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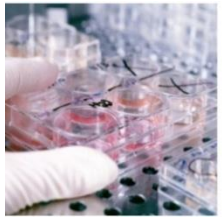
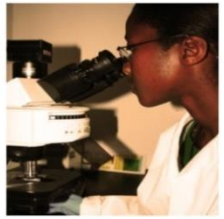


How the laboratory can help prevent the emergence of multidrug resistant gonococci in Africa

Dumisile Venessa Maseko
Centre for HIV & STIs

ASLM 2014
AFRICAN SOCIETY FOR LABORATORY MEDICINE

Innovation and Integration of Laboratory and Clinical Systems
Reshaping the Future of HIV, TB, Malaria, Flu,
Neglected Tropical Diseases and Emerging Pathogens in Africa

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"To timeously, consistently and accurately isolate and identify Neisseria gonorrhoeae with the appropriate antimicrobial sensitivity results"

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Neisseria gonorrhoeae

- Gram negative coccus
- Exclusive human pathogen
- Transmission usually by sexual intercourse
- Resides in a variety of anatomical niches
- Gonococci are naturally competent for DNA transformation
- DNA transformation is important for antigenic variation, DNA repair and antimicrobial resistance
- Antimicrobial resistant determinants may also be expressed on plasmids

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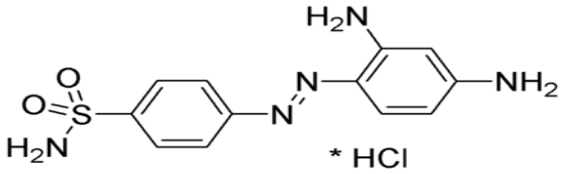
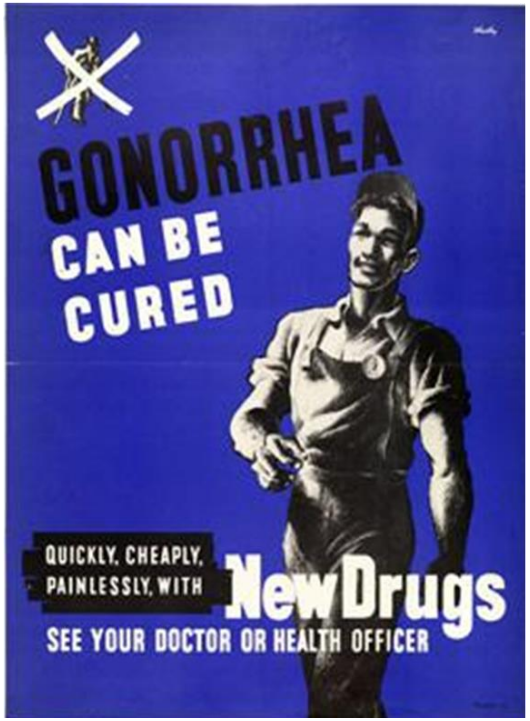
"The emergence and spread of drug-resistant pathogens has accelerated . Drug resistance costs vast amounts of money, and affects vast numbers of lives. The trends are clear and ominous. No action today means no cure tomorrow. At a time of multiple calamities in the world, we cannot allow the loss of essential medicines – essential cures for many millions of people – to become the next global crisis".

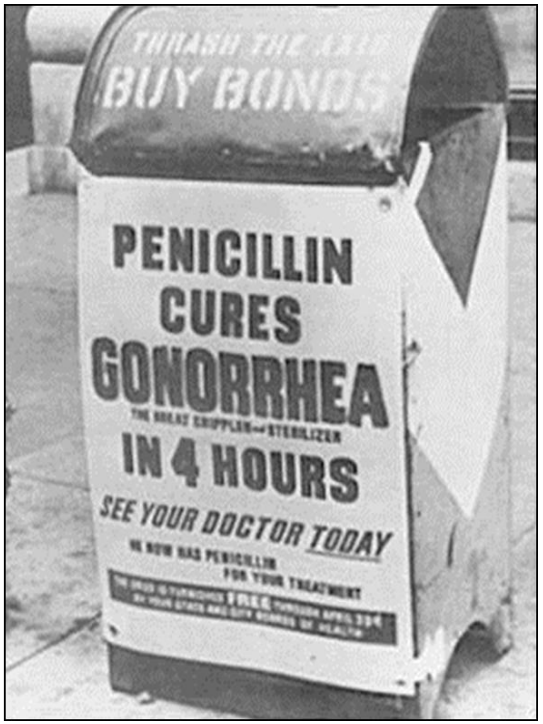
Statement of WHO Director-General, Margaret Chan on World Health Day 2011

Prontosil



Sulphaniliamide





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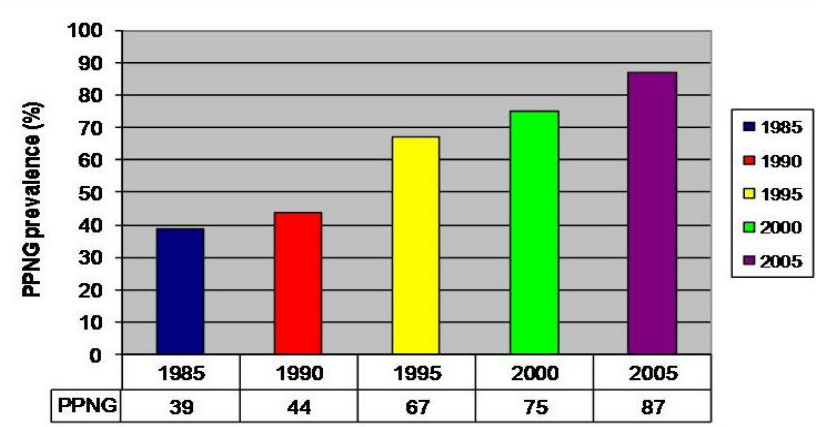
Plasmid-Mediated Resistance

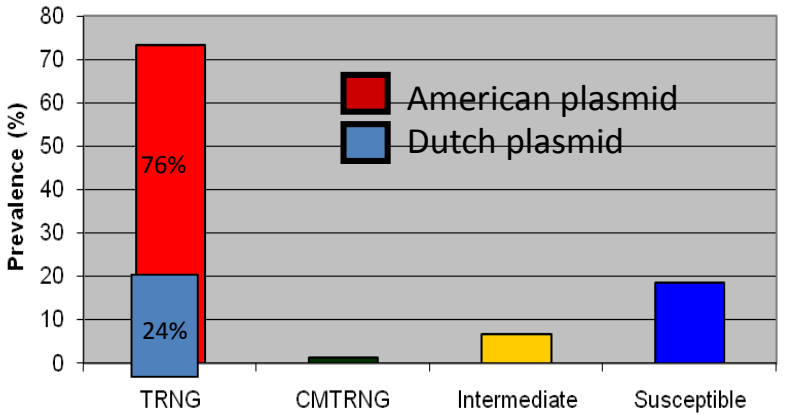
PENICILLIN

- First reported in UK & USA in 1976
- The 3.2 MDa African and 4.4 MDa Asian plasmids are identical except for a 2.1 kb deletion
- Further plasmid variants have been identified

TETRACYCLINE

- Plasmid-mediated resistance (TRNG), with MIC > 10 mg/L, first appeared in the Netherlands (1985) and USA (1986)
- 25.2 MDa plasmid
- Dutch and American TRNG strains have different phenotypes





Manuel de formation des prestataires de soins sur la prise en charge syndromique des IST au Cameroun, Ministry of Public Health, April 2007; Fayemiwo S *et al.*, Sex. Transm. Infect. 2011;**38**:329-333

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Fluoroquinolone Resistant Gonorrhoea

Sub-Saharan Africa

- **South Africa**
  - 42%, 248 MUS cases in Durban, 2005
  - 29%, 288 MUS cases in JHB/CPT, 2007
- **Mozambique**
  - 29%, 55 MUS/VDS cases in Maputo, 2005
- **Namibia**
  - 48%, 52 MUS cases in Oshakati, 2007
- **Kenya**
  - 53%, 154 M/F STI clinic patients in 2009/10
- **Uganda**
  - 83%, 148 CSW in Kampala, 2008/09

