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Neisseria gonorrhoeae: Antimicrobial resistance

Dr Helen Fifer
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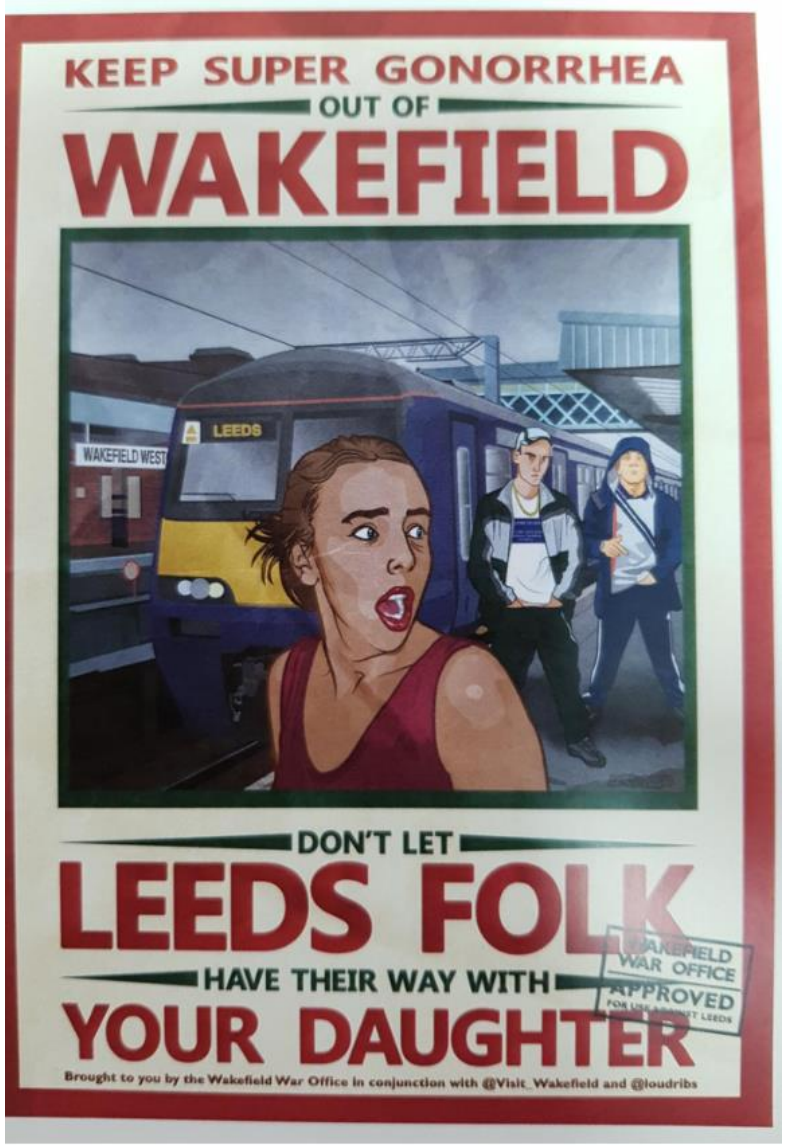
National Infection Service
Public Health England

Super gonorrhoea



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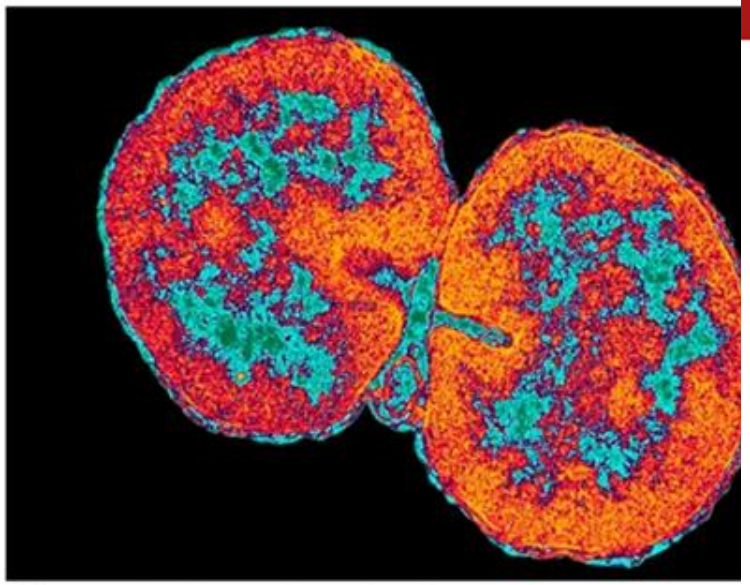
Sexual health

Drug-resistant gonorrhoea outbreak sparks England-wide alert

'The implication is there's a lot more of this strain out there and we need to st… quickly as possible,' sexual health expert says



Neisseria gonorrhoeae, the bacterium that causes the sexually transmitted disease gonorrhoea. Photograph

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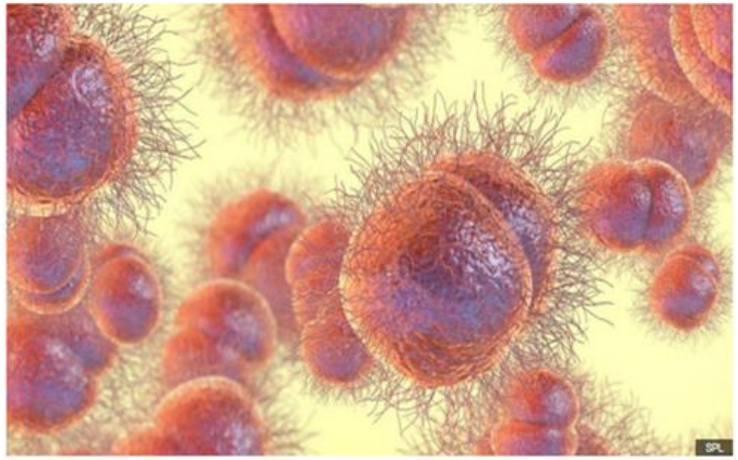
Health

'Super-gonorrhoea' outbreak in Leeds

By James Gallagher
Health editor, BBC News website

18 September 2015 | Health



Highly drug-resistant gonorrhoea is spreading in the north of England with an outbreak centred in Leeds, sexual health doctors have told the BBC.

World's worst super gonorrhoea

THE Sun

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STI ALERT World first as Brit bloke catches 'super gonorrhoea' that's resistant to TWO vital antibiotics from woman in Asia

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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

The Telegraph

News

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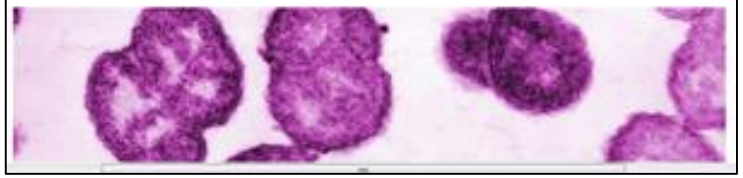
News

Scramble to stop spre gonorrhoea as British 'worst ever' case



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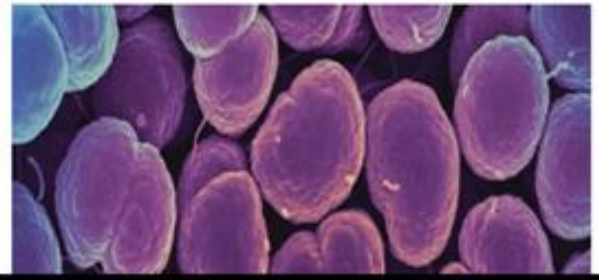
News › Health

UK man catches 'world's worst' case of super-gonorrhoea in south-east Asia

TOM POWELL



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WHAT HI-FI? AWARDS 2017 "This is as good as TV gets." sky

News › Health

Man contracts 'super'-gonorrhoea that cannot be cured with usual antibiotics

'This is the first time a case has displayed such high-level resistance to both of these drugs and to most other commonly used antibiotics'

