Are we entering an era of untreatable gonorrhoea?

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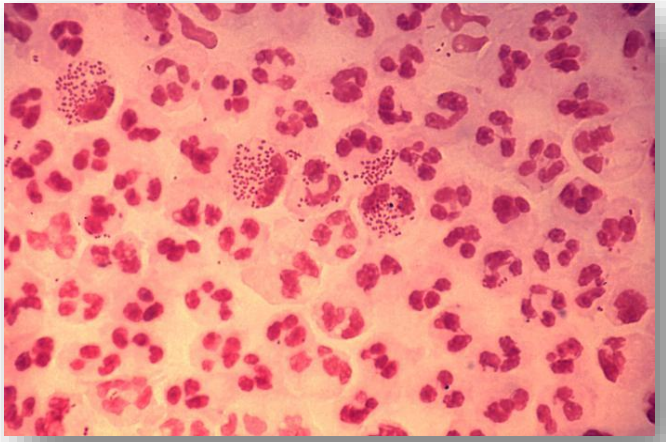
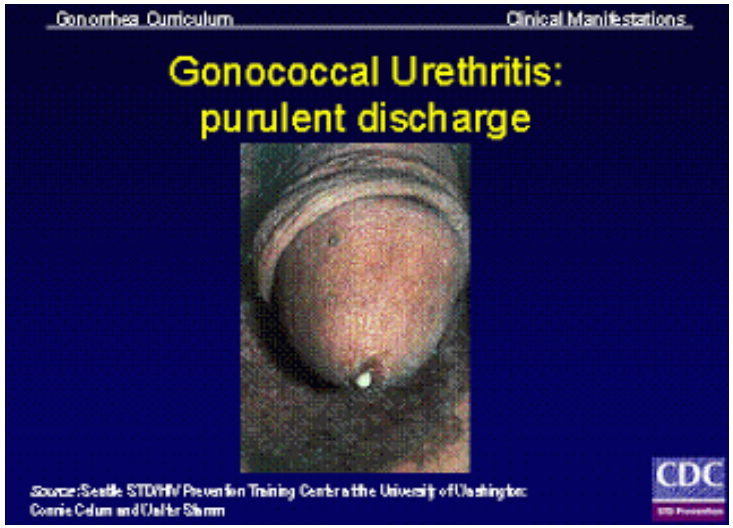
NATIONAL HEALTH LABORATORY SERVICE

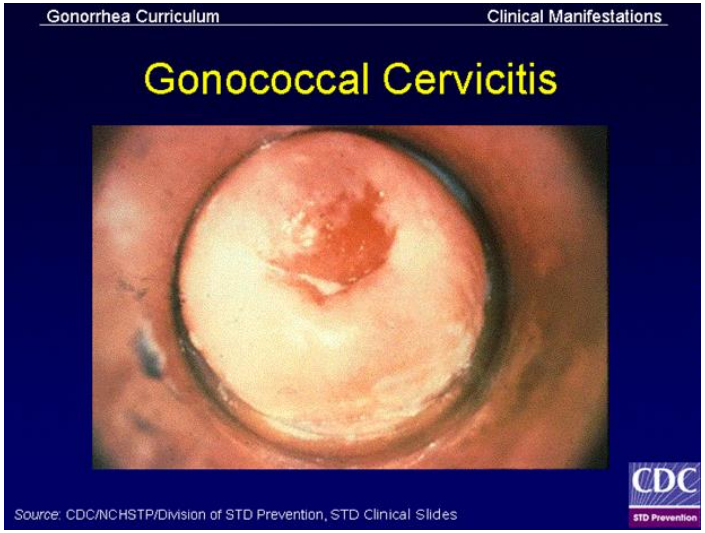
Gonorrhoea

- “Flow of seed” (Greek)
- “The clap” – derived in 1378 from the name of a Parisian brothel (Les Clapiers)
- Caused by *Neisseria gonorrhoeae*
  - sexually transmitted
  - obligate pathogen of humans