Moodley P *et al.*, Lancet 2005;**366**:1159; Lewis DA *et al.*, Sex. Transm. Infect. 2008;**84**:352-355;
Apalata T *et al.*, Sex. Transm. Dis. 2009;**36**:341-343; Lagacé-Wiens *et al.*, Sex. Transm. Dis. 2012;**39**:332-334;
Vandepitte *et al.*, Sex. Transm. Infect. 2014;**41**:233-237

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Prevalence of Resistance to Antimicrobial Agents 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%

Ito M *et al.*, Antimicrob. Agents Chemother. 2004;**48**:3185-3187

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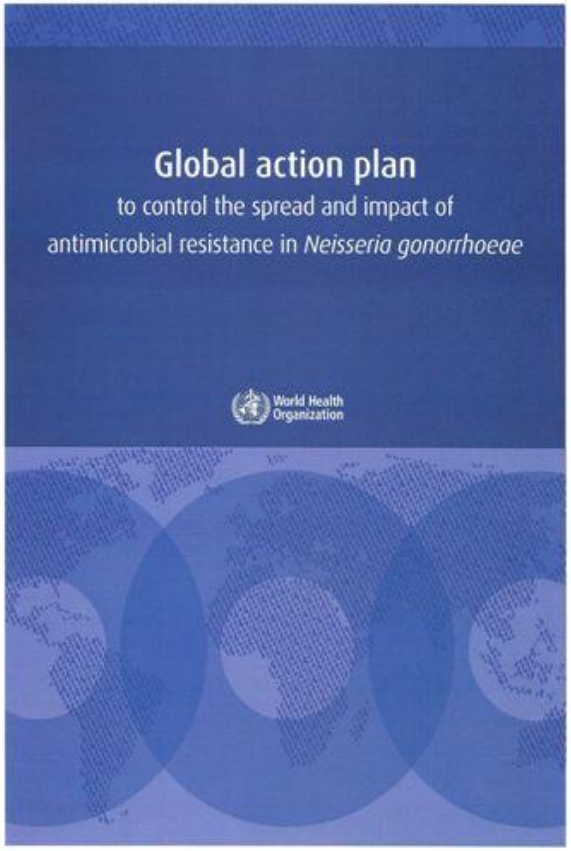
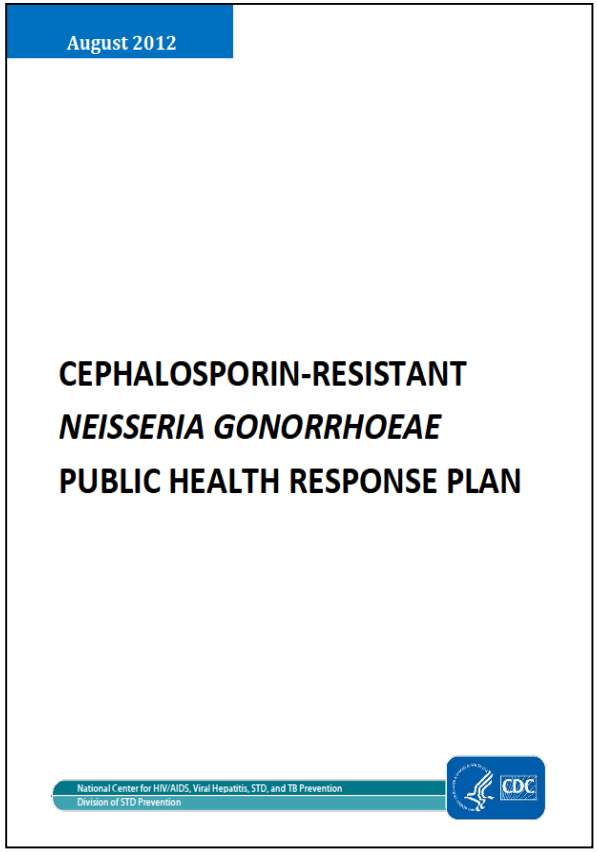
Response Plans to Aid the Control of Cephalosporin-Resistant Gonorrhoea





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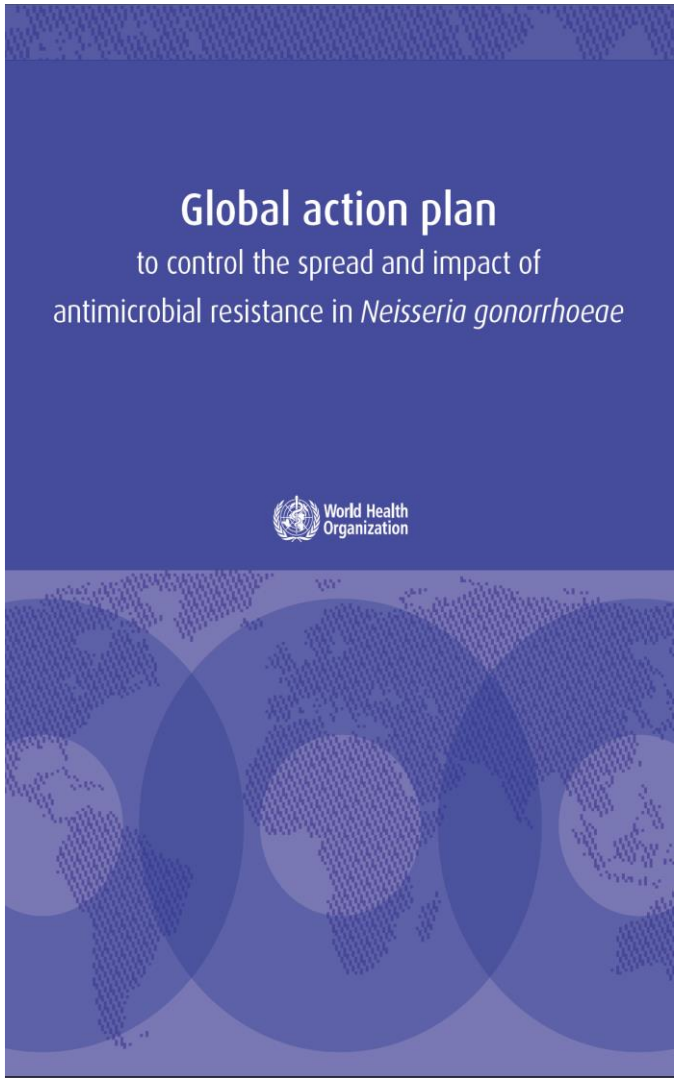


	Policy	Norms	Surveillance	Containment and implementation	Capacity building (clinicians and laboratory technicians)	Communication and education strategy for general public and key populations	Advocacy and political engagement	Drug regulation	Drug rational prescription	Early warning system	Resource mobilization	Research
World Health Organization (WHO)	x	x			x	x	x			x	x	x
Donor agencies	x				x	x	x				x	x
Ministries of health and STI programme managers	x	x	x	x	x	x	x	x		x	x	x
National public health laboratoriess			x			x				x		x
Private sector and NGOs			x	x	x	x			x	x		x
Clinicians			x			x			x	x		x
WHO Gonococcal Antimicrobial Surveillance Programme (GASP) networks			x		x	x	x			x	x	x
Researchers					x					x		x

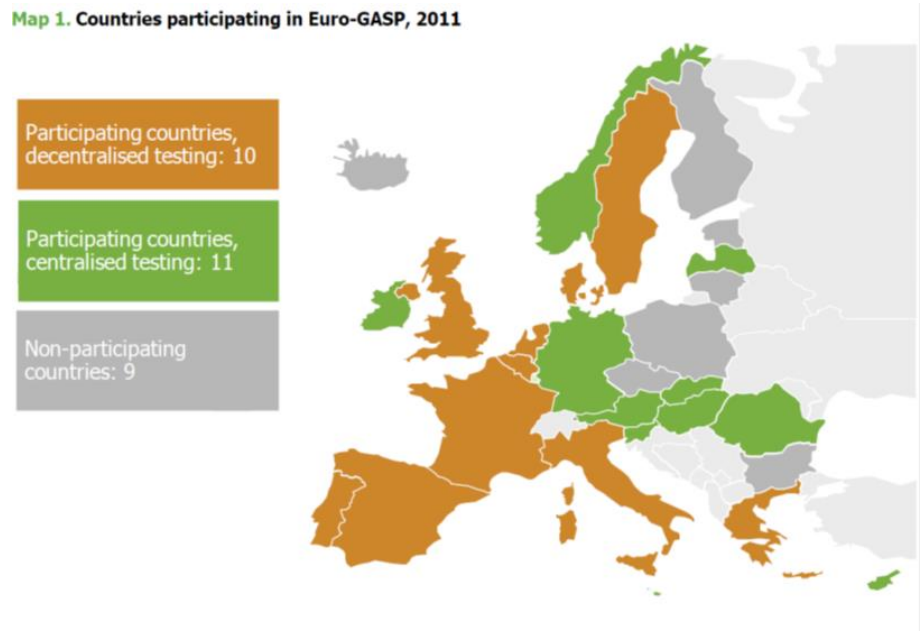
Sexually Transmitted Diseases, February 2006, Vol. 33, No. 2, p.87–95
DOI: 10.1097/01.olq.0000187231.28812.29

