



NICD

Communicable Diseases Surveillance Bulletin



August 2005

*A quarterly publication of the National Institute for Communicable Diseases (NICD)
of the National Health Laboratory Service (NHLS)*



Healthcare workers in protective clothing burn disposable hospital waste in a field “drum” incinerator using diesel fuel, provincial hospital, Uige, northern Angola, where the 2005 Marburg haemorrhagic fever outbreak was first recognized.

CONTENTS

| | |
|---|----------|
| <i>Epidemic prone disease surveillance table.....</i> | <i>2</i> |
| <i>Deadly course of the 2005 Marburg haemorrhagic fever outbreak in Angola.....</i> | <i>3</i> |
| <i>Quinolone resistance in enteric bacteria.....</i> | <i>5</i> |
| <i>Ciprofloxacin resistant gonococci.....</i> | <i>7</i> |

This bulletin is available on the NICD website : <http://www.nicd.ac.za>

Requests for e-mail subscription are invited - please send request to Mrs Liz Millington : lizm@nicd.ac.za

Material from this publication may be freely reproduced provided due acknowledgement is given to the author, the Bulletin and the NICD

| EPIDEMIC PRONE DISEASE SURVEILLANCE : JANUARY-JUNE | | CUMULATIVE | ECP | FSP | GAP | KZP | LPP | MPP | NCP | NWP | WCP | RSA |
|--|---------------|---------------|----------|------------|------------|----------|----------|----------|----------|------------|--------------|------------|
| AFP, cases from whom specimens have been received | < 15 years | 2004 2005 | 7 11 | 6 13 | 16 15 | 17 27 | 41 16 | 9 5 | 1 1 | 11 18 | 13 8 | 131 114 |
| | All ages | 2004 2005 | 0 549 | 0 0 | 140 33 | U 66 | 0 1 | 3 1 | 0 0 | 1 1 | 0 12 | 144 663 |
| Rubella, IgM positive results from measles IgM negative patients | All ages | 2004 2005 | 43 81 | 2 2 | 33 24 | U 31 | 8 5 | 27 21 | 2 1 | 27 9 | 5 9 | 147 183 |
| | All ages | 2004 2005 | 0 0 | 1 0 | 0 0 | 0 0 | 0 0 | 0 0 | 1 0 | 2 0 | 0 0 | 4 0 |
| Rabies, human | All ages | 2004 2005 | 0 1 | 0 1 | 0 0 | 6 0 | 0 0 | 1 0 | 0 0 | 0 0 | 0 0 | 7 2 |
| | All ages | 2004 2005 | 3 5 | 5 7 | 57 66 | 11 8 | 0 1 | 3 5 | 1 0 | 2 1 | 22 15 | 104 108 |
| <i>Haemophilus influenzae</i> , invasive | Age < 5 years | 2004 2005 | 0 3 | 0 1 | 1 6 | 1 1 | 0 0 | 0 1 | 0 0 | 0 0 | 3 2 | 5 10 |
| | | 2004 2005 | 0 0 | 2 1 | 16 17 | 2 0 | 0 0 | 0 1 | 0 0 | 0 0 | 6 0 | 26 20 |
| | 2004 2005 | 1 0 | 2 0 | 2 8 | 4 2 | 0 0 | 0 0 | 1 0 | 1 0 | 1 0 | 4 5 | 16 15 |
| | 2004 2005 | 11 4 | 10 8 | 47 99 | 10 5 | 1 3 | 4 3 | 2 2 | 11 2 | 30 27 | 126 153 | |
| | 2004 2005 | 57 99 | 93 77 | 820 912 | 199 199 | 33 31 | 82 94 | 8 15 | 42 45 | 239 210 | 1573 1682 | |
| Meningococcal disease | Age < 5 years | 2004 2005 | 26 38 | 36 31 | 294 261 | 66 73 | 11 11 | 20 22 | 3 4 | 13 12 | 103 87 | 572 539 |
| | | 2004 2005 | 11 4 | 20 21 | 238 296 | 58 67 | 7 6 | 16 21 | 0 4 | 9 16 | 65 56 | 424 511 |
| | 2004 2005 | 3 10 | 12 5 | 76 104 | 16 21 | 4 6 | 9 12 | 0 1 | 2 2 | 24 23 | 146 184 | |
| <i>Salmonella</i> species - invasive isolates | All ages | 2004 2005* | 4 33 | 11 10 | 357 244 | 41 34 | 4 6 | 8 19 | 0 0 | 5 2 | 37 38 | 467 386 |
| | All ages | 2004 2005* | 78 92 | 18 9 | 121 109 | 56 75 | 22 9 | 1 27 | 0 2 | 21 13 | 86 46 | 403 382 |
| <i>Salmonella typhi</i> | All ages | 2004 2005* | 0 11 | 0 0 | 12 5 | 5 6 | 3 1 | 7 14 | 0 0 | 0 0 | 6 6 | 39 43 |
| <i>Shigella</i> species | All ages | 2004 2005* | 72 81 | 19 22 | 138 139 | 72 82 | 23 10 | 5 12 | 0 1 | 5 3 | 190 98 | 524 448 |
| | | 2004 2005 | 23 0 | 0 0 | 3 0 | 0 0 | 0 0 | 213 0 | 0 0 | 28 0 | 0 0 | 267 0 |

