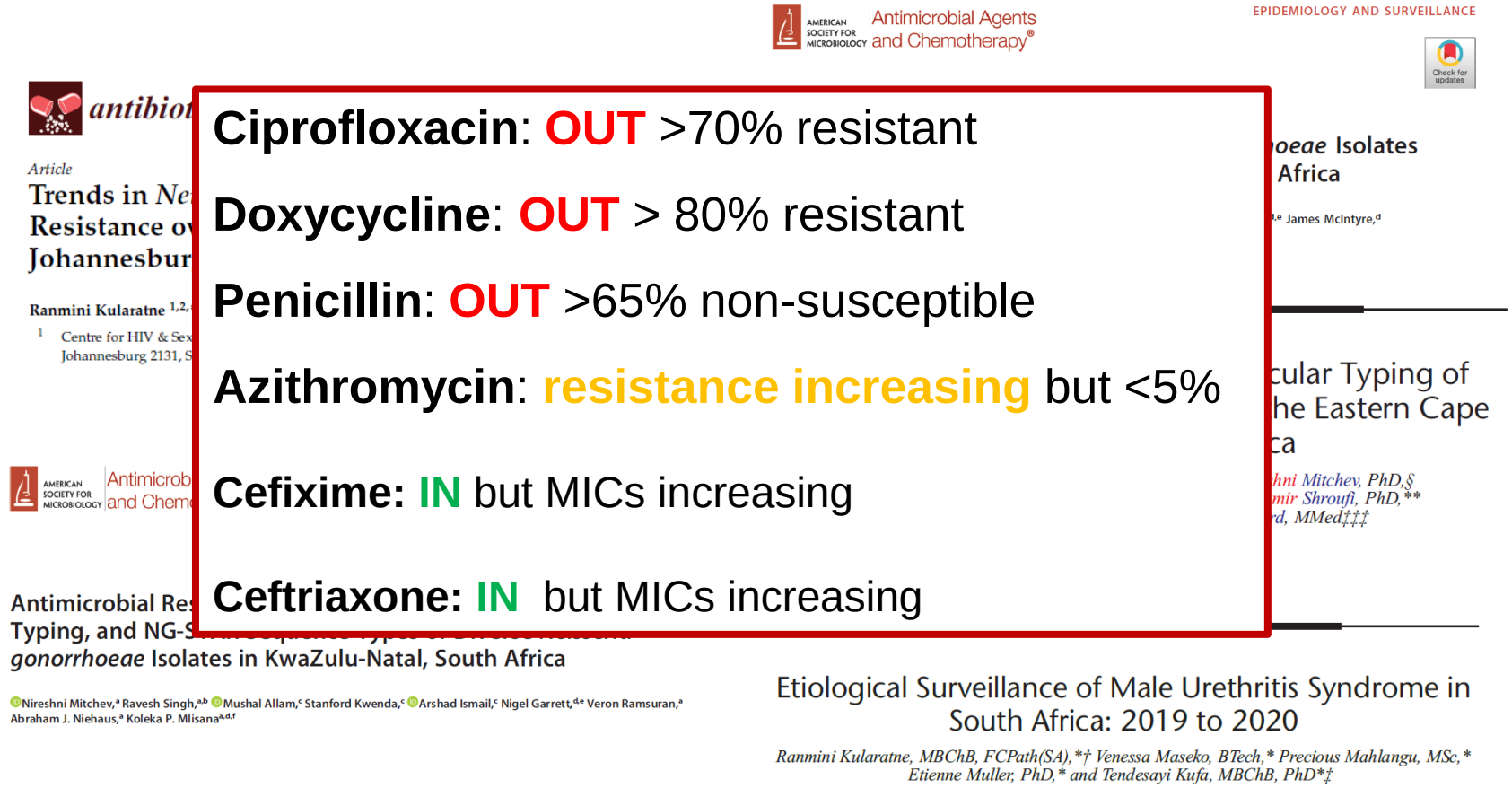
ORIGINAL STUDY

Etiological Surveillance of Male Urethritis Syndrome in South Africa: 2019 to 2020

Ranmini Kularatne, MBChB, FCPath(SA),† Venessa Maseko, BTech,* Precious Mahlangu, MSc,* Etienne Muller, PhD,* and Tendesayi Kufa, MBChB, PhD*‡*