Challenges in the Control of Gonorrhea in South America and the Caribbean: Monitoring the Development of Resistance to Antibiotics

JO-ANNE R. DILLON, PHD,*† MARTHA RUBEN, MD, PHD,* HUI LI, MSC,* GRACIELA BORTHAGARAY, MSC,‡
CAROLINA MA´ RQUEZ, PHD,‡ SUSANA FIORITO, MD,§ PATRICIA GALARZA, MSC,§ JOSE´ LUIS PORTILLA, MSC,
LILIA LEO´ N, BSC,¶ CLARA INE´ S AGUDELO, BSC,** OLGA MARINA SANABRIA, BSC,** AURORA MALDONADO, RT, BSC,†† AND PARIMI PRABHAKAR, MD‡‡

Surveillance of antibiotic resistance in *Neisseria gonorrhoeae* in the WHO Western Pacific and South East Asian Regions, 2010

Monica M Lahra for the WHO Western Pacific and South East Asian Gonococcal Antimicrobial Surveillance Programmes



APMIS. 2011 Sep;119(9):643-649. doi: 10.1111/j.1600-0463.2011.02780.x. Epub 2011 Jun 17.

Gonorrhoea surveillance, laboratory diagnosis and antimicrobial susceptibility testing of Neisseria gonorrhoeae in 11 countries of the eastern part of the WHO European region.

Unemo M, Shipitsyna E, Domeika M; the Eastern European Sexual and Reproductive Health (EE SRH) Network Antimicrobial Resistance Group.

National Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden Laboratory of Microbiology, the DO Ott Research Institute of Obstetrics and Gynecology, St. Petersburg, Russia Department of Medical Sciences, Uppsala University, Uppsala, Sweden

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Festschrift: Antimicrobial-resistant gonorrhoea in Africa

Antimicrobial-resistant gonorrhoea in Africa: An important public health threat in need of a regional gonococcal antimicrobial surveillance programme

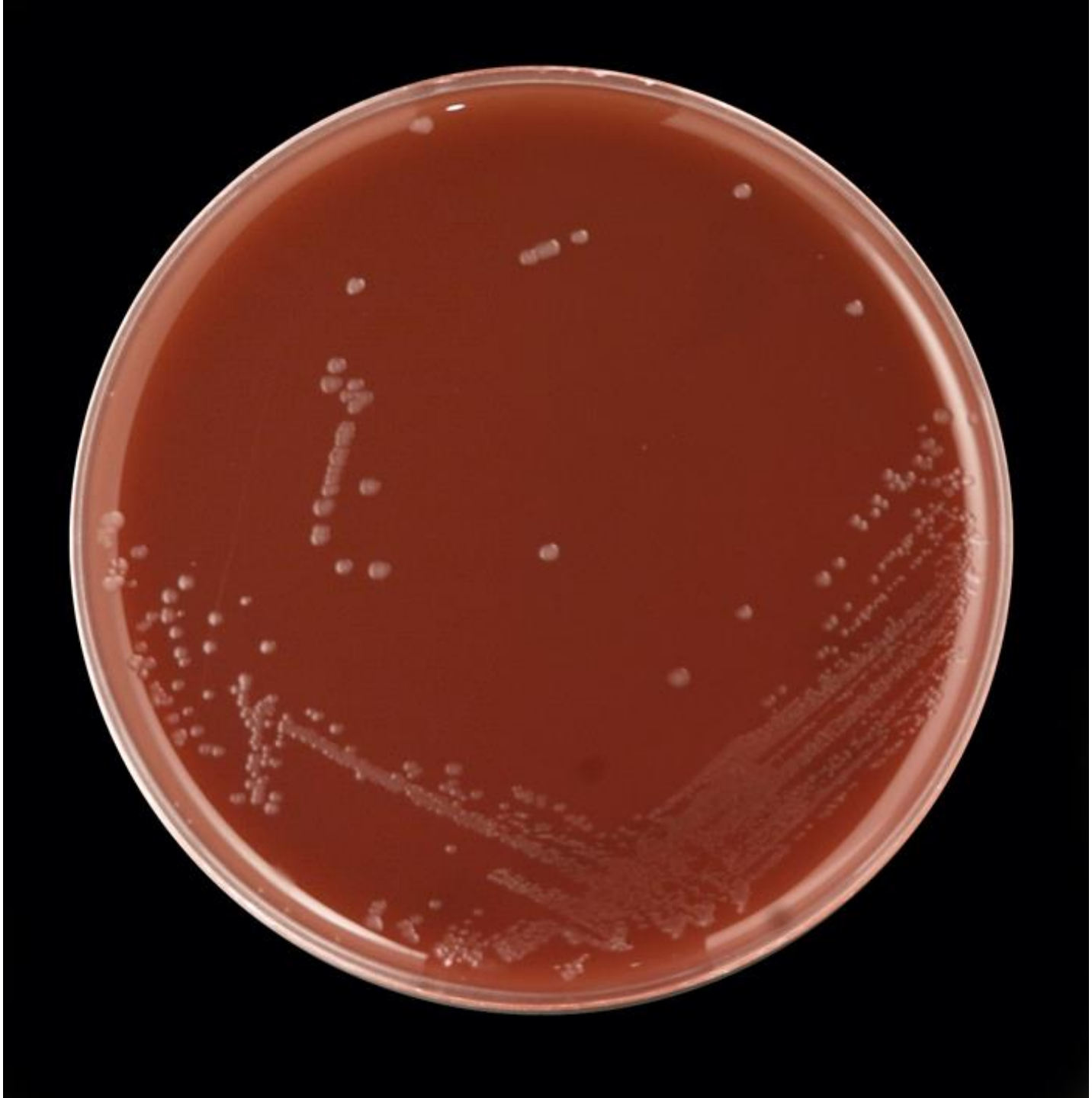
DA Lewis

David Lewis, Sexually Transmitted Infections Reference Centre, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg; Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg; Division of Microbiology, University of Cape Town, Cape Tow; and London School of Hygiene and Tropical Medicine, London.
E-mail: davidl@nicd.ac.za

ORIGINAL STUDY

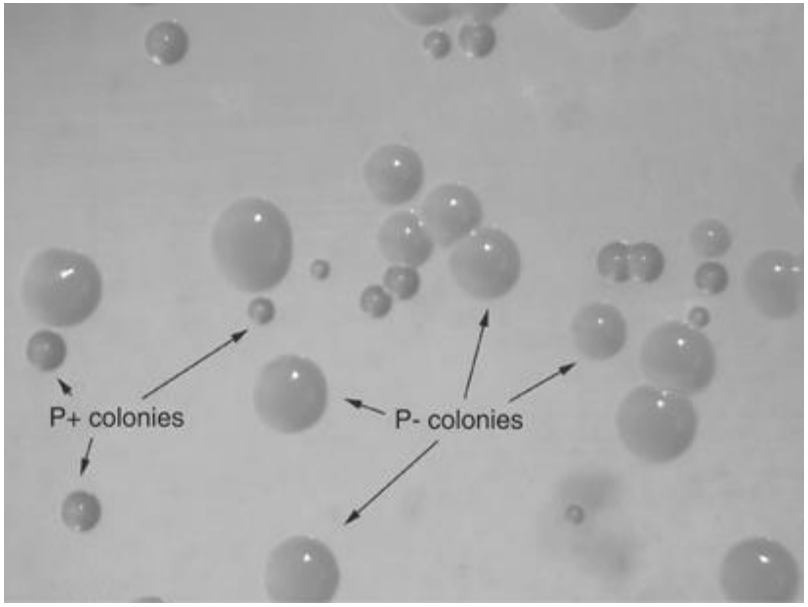
Etiology and Antimicrobial Susceptibility of Pathogens Responsible for Urethral Discharge Among Men in Harare, Zimbabwe