Staff Reporter

808

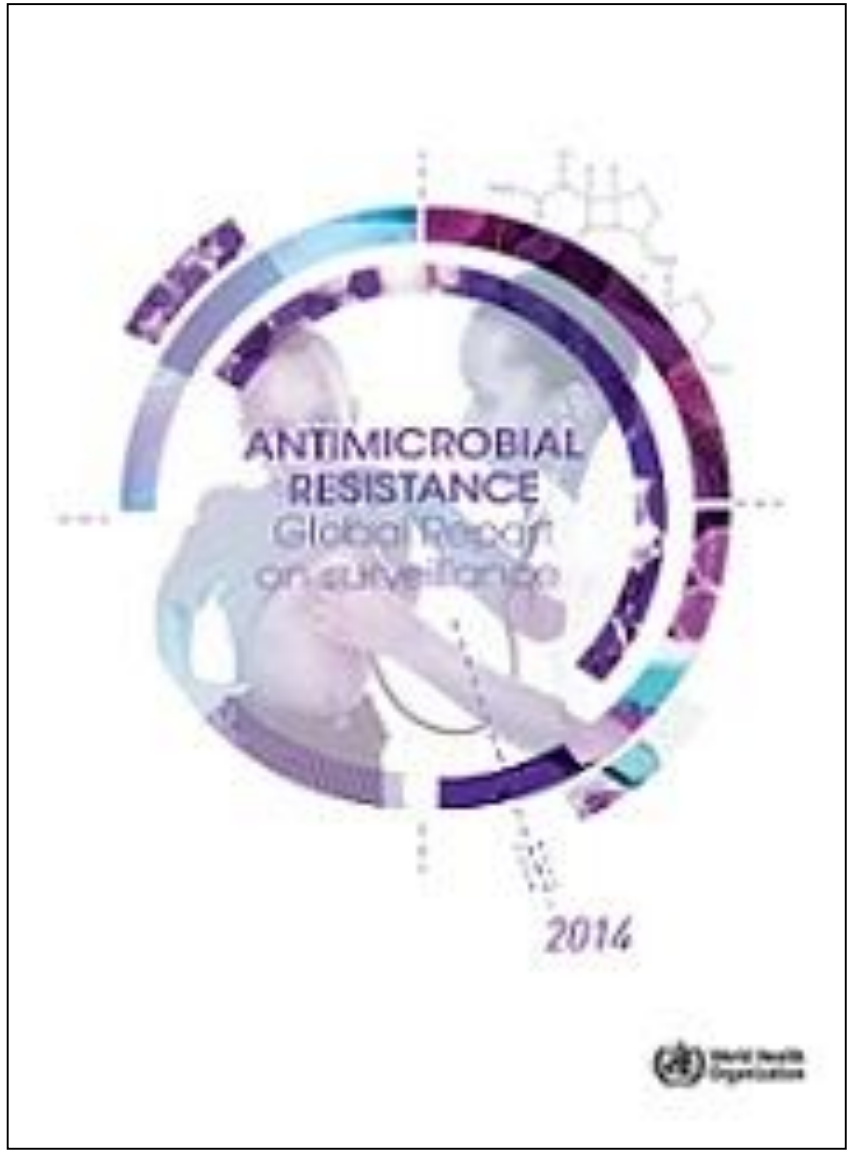
Resistance

Neisseria gonorrhoeae among 9 bacteria of international concern

WHO Global Report on Antimicrobial Resistance

N. gonorrhoeae drug resistance classified as ‘urgent public health threat’

CDC, 2013



Response plans

- Strengthen the surveillance of gonococcal AMR
- Maintain and develop capacity for culture and susceptibility testing
- Increase awareness of appropriate use of antimicrobials
- Establish a strategy for timely treatment failure detection

N. gonorrhoeae treatments & resistance timeline

Sulphonamide **1930s** **1940s**

Penicillin **1943** **1950s** *PBP, efflux pumps, pili, porins*

1976 *B-lactamase (PPNG)*

Tetracycline **1962** **1985** *Ribosomes, efflux pumps, pili, porins, TET-M (TRNG)*

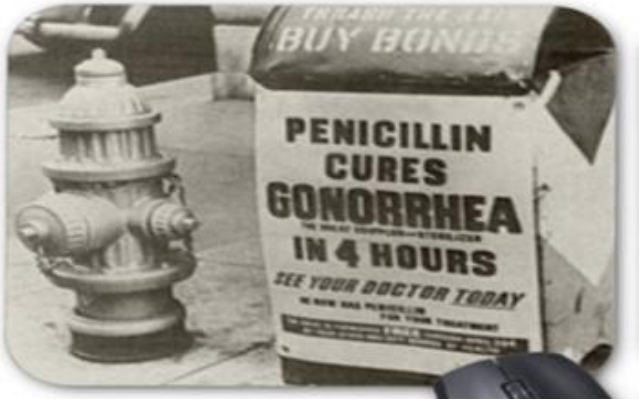
Ciprofloxacin **1987** **1991** *DNA topoisomerase / gyrase*

Azithromycin **1983** **1999** 23S rRNA, *efflux pumps*

Cefixime **1983** **2001** *PBP, efflux pumps, porins*

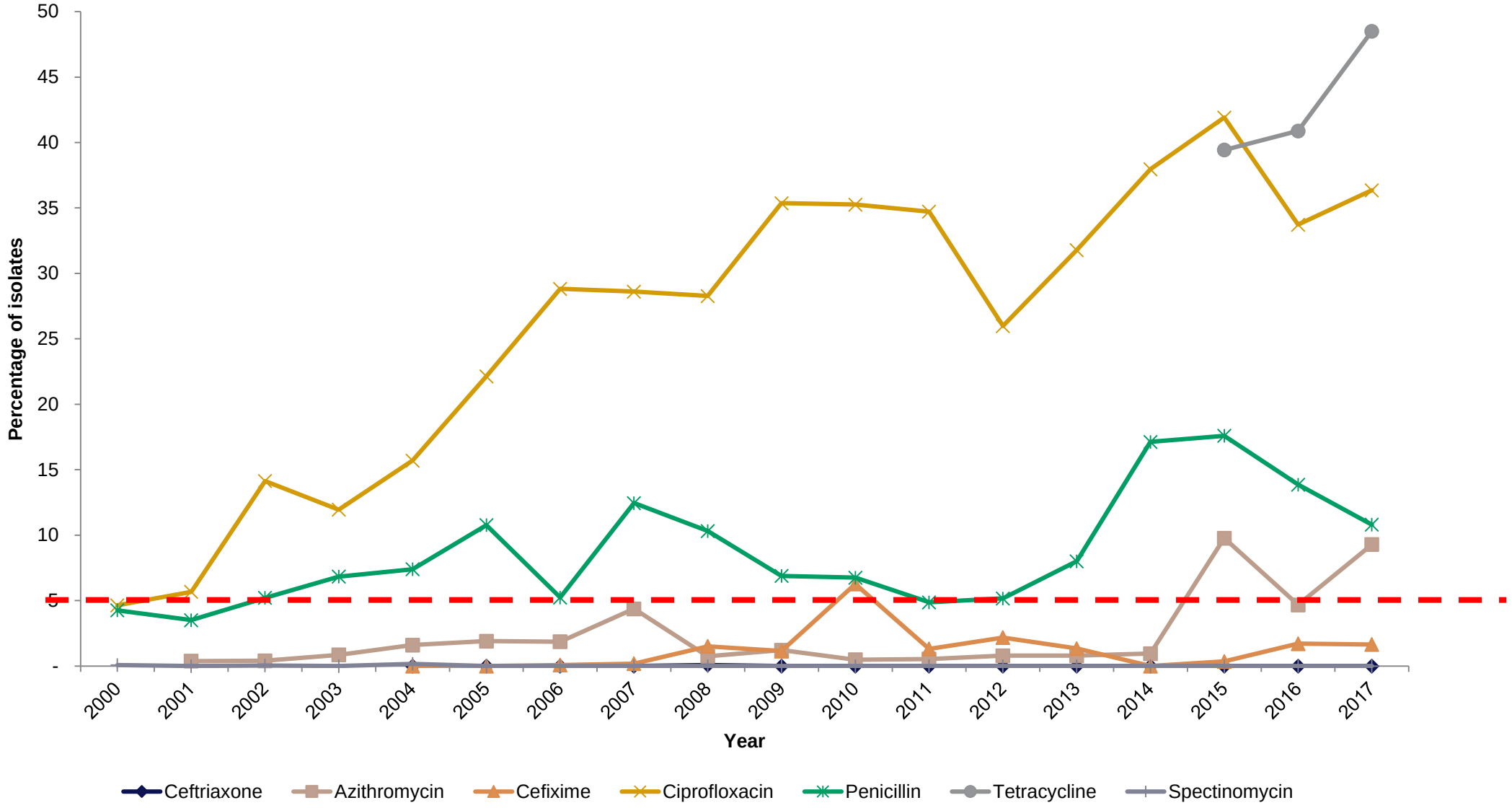
Ceftriaxone **1980** **2011**

Super bug??



