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

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According to the World Health Organization’s (WHO) prevalence and incidence estimates for 2005, gonorrhoea is the second most common sexually transmitted bacterial infection worldwide. Antimicrobial resistance among gonococci is worsening and multidrug-resistant strains, no longer responsive to oral cephalosporins, are now circulating in the Western Pacific region and emerging in other parts of the world. Sustainable high-quality antimicrobial resistance surveillance programmes for Neisseria gonorrhoeae exist in only a few countries. With the exception of South Africa, gonococcal antimicrobial resistance surveillance data are few or absent for most of Africa. There is thus an urgent need to revitalise gonococcal laboratory-based surveillance on the continent. In order to respond to this challenge, renewal of the WHO Gonococcal Antimicrobial Surveillance Programme is now taking place in various regions of the world, including sub-Saharan Africa, where the National Institute for Communicable Diseases, a division of the National Health Laboratory Service, has been asked to play a leading role.

Introduction and tribute

Globally, the World Health Organization (WHO) estimates that about 88 million new cases of gonococcal infections occurred in 2005, making it the second most common sexually transmitted bacterial infection worldwide. This paper reviews the evolution of antimicrobial resistance in Neisseria gonorrhoeae to date, with a focus on the current situation in Africa, and then discusses the public health threat of drug-resistant gonorrhoea. Renewed efforts to revitalise gonococcal antimicrobial resistance surveillance in Africa by the Sexually Transmitted Infections Reference Centre at the National Institute for Communicable Diseases (NICD), a division of South Africa’s National Health Laboratory Service (NHLS), in collaboration with the WHO, will be discussed.

Prof Barry Schoub, former Executive Director of the NICD, had a vision for the NICD/NHLS, to rise to the challenge of improving public health across the African continent. The recent achievements of the NICD/NHLS in relation to the Gonococcal Antimicrobial Surveillance Programme’s (GASP) activities in Africa form part of that vision and were only made possible as a result of Prof Schoub’s constant support and encouragement.

Overview of the evolution of antimicrobial resistance in N. gonorrhoeae, with special reference to Africa

In the pre-antibiotic era, gonococcal infections caused significant morbidity and mortality, through genital tract complications and disseminated infections. The first major breakthrough came in 1935 with the discovery of sulphamethoxazole; the benefit was short-lived and significant bacterial resistance to sulphonamides had developed by 1944. Penicillin was subsequently introduced in 1943 as a treatment for sulphonamide-resistant gonorrhoea. Penicillin quickly became the drug of choice for gonorrhoea and cure rates with small total doses of penicillin exceeded 95%. With constant exposure to this antibiotic, penicillin minimum inhibitory concentrations (MICs) increased incrementally as a result of step-wise mutations in several key genes (penA, penB, pem, mtr and pem). These rising MICs were initially countered by elevation of the total dose of penicillin prescribed for patients, aided by the addition of probenecid. Eventually chromosomal resistance emerged, which marked the beginning of the end for penicillin as a cheap and effective therapy for gonorrhoea.

The final nail in penicillin’s coffin came abruptly in 1976, with the emergence and rapid spread of transferable plasmid-mediated high-level resistance to penicillin mediated by TEM-1 β-lactamase production. Following the initial description of the prototype “Asia” and “Africa” plasmids in penicillinase-producing N. gonorrhoeae isolates, a number of deletion or insertion derivatives have been described, including most recently the “Johannesburg”plasmid, reported from the NICD/NHLS in South Africa.

Tetracyclines, discovered in the late 1940s, were used initially to treat gonorrhoea in penicillin-allergic patients and for the management of post-gonococcal urethritis. As with penicillin, gonococci became less susceptible to tetracycline because of mutations in several genes (rpsJ, penB, mtr, tet), which
eventually led to chromosomal resistance. High-level plasmid-mediated tetracycline-resistant \( \text{N. gonorrhoeae} \) (TRNG) isolates were first reported in the USA in 1985, and shortly afterwards in the Netherlands.\(^{7,8}\) TRNG is now widespread and highly prevalent in many countries, as exemplified by the 73% prevalence recently reported from Johannesburg by NICD/NHLS researchers.\(^6\)

Co-trimoxazole, a combination of sulphamethoxazole and trimethoprim, was introduced with some initial success in the 1970s in various parts of the world, including Africa. Resistance soon developed, mainly to the sulphonamide component, as gonococcal dihydrofolate reductase has low affinity for trimethoprim.