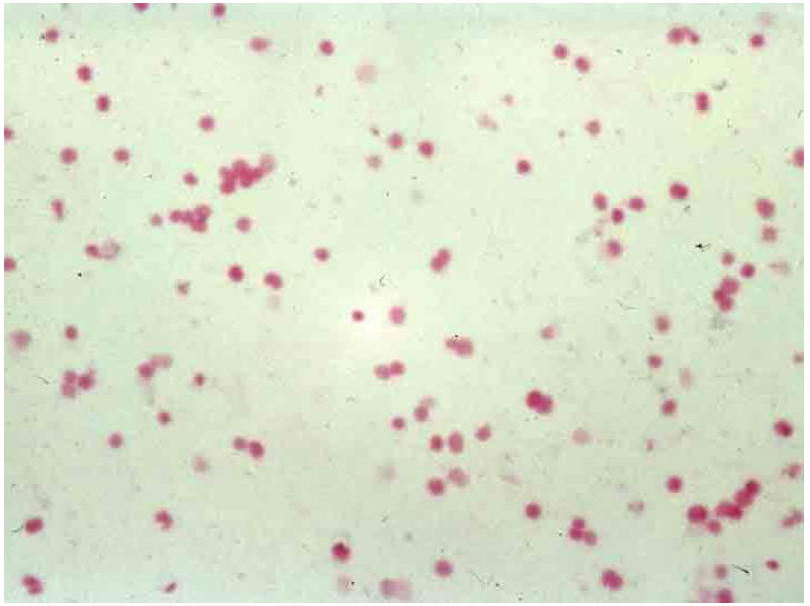
Simbarashe Takuva, MBChB, MSc,† Owen Mugurungi, MD, MSc,‡ Junior Mutsvangwa, MPhil,§ Anna Machiha, RGN, BSc,‡ Albert C. Mupambo, MBChB,¶ Venessa Maseko, BTech,* Fatim Cham, PhD,||** Stanley Mungofa, MD, MPH,¶ Peter Mason, FRCPath, PhD,§ and David A. Lewis, FRCP(UK), PhD*††‡‡*



Presumptive Identification - I

- Gonococci may have several colony types that are related to piliation
  - Piliated colonies are small (0.5 mm diameter), glisten and are raised
  - Non-piliated colonies are larger (1mm diameter), flatter and do not glisten





- Gram negative single, diplococci and, in young cultures, tetrad cocci

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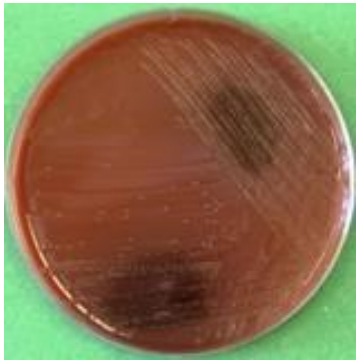
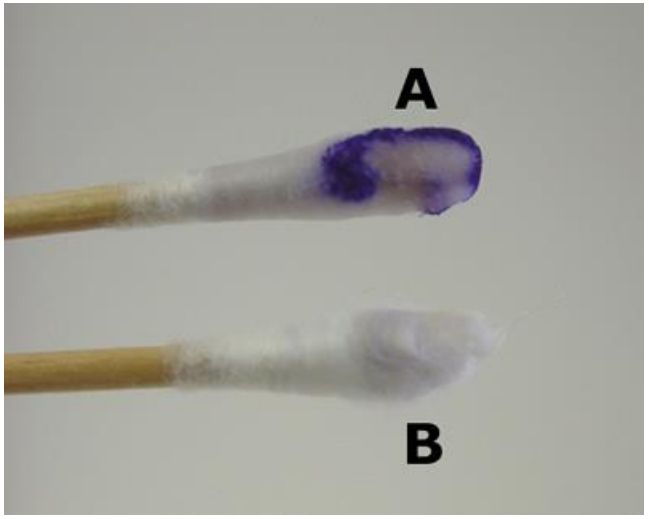
Presumptive Identification - II

- Oxidase positive

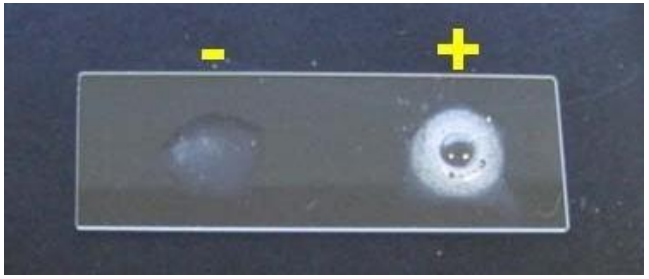




A = oxidase positive

B = oxidase negative

- Catalase positive*



+ = catalase positive

- = catalase negative

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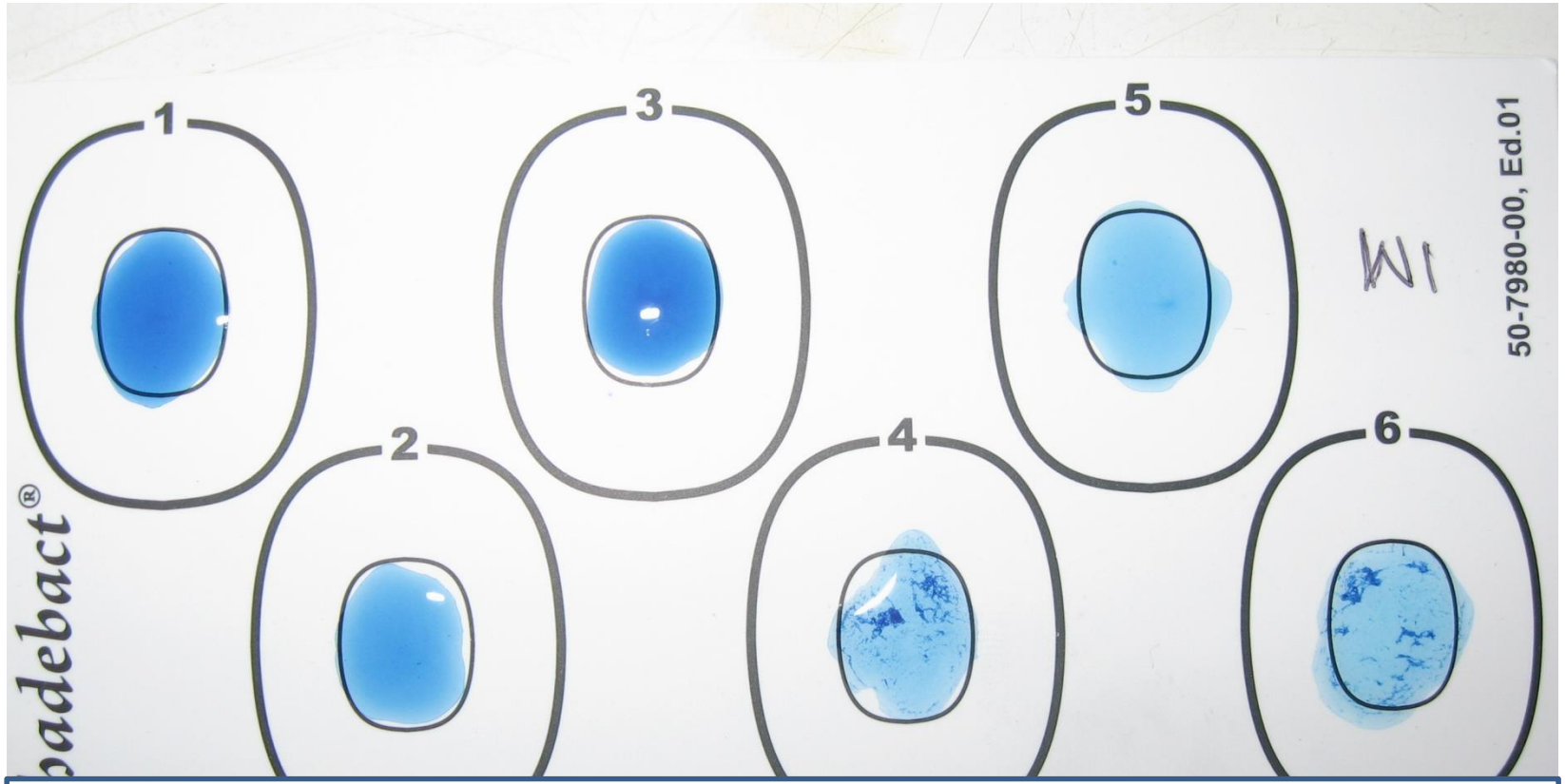
Phadebact Monoclonal GC Test