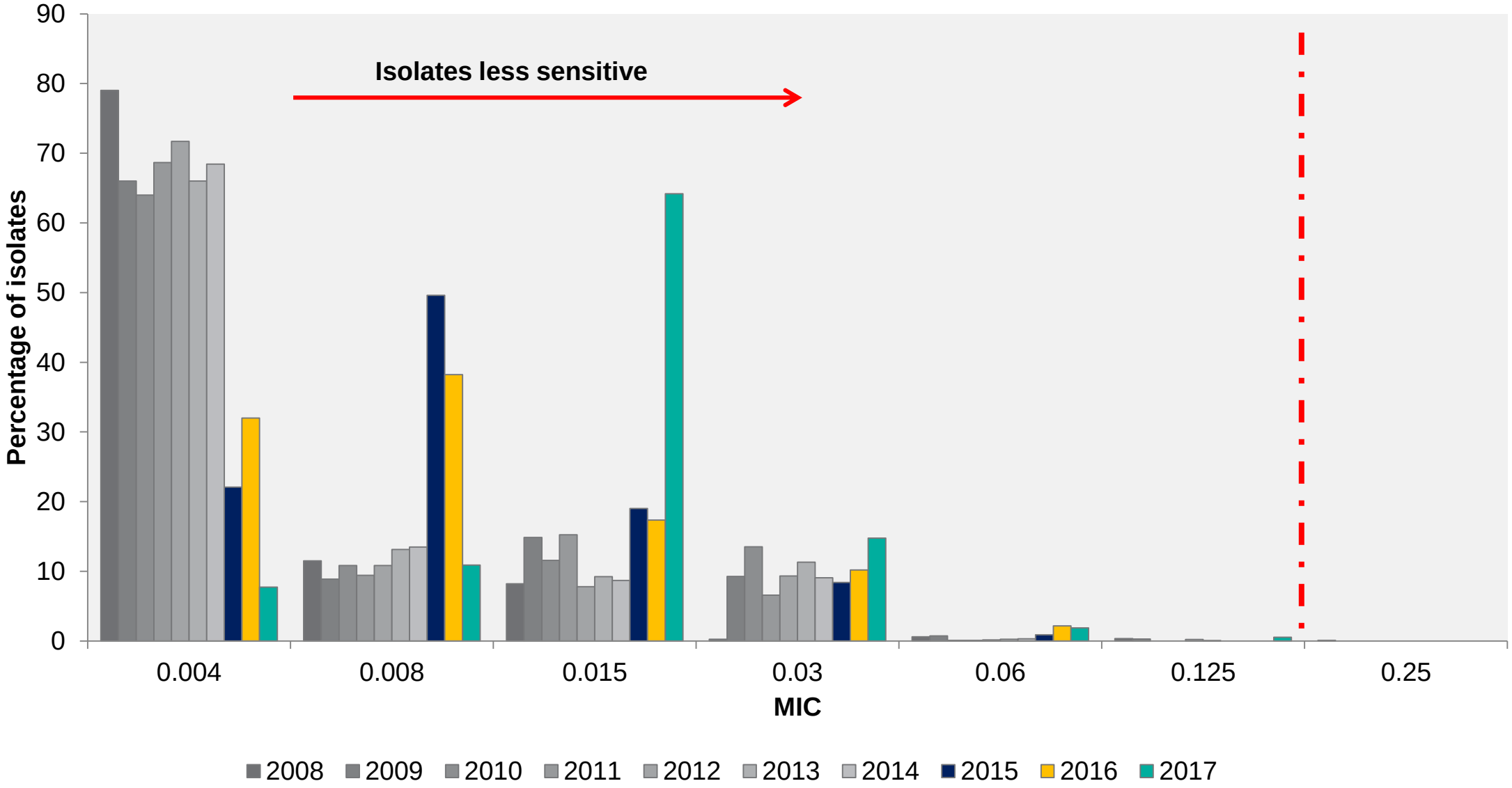
Adapted from: Unemo & Shafer, Ann. N. Y. Acad. Sci. 1230 (2011) E19-E28