Neisseria gonorrhoeae AMR in South Africa

- Antimicrobial resistance surveillance at sentinel sites
- Research data



Ciprofloxacin: **OUT** >70% resistant

Doxycycline: **OUT** > 80% resistant

Penicillin: **OUT** >65% non-susceptible

Azithromycin: **resistance increasing** but <5%

Cefixime: IN but MICs increasing

Ceftriaxone: IN but MICs increasing

Addressing NG AMR in South Africa

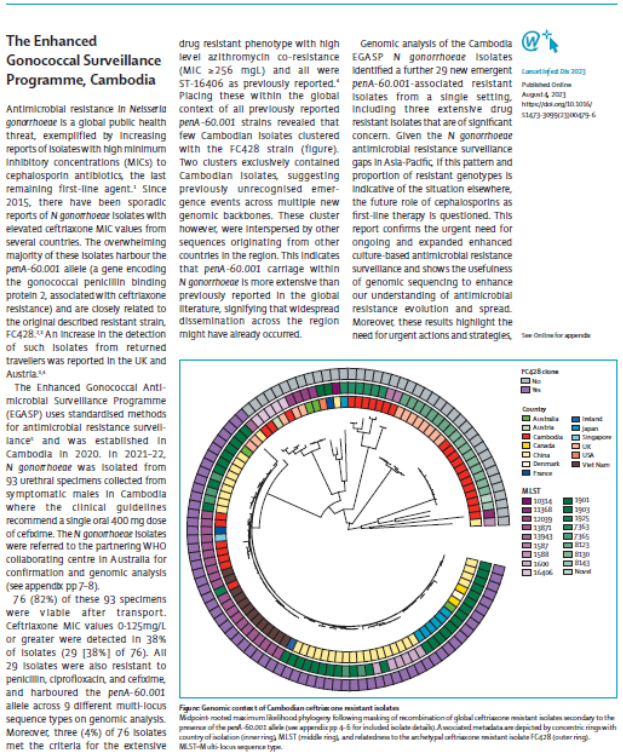
- **Important data gaps to inform treatment guidelines**
  - Limited scale of NG AMR surveillance
  - Limited data of core groups (MSM)
  - No data of oropharyngeal *Neisseria gonorrhoeae*

Country (no. cases; country of infection), year	Therapy	MIC of CRO/AZM (mg L^{-1})	CRO $fT_{>MIC}$ (h)[A]	ML ST ST/NG-MAST ST/NG-STAR type/PBP2 allele	Site of failure	Final successful treatment
Australia (n = 2; Australia), 2007[28]	CRO 250 mg × 1	0.016–0.03/ND	41.4–50.3	ND/5, 2740/ND/ND	Pharynx	CRO 500 mg × 1/CRO 1 g × 1
Japan (n = 1; Japan), 2009[9]	CRO 1 g × 1	4.0/1	0	7363/4220/226/37.001 (mosaic)	Pharynx	None[B]
Sweden (n = 1; Japan), 2010[30]	CRO 250 mg × 1 and CRO 500 mg × 1	0.125–0.25/0.5	15.6–32.8	1901/2958/1399/71.001 (mosaic)	Pharynx	CRO 1 g × 1
Australia (n = 1; Australia), 2010[29]	CRO 500 mg × 1	0.03–0.06/0.25–0.5	41.3–49.9	ND/4950 (genogroup 1407)/ND/ND	Pharynx	AZM 2 g × 1
Slovenia (n = 1; Serbia), 2011[26]	CRO 250 mg × 1	0.125/0.5	24.3	1901/1407/90/34.001 (mosaic)	Pharynx	CRO 250 mg × 1 plus AZM 1 g × 1
Australia (n = 2; Australia), 2011[27]	CRO 500 mg × 1	0.03–0.06	41.3–49.9	1901/225, new variant of 225/ND/ND	Pharynx	CRO 1 g × 1 plus AZM 2 g × 1/CRO 1 g × 1
Sweden (n = 3; Sweden), 2013–2014[25]	CRO 500 mg × 1	0.064–0.125/1–2	32.8–41.3	1901/3149, 3149, 4706 (genogroup 1407)/90/34.001 (mosaic)	Pharynx	CRO 1 g × 1
UK (n = 1; Japan), 2014[35]	CRO 500 mg × 1 plus AZM 1 g × 1	0.25/1	24.3	1901/12133/22/10.001 (mosaic)	Pharynx	CRO 1 g × 1 plus AZM 2 g × 1
France (n = 1; France), 2017[19]	CRO 250 mg × 1 plus DOX 100 mg × 2 daily, 7 days	0.5/0.5	6.6	1903/3435/233/60.001 (mosaic)	Pharynx	Lost to follow-up
UK (n = 1; Thailand), 2018[22]	CRO 1 g × 1 plus DOX 100 mg × 2 daily, 7 days	0.5/>256	24.3	12039/16848/996/60.001 (mosaic)	Pharynx	ETP 1 g × 1, 3 days
UK (n = 1; UK[C]), 2018[21]	CRO 1 g × 1	1/0.5	15.6	1903/1614/233/60.001 (mosaic)	Rectum, urogenital tract	ETP 1 g × 1, 3 days