WI

WII/III



Escherichia coli negative control	*N. gonorrhoeae* WHO control K	*N. gonorrhoeae* WHO control P

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API-NH for *Neisseria* species

API-NH Reading Table

READING TABLE

Test		Results: Negative	Positive
PEN	Penicillinase	blue	yellow, yellow-green, yellow-blue
GLU	Glucose	red or red-orange	yellow or orange
FRU	Fructose		
MAL	Maltose		
SAC	Saccharose/Sucrose		
ODC	Ornithine decarboxylase	yellow-green or grey-green	blue
URE	Urease	yellow	pink-violet
LIP	Lipase	pale grey or colorless	blue
PAL	alkaline phosphatase	pale yellow or Colorless	yellow
BGAL	beta galactosidase	colorless	yellow
ProA	proline arylamidase	pale orange or yellow (brown if LIP+)	orange
GGT	gamma glutamyl transferase	pale orange or Yellow (yellow-orange if PAL+)	orange
IND	indole	colorless	pink

HINT: If the test reads any color other than that clearly defined as "positive", call it negative.

glu fru mal sac odc ure lip pal gal proA ggt ind

+ - - - - - - - - + - -

1	2	4	1	2	4	1	2	4	1	2	4

Numerical profile **1 0 0 1**

Organism: ***Neisseria gonorrhoeae***

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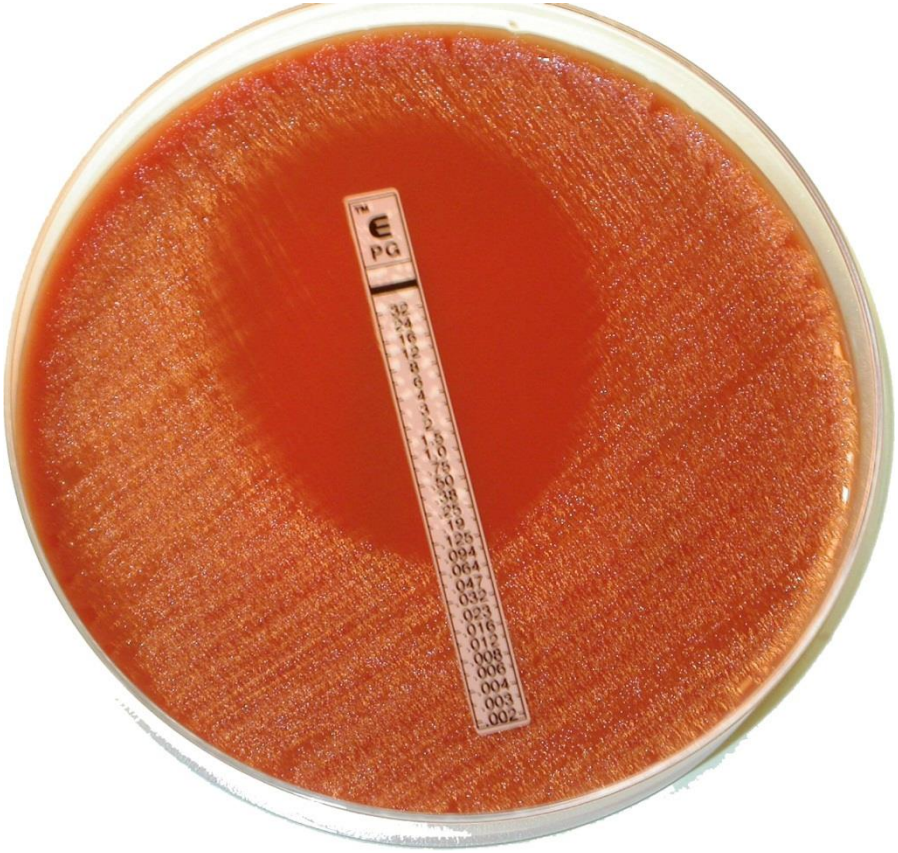
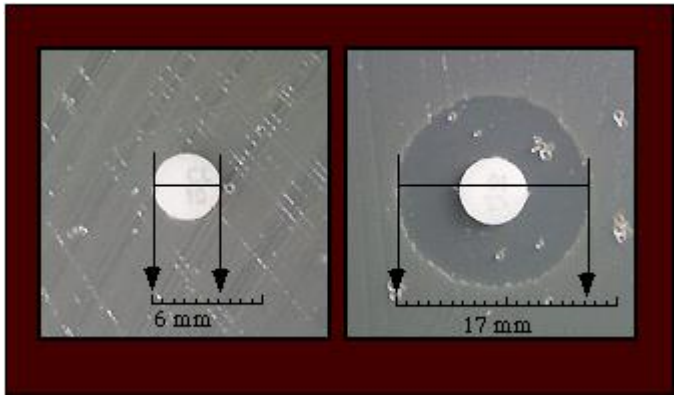
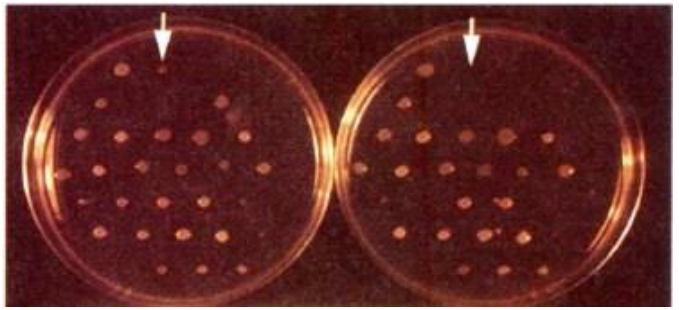
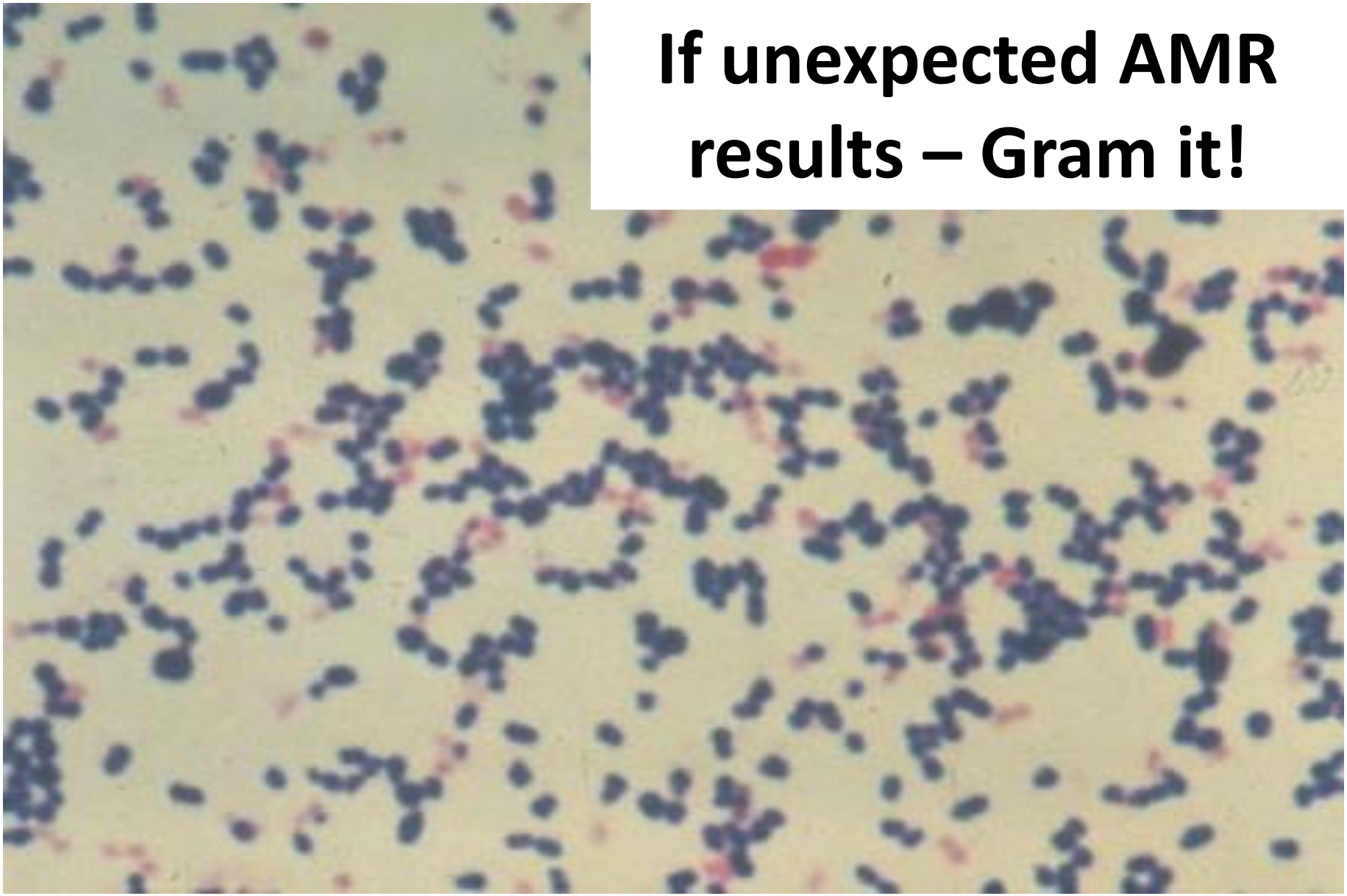
Antimicrobial sensitivity testing