DEADLY COURSE OF THE 2005 MARBURG HAEMORRHAGIC FEVER (MHF) OUTBREAK IN ANGOLA

Janusz T Paweska, Special Pathogens Unit (SPU), NICD

INTRODUCTION

Since the first outbreaks of Marburg in 1967 in Germany and Ebola in 1976 in Zaire, filovirus epidemics have been rare. However, since 2001, simultaneous Ebola outbreaks in humans, great apes and other primates have occurred each year in Gabon and the Republic of Congo. To date there have been 7 known outbreaks of Marburg (6 in Africa) with the most recent confirmed in northern Angola. Despite large-scale international support, the Angolan outbreak of Marburg haemorrhagic fever (MHF) is now the largest and deadliest on record.

BRIEF OUTBREAK HISTORY AND ITS CONTROL

10 March: The WHO Epidemiological Focal Point for childhood immunisation in Angola approaches the NICD to test specimens from fatal haemorrhagic cases in Uige Province, Angola, among hospitalised children and one of their nurses. The NICD cannot assist with laboratory testing as the maximum-bio-security laboratory (BSL-4), the only one on the African continent, has been shut down since April 2004 for major renovation and upgrading. The SPU assist in the shipping of specimens from Angola to the Centres for Disease Control and Prevention (CDC), Atlanta, USA.

21 March: The CDC identify Marburg virus as the cause of death, with severe haemorrhagic manifestations in an increasing number of patients, and linked mostly to a single paediatric ward in the main hospital in Uige. Retrospective epidemiological analysis, embracing the period 13 October 2004 - 23 March 2005, identifies 102 cases. Of these, 95 were fatal; about 75% occurred in children under 5 years of age. In adults, cases include a small number of health care workers. Diagnostic confirmation prompts international response that begins the day after the CDC's findings were publicised. The WHO immediately support the Angolan Ministry of Health (AMH) in efforts to control the outbreak, including technical support for case management, contact tracing and surveillance, infection control and raising awareness in the community. Further technical support is promptly provided by experts from the Inter-Country Programme for Southern Africa, the Regional WHO Office for Africa, many institutions in the Global Outbreak Alert and Response Network (GOARN) including laboratory staff from Canada, Germany, South Africa and the USA, Médecins Sans Frontières (MSF) from Belgium, France, Holland and Spain, UNICEF, the World Food Programme, and other humanitarian aid organisations.

29 March: 124 cases (117 deaths) in total reported from Uige, Cabinda, and Luanda provinces; all originating from Uige. Infectious disease control experts from the UK and SA have begun to provide on-site assistance in infection control in Luanda and

Uige as well as in training health care staff in all provinces. Most urgent is to disinfect hospital wards and homes where patients have died, collect and bury corpses, intensify social mobilisation activities, and provide logistic support and equipment.

2 April: 163 cases (150 deaths) in total reported from Uige, Luanda, Cabinda, Malange, and Kuanza Norte provinces. WHO works with the AMH to finalise a national plan of action for outbreak control but its implementation will require significant assistance from the international community.

6 April: Total case count: 200 (173 deaths); Kuanza Sul reports its first case, bringing the number of affected provinces to six.