Resistance to selected antimicrobials: GRASP 2000-2017

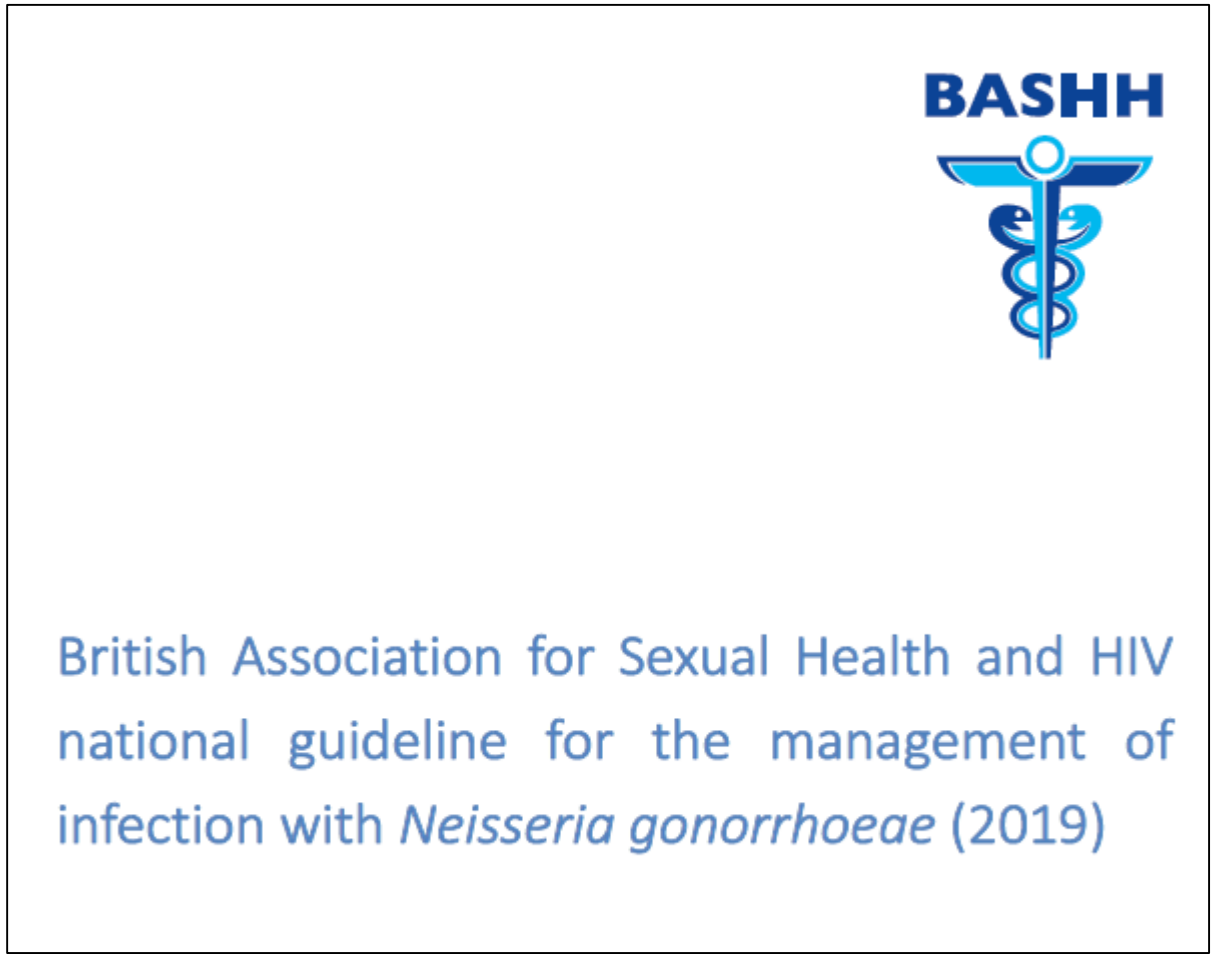


Ceftriaxone MIC distribution: 2008 to 2017

- Shift in the modal MIC from 0.008 mg/L in 2016 to 0.015 mg/L in 2017



Change to ceftriaxone 1g monotherapy



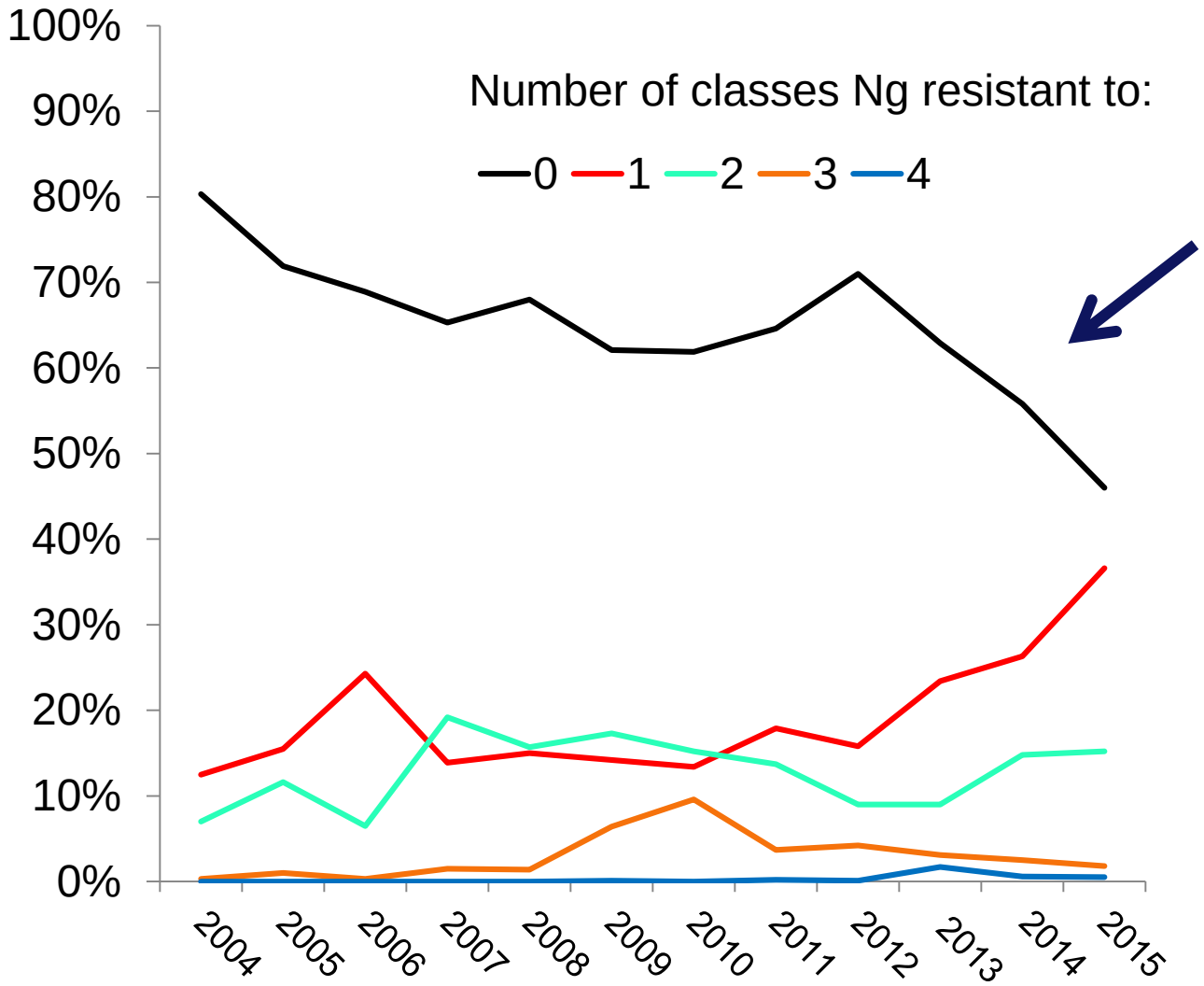
What is MDR and XDR?

Difficult to define due to changing first-line treatments over time and internationally.
Definition proposed by Tapsall *et al* (2009):

MDR-NG
Resistance to 1 or more of ceftriaxone, cefixime or spectinomycin
Plus
Resistance to 2 or more of penicillin, ciprofloxacin and azithromycin

XDR-NG
Resistance to 2 or more of ceftriaxone, cefixime or spectinomycin
Plus
Resistance to 3 or more of penicillin, ciprofloxacin and azithromycin

Resistance to classes of antimicrobials; GRASP 2004–2015



Proportion fully susceptible fell from 80% to 46%

MDR definition adapted to reflect treatment guidelines

MDR-NG more common among

- Heterosexual men (4.6%) compared to MSM (3.3%) or women (2.5%)
- Older patients
- Recent sex abroad

GRASP, n=16,242

Clifton et al. Prevalence of and factors associated with MDR Neisseria gonorrhoeae in England and Wales between 2004 and 2015: analysis of annual cross-sectional surveillance surveys. JAC 2018 Apr 1;73(4):923-932.

High-level ceftriaxone resistance, 2009-2011

Year	Country	MLST ST	NG-MAST ST	CTX MIC	Gender & Sexual orientation	Infection site	Ref
2009	Japan - H041	7363	4220	2-4mg/L	Female	Pharynx	AAC, 2011; 55: 3538-45
2010	France - F89	1901	1407	1-2mg/L	MSM	Urethra	AAC, 2012; 56: 1273-1280
2011	Spain – F89	1901	1407	1-2mg/L	MSM	Urethra	JAC, 2012; 67: 1858-1860

First reported case of gonorrhoea failing treatment with dual therapy, 2015

The NEW ENGLAND JOURNAL of MEDICINE

2. Hecht S, Haig C, Chase AM. The influence of light adaptation on subsequent dark adaptation of the eye. J Gen Physiol 1937; 20:831-50.
3. Lamb TD, Pugh EN Jr. Dark adaptation and the retinoid cycle of vision. Prog Retin Eye Res 2004;23:307-80.
4. Cameron AM, Mahroo OA, Lamb TD. Dark adaptation of human rod bipolar cells measured from the b-wave of the scotopic electroretinogram. J Physiol 2006;575:507-26.

DOI: 10.1056/NEJMc1514294

Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea

TO THE EDITOR: Resistance to all antimicrobial agents has developed in some *Neisseria gonorrhoeae* strains. Dual antimicrobial therapy (ceftriaxone plus azithromycin) is a recommended first-line empirical treatment in many countries.[1-3] We describe treatment failure with dual therapy in a patient with gonorrhea.

In December 2014, a heterosexual man presented to a sexual health clinic in the United Kingdom with a 2-week history of urogenital

On day 98, *N. gonorrhoeae* was detected in a pharyngeal sample on the nucleic acid amplification test and culture. The patient received one dose of ceftriaxone at a dose of 1 g intramuscularly plus azithromycin at a dose of 2 g orally.[3] At the test of cure on day 112, the pharyngeal specimen was negative (according to the nucleic acid amplification test). Initial pretreatment specimens were unavailable for further analysis.

Cooperative Recognition of Internationally Disseminated Ceftriaxone-Resistant *Neisseria gonorrhoeae* Strain

Monica M. Lahra, Irene Martin, Walter Demczuk, Amy V. Jennison, Ken-Ichi Lee, Shu-Ichi Nakayama, Brigitte Lefebvre, Jean Longtin, Alison Ward, Michael R. Mulvey, Teodora Wi, Makoto Ohnishi, David Whiley

Emerg Infect Dis. 2018

	Country, Date	PenA	NG-STAR	MLST	NG-MAST
FC428	Japan, 2015	PenA60	233	1903	3435
FC460	Japan, 2015	PenA60	233	1903	3435
A7536	Australia, Aug 2017	PenA60	233	1903	15925
47707	Canada, Jan 2017	PenA60	233	1903	1614
A7846	Australia, Apr 2017	PenA60	233	1903	1614
F89	France, 2010	PenA42	16	1901	1407

All patients had Asian travel link

Ceftriaxone MICs 0.5-1mg/L, Azithromycin MICs 0.25-1.0mg/L

Surveillance gaps – 0.1% of the estimated 80M cases have AST

Multidrug-resistant *Neisseria gonorrhoeae* infection with ceftriaxone resistance and intermediate resistance to azithromycin, Denmark, 2017

David Terkelsen[1,2], Jacob Tolstrup[2,3], Camilla Hundahl Johnsen[4], Ole Lund[4], Helle Kiellberg Larsen[3], Peder Worning[1], Magnus Unemo[5,7], Henrik Westh[1,6,7]

Euro Surveill. 2017

Multidrug-resistant *Neisseria gonorrhoeae* failing treatment with ceftriaxone and doxycycline in France, November 2017