Clinical Presentation

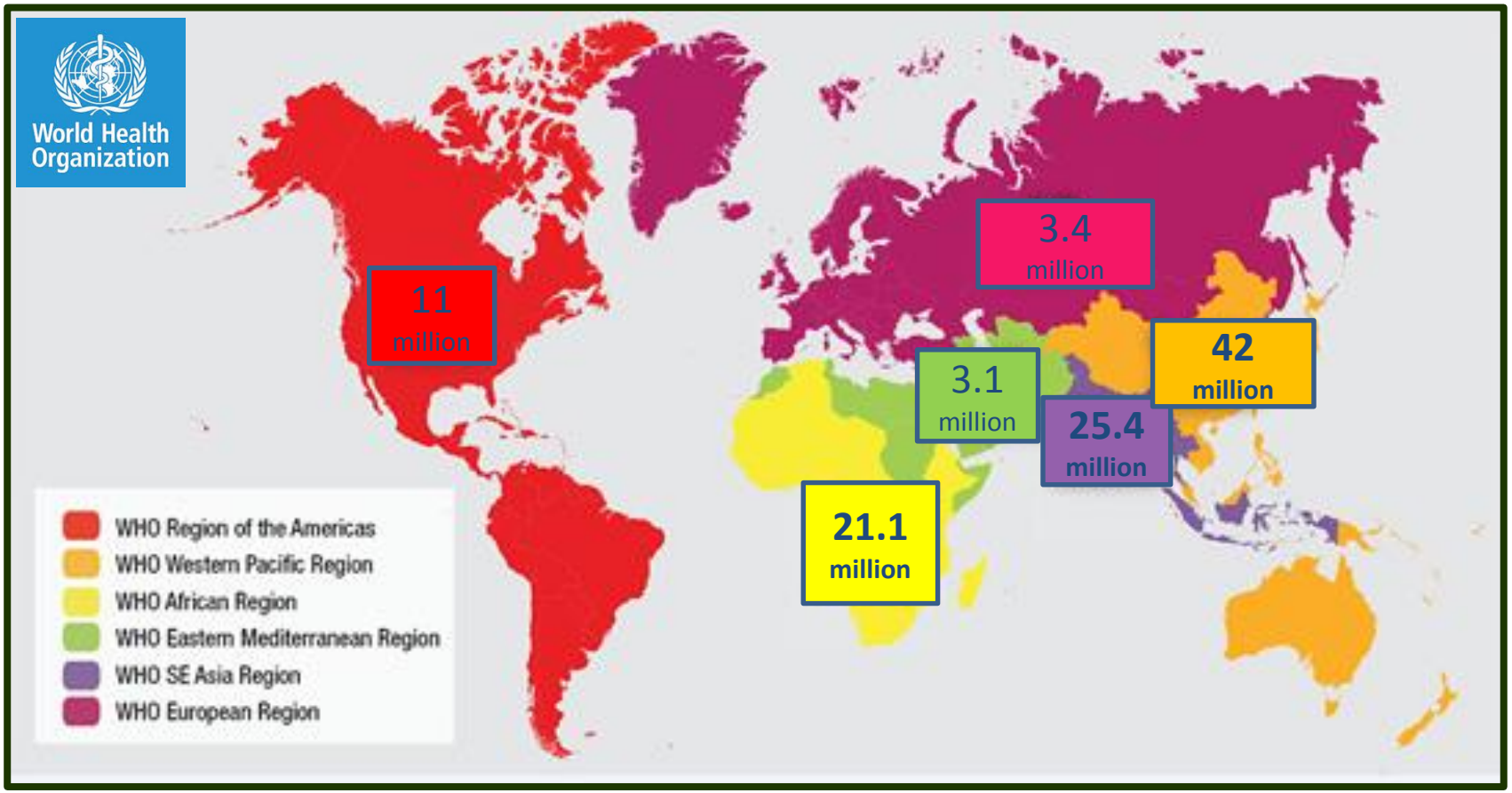


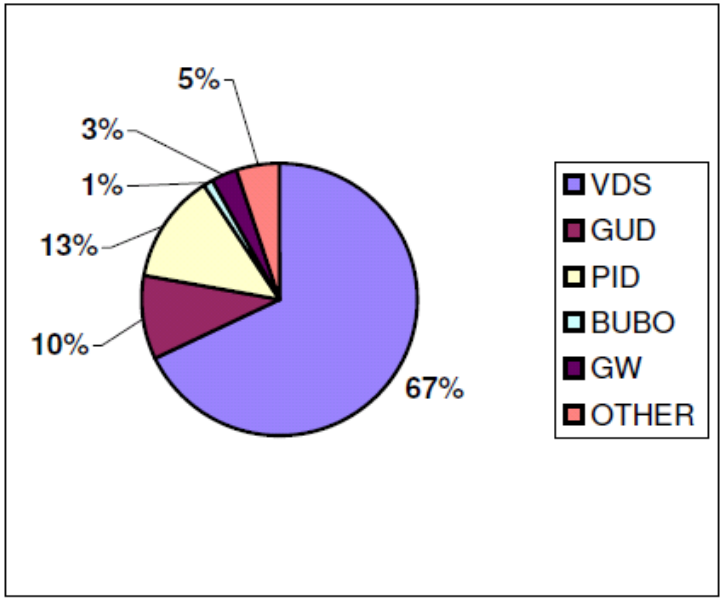


- **Complications**
  - PID
  - Ectopic pregnancy
  - Epidymo-orchitis
  - Disseminated gonococcal infection
  - Infertility

Epidemiology

- 2008 (WHO): 106 million new cases globally
  - 21% increase since 2005





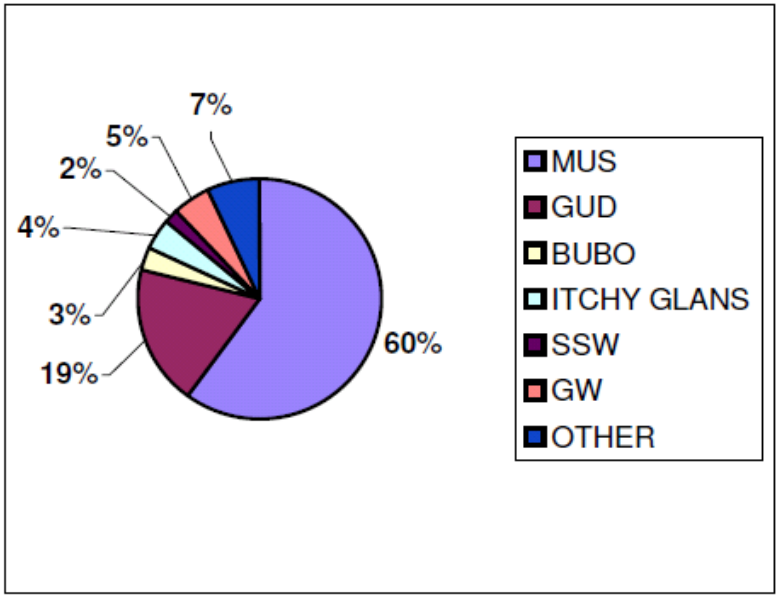
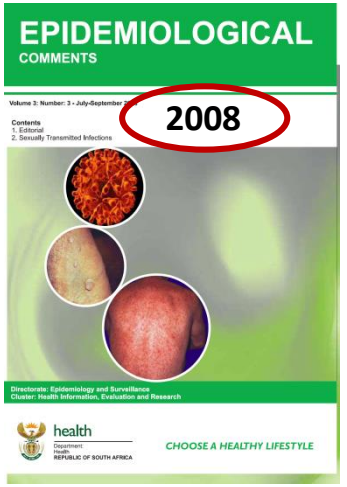


Figure 5: Distribution of STI syndromes in both females and males, South Africa, 2000 - 2007

MICROBIOLOGICAL SURVEILLANCE

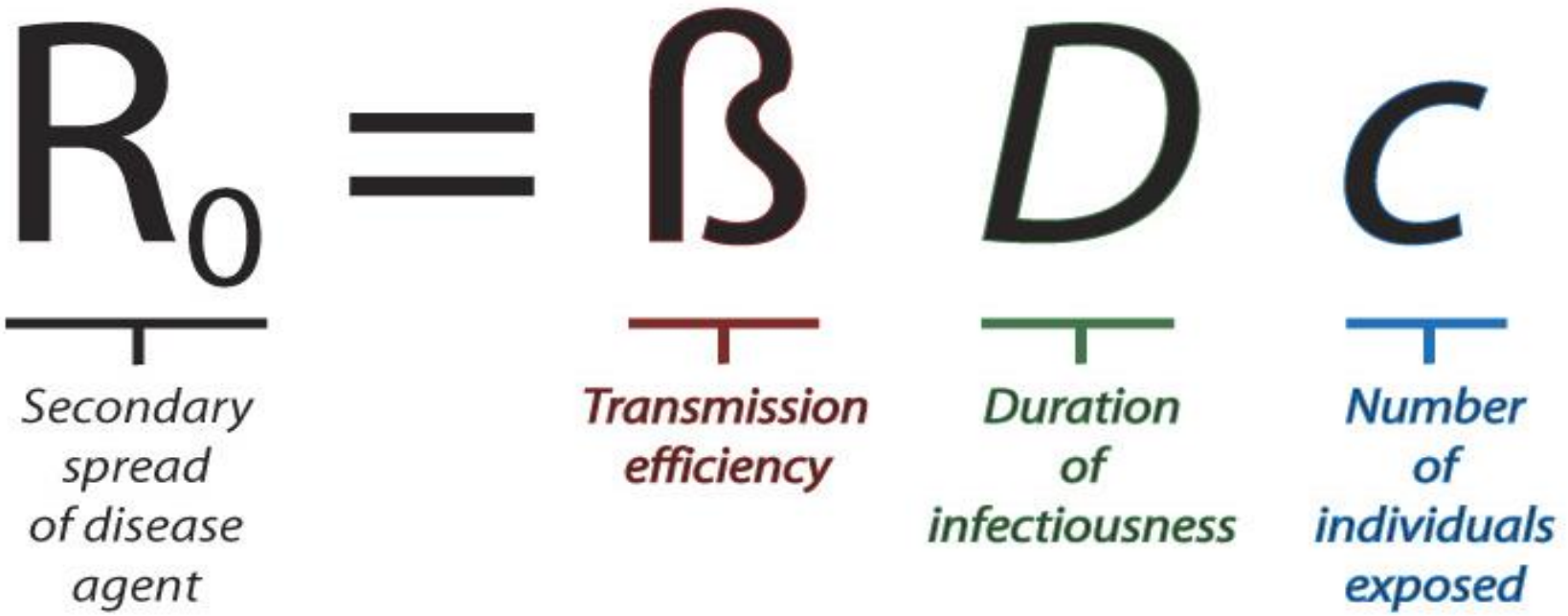
Gauteng 2007 Surveillance Report, STI Reference Centre, NICD



Prevalence of gonococcal infection:

- **MUS – 71% (n=217)**
- VDS – 13.1% (n= 206)

Major public health concern



- **Short incubation period**
- **High transmission efficiency. Co-efficient of infection:**
  - **female to male = 0.6; male to female = 0.7**

Major public health concern

- Fivefold increase in HIV transmission[1]
- Asymptomatic urogenital infections in ≥ 50% infected women
- Rectal and pharyngeal gonorrhoea (MSM) mostly asymptomatic
- Eradication from oropharynx more difficult than from urogenital sites[2]
  - Differential concentration of antimicrobials
  - Selection for antimicrobial resistance
- Remarkable capacity acquire genetic antimicrobial resistance determinants