If unexpected AMR results – Gram it!



Journal of Antimicrobial Chemotherapy (2009) **63**, 1142–1151
doi:10.1093/jac/dkp098
Advance Access publication 24 March 2009

JAC

Phenotypic and genetic characterization of the 2008 WHO *Neisseria gonorrhoeae* reference strain panel intended for global quality assurance and quality control of gonococcal antimicrobial resistance surveillance for public health purposes

Magnus Unemo[1]*, Oskar Fasth[1], Hans Fredlund[1], Athena Limnios[2] and John Tapsall[2]

[1]National Reference Laboratory for Pathogenic Neisseria, Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden; [2]WHO Collaborating Centre for STD, Microbiology Department, The Prince of Wales Hospital, Randwick, Sydney, Australia

Received 22 December 2008; returned 11 February 2009; revised 24 February 2009; accepted 26 February 2009

Table 4. Antimicrobial susceptibility/resistance phenotypic and genetic characteristics present in the 2008 WHO *N. gonorrhoeae* reference strain panel, intended for global quality assurance and quality control of AMR testing and surveillance

Characteristics	WHO reference strain							
	F	G	K	L	M	N	O	P
β-Lactamase production (PPNG)[a]	—	—	—	—	Pos	Pos	Pos	—
Penicillin G (0.032 to >32)[b]	S (0.032)	I (0.5)	CMRNG[a] (2)	CMRNG[a] (2)	PPNG[a] (8)	PPNG[a] (8)	PPNG[a] (>32)	I (0.25)
Ampicillin (0.032–24)[b]	S (0.032)	I (0.25)	I (2)	I (2)	PPNG[a] (8)	PPNG[a] (4)	PPNG[a] (24)	S (0.064)
Cefuroxime (0.064–12)[b]	S (0.064)	I (0.5)	R (12)	R (8)	I (0.5)	I (0.25)	I (1)	I (0.125)
Cefixime (<0.016–0.5)[b]	S (<0.016)	S (<0.016)	NS[c] (0.5)	NS[c] (0.25)	S (<0.016)	S (<0.016)	S (0.016)	S (<0.016)
Ceftriaxone (<0.002–0.125)[b]	S (<0.002)	S (0.008)	NS[c] (0.064)	NS[c] (0.125)	S (0.012)	S (0.004)	S (0.032)	S (0.004)
Ertapenem[d] (0.004–0.125)[b]	S (0.004)	S (0.008)	NS[c] (0.125)	NS[c] (0.064)	S (0.012)	S (0.008)	S (0.032)	S (0.008)
Erythromycin (0.5–4)[b]	S (0.5)	I (1)	I (1)	I (2)	I (1)	S (0.5)	I (1)	R (4)
Azithromycin (0.125–2)[b]	S (0.125)	S (0.25)	S (0.25)	I (0.5)	S (0.25)	S (0.125)	S (0.25)	R (2)
Ciprofloxacin (0.004 to >32)[b]	S (0.004)	LLR[e] (0.125)	HLR[e] (>32)	HLR[e] (>32)	R (2)	R (4)	S (0.008)	S (0.004)
Spectinomycin (16 to >1024)[b]	S (32)	S (16)	S (16)	S (16)	S (16)	S (16)	R (>1024)	S (16)
Kanamycin[d] (8–32)[b]	S (16)	S (16)	S (16)	S (32)	S (16)	S (16)	S (16)	S (8)
Gentamicin[d] (2–8)[b]	S (4)	S (4)	S (2)	S (8)	S (4)	S (4)	S (4)	S (4)
Tetracycline (0.25–32)[b]	I (0.25)	TRNG[f] (32)	R (2)	R (4)	I (1)	TRNG[f] (16)	I (1)	I (0.5)
Rifampicin[d] (0.125 to >32)[b]	S (0.125)	S (0.5)	S (0.5)	S (0.5)	R (>32)	R (>32)	S (0.25)	R (>32)
penA mosaic allele			yes[g]					

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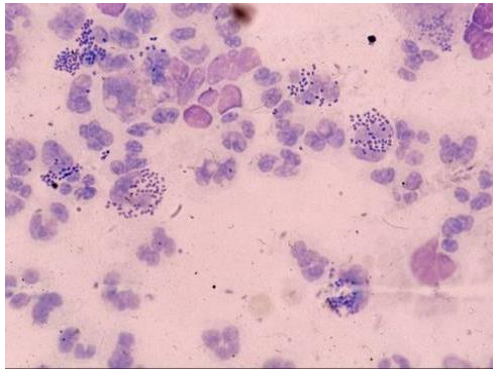
Improving Early Detection of Gonococcal Infection in Men and Women

Microscopy



Methylene blue stain (urethral smear)

- Early detection and prompt treatment of *N. gonorrhoeae*
- Most resource-poor countries lack facilities to make a laboratory diagnosis of gonorrhoea at the primary health care level, e.g. Gram strain +/- culture
- Delays in laboratory reporting hinder timely treatment
- The syndromic approach is a tool to improve management of individuals with STI-related symptoms – not useful for asymptomatic infections
- Antimicrobial resistance epidemiology should ideally be available locally
- If not available, undertake local studies or use regionally-available data until this can be achieved

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

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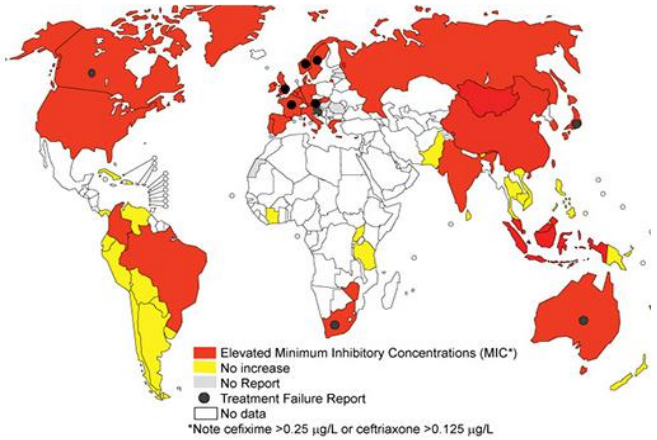
Strengthening Surveillance

- Laboratories that can culture and accurately identify resistant organisms are required
- Standardized methods and appropriate use of controls are required
- Laboratory strengthening, through training of technologists and implementation of quality-assurance systems, is essential
- Laboratories should be part of national, regional and international networks
- Surveillance data must be analysed, reported and acted upon in a prompt manner on a regular basis

Training Tanzanian technologists



Data on gonococci with elevated MICs to cephalosporins (WHO Gonococcal Antimicrobial Surveillance Project, 2012)