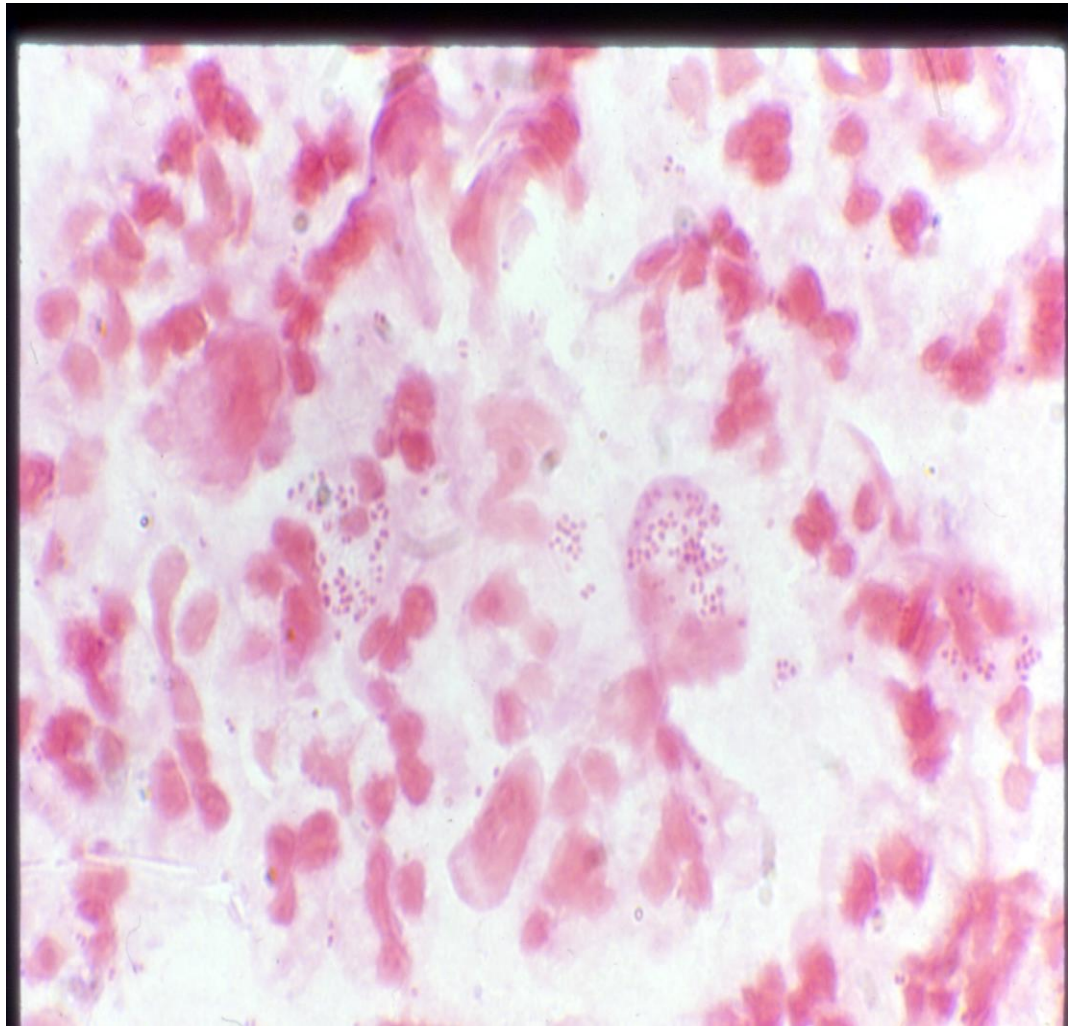
Thibault Poncin[1,2], Sebastien Fouere[4], Aymeric Braille[1,2], Francois Camelena[1,2,3], Myriem Agsous[1,2], Cecile Bebear[5], Sylvain Kumanski[2], Florence Lot[6], Severine Mercier-Delarue[1], Ndeindo Ndeikoundam Ngangro[6], Maud Salmona[1], Nathalie Schnepf[1,2], Julie Timsit[4], Magnus Unemo[7], Beatrice Bercot[1,2,3]

Euro Surveill. 2018

Both have the FC428 penA

UK February 2018

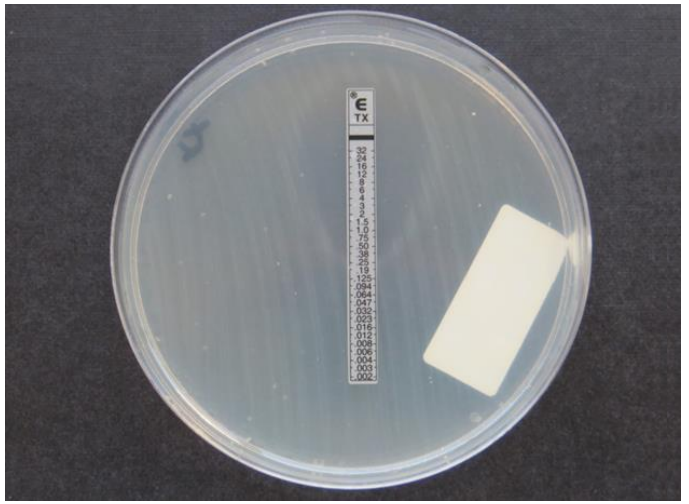
- Heterosexual male in his 50s
- 4 days urethral discharge and dysuria
- One UK female partner for 6 months
- Sex with Thai female in Thailand, a few weeks earlier
- Ceftriaxone 1g IM plus doxycycline 7 days



PHE reference Lab: MIC Results

Culture: *Neisseria gonorrhoeae*

- Ceftriaxone R (MIC 0.5mg/L)
- Cefixime R (MIC 2 mg/L)
- Penicillin I (MIC 1 mg/L)
- Azithromycin R (MIC >256mg/L)
- Ciprofloxacin R (MIC >32mg/L)
- Tetracycline R (MIC 32 mg/L)
- Spectinomycin S (MIC 8 mg/L)
- Gentamicin MIC 2 mg/L
- Ertapenem MIC 0.032 mg/L



First ever global report of XDR GC with HLAziR and ceftriaxone resistance

What would you do now?

1. Give spectinomycin plus azithromycin
2. Give spectinomycin alone
3. Give gentamicin plus azithromycin
4. Give gentamicin alone
5. Give ertapenem
6. Wait for TOC

Day 13: recalled for spectinomycin

- Asymptomatic
- Urine NAAT negative
- Denied any sexual contact since treatment
- Spectinomycin 2g IM

Incident management

- Emergence of dual resistance to last remaining treatment options is a global public health threat
- Control spread
  - Case management: TOC, including pharyngeal test
  - Partner notification: UK and Thailand ?any others
- Thai authorities notified via IHR (WHO)
- EWRS notification
- PHE Briefing Note and HPR publication

3 weeks later

- Remained asymptomatic
- Urine NAAT negative
- **Pharyngeal GC culture positive,** same antibiogram
- Denied any sexual contact since treatment
- UK partner NAAT negative
- Thai partner could not be contacted

What would you do now?

1. Give gentamicin plus azithromycin
2. Give gentamicin alone
3. Give ertapenem
4. Give penicillin
5. Wait 2 weeks and repeat test