Unemo M et al. Sex Health 2019

Addressing NG AMR in South Africa

- **Lack of access to routine diagnostic testing**
  - Management of treatment failure
  - Identification of potential outbreaks



The Enhanced Gonococcal Surveillance Programme, Cambodia

Antimicrobial resistance in *Neisseria gonorrhoeae* is a global public health threat, exemplified by increasing reports of isolates with high minimum inhibitory concentrations (MICs) to cephalosporin antibiotics, the last remaining first-line agent.[1] Since 2015, there have been sporadic reports of *N gonorrhoeae* isolates with elevated ceftriaxone MIC values from several countries. The overwhelming majority of these isolates harbour the *penA*-60.001 allele (a gene encoding the gonococcal penicillin binding protein 2, associated with ceftriaxone resistance) and are closely related to the original described resistant strain, FC428.[2,3] An increase in the detection of such isolates from returned travellers was reported in the UK and Austria.[3,4]

The Enhanced Gonococcal Antimicrobial Surveillance Programme (EGASP) uses standardised methods for antimicrobial resistance surveillance[5] and was established in Cambodia in 2020. In 2021–22, *N gonorrhoeae* was isolated from 93 urethral specimens collected from symptomatic males in Cambodia where the clinical guidelines recommend a single oral 400 mg dose of cefixime. The *N gonorrhoeae* isolates were referred to the partnering WHO collaborating centre in Australia for confirmation and genomic analysis (see appendix pp 7–8).

76 (82%) of these 93 specimens were viable after transport. Ceftriaxone MIC values 0·125 mg/L or greater were detected in 38% of isolates (29 [38%] of 76). All 29 isolates were also resistant to penicillin, ciprofloxacin, and cefixime, and harboured the *penA*-60.001 allele across 9 different multi-locus sequence types on genomic analysis. Moreover, three (4%) of 76 isolates met the criteria for the extensive drug resistant phenotype with high level azithromycin co-resistance (MIC ≥256 mg/L) and all were ST-16406 as previously reported.[4] Placing these within the global context of all previously reported *penA*-60.001 strains revealed that few Cambodian isolates clustered with the FC428 strain (figure). Two clusters exclusively contained Cambodian isolates, suggesting previously unrecognised emergence events across multiple new genomic backbones. These cluster however, were interspersed by other sequences originating from other countries in the region. This indicates that *penA*-60.001 carriage within *N gonorrhoeae* is more extensive than previously reported in the global literature, signifying that widespread dissemination across the region might have already occurred.

Genomic analysis of the Cambodia EGASP *N gonorrhoeae* isolates identified a further 29 new emergent *penA*-60.001-associated resistant isolates from a single setting, including three extensive drug resistant isolates that are of significant concern. Given the *N gonorrhoeae* antimicrobial resistance surveillance gaps in Asia-Pacific, if this pattern and proportion of resistant genotypes is indicative of the situation elsewhere, the future role of cephalosporins as first-line therapy is questioned. This report confirms the urgent need for ongoing and expanded enhanced culture-based antimicrobial resistance surveillance and shows the usefulness of genomic sequencing to enhance our understanding of antimicrobial resistance evolution and spread. Moreover, these results highlight the need for urgent actions and strategies,

Published Online August 4, 2023

See Online for appendix

Figure: Genomic context of Cambodian ceftriaxone resistant isolates

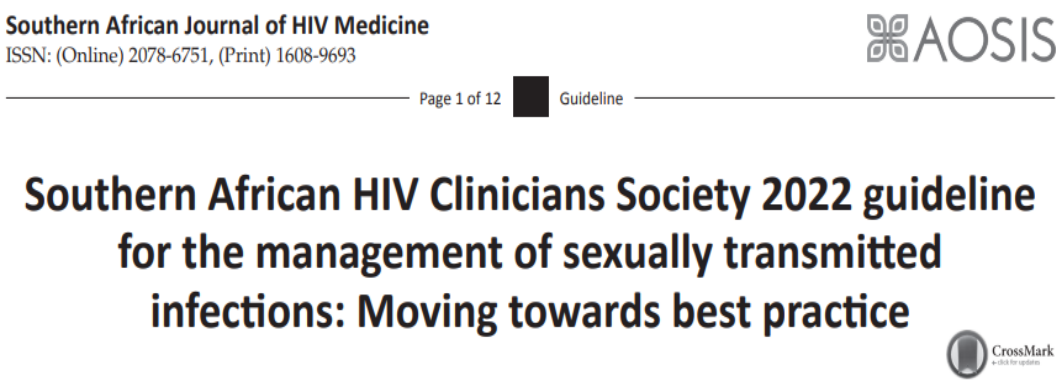
Midpoint-rooted maximum likelihood phylogeny following masking of recombination of global ceftriaxone resistant isolates secondary to the presence of the *penA*-60.001 allele (see appendix pp 4–6 for included isolate details). Associated metadata are depicted by concentric rings with country of isolation (inner ring), MLST (middle ring), and relatedness to the archetypal ceftriaxone resistant isolate FC428 (outer ring). MLST=Multi-locus sequence type.