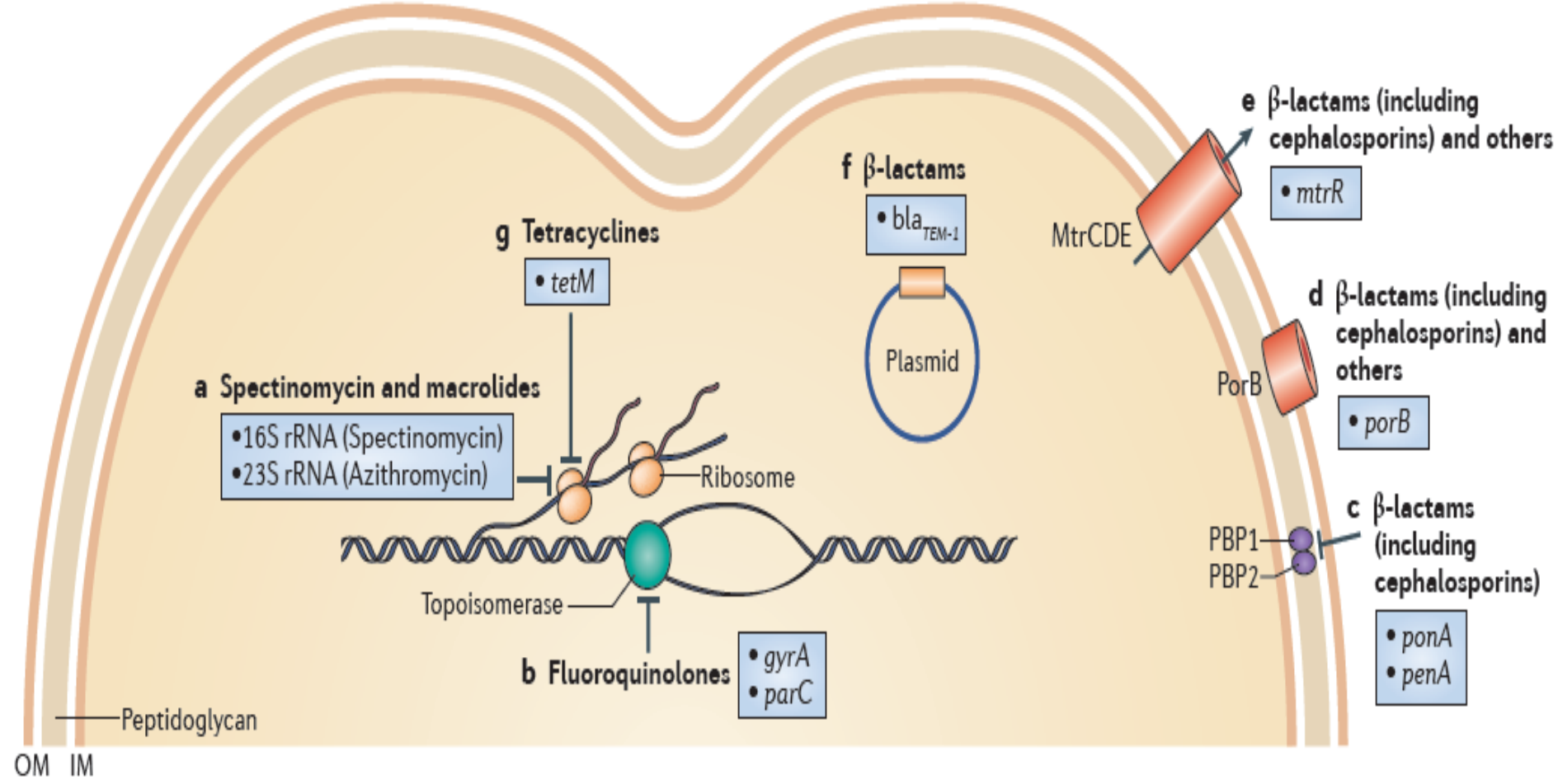
[1]WHO/RHR/11.14 2011
[2]Curr Opin Infect Dis 2014; 27 (3): 282-283

Mechanisms of antimicrobial resistance in *Neisseria gonorrhoeae*

Plasmid or chromosome mediated

- 1. Antimicrobial destruction/ modification by enzymes
- 2. Target modification or protection leading to reduced affinity
- 3. Decreased antimicrobial influx (porin mutations)
- 4. Increased antimicrobial efflux (upregulation of efflux pumps)