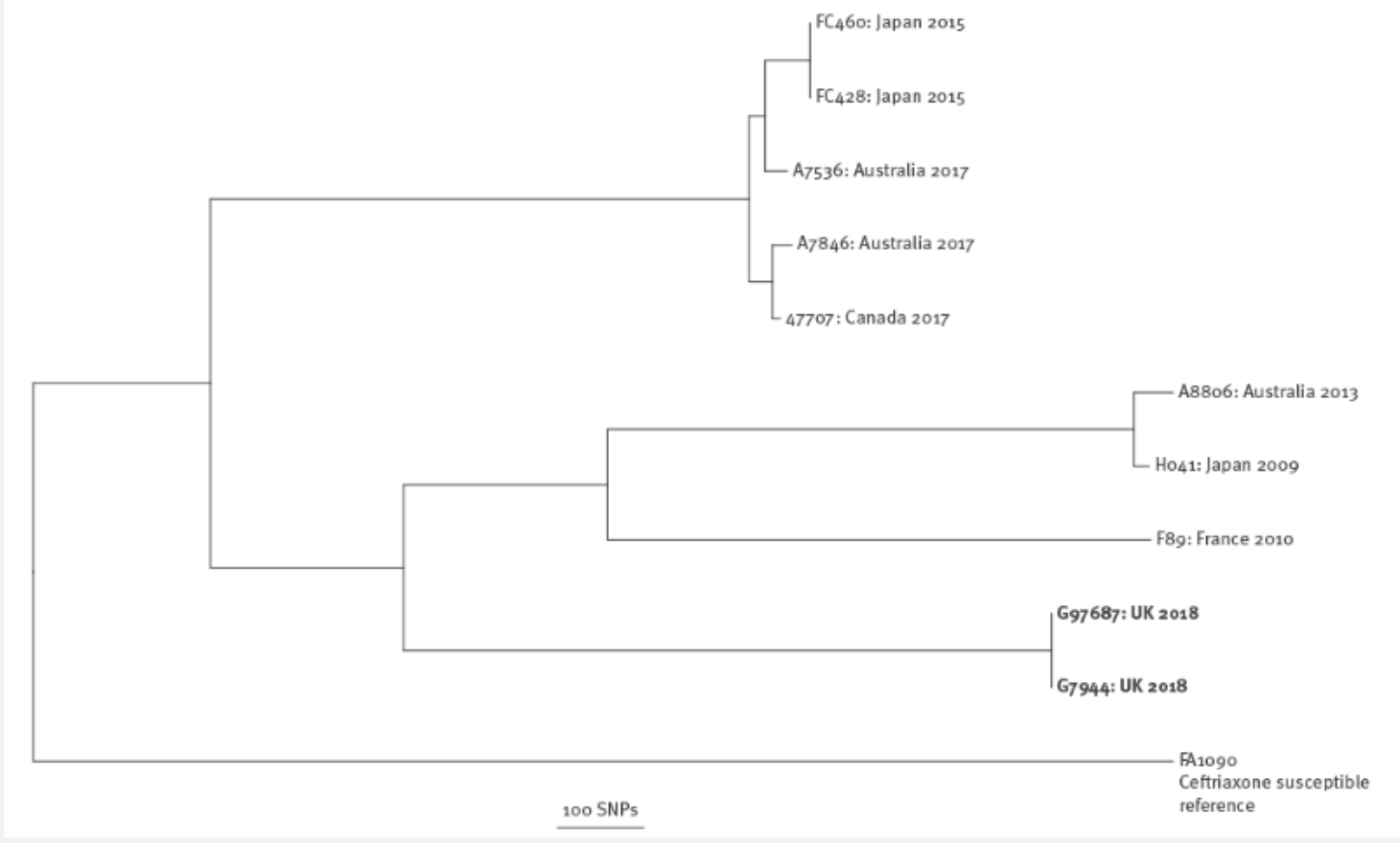
Ertapenem

- Treated with 3 days ertapenem 1g IV
- Why ertapenem?
  - Ertapenem shown to have *in vitro* microbiological activity against NG (Livermore *et al* JAC 2004)
  - Evaluated against MDR and XDR strains, MICs of ertapenem tend to parallel those of ceftriaxone, however isolates with high ceftriaxone MICs (0.5-4mg/L) had lower ertapenem MICs (0.016-0.064mg/L) (Unemo *et al* AAC 2012)
  - No clinical data
  - Pragmatic dosing regimen chosen by expert opinion

Gonorrhoea treatment failure caused by a *Neisseria gonorrhoeae* strain with combined ceftriaxone and high-level azithromycin resistance, England, February 2018

David W Eyre[1,2], Nicholas D Sanderson[2], Emily Lord[3], Natasha Regisford-Reimmer[3], Kevin Chau[2], Leanne Barker[2], Markus Morgan[3], Robert Newnham[3], Daniel Golparian[4], Magnus Unemo[4], Derrick W Crook[2,5,6], Tim EA Peto[2,6], Gwenda Hughes[5], Michelle J Cole[5], Helen Fifer[5], Anne Edwards[3,7], Monique I Andersson[3,7]

Figure 1 Genetic relatedness with previous ceftriaxone resistant isolates of *Neisseria gonorrhoeae* case imported from Thailand to England, February 2018



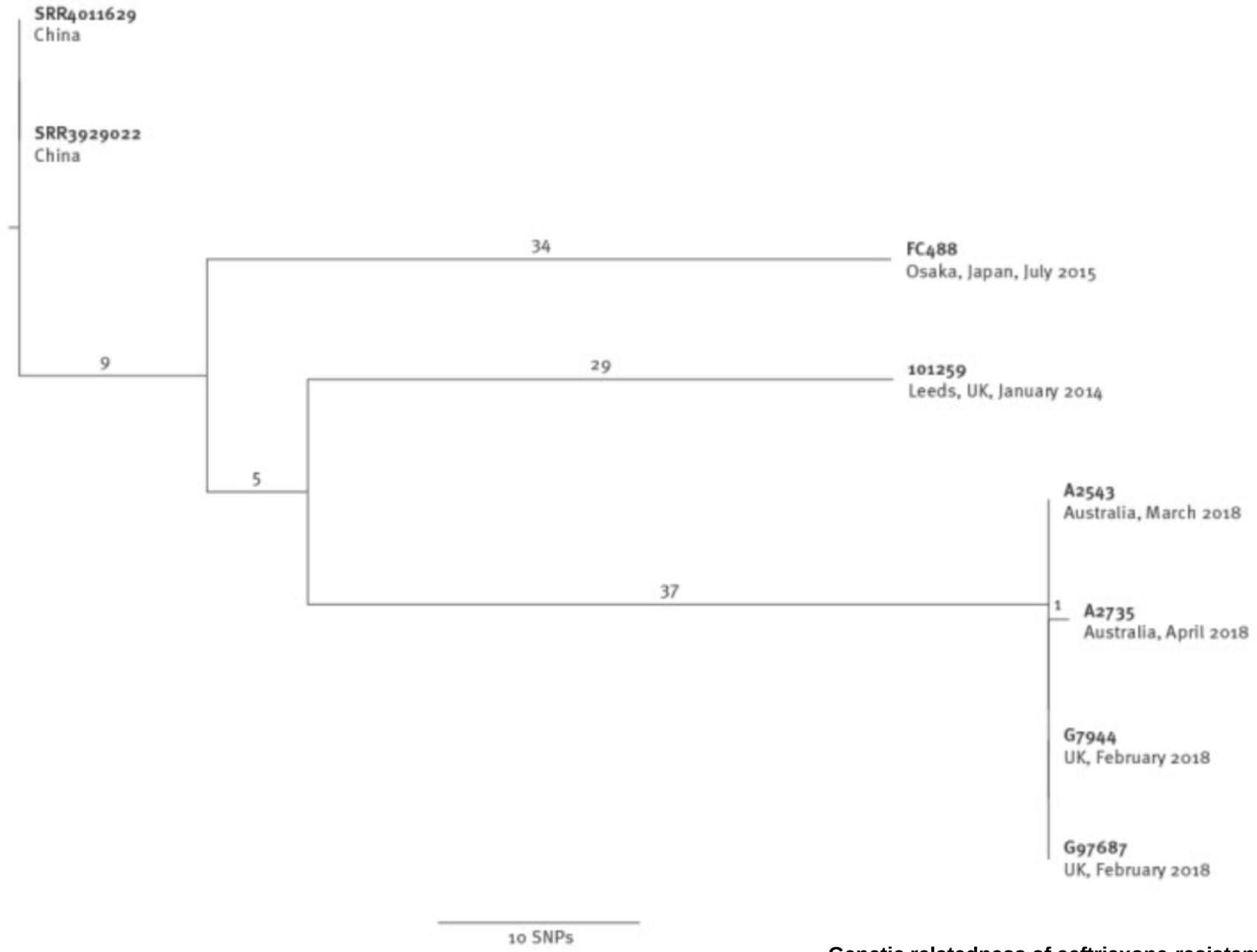
THE LANCET
Infectious Diseases
Volume 18, Issue 7, July 2018, Pages 717-718

Correspondence

Genetic characterisation of *Neisseria gonorrhoeae* resistant to both ceftriaxone and azithromycin

David M Whiley [a] ✉, Amy Jennison [b], Julie Pearson [c], Monica M Lahra [d]

- Two isolates, Australia 2018 = identical and epidemiologically unrelated
- Phenotypically similar to the UK isolate

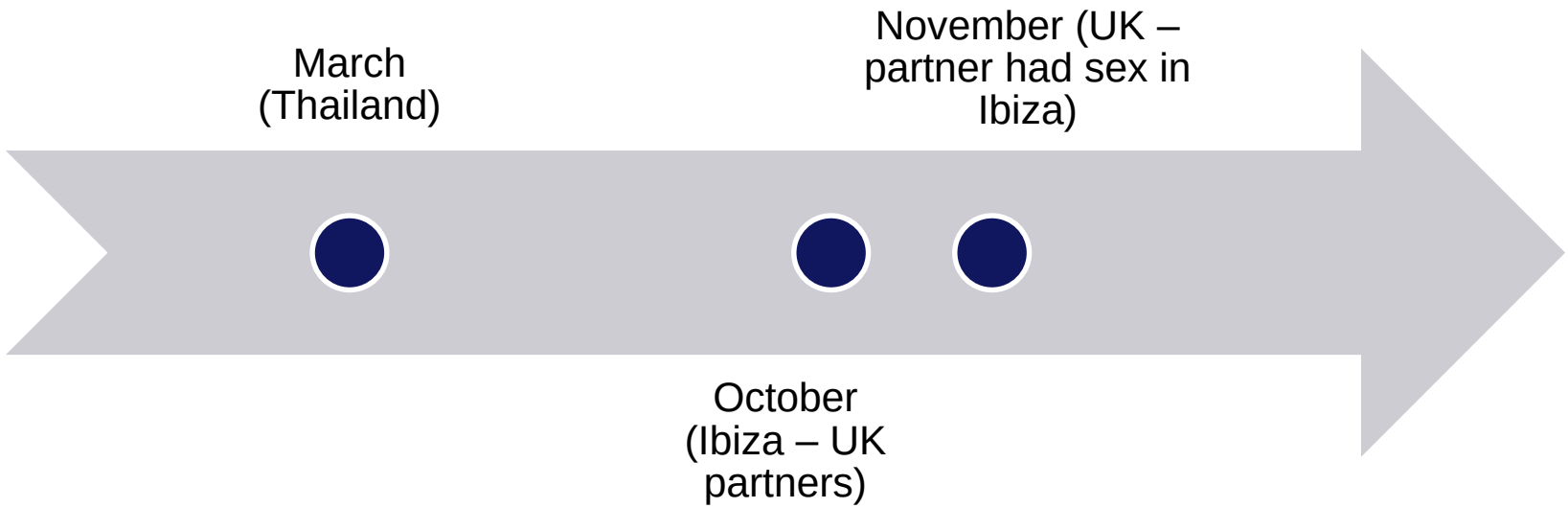


Genetic relatedness of ceftriaxone-resistant and high-level azithromycin resistant *Neisseria gonorrhoeae* cases, United Kingdom and Australia, February to April 2018.
Jennison AV et al. Euro Surveill. 2019 Feb;24(8).