Spectinomycin was developed and marketed specifically for the treatment of gonorrhoea, particularly penicillinase-producing \( \text{N. gonorrhoeae} \) infections in the early 1960s, although its use has been limited on the African continent because of high cost and limited accessibility. Experience with spectinomycin in the Republic of Korea in the 1980s, where it was introduced to treat gonorrhoea in US military personnel, demonstrated the ease with which chromosomal resistance can develop to the agent when it is widely used in clinical practice.\(^9\) Kanamycin is cheap and is used to treat gonorrhoea in some resource-poor countries, for example Zimbabwe and Mozambique. Gentamicin has been the first-line therapy for gonorrhoea in Malawi for approximately 15 years, where the observation that gonococci appear to have retained susceptibility during this period has raised the possibility that this drug could be used in future "rescue therapies" for multi-resistant \( \text{N. gonorrhoeae} \) infections.\(^{10}\)

Clinical and laboratory susceptibility data have demonstrated that erythromycin is of limited use in gonorrhoea treatment, because of the ease with which macrolide resistance develops.\(^{11}\) Azithromycin, however, is more active against gonococci and has the advantage of single-dose oral therapy. The WHO does not recommend azithromycin as a first-line agent for treatment of gonorrhoea, because of concerns over the ease of development of resistance and the side-effects of the required 2 g dose required to treat gonorrhoea effectively.\(^{2,12}\) Such concerns are supported by the observation that in vitro resistance to azithromycin is now emerging in several countries, perhaps as a consequence of the widespread use of this drug in sexually transmitted infection (STI) clinics to treat presumptive or confirmed chlamydial infections.\(^{13}\)

Fluoroquinolones, for example ciprofloxacin, were widely used to treat gonorrhoea from the mid-1980s onwards. Treatment failure of the lower 250 mg single oral dose was first reported in 1990, following which the recommended treatment dose was raised to single-dose 500 mg.\(^{14}\) However, it was not long before clinical resistance emerged to the higher dose as well, initially in the Asia-Pacific region and later on a global scale.\(^7\) Quinolone-resistant \( \text{N. gonorrhoeae} \) (QRNG) isolates contain point mutations in the chromosomal \( qyrA \) and \( parC \) genes, which encode for DNA gyrase and topoisomerase IV, respectively. Quinolones, such as ciprofloxacin and norfloxacin, have been widely used in many African countries to treat gonorrhoea over the past decade and, until 2003, there was little or no recorded resistance, mainly due to the fact that there was no laboratory-based antimicrobial surveillance in countries using these drugs. The emergence of QRNG as a public health problem in Africa was first reported from South Africa, where QRNG first appeared dramatically at 22% prevalence in a survey conducted in KwaZulu-Natal in 2003; subsequent surveys, mostly coordinated by the NICD/NHLS, have demonstrated substantial levels of resistance in most of South Africa’s other eight provinces.\(^{15-17}\)

With the loss of quinolones, many non-African countries opted to treating gonorrhoea with oral cephalosporins or, particularly when these were not available, intramuscular ceftriaxone. Within Africa, country examples where cefixime has replaced quinolones to treat presumptive gonorrhoea include Ghana (2008), Namibia (2008) and South Africa (2008). Of global concern, gonococci exhibiting in vitro decreased susceptibility, and now clinical resistance, have emerged in Japan in recent years.\(^{18,19}\) Gonococci with reduced susceptibility and resistance to oral cephalosporins, caused in major part by acquisition of mosaic \( penA \) genes, are spreading within the Asia-Pacific region and emerging in other regions of the world.\(^2\) Of note, UK- and USA-based surveillance programmes have reported "MIC creep" for both oral cephalosporins and ceftriaxone, mirroring what was observed with penicillin and tetracycline in the 1940-50s.\(^{20}\) Several countries have now turned to intramuscular ceftriaxone as the last available treatment for gonorrhoea.\(^{21}\)

**The public health threat of drug-resistant gonorrhoea and the need to strengthen gonococcal control programmes in Africa**

For Africa, the emergence of multidrug-