Mechanisms of antimicrobial resistance in *Neisseria gonorrhoeae*



Nature Rev Microbiol 2014;12: 223-229

Resistance evolution in *Neisseria gonorrhoeae*

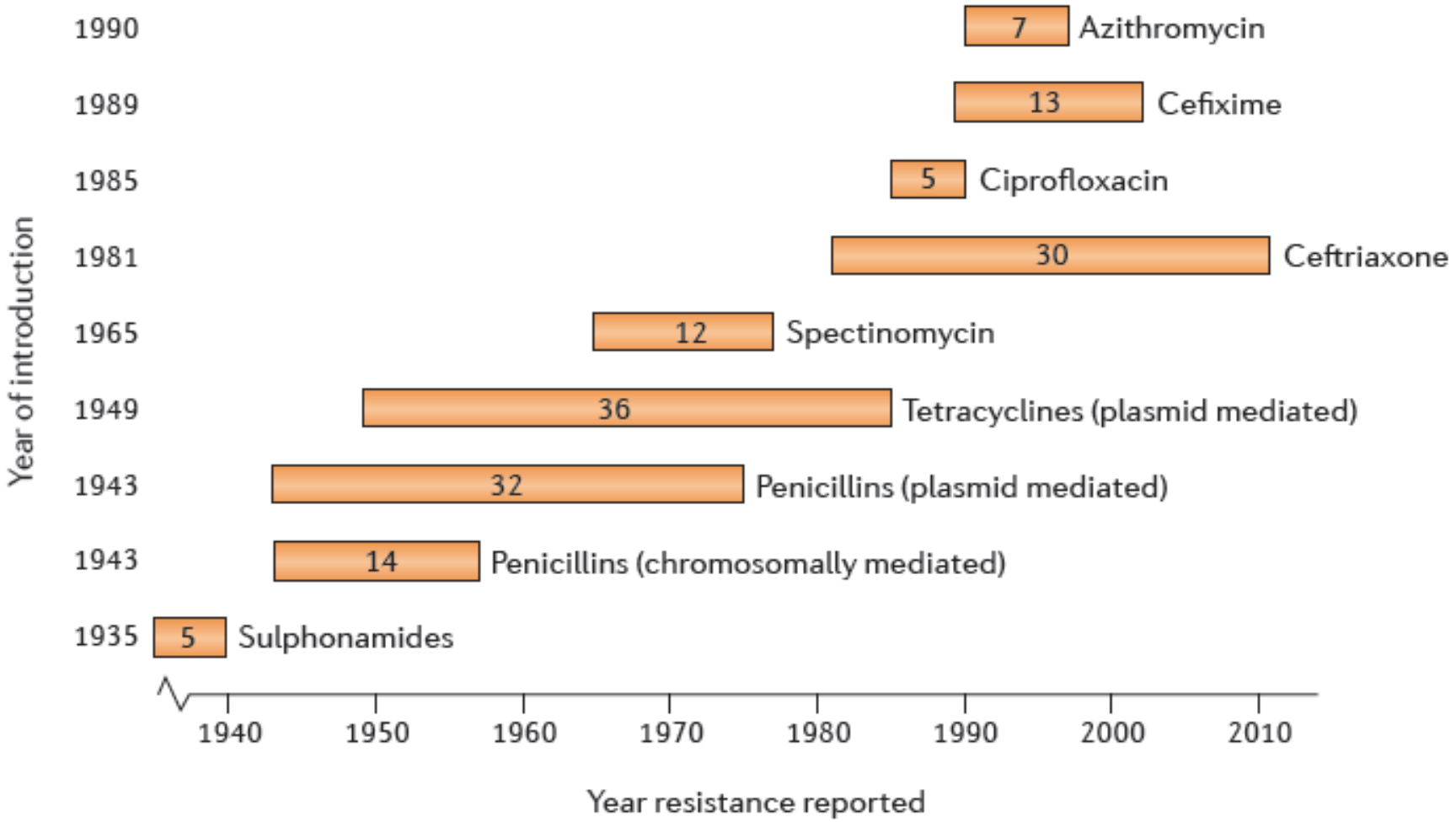


Figure 1 | **The history of *Neisseria gonorrhoeae* antimicrobial resistance.**

Nature Rev Microbiol 2014;12: 223-229

Antimicrobial resistance and gonococcal fitness

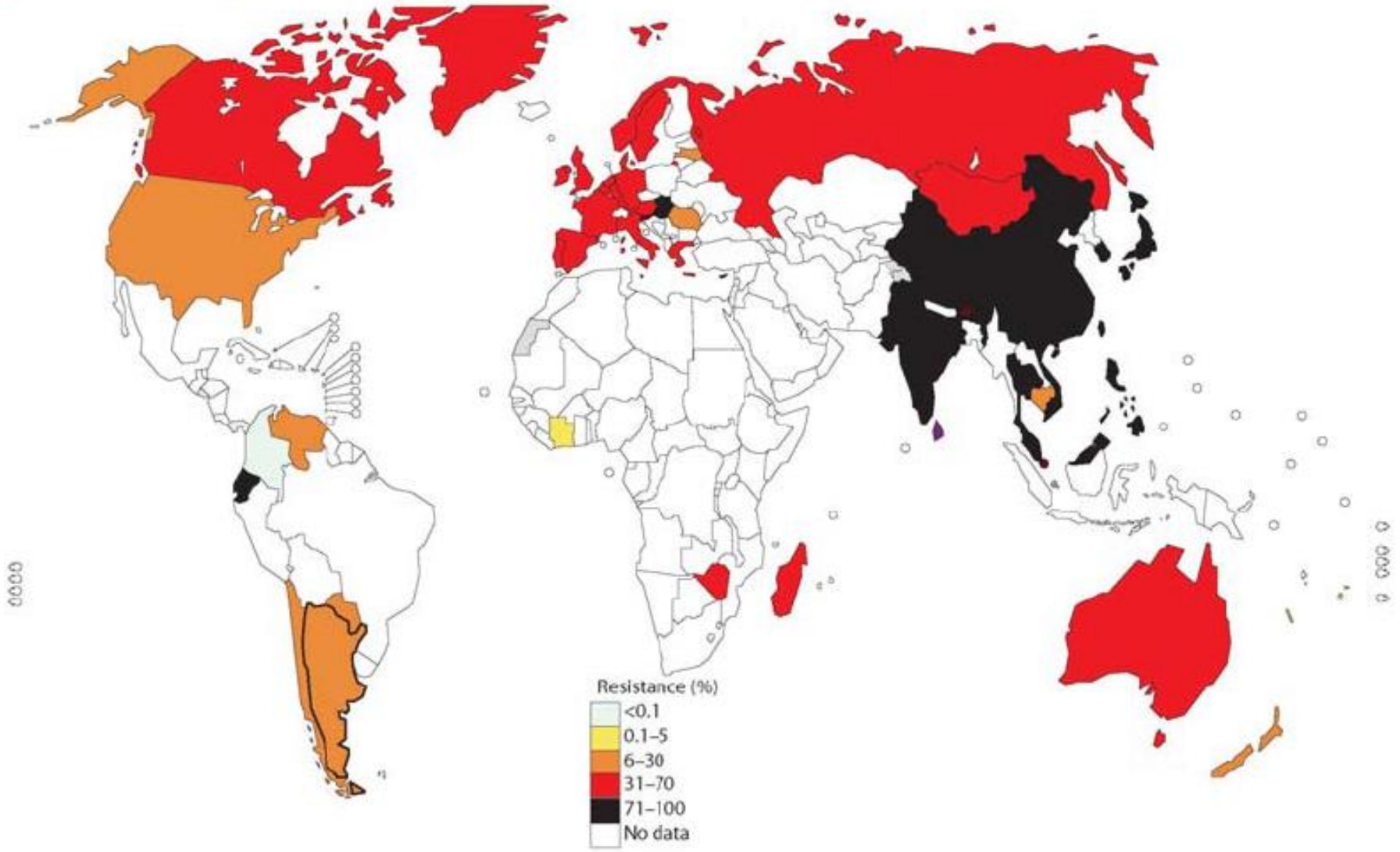
- In *Neisseria gonorrhoeae*, antimicrobial resistance does not appear to confer a fitness cost
  - Resistance mutations persist in the absence of antimicrobial selection pressure

- Some resistance determinants (*gyrA* mutations, MtrCDE efflux pumps) may enhance biological fitness

- Fitness retained due to additional compensatory/ stabilizing/ repairing mutations

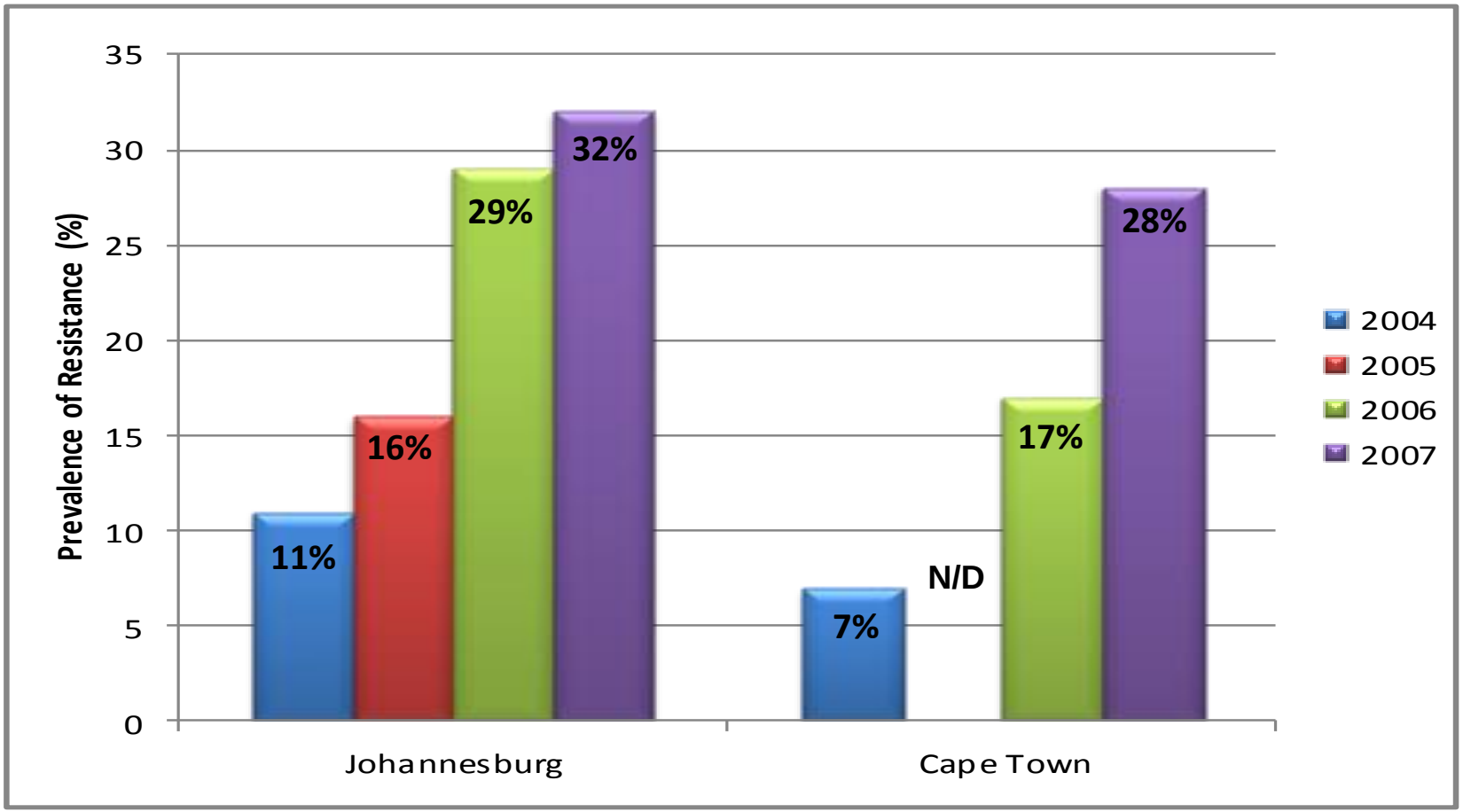
Clin Micro Rev 2014; 27(3): 587-612

Proportion of *N. gonorrhoeae* strains resistant to ciprofloxacin and/or other quinolones reported in countries, 2010



Source: GASP 2013

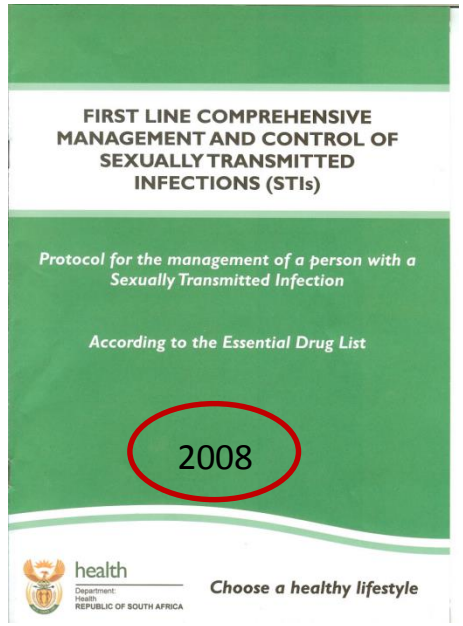
Rise of Ciprofloxacin-resistant Gonorrhoea in South Africa



The ciprofloxacin resistant phenotype was significantly associated with HIV serostatus (p = 0.034).