Further Actions

- NaTHNac: STI advice for travellers
- ECDC Rapid Risk Assessment
- Review of guidelines: pharyngeal testing

Further XDR cases….

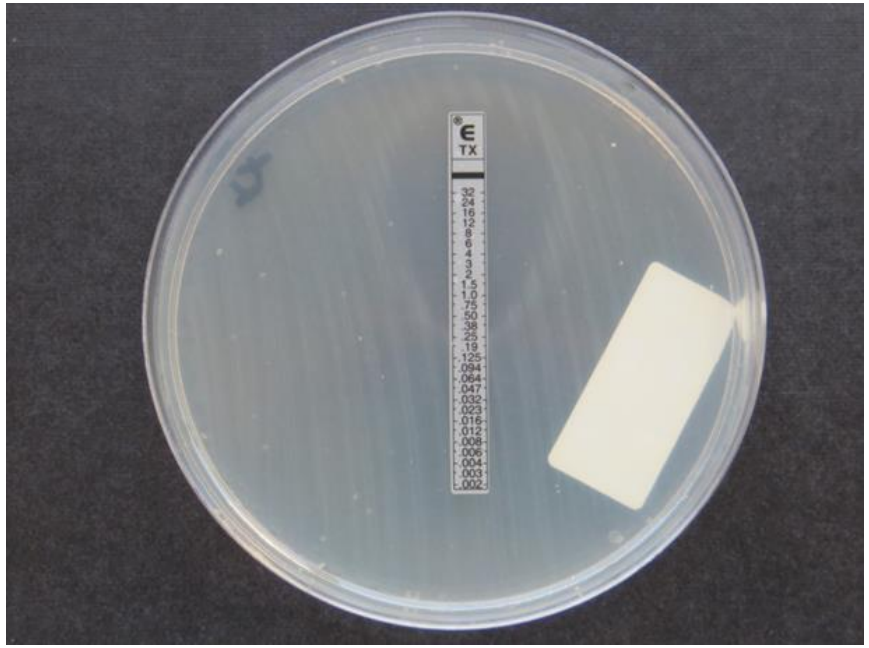


October 2018: case 1

- Female with dysuria
- >1 partner in Ibiza (all UK men, not contactable)
- VVS NAAT positive
- Ceftriaxone 500mg plus azithromycin 1g

Culture results:

Ceftriaxone R	MIC 1.0 mg/L
Cefixime R	MIC 2.0 mg/L
Penicillin R	MIC 2.0 mg/L
Tetracycline R	MIC 2.0 mg/L
Ciprofloxacin R	MIC > 32 mg/L
Azithromycin I	MIC 0.5 mg/L
Spectinomycin S	MIC 8.0 mg/L
Gentamicin	MIC 4.0 mg/L
Ertapenem	MIC 0.032 mg/L



What would you do now?

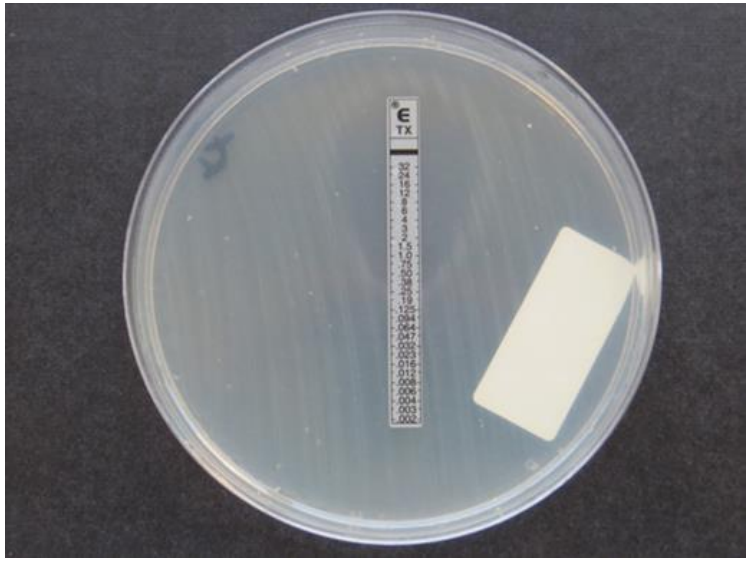
1. Give ceftriaxone 1g plus azithromycin 2g
2. Give gentamicin plus azithromycin
3. Give gentamicin alone
4. Give ertapenem
5. Wait for TOC

November 2018: case 2

- Asymptomatic female attended for screen, 2 weeks after unprotected vaginal, oral and anal sex with UK-resident man who had been in Ibiza
- Positive vaginal and rectal NAATs, negative throat NAAT (culture-negative all sites)
- 1 week later treated with ceftriaxone 1 g and at this visit reported rectal symptoms
- Initially responded clinically but symptoms relapsed,10 days later visited GP

Endocervical culture results:

Ceftriaxone R	MIC 1.0 mg/L
Cefixime R	MIC 2.0 mg/L
Penicillin R	MIC 2.0 mg/L
Tetracycline R	MIC 2.0 mg/L
Ciprofloxacin	MIC > 32 mg/L
Azithromycin I	MIC 0.5 mg/L
Spectinomycin S	MIC 8.0 mg/L
Gentamicin	MIC 4.0 mg/L
Ertapenem	MIC 0.032 mg/L



What would you do?

1. Give ceftriaxone 1g plus azithromycin 2g
2. Give gentamicin plus azithromycin
3. Give gentamicin alone
4. Give ertapenem
5. Wait and repeat tests in 2 weeks

Clinic 4 days later

Culture and NAAT-positive at both the rectum and cervix but not the throat
Treated with gentamicin 240mg plus azithromycin 2g

1 week later: no improvement in symptoms

What would you do now?

1. Give ceftriaxone 1g plus azithromycin 2g
2. Repeat gentamicin plus azithromycin
3. Give ertapenem
4. Wait for TOC

Further treatment

- IV ertapenem 1 g once daily for 3 days
- Symptoms resolved
- TOC 2 weeks later negative at both sites