First joint outbreak assessment: Not only is the Angolan outbreak already the largest on record, and with the highest fatality rate, but is also the first to occur in an urban setting, reaching a very high transmission level. Uige, which remains the epicentre of the outbreak, has 500 000 inhabitants; Luanda, where some cases have occurred, has a population of close to 3 million. A top priority is to prevent the virus from becoming established in densely populated urban or peri-urban environments. As the incubation period of Marburg disease could be as short as 3 days, rapid and efficient contact tracing is vital towards containing the outbreak. Effective management of contacts needs timeous isolation of cases prior to the onset of symptoms to limit the risk of further transmission. Other needs include the protection of front-line staff, strengthening infection control in isolation wards, improved transportation of suspected cases to designated isolation wards, and education of the public to encourage protective behaviours and improve compliance with control measures.

Decades of civil unrest have left Angola with a severely impaired health infrastructure, a hospital system in urgent need for basic equipment and supplies and inadequate communication and transportation systems. These factors hamper disease containment, which depends on active surveillance for rapid detection of cases and isolation in specially designated and equipped facilities, and the rapid tracing of contacts. Deaths amongst doctors and nurses undermine the morale of hospital staff already working under difficult circumstances. Also, landmines remain scattered over a vast area making transportation by rail and road dangerous, often requiring staff and equipment to be airlifted. Intensified surveillance in Uige has revealed that some patients are dying within the community, creating an urgent need to organise services for their safe collection and burial.

Cases in front-line health care workers indicate the need for protective equipment and training in their use. The manifestations of MHF and the high fatality rate cause great anxiety in affected populations, increasing the risk of people fleeing from affected to unaffected areas, thereby contributing to the wider spread of the disease. Control measures are socially disruptive, and so add to public unease; in Uige, some people are reluctant to seek treatment or remain in hospital. Overall, there is an urgent need to strengthen the hospital system and to restore public confidence.

7 April: 205 cases (180 deaths) now reported including the first 6 from Zaire Province; bringing the number of affected provinces to seven. Vehicles are attacked and damaged by local residents forcing mobile surveillance teams in Uige to suspend operations. The situation does not improve subsequently, and discussions are held with the provincial authorities to find solutions. The symptoms of MHF and frequent deaths create a high level of fear, aggravated further by a lack of public understanding of the disease. Because the disease has no cure, hospitalisation is not associated with a favourable outcome, further eroding confidence in the medical care system. Two medical anthropologists are now in Uige and will be joined soon by experts in social mobilisation from Angola, the DRC and Mozambique.

8 April: WHO launches an international appeal for funding. US\$ 2.4 million is needed to intensify operations in the field. Specialised international staff and equipment have been deployed rapidly and measures are beginning to have an impact; however, the control of the outbreak will require intensified and sustained technical operational and logistic support, additional supplies and most urgently personal protective equipment.

12 April: Cases now number 235 (215 deaths). The isolation ward at the province's 400-bed hospital, especially equipped and staffed for the care of Marburg patients, stands empty despite cases and known deaths in the community. The community does not accept the concept of isolation. Family members and others who refuse to allow patients to be cared for in the isolation facility are being informed how to protect themselves from infection and given appropriate supplies. Disinfectants are on urgent order by WHO. International experts begin training staff at the provincial hospital to reduce the risk of nosocomial infection. Fever-screening units are established to ensure that all persons admitted to hospital are initially screened for symptoms of MHF before admission to the general wards. Apart from continuing security concerns, another pressing problem is poor access to remote communities in Uige Province resulting in poor surveillance. Using a military helicopter, international workers begin the pre-positioning of supplies and equipment needed for outbreak control in these areas.

14 April: 224 cases (207 deaths) now reported. Meetings in Uige were held with traditional community leaders (Sobas) who have been temporarily released

from their current duties to accompany the surveillance and medical teams in their search for cases and collection of bodies.

19 April: Total case count: 266 (239 deaths). A team of 28 Angolese health care professionals arrive in Uige to provide further outbreak control support. Teams investigating recent deaths within the community determine that some families administer injections to patients while providing care in their homes, a high-risk practice which can perpetuate transmission. Educational messages and materials communicating the associated dangers were developed and will be added to the information already provided to communities.