Lewis *et al*., Sex Transm Infect 2008; 84: 352-355

MALE URETHRITIS SYNDROME (MUS)



Patient complains of urethral discharge or dysuria

Take history and examine.
Milk urethra, if no visible discharge.
Emphasise HIV testing.

Discharge and/or dysuria present?

YES

Treat with:

- **Cefixime**, oral, 400 mg single dose**
AND
- **Doxycycline**, oral, 100 mg twice daily for 7 days

Ask patient to return in 7 days if symptoms persist

If symptoms persist

- Unprotected intercourse?
- Poor adherence?

NO

Treat with:

- **Metronidazole** 2g immediately as a single dose

Ask patient to return in 7 days if symptoms persist

YES

Repeat treatment

Improved?

NO

Treatment failure: Refer

YES

Discharge patient

Extended-spectrum cephalosporin (ESC) resistance in *Neisseria gonorrhoeae*

- ESCs: last antimicrobial class suitable for widespread single-dose single-agent treatment.
  - Cefixime is the only oral ESC that met criteria for effective treatment of pharyngeal gonorrhoea (≥ 95% cure rate).
  - SA: cefixime 400mg single-dose introduced into STI syndromic management guidelines (MUS, VDS) in 2008.

- Japan: in the 1990s a variety of oral ESCs with suboptimal efficacy and dosing regimens used in monotherapy
  - cephalosporin MIC creep & ultimate treatment failure with cefixime

JAC 2010; 65: 2141-2148

Extended-spectrum cephalosporin (ESC) resistance in *Neisseria gonorrhoeae*

- The primary resistance determinant is a specific alteration in *pen*A gene that encodes PBP2
  - Transformation due to acquisition & incorporation of *pen*A gene sequences from commensal *Neisseria* species in oropharynx

(*N. perflava, N. sicca, N. cinerea, N flavescens*)

Mosaic *pen*A gene → mosaic PBP2

Criteria for decreased susceptibility to cephalosporins

Drug	MICs (mg/l)
Cefixime	≥0.25
Ceftriaxone	≥0.125

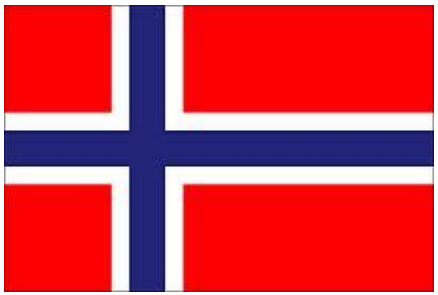
WHO 2012

Prevalence of Gonococcal Antimicrobial Resistance in Central Japan (1999-2002)

Gonococcal Phenotype	1999-2000 N = 91	2001 N = 150	2002 N = 221
PPNG	1.1%	0.7%	0.5%
TRNG (MIC ≥ 16mg/l)	2.2%	0.7%	0.5%
CMRNG Pen (MIC ≥ 2mg/l)	2.2%	59.3%	73.3%
CMRNG Tet (MIC ≥ 2mg/l)	11.0%	53.7%	68.8%
QRNG Levofloxacin (MIC ≥ 1mg/l)	27.5%	53.3%	78.3%
Cefixime decreased susceptibility (MIC ≥ 0.5mg/l)	0%	26.0%	30.3%
Ceftriaxone decreased susceptibility (MIC ≥ 0.5mg/l)	0%	0%	0.9%
Spectinomycin resistance (MIC ≥ 128mg/l)	0%	0.7%	0%

Antimicrob. Agents Chemother. 2004; 48: 3185-3187

Emergence of Clinically Confirmed Cefixime Treatment Failures in Europe



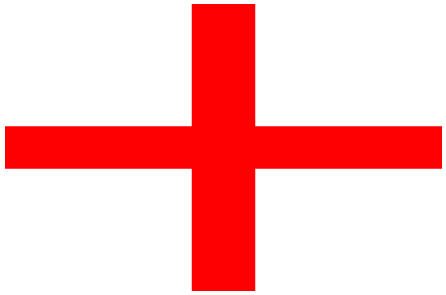
RAPID COMMUNICATIONS

Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010

M Unemo (magnus.unemo@orebroll.se)[1], D Golparian[1], G Syversen[2], D F Vestrheim[3,4], H Moi[3,5]
1. Swedish Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden
2. Department of Microbiology, Oslo University Hospital, Ullevål, Oslo, Norway
3. Olafiaklinikken, Oslo University Hospital, Oslo, Norway
4. Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway
5. Faculty of Medicine, University of Oslo, Oslo, Norway

Citation style for this article:
Unemo M, Golparian D, Syversen G, Vestrheim DF, Moi H. Two cases of verified clinical failures using internationally recommended first-line cefixime for gonorrhoea treatment, Norway, 2010. Euro Surveill. 2010;15(47):pii=19721. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19721

Article published on 25 November 2010



RAPID COMMUNICATIONS

Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010

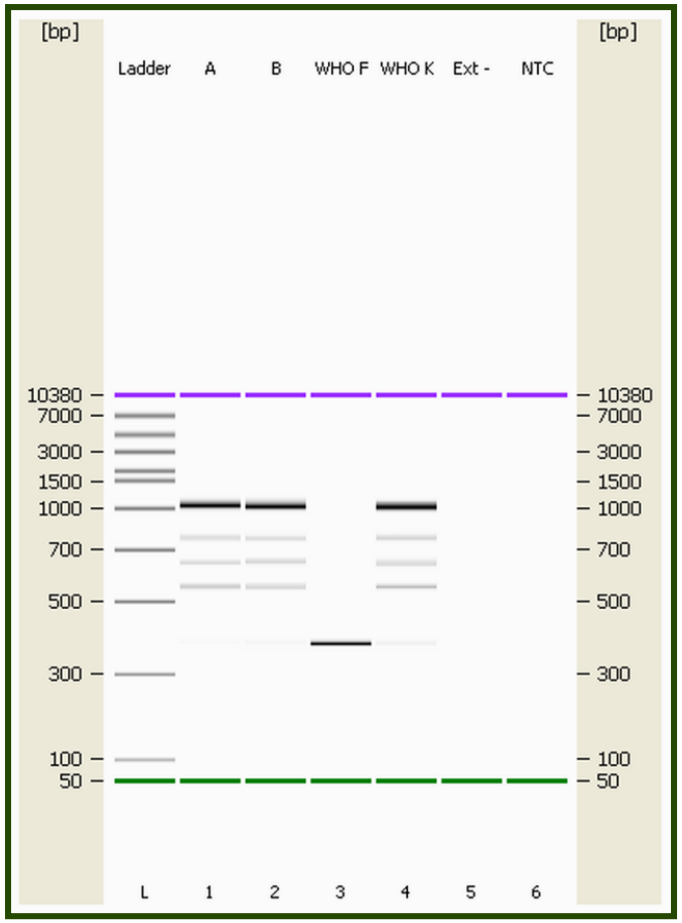
C A Ison (catherine.ison@hpa.org.uk)[1], J Hussey[2], K N Sankar[3], J Evans[4], S Alexander[1]
1. Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency, London, United Kingdom
2. Carlton Street Clinic, Blyth, Northumberland, United Kingdom
3. New Croft Centre, Newcastle upon Tyne, United Kingdom
4. Health Protection Agency North East, Newcastle General Hospital, Newcastle upon Tyne, United Kingdom