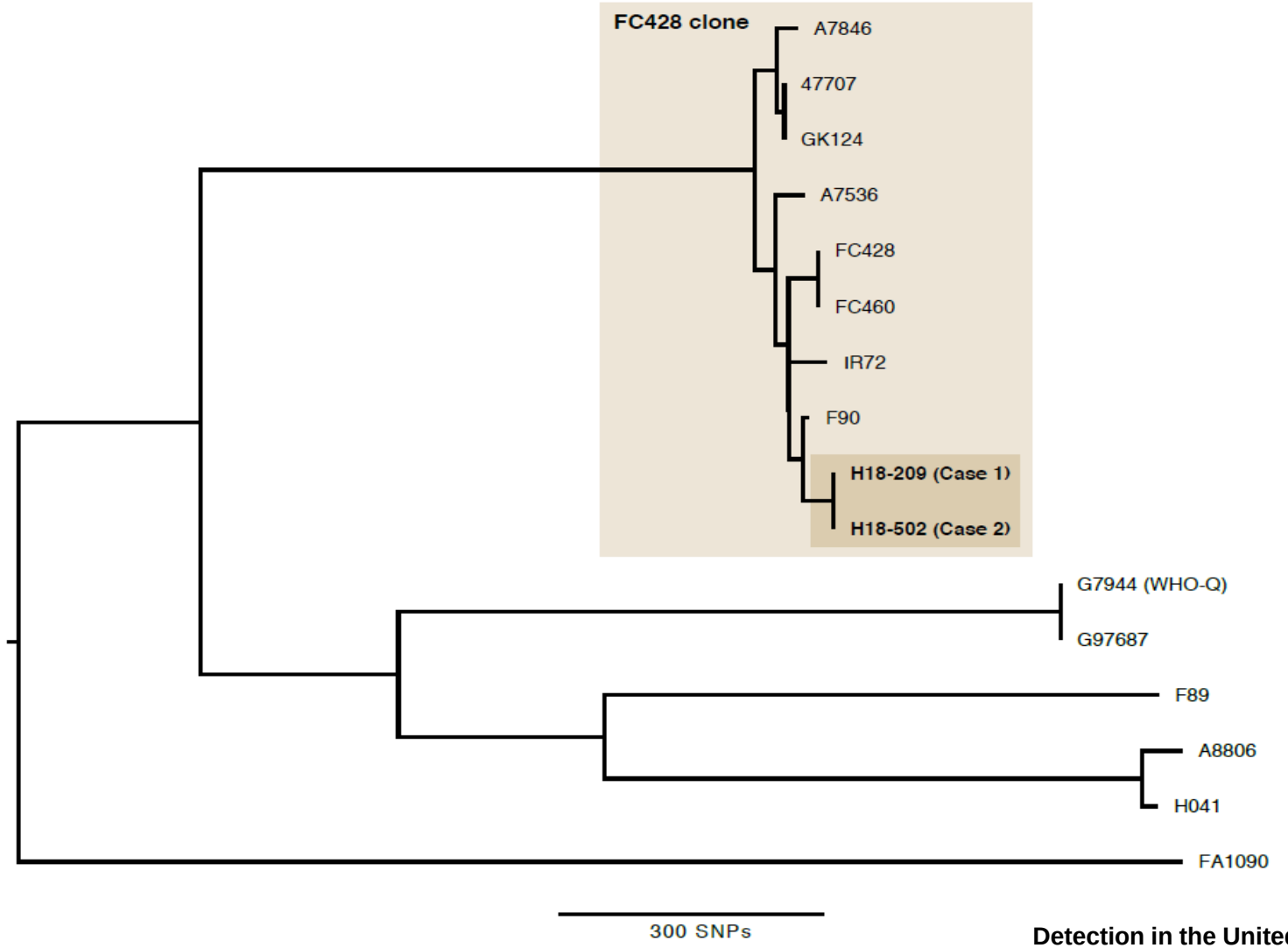
Partner notification

- ‘Ibiza’ contact was asymptomatic, negative urine NAAT
- Case 2 had unprotected oral sex and protected vaginal sex with new male partner 8 days after receiving the first treatment (ceftriaxone), before her symptoms relapsed
- This partner was NAAT-positive at the pharynx (culture negative) and negative urine NAAT

How would you treat this partner?

1. Give ceftriaxone 1g plus azithromycin 2g
2. Give ceftriaxone 1g alone
3. Give azithromycin 2g alone
4. Give gentamicin plus azithromycin
5. Give ertapenem

Identical WGS, FC428 clone



Detection in the United Kingdom of the *Neisseria gonorrhoeae* FC428 clone, with ceftriaxone resistance and intermediate resistance to azithromycin, October to December 2018.
Eyre et al. Eurosurveillance 2019 Mar;24(10)

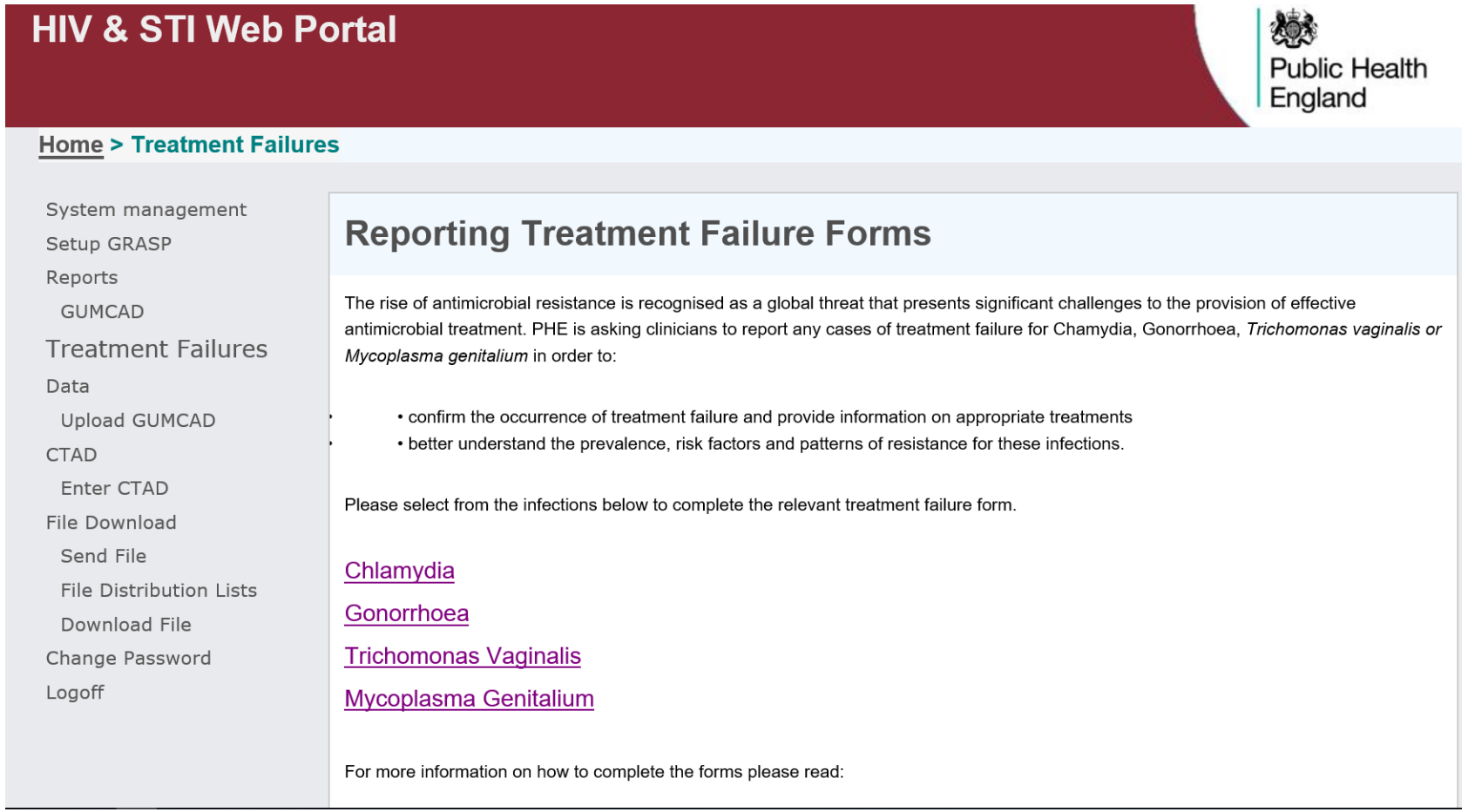
What does this mean?

- The ‘Ibiza’ contact of Case 2 had an epidemiological link to the same sexual network as Case 1, and given the sequencing results, is likely to have been the source of Case 2’s infection, and to have spontaneously cleared his infection
- Evidence of transmission of FC428 clone occurring within Europe. As the transmission between our cases is likely to have occurred between UK residents visiting Ibiza, there is a risk that further undetected transmission has occurred.
- PHE has introduced enhanced monitoring to ensure all ceftriaxone-resistant isolates identified by primary labs are sent to Ref lab for confirmation and investigation promptly to help reduce further spread.

Identifying ceftriaxone resistance

	Number reported resistant by primary labs (2018)	Number sent to Ref lab (2018)	Number of cases confirmed as resistant	Proportion sent to Ref lab (2018)	Proportion sent to Ref lab (2015)
Ceftriaxone R	58	45	3	76%	19%
Azithromycin R	1419	712	n/a	50%	31%
Total	1477	757		51%	28%

http://hivstiwebportal.phe.org.uk/login.aspx



What's next?

New therapies lacking; no new anti-GC agent entered Phase II-III since 2015

Clear medical need; commercial opportunity less certain

New agents

Solithromycin (macrolide family): Phase III clinical trial failed non-inferiority, and concerns re liver toxicity preventing dosing adjustments

Delafloxacin (fluoroquinolone) - failed non-inferiority

Gepotidacin (type IIA topoisomerase inhibitor) Promising phase II clinical trials, but concerning that resistance was seen in treatment failures

Zoliflodacin (type IIA topoisomerase inhibitor) Promising phase II clinical trials. To start phase III

Other options

Antimicrobial susceptibility detection at point of care

Vaccine

'Older' agents

Use of ‘older’ antimicrobials

- Ertapenem, Fosfomycin, Rifampicin, Piperacillin-tazobactam
- Cases of ceftriaxone resistance, allergy, and in novel dual antimicrobial regimens
- Lack of appropriate pharmacokinetic/pharmacodynamic parameters for gonorrhoea and known correlates between MIC and treatment outcome
- AMR determinants already exist in the gonococcal population (ertapenem and rifampicin) or resistance might emerge rapidly (fosfomycin)
- Dutch double-blind randomized clinical noninferiority trial: ceftriaxone 500mg IM vs ertapenem 1g IM vs gentamicin 5mg/kg IM vs fosfomycin 6g PO

Thank you

Thank you to Michelle Cole, Gwenda Hughes, and GRASP team

Helen.fifer@phe.gov.uk