Second assessment of the outbreak: The features of MHF and the conditions in Angola have been an extreme test for the capacity of the international community to hold MHF at bay. Two factors make the rapid detection of MHF difficult: its extreme rarity and similarity to other diseases seen in countries where deaths from infectious diseases are common. Previous experience with filovirus epidemics indicates that the outbreak can be ended using classic public health interventions: rapid detection and isolation of patients, tracing and management of their close contacts, infection control in hospitals, and protective clothing for staff. These straightforward measures are, however, complicated by the sudden onset, dramatic symptoms, rapid deterioration of patients and the absence of a vaccine or effective treatment and invariably instil great anxiety in affected populations. This anxiety can hamper control operations, especially when communities begin to conceal cases (and bodies) because of their suspicions around the 'safety' of hospitals. This is understandable as most patients with laboratory-confirmed MHF die within a day or two following admission and staff from the mobile teams, fully suited in protective gear, is seen to take away loved ones seldom to be seen again alive.

Although community attitudes are improving, hostility towards the mobile teams is still of concern. Efforts to sensitise affected communities continue, with local volunteers supported by Portuguese-speaking experts from Brazil and Mozambique. It is believed that the risk for international spread is low. No foreign nationals, with the exception of those involved in the direct care of patients, have been infected. All the essential containment measures are being applied with extensive international support, including more than 60 international staff drawn from institutions in the GOARN, and the cooperation of national authorities and experts. Needs, which have ranged from hand-held radio sets to vehicles, protective equipment, disinfectants, and specialised staff, have been rapidly communicated and immediately met. An important present goal is to transfer skills and responsibilities for outbreak response to national staff.

27 April: Case count: 275 (255 deaths). With all control measures (teams, equipment, and protocols)

in place, extreme care must be taken to guard against any practices that could again amplify transmission, potentially setting back containment efforts by several weeks. The investigation of several recent deaths in Uige indicates a clear link between home-based treatments using unsafe syringes and the spread of Marburg virus. A massive door-to-door campaign, supported by banners and posters throughout Uige municipality, was launched yesterday to inform residents of the associated dangers and to collect and safely destroy syringes.

3 May: 308 cases (277 deaths) now reported. Uige Province remains the epicentre of the outbreak. The large increase in the number of reported cases for Uige is the result of retrospective investigations. Procedures and assigned responsibilities for safe infection control at the provincial hospital in Uige have been agreed on by ministry officials, WHO, and MSF. Teams are giving particular attention to screening and admission procedures to prevent suspected cases being treated in open wards. Massive public information campaigns aimed at ending unsafe injections continued this week. New vehicles provided by the Angolan government help in greater mobility to follow contacts and investigate suspect cases and deaths.

10 May: 316 cases (276 deaths) now reported; the municipality of Uige remains the most severely affected in the province, and where new cases have been identified in the last few days. As some chains of transmission are still ongoing, mobile teams are investigating suspect cases and following contacts. Religious leaders have joined the information campaign against the use of unsafe injections.

17 May: 337 cases (311 deaths) now reported. No cases have been reported outside Uige for the past five weeks. The isolation unit at Uige's provincial hospital is in use, infection control in the hospital has

improved, and safe burial practices are followed. A campaign to stop home treatment of patients using unsafe injections resulted in the collection and disposal of a large number of needles and syringes. Support from religious and community leaders allow surveillance teams to operate more smoothly, increasing the efficiency of case finding and contact tracing. New cases, linked to exposure in homes and at funerals, indicate that public understanding of the disease needs still to be improved.

26 May: 399 cases (335 deaths) now reported. Local and international staff continue to identify cultural practices that create opportunities for exposure. Around 200 traditional healers have been trained in ways to reduce risks to themselves and their clients and were given masks and gloves. To date, at least two traditional healers have died of MHF.

5 June: 423 cases (357 deaths) now reported; the vast majority from Uige Province, where the respective totals are 412 and 346. The number of new cases reported in Uige municipality has declined considerably, with only 1 new confirmed case detected in the past week.

10 July: Following the review of data by the Outbreak Response Team, the AMH has reported a total of 351 cases and 312 deaths from MHF; 64 contacts are being followed up in Uige Province. The team continues to receive and investigate alerts to potential cases.

28 July: 388 cases (323 deaths) reported, 157 laboratory-confirmed; 45 contacts are being followed up in the municipality of Songo and Uige Province.

Marburg virus took its deadly course again and left some traces but neither its source in nature nor the date of the initial MHF cases in Angola could yet be identified.

ACKNOWLEDGEMENTS

The author wishes to thank: WHO and NICD-NHLS for facilitating his mission to Angola to take part in the outbreak control, and visit the Canadian mobile laboratory, Uige, and the CDC laboratory for Marburg diagnosis, Luanda; Daniel Kertesz from WHO Epidemiological Focal Point, Luanda and Dr Fernando del Castillo, CDC Luanda, for providing some materials for this report.