Citation style for this article:
Ison CA, Hussey J, Sankar KN, Evans J, Alexander S. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. Euro Surveill. 2011;16(14):pii=19833. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19833

Article published on 7 April 2011

Emergence of Cefixime Resistant Gonococci and Cefixime Treatment Failure in South Africa

Lewis *et al*. JAC 2013; 1-4

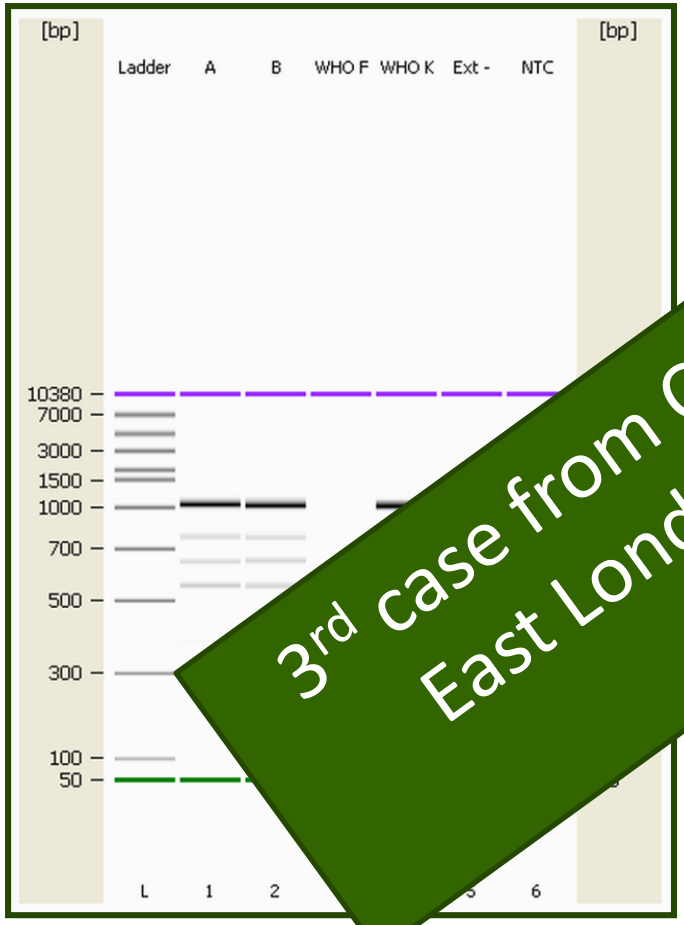


Antibiotic	Patient A (mg/L, agar dilution)	Patient B (mg/L, agar dilution)
Cefixime	0.25	0.25
Ceftriaxone	0.128	0.064
Penicillin	4 (β-lactamase –ve)	4 (β-lactamase –ve)
Tetracycline	4	4
Ciprofloxacin	> 16	> 16
Spectinomycin	32	32
Gentamicin	8	8
Azithromycin	0.5	1

- Phadebact serogroup WII/WIII
- NG-MAST ST 4822 (*porB* 1903; *tbpB* 29)
- MLST ST 1901
- Mosaic XXXIV (same as F89, MSM-linked)
- A-deletion in *mtrR* promoter
- *penB* mutations: G101K, A102N
- *ponA* mutation: L421P

Emergence of Cefixime Resistant Gonococci and Cefixime Treatment Failure in South Afri

Lewis *et al*. JAC 2013; 1-4



Antibiotic		t B gar dilution)
Cefixime		
Ceftri		0.064
	)	4 (β-lactamase –ve)
		4
		> 16
		32
	8	8
	ycin 0.5	1

3rd case from Cape Town and 4th case from East London with identical NG MAST genotype

- Phadebact serogroup WII/WIII
- NG-MAST ST 4822 (*porB* 1903; *tbpB* 29)
- MLST ST 1901
- Mosaic XXXIV (same as F89, MSM-linked)
- A-deletion in *mtrR* promoter
- *penB* mutations: G101K, A102N
- *ponA* mutation: L421P

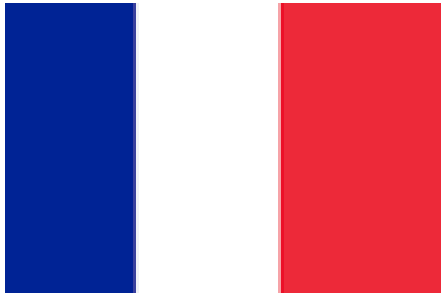
The World's First Confirmed Gonococcal Isolate Resistant to Ceftriaxone (XDR)

- Gonococcal strain isolated from the pharynx of a female sex worker in Kyoto, Japan (H041) in 2009
- Confirmed as *N. gonorrhoeae* by 7 tests
- MIC to ceftriaxone 2-4 µg/ml and to cefixime 8 µg/ml
- Resistant to most beta-lactams including piperacillin/tazobactam fluoroquinolones, macrolides, tetracycline, co-trimoxazole, chloramphenicol and nitrofurantoin
- Susceptible to spectinomycin, rifampicin and imipenem

Antimicrob Agents Chemother 2011; 55 (7): 3538-3545

Emergence of Clinically Confirmed Ceftriaxone Treatment Failures in Europe (F89 XDR)

NG-MAST ST1407; MLST ST1901



AAC
Journals.ASM.org

High-Level Cefixime- and Ceftriaxone-Resistant *Neisseria gonorrhoeae* in France: Novel *penA* Mosaic Allele in a Successful International Clone Causes Treatment Failure

Magnus Unemo,[a] Daniel Golparian,[a] Robert Nicholas,[b] Makoto Ohnishi,[c] Anne Gallay,[d] and Patrice Sednaoui[e]

WHO Collaborating Centre for Gonorrhoea and Other STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden[a]; Department of Pharmacology, University of North Carolina, Chapel Hill, North Carolina, USA[b]; National Institute of Infectious Diseases, Tokyo, Japan[c]; Institut de Veille Sanitaire, Saint-Maurice, France[d]; and Institut Alfred Fournier, Centre National de Référence des Gonocoques, Paris, France[e]

J Antimicrob Chemother 2012; **67**: 1858–1860
doi:10.1093/jac/dks162 Advance Access publication 7 May 2012