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

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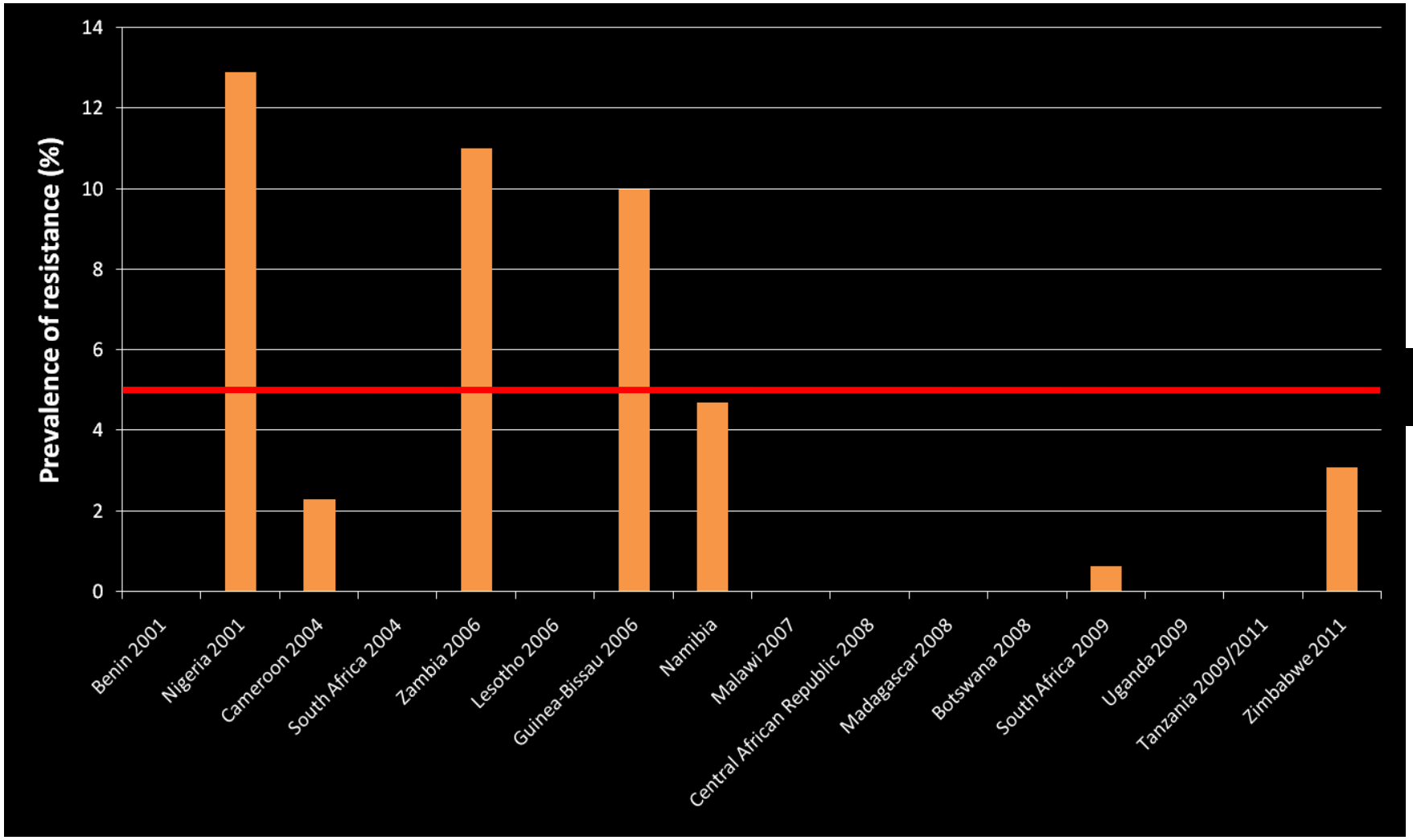
Decreased Susceptibility to Ceftriaxone (2001-2011)



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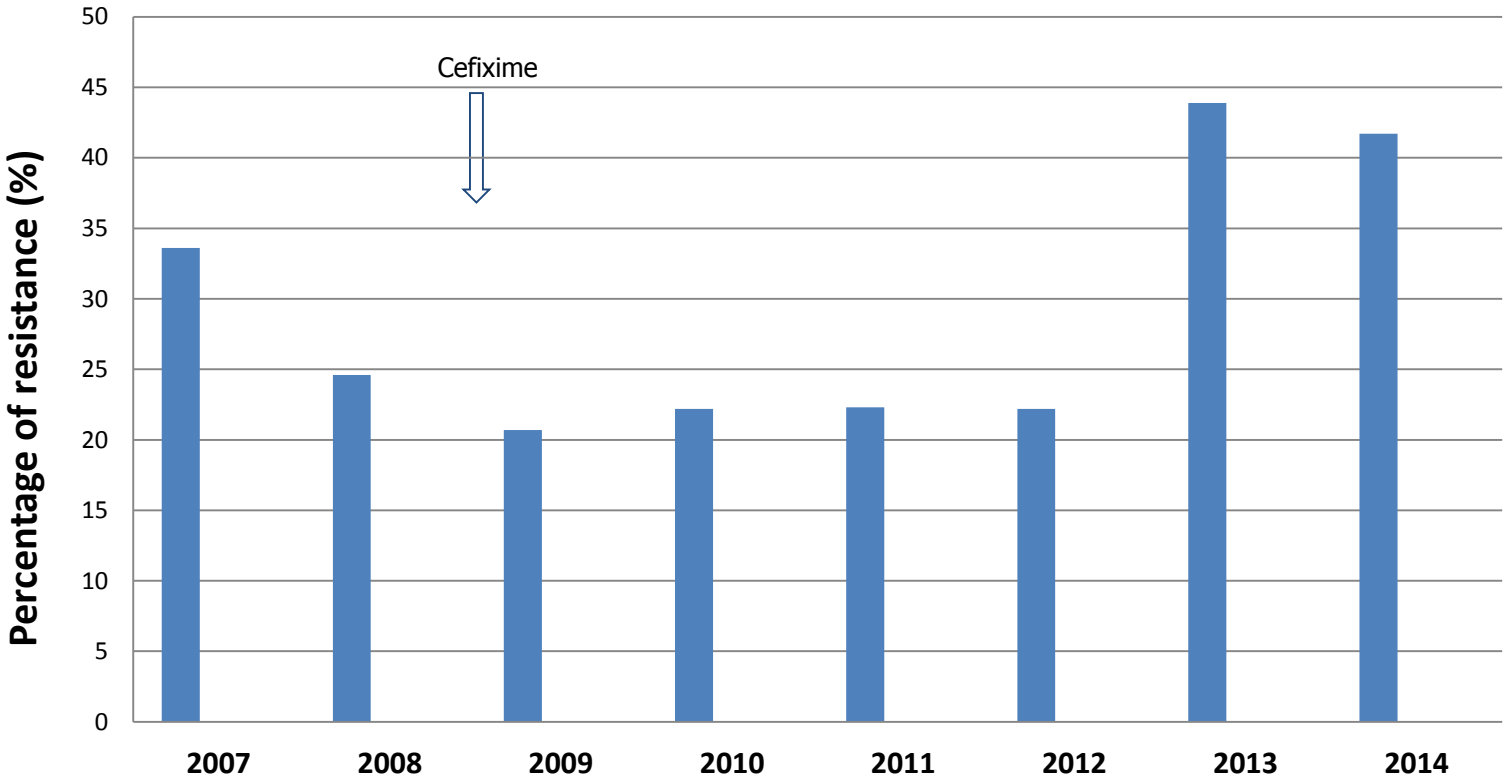
Ciprofloxacin Resistance in South Africa (2007-2014)