REFERENCES

- CDC. Brief Report: Outbreak of Marburg virus hemorrhagic fever – Angola, October 1 2004-March 29 2005. MMWR , 2005, March 30, 54(Dispatch):1-2
- R&PG News. Marburg haemorrhagic fever in Angola. Available at:http://www.rxpnews.com/world/epidemics/hemorrhagicfevers/marburg/article_1227.shtml
- R&PG News. Assessment of the Marburg haemorrhagic fever outbreak. Available at: http://www.rxpnews.com/world/epidemics/hemorrhagicfevers/marburg/article_1227.shtml
- World Health Organization. Marburg haemorrhagic fever in Angola – updates. Available at: <http://www.who.int/csr/don/> 2005.

QUINOLONE RESISTANCE IN ENTERIC BACTERIA

Sandrama Nadan and Karen Keddy, Enteric Diseases Reference Unit (EDRU), NICD

In 1962, during the synthesis and purification of the anti-malaria agent, chloroquine, a quinolone derivative, nalidixic acid, was discovered. This agent was active against gram-negative bacteria. It was able to accumulate in high concentrations in urine, leading to its primary use in urinary tract infections (UTIs). The addition of a fluorine atom increased its activity and by the early 1990s fluoroquinolones, with activity

against gram negative and gram-positive bacteria as well as anaerobes, were introduced into clinics¹.

The early quinolones such as nalidixic acid had poor systemic distribution and limited activity. They were used mainly for gram negative UTIs. The next generation, the fluoroquinolones, such as ciprofloxacin and ofloxacin, were absorbed more rapidly and showed

increased activity against gram-negative bacteria. These are broad-spectrum agents with enhanced activity against both gram-negative and gram-positive organisms, highly effective for treatment of a variety of clinical and veterinary infections. They may be used in treatment of bacteraemia, respiratory tract infections, osteomyelitis, enteric and gonococcal infections as well as prophylactics for neutropaenic patients. These agents have the advantages of a wide range of activity, good oral absorption and tissue penetration. They have a relatively long serum elimination half-life that allows for once or twice daily dosing and a relatively low incidence of serious side effects and drug interactions are predictable. However, not all fluoroquinolones share these characteristics and several of these drugs pose expensive alternatives to other regimens.

Quinolones are bactericidal and exhibit concentration-dependant killing. The antimicrobial action is initiated by penetration of the organism via porins on the outer membrane or directly past the lipid membrane, then crossing the internal membrane to arrive at the cytoplasm. The drug inhibits two enzymes that are required for bacterial DNA synthesis, DNA gyrase and topoisomerase IV. The fluoroquinolone binds with the subunits of the DNA gyrase, initiating the formation of loose DNA ends which are cleaved by nucleases, resulting in cell death¹.

However, as with most antimicrobial agents, the extensive use of fluoroquinolones in humans and animals has generated the appearance of bacterial resistance. Control has to be exerted over the use of fluoroquinolones in clinical and veterinary settings. Some bacteria can infect across species and may result in the concomitant spread of resistance factors between human and animals².

Resistance to quinolones in gram negative bacteria e.g. *Escherichia coli* and *Salmonella* is mainly caused by single point mutations in the gene *gyrA*, which encodes the A subunit of DNA gyrase^{1,3}. Chromosomal mutations alter the target region where the drug binds to the bacterial enzyme, reducing the quinolone affinity for the target site. The bacterial genes encoding

for the porin proteins and efflux capabilities may undergo mutations, reducing the number of effective porin proteins which cause the bacterial outer membrane to become less permeable. Consequently lesser amounts of the drug reach the target enzyme in the cytoplasm. An increase in the number of active expulsion pumps responsible for the elimination of toxic compounds (efflux pumps) enhances the organism's total efflux capability, increasing quantities of the drug pumped out of the cell.

Plasmids and integrons encoding resistance, such as chromosomal genes of DNA enzymes encoding mutations for quinolone resistance (*qnr*), have also been implicated in the surge and spread of resistant organisms^{1,4}. This has been reported in a *Shigella dysenteriae* strain but was not subsequently verified¹. *In vitro* studies using *E. coli* have demonstrated protection of the organism from the action of nalidixic acid by expression of genetic sequence *qnr*.