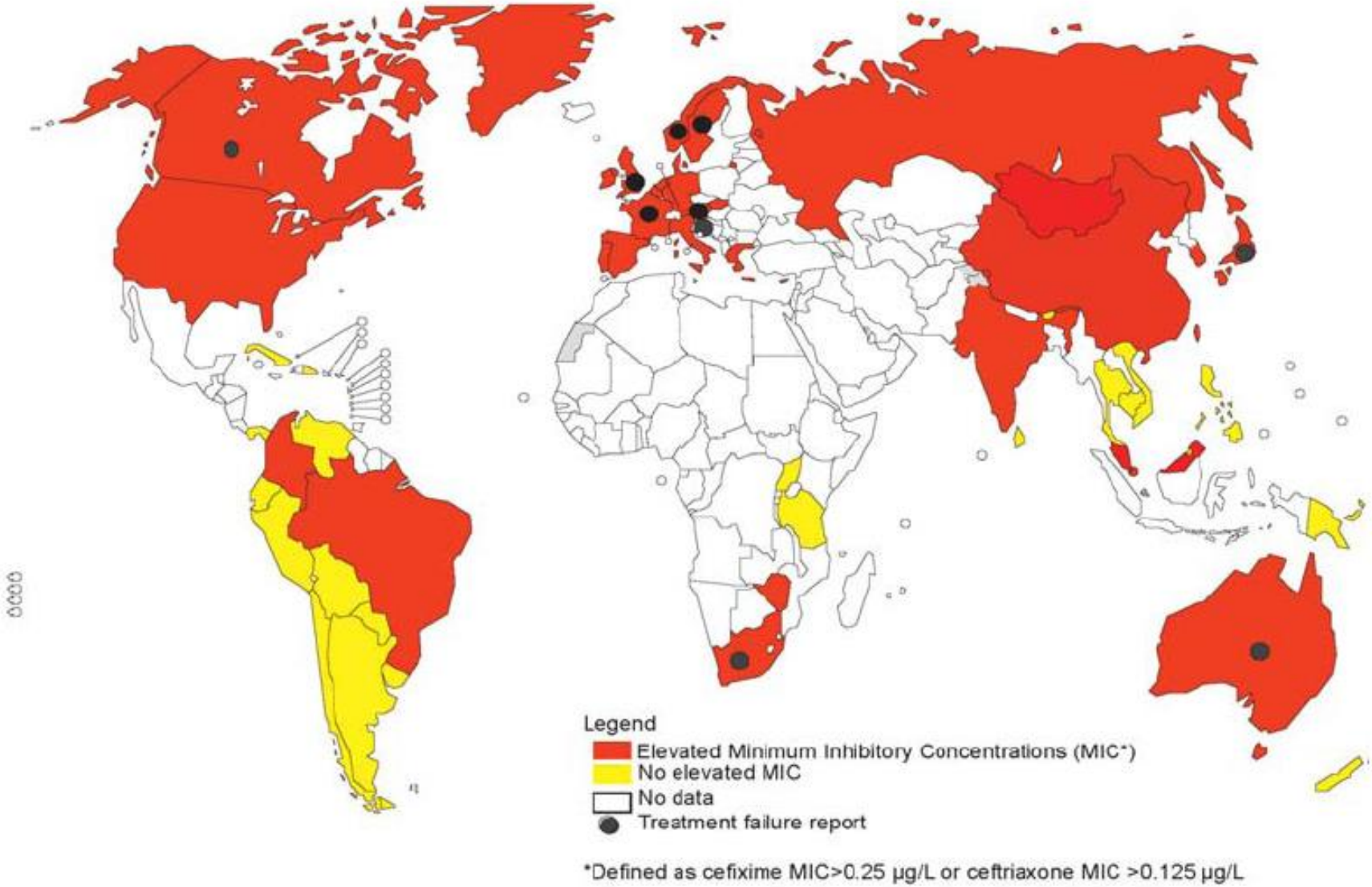
Journal of Antimicrobial Chemotherapy

Molecular characterization of two high-level ceftriaxone-resistant *Neisseria gonorrhoeae* isolates detected in Catalonia, Spain

Jordi Cámara[1], Judit Serra[2], Josefina Ayats[1], Teresa Bastida[3], Dolors Carnicer-Pont[4], Antònia Andreu[2] and Carmen Ardanuy[1]*

[1]Microbiology Department, Hospital Universitari de Bellvitge-Universitat de Barcelona-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain; [2]Microbiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [3]Microbiology Department, 'Esperit Sant' Regional Hospital, Santa Coloma de Gramenet, Spain; [4]Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), Institut Català d'Oncologia, Badalona, Barcelona, Spain

Countries with documented elevated minimum inhibitory concentrations to cefixime and/or ceftriaxone, 2010



Source: GASP 2013

Multi-Drug and Extensively-Drug Resistant *Neisseria gonorrhoeae* (MDR-NG and XDR-NG)

MDR-NG: resistant to ≥ 1 class I antibiotic PLUS resistant to ≥ 2 class II antibiotics

XDR-NG: resistant to ≥ 2 class I antibiotics PLUS resistant to ≥ 3 class II antibiotics

Class I antibiotics (currently recommended for use)	**Class II antibiotics** (used less frequently or proposed for more extensive use)
Injectable extended spectrum cephalosporins	Penicillins
Oral extended spectrum cephalosporins	Fluoroquinolones
Spectinomycin	Azithromycin
	Aminoglycosides
	Carbapenems

Expert Rev Anti Infect Ther 2009; 7: 822-834

ESC Strategies (pre-emptive) to limit spread of MDR-NG and XDR-NG

- 1. National change in recommended first line therapy for gonorrhoea from oral cefixime to injectable ceftriaxone.

- 2. Dual antimicrobial therapy to treat gonorrhoea

Table 1. Various dosing regimens of ceftriaxone for *Neisseria gonorrhoeae* throughout the world

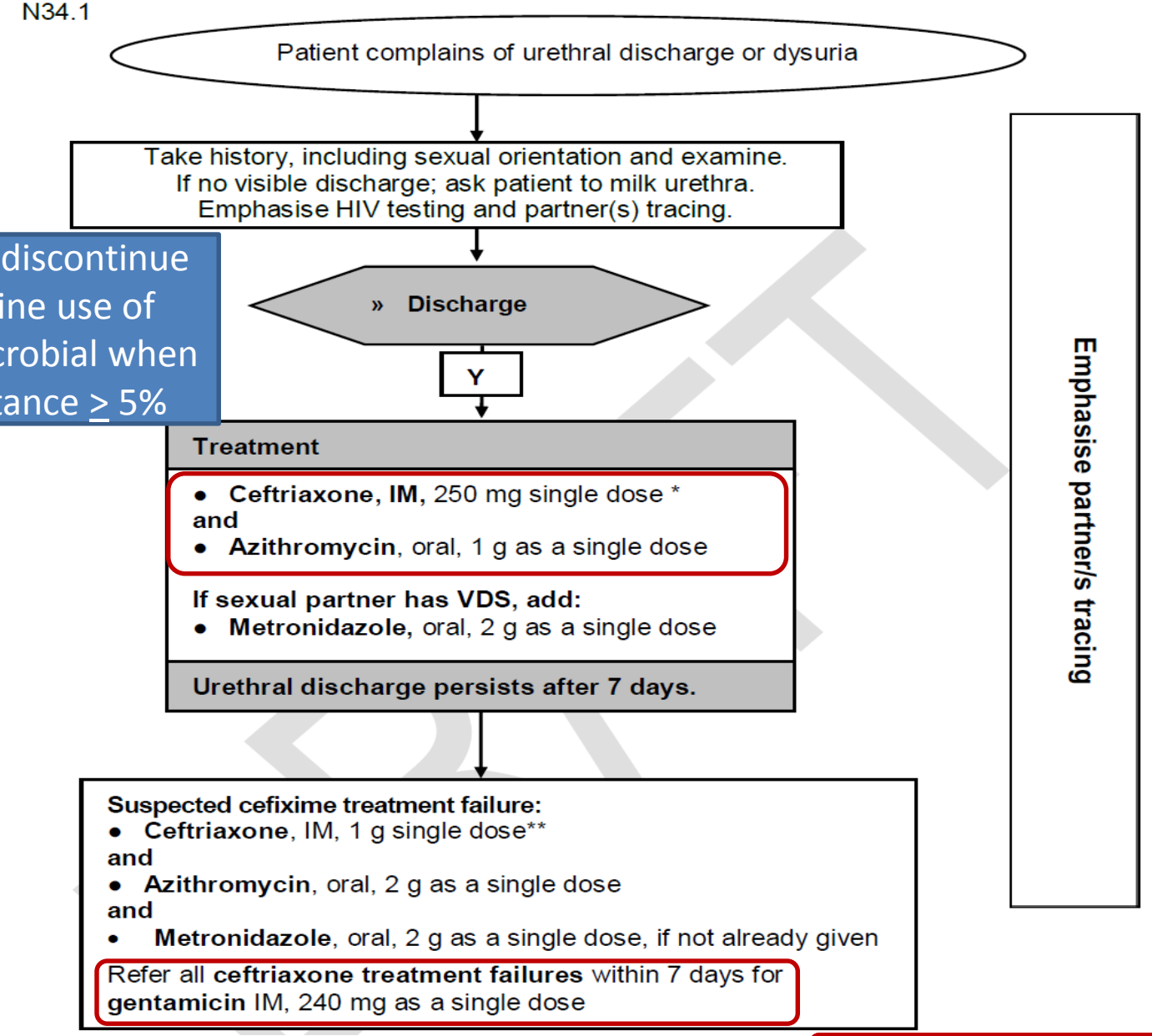
Country	Ceftriaxone dose	Combination therapy recommended?	Recommended second agent
United States	250 mg IM	Yes	Azithromycin (preferred) or doxycycline
United Kingdom	500 mg IM	Yes	Azithromycin
Europe	500 mg IM	Yes	Azithromycin
Japan	1g IV	No	
Canada	250 mg IM or 800 mg cefixime PO[a]	Yes	Azithromycin