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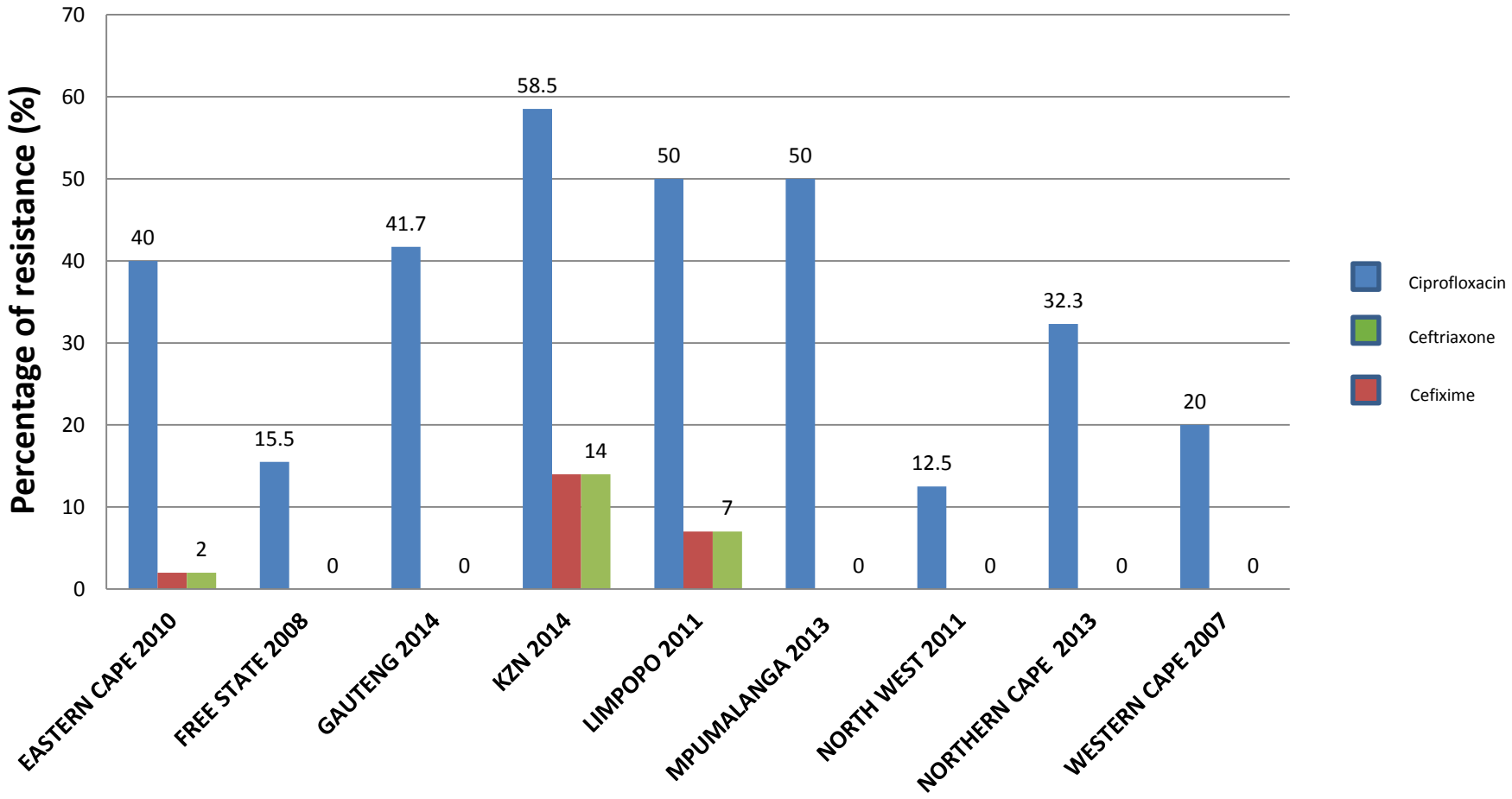
GC AMR patterns in South Africa (2007-2014)



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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

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- Isolates from MSM in 3 South African cities: JHB (A/B), Cape Town (C), East London (D)
- All had identical NG-MAST genotypes (ST4822); A & B had the same MLST profile (ST1901)
- Isolate B failed two sequential courses of cefixime 400 mg p.o. stat.

GASP Sustainability

Meeting to review Afro-GASP - Zimbabwe

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Challenges - I

- **Specimen collection** – loss of skill by nurses trained in syndromic management, need for ethical and other committee approval, costs for these approvals, lack of appreciation by national health ministries that these surveys should be a routine part of syndromic management
- **Media preparation** – problems with obtaining reagents, media QC and contamination
- **AMR testing** – deskilled laboratory staff following implementation of syndromic management, lack of skills retention in public health laboratories, lack of training opportunities
- **Contamination** - after primary *N. gonorrhoeae* isolation/identification and/or during the AMR testing process, lack of attention to repeat Gram staining, lack of appreciation of the need to repeat spurious results
- **Stocking** – lack of access to -70^{o}C freezers, inadequate volumes of bacteria, use of old bacterial cultures, failure to do this in duplicate, use of only one freezer to store specimens, electrical power cuts and lack of generators

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Challenges - II

- **Transport of Specimens** – high rate of loss of gonococci in transit, unable to confirm potentially important findings
- **Quality Control** – until recently, lack of a regional approach in terms of quality control (new WHO control strains, setting up of EQA programme)
- **Reference Laboratory Support** - lack of *N. gonorrhoeae*-competent laboratories in the region at present, need for training and skills development, laboratories still being asked to send their stains out of Africa for EQA exercises and specialised molecular resistance testing
- **Funding** - lack of funding remains a key challenge, competition with other non-STI HIV prevention activities, loss of interest in STIs by donor funding agencies post-ACV trials
- **In-country Commitment** - lack of national prioritisation to support GASP activities, slow action in terms of changing national STI treatment guidelines
- **Leadership** – Limited leadership in the Afro Region to support the GASP programme and to engage in dialogue with National Health Ministers

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- Strict implementation of action/ response plans
- Dual Antimicrobial treatment regimens where indicated
- **Gonococcal antimicrobial surveillance programs**
- Intensified research activities

SPECIAL FOCUS | Non-viral sexually transmitted infections Editorial

Challenges with gonorrhea in the era of multi-drug and extensively drug resistance – are we on the right track?

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Neisseria gonorrhoeae has retained antimicrobial resistance to drugs previously recommended for first-line empiric treatment of gonorrhea, and resistance to ceftriaxone, the last option for monotherapy, is evolving. Crucial actions to combat this developing situation include implementing response plans; considering use of dual antimicrobial regimens; enhancing surveillance of gonorrhea, gonococcal antimicrobial resistance, treatment failures and antimicrobial use/misuse and improving prevention, early diagnosis, contact tracing and treatment. The ways forward also include an intensified research to identify novel antimicrobial resistance determinants and develop and evaluate appropriate use of molecular antimicrobial resistance testing, ideally point-of-care and with simultaneous detection of gonococci, to supplement culture-based methods and ideally guide tailored treatment. It is crucial with an enhanced understanding of the dynamics of the national and international emergence, transmission and evolution of antimicrobial-resistant gonococcal strains. Genome sequencing combined with epidemiological metadata will detail these issues and might also revolutionize the molecular antimicrobial resistance testing. Ultimately, novel antimicrobials are essential and some antimicrobials in development have shown potent *in vitro* activity against gonococci. Several of these antimicrobials deserve further attention for potential future treatment of gonorrhea.

Gonorrhea is a major public health concern globally that requires immediate international public health resources and attention. The WHO estimated that the global burden of gonorrhea in adults was 106 million cases in 2008, a 21% increase compared to 2005 [1]. The transmission of *Neisseria gonorrhoeae* can be controlled only through effective prevention, diagnostics and particularly antimicrobial treatment of patients and traced contacts. Untreated infections can result in severe reproductive complications, leading to infertility or loss of life through ectopic pregnancy or promoted transmission of other sexually transmitted infections, including HIV. Unfortunately, *N. gonorrhoeae* has developed antimicrobial resistance to all drugs introduced for treatment of gonorrhea [2–5]. In most countries globally, the only remaining options for empiric first-line monotherapy are the extended-spectrum cephalosporins, cefixime and ceftriaxone. However, treatment failures, particularly with cefixime and more rarely with the more potent ceftriaxone (mainly pharyngeal gonorrhea), have been verified in Japan, Australia, several European countries, Canada and South Africa [4,6,7]. Furthermore, multidrug-resistant gonococcal strains are common, and the first extensively drug resistant *N. gonorrhoeae* isolates with high-level ceftriaxone resistance were recently found [2–5].

As a response to this international spread of multi-drug-resistant and extensively drug resistant gonococcal strains and possible emergence of untreatable gonorrhea, the WHO, US CDC and European CDC have published a global action plan and regional response plans [2,8–10]. These

EXPERT REVIEWS

Keywords: antimicrobial resistance • cefixime • ceftriaxone • gonorrhea • *Neisseria gonorrhoeae* • surveillance • treatment • WHO