It is suggested that organisms develop resistance as the result of exposure to the antibiotic. Plasmid-mediated transfer may not follow this norm, but rather create a whole new population of quinolone-resistant enteric bacteria. Table 1 indicates the increasing levels of quinolone resistance in isolates of *Salmonella typhimurium*, encountered in the antimicrobial susceptibility laboratory of EDRU for the period 2003 and 2004⁵.

Increasing quinolone resistance has resulted in altering the recommendation to use nalidixic acid in the treatment of bacillary dysentery in adults. The Essential Drug List now recommends the use of ciprofloxacin in adults⁶. Although the recommendation to use nalidixic acid in children has been retained⁶, other authors have postulated that fluoroquinolones may be justifiable for use in children as well for treatment of severe *Shigella* dysentery or typhoid fever⁷. Laboratory testing for nalidixic acid as well as fluoroquinolone susceptibility is critical, as resistance to the former antimicrobial may result in poor patient response to fluoroquinolone therapy, and increased dosages of fluoroquinolone may be required to overcome this effect⁸.

Table 1 :Incidence of quinolone resistance in *Salmonella typhimurium* 2003-2004, EDRU, NICD⁵.

| PROVINCE | 2003 | | | | | 2004 | | | | | | |
|---------------|-------------------------|--------|-----------------------------|--------|----------------------------|-------------------------|-----|-----------------------------|-----|----------------------------|----|--------|
| | Total isolates received | | Resistant to Nalidixic acid | | Resistant to Ciprofloxacin | Total isolates received | | Resistant to Nalidixic acid | | Resistant to Ciprofloxacin | | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | | |
| Eastern Cape | 16 | (3) | 2 | (12.5) | 0 | (0) | 72 | (8.7) | 0 | (0) | 0 | (0) |
| Free State | 26 | (4.9) | 15 | (57.7) | 0 | (0) | 28 | (3.4) | 13 | (46.4) | 1 | (3.6) |
| Gauteng | 361 | (68.4) | 57 | (15.8) | 0 | (0) | 500 | (60.8) | 156 | (31.2) | 3 | (0.6) |
| KwaZulu Natal | 16 | (3) | 3 | (18.8) | 0 | (0) | 115 | (14) | 41 | (35.7) | 24 | (20.9) |
| Limpopo | 0 | (0) | 0 | (0) | 0 | (0) | 10 | (1.2) | 0 | (0) | 0 | (0) |
| Mpumalanga | 9 | (1.7) | 0 | (0) | 0 | (0) | 15 | (1.8) | 1 | (6.7) | 0 | (0) |
| North West | 12 | (2.3) | 0 | (0) | 0 | (0) | 12 | (1.5) | 1 | (8.3) | 0 | (0) |
| Western Cape | 88 | (16.7) | 2 | (2.3) | 0 | (0) | 71 | (8.6) | 3 | (4.2) | 0 | (0) |
| Total | 528 | (100) | 79 | (15.0) | 0 | (0) | 823 | (100) | 215 | (26.1) | 28 | (3.4) |

References

1. Ruiz J. mechanisms of resistance to quinolones: target alteration, decreased accumulation and DNA gyrase protection. *J Antimicrob Chemother* 2003; 51: 1109-1117.
2. Malorny B, Schroeter A, Helmuth R. Incidence of Quinolone resistance over the period 1986 to 1998 in veterinary *Salmonella* isolates from Germany. *Antimicrob Agents Chemother* 1999; 43: 2278-2282.
3. Fact Sheet: Quinolones and the clinical laboratory. <http://www.cdc.gov/ncidod/hip/Lab/FactSheet/quinolones.htm>
4. Poirel L, Rodríguez-Martínez JM, Mammari H, Liard A, Nordmann P. Origin of plasmid-quinolone resistance determinant QnrA. *Antimicrob Agents and Chemother* 2005; 49: 3523-3525.
5. Mnyameni FS, Kruger T, Sooka A, Keddy KH. Quinolone resistance of *Salmonella* Typhimurium in South Africa, 2003-2004. 18 th national Congress of the Society of Medical Laboratory Technologists of South Africa, Cape Town Civic Centre, Cape Town, South Africa, 29 April - 2 May 2005.
6. Essential Drug List and Standard Treatment Guidelines. <http://www.hst.org.za/uploads/files/edlphc2003.pdf>.
7. Gendrel D, Chalumeau M, Moulin F, Raymond J. Fluoroquinolones in paediatrics: a risk for the patient or the community? *Lancet Infect Dis* 2003; 3: 537-46.
8. Crump JA, Barrett TJ, Nelson JT, Angulo FJ. Re-evaluating fluoroquinolone breakpoints for *Salmonella enterica* serotype Typhi and for nontyphoidal salmonellae. *Clin Infect Dis* 2003; 37: 75-81