Curr Opin Infect Dis 2014; 27 (1): 62-67

Curr Opin Infect Dis 2014; 27 (3): 282-287

12.3 MALE URETHRITIS SYNDROME (MUS)

N34.1



WHO: discontinue routine use of antimicrobial when resistance ≥ 5%

Box 1
Case definition – *Neisseria gonorrhoeae* cephalosporin treatment failure

A person who has received appropriate treatment for gonococcal infection with one of the recommended cephalosporin regimens (for example, ceftriaxone or cefixime)

AND

One of the following positive tests for *N. gonorrhoeae*:

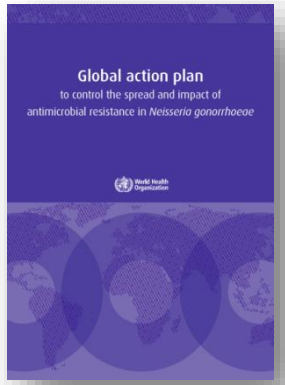
- the presence of intracellular Gram-negative cocci on microscopy taken at least 72 h after completion of treatment; or
- isolation of *N. gonorrhoeae* by culture taken at least 72 h after completion of treatment; or
- a positive nucleic acid amplification test (NAAT) taken 2–3 weeks after completion of treatment.

AND

No history of sexual contact reported during the post-treatment follow-up period.

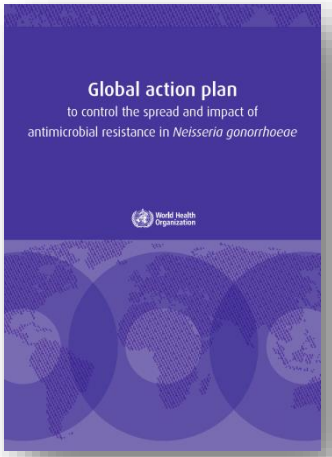
WHO Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae* (2012)

WHO: Global action plan to control spread and impact of AMR NG (2012)



- 1. Improving early detection of infection
  - Effective prevention diagnosis and control of gonorrhoea
- 2. Appropriate and effective treatment for patients and sexual partners
  - Awareness on correct use of antibiotics among HCW, esp in key populations e.g. MSM, CSW
- 3. Systematic monitoring, early detection and follow-up of treatment failures
  - Standard case definition for treatment failure
- 4. Effective drug regulations and prescription policies
  - Prevent unrestricted access, inappropriate selection

WHO: Global action plan to control spread and impact of AMR NG (2012)



- 5. Laboratory capacity strengthening
  - Awareness among clinicians regarding resistant NG
  - Strengthen HCW skills in specimen collection
  - Train laboratory personnel

- 6. Strengthen antimicrobial resistance surveillance in high burden countries
  - Standardized protocols for testing, external quality assurance programs
  - Regional networks of laboratories that perform quality-assured NG culture/ antimicrobial susceptibility.

- 7. Research
  - New molecular methods for detection and monitoring of resistance
  - ID alternative therapeutic strategies/ novel antimicrobials/ vaccine

WHO: Regional response plan (2012) – ESC resistance

- Local health departments should initiate epidemiological assessments to monitor spread in affected area:
  - 1. Review of clinical records to ID additional cases of treatment failure
  - 2. Epidemiological assessment to ID demographic and behavioural risk factors
  - 3. Design and implementation of clinic-based activities to enhance case detection
    - Targeted screening
    - ***Test-of-cure using culture for key populations***
  - 4. Enhance laboratory capacity for culture/ susceptibility testing
  - 5. Enhance local surveillance activities
  - 6. **Prioritize notification of sexual contacts**

WHO Global Antimicrobial Surveillance network (GASP) – baseline report 2012

Number of countries participating in the Gonococcal Antimicrobial Surveillance Programme (GASP) network

WHO Region	Regional GASP focal points	Number of countries participating
Africa	Currently none	5
	Formerly, until February 2012, Sexually Transmitted Infections Reference Centre, National Health Laboratory Service, Johannesburg, South Africa	
The Americas	Sexually Transmitted Infections Reference Centre, National Institute of Infectious Disease, Buenos Aires, Argentina	13 plus Canada and the USA
	University of Saskatchewan, Saskatoon, Canada	
	Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, USA	
The Eastern Mediterranean	STD Laboratory, Bacterial Department, National Institute of Hygiene, Rabat, Morocco	1
Europe	Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency Centre, London, UK	22
	WHO Collaborating Centre for Gonorrhoea and Other STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden	
South-East Asia	WHO GASP South-East Asia Regional Reference Laboratory, VMMC and Safdarjang Hospital, New Delhi, India	6
Western Pacific	WHO Collaborating Centre for STD – South Eastern Area Laboratory Services (SEALS), The Prince of Wales Hospital, Sydney, Australia	15

Status of the data: Gonococcal Antimicrobial Susceptibility Programme

Although 62 countries participate in the GASP network, only 50 countries had available data for 2009–2010 on ceftriaxone (or cefixime), azithromycin, and quinolones (Table 3). Data on quinolones are the most widely available data (all countries reporting), whereas data on ceftriaxone (or cefixime) were available for 32 countries and on azithromycin for 29 countries.

Future developments (Therapeutics)

- **1. Alternative single dose options**
  - Spectinomycin: costly, low cure rate for pharyngeal NG, rapid emergence of resistance
  - Gentamicin: limited *in vitro* data; need efficacy data for extragenital NG
  - Azithromycin: ESC non-susceptible NG show reduced susceptibility; high level resistance with monotherapy; side effects associated with 2g dose

- **2. Novel treatment options**
  - Ertapenem: increasing MICs seen in ESC non-susceptible NG; parenteral
  - Tigecycline: active *in vitro* against ESC non-susceptible strains; use in urogenital infections questionable; parenteral
  - **Solithromycin: fluoroketolide undergoing phase 2 clinical trials**
  - **New broad-spectrum fluoroquinolones: avarofloxacin, delafloxacin**

- **3. New targets**
  - Novel inhibitors of bacterial topoisomerases/ efflux pumps
  - Therapeutic vaccine

Curr Opin Infect Dis 2014; 27(14): 62-67
JAC 2014; 69: 2086-2090

Future developments (Diagnostics)

- **1. Resistance prediction by genotype association**
  - NG-MAST: DNA sequencing of two variable outer membrane protein genes (*porB* & *tbpB*)
  - NG-MAST sequence types in a given geographical area possess similar resistance profiles **(e.g. NG-MAST ST 1407 related to XDR strain F89)**
  - Need representative number of sample isolates from a region for an unbiased assessment of resistance

- **2. Detection of specific genetic mechanisms of resistance**
  - Chromosomal resistance relies on synergistic effect of multiple mutations
  - Need to define targets that are fundamental to resistance **(e.g. *gyrA* PCR for quinolone resistance)**

- **Molecular surveillance**
  - International database of NG *penA* ST associated with ESC resistance
  - ***Complementary to culture-based surveillance***

Nature Rev Microbiol 2014; 12: 223-229

Key Points

- 1. Incidence of gonorrhoea increasing worldwide
- 2. Antimicrobial resistance in NG increasing, XDR strains characterized by high ESC MICs
- 3. Use of high dose ceftriaxone as national first line therapy may slow spread of XDR NG
- 4. Combination treatment with azithromycin may curtail emergence of XDR NG
- 5. Enhanced national and regional **culture-based surveillance** (public & private sectors) essential, particularly in key populations
  - Political advocacy, evidence-based guidelines, funding, and ***investment in laboratory infrastructure & training***

"Although we have not yet had the 'knockout' punch, the gonococcus appears to be winning on points"

Lewis, D. Sex Transm Infect 2010; 86: 415-421