- **Recent data from Cambodia**
  - 29/76 (38%) of isolates resistant to ceftriaxone
  - Multiple sequence types
- **Without diagnostic testing, how would we know if these infections occur in South Africa?**

Ouk V et al. Lancet Infect Dis 2023

Addressing NG AMR in South Africa

- **Recent developments and good news..**

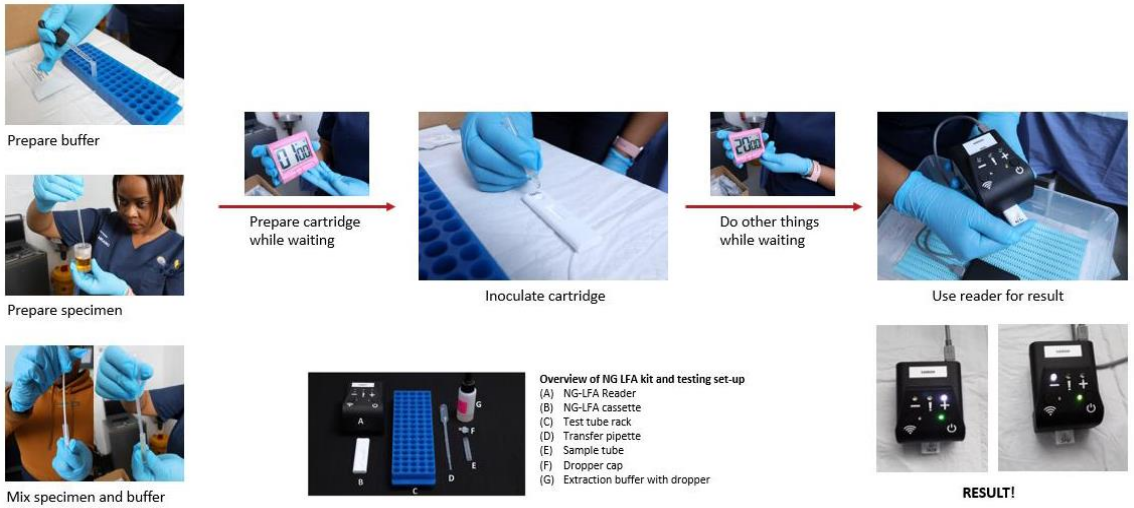


Ceftriaxone dose increased to 500mg to improve treatment outcomes and prevent resistance

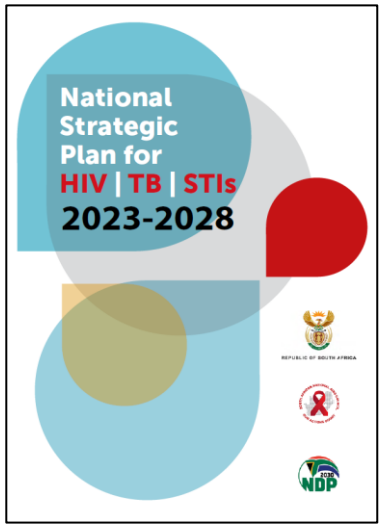
Zoliflodacin as potential new treatment option

Addressing NG AMR in South Africa

- **Recent developments and good news**



First point-of-care test for *Neisseria gonorrhoeae* in syndromic management settings developed



National recognition and efforts to reduce burden of *Neisseria gonorrhoeae* by 2030

Peters RPH et al. Lancet 2023
De Vos et al. PLoS One 2023

In summary

- NG AMR is not a matter of '***if***' but rather of '***how soon***'
- Concerning data of ceftriaxone-resistant gonorrhoea in Asia
- Public health should take priority and prepare for NG AMR:
  - Close epidemiological data gaps
  - Expand AMR surveillance
  - Ensure access to diagnostic testing
  - Strengthen treatment regimens and options

Thank you

“It always seems impossible until it’s done”

Remco Peters
remcop@foundation.co.za