CIPROFLOXACIN RESISTANT GONOCOCCI

David Lewis, Sexually Transmitted Infections Reference Centre (STIRC), NICD

INTRODUCTION

Fluoroquinolones were recommended for the primary treatment of gonorrhoea from the late 1980s due to increasing gonococcal resistance to penicillin, spectinomycin and tetracyclines. Decreased susceptibility and resistance to quinolones have been worsening worldwide, with the result that many countries have been forced to abandon this group of antimicrobial agents for the treatment of gonorrhoea. Quinolone resistant gonococci (QRNG) are those determined to have a ciprofloxacin minimum inhibitory concentration (MIC) of greater or equal to 1 mg/L. The World Health Organisation (WHO) recommends a change in first-line therapy for gonorrhoea if less than 95% of patients can be reliably cured with the first-line antimicrobial agent. Ciprofloxacin currently remains the first-line agent used to treat presumptive gonococcal infections in patients with sexually transmitted infections (STIs) attending primary health care clinics in South Africa.

ASSOCIATION BETWEEN MIC & CLINICAL FAILURE

Some countries initially used a 250mg ciprofloxacin single dose to treat gonorrhoea. Treatment failure with such a dose was first reported in London in 1990. A single 500mg dose is now recommended for the treatment of susceptible isolates, although resistance to such therapy has now been widely reported. The first gonococcal strains failing therapy with 250mg ciprofloxacin had MICs in the range of 0.06 mg/L to 0.25 mg/L. Post-treatment isolates from gonorrhoea failing to respond to 500mg ciprofloxacin typically have MICs \geq 1mg/L.

RISING RESISTANCE OUTSIDE SOUTH AFRICA

a) Europe

Within the United Kingdom (UK), antimicrobial resistance surveillance in London demonstrated a gradual increase in gonococcal resistance to ciprofloxacin over the period 1986-1997. By 2002, QRNG accounted for 9.7% of all isolates and a national decision was made to change therapy for gonorrhoea to 3rd generation cephalosporins. Surveillance data in the UK demonstrate that resistance levels varied

widely throughout the country and that many of the early resistant strains were imported from other countries in Europe and the Far East. Recently a surveillance network was set up in Europe to monitor STIs. In 2004, gonococcal resistance was surveyed in 12 European countries. QRNG accounted for between 7.6% and 53.1% of each country's isolates (average 31%).

b) WHO Western Pacific Region

High rates of QRNG have been detected for a number of years in many countries within the Far East, where ofloxacin and other quinolones were used to treat presumptive gonococcal infections since the late 1980s. WHO regularly monitors resistance rates in a number of countries within the Western Pacific Region. Most countries have shown a sustained rise in resistance throughout the 1990s and onwards. (Figure 1).

c) WHO South-East Asian Region

Rising levels of QRNG have been reported in India and Bangladesh, but not Sri Lanka, since the mid-1990s (Figure 2).

RISING RESISTANCE IN SOUTH AFRICA

A high level of ciprofloxacin resistant gonorrhoea in South Africa (22%) was first reported among isolates tested in Durban in 2003 by Moodley et al. (*Int. J. Antimicrobial Agents* 2004;24:192-193). More recent data on ciprofloxacin resistance in gonococci isolated in several provinces within South Africa were reported at the 1st Joint Congress of The Federation of Infectious Diseases Societies in Southern Africa (24-27 July 2005, Programme and Abstract Book): A survey undertaken in 2004 as part of South Africa's newly-established National STI Surveillance Programme demonstrated marked variation in ciprofloxacin resistance: Durban 24%, Johannesburg 11%, Umtata 10%, Pietermaritzburg 8%, Cape Town 7% and Pretoria (MEDUNSA) 0%; 2005 data from Durban (42%) and Johannesburg (16%) show marked increases in resistance; detection of QRNG in Pretoria (MEDUNSA) was also reported in a recent 2005 survey. It is clear that there is now an urgent need to change first line therapy for presumptive gonococcal infection in the

syndromic management protocols in use in primary health care facilities. The National Department of Health is aware of the severity of the problem.

MECHANISMS OF QUINOLONE ACTION AND RESISTANCE

Ciprofloxacin inhibits bacterial DNA synthesis by acting on DNA gyrase, a type II topoisomerase which inserts negative supercoils into DNA. Resistance in *Neisseria gonorrhoeae* is associated with mutations resulting in amino acid changes in the: a) A subunit (GyrA) and the B subunit (GyrB) of DNA gyrase and b) parC-encoded subunit of topoisomerase IV.

In gonococci, *gyrB* gene mutations confer low level resistance to nalidixic acid only. Decreased susceptibility and resistance to ciprofloxacin is associated with gonococcal *gyrA* gene mutations. In contrast, *parC* mutations are only seen in association with *gyrA* mutations in QRNG; they do not occur in gonococci exhibiting decreased susceptibility to ciprofloxacin. Mutations in the *gyrA* and *parC* genes may be characterised by DNA sequencing of quinolone resistance determining regions (QRDRs). The transfer of both *gyrA* and *parC* mutations between gonococci by transformation has been demonstrated in vitro. The presence of transformation sequences downstream of *gyrA* suggests that transformation may be important in vivo.

MANAGEMENT OF RESISTANT GONORRHOEA

Clinicians should be alert to the rising levels of

ciprofloxacin resistance in South Africa and consider this as a possibility in all patients not improving on current first-line STI syndromic management. Many of the QRNG isolated in South Africa also exhibit high level resistance to tetracyclines, so the co-administration of doxycycline to manage patients with male urethritis syndrome, vaginal discharge and lower abdominal pain syndrome (women) should not be relied upon. In particular, patients from (or with sexual partners in) KwaZulu-Natal should be closely monitored as they are at highest risk of acquiring a QRNG strain. If in doubt, a urethral or endocervical swab should be sent to a laboratory capable of growing *N. gonorrhoeae* and antimicrobial susceptibility testing performed to guide therapy in case of treatment failure. The need for effective contact tracing of patients with QRNG cannot be over-emphasised.

Gonococci are still susceptible to cephalosporins and no confirmed resistant strains have been reported in South Africa to date. Patients with QRNG can be reliably treated with cefixime 400mg as a single oral dose or with ceftriaxone 250mg as a single intramuscular dose. Spectinomycin still has activity against gonococci although this should be reserved for special situations, e.g. severe penicillin allergy. However, resistance occurs quite quickly, limiting its usefulness in the longer term. It is possible that gonococcal infections will need combination therapy once resistance to cephalosporins develops as there are no other options at present for management.

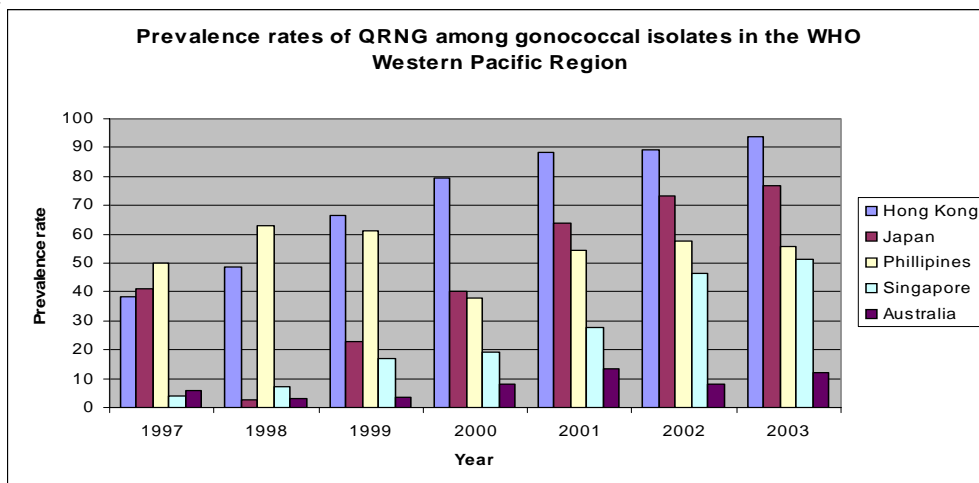


Figure 1 (Source WHO)

Figure 2 (Source: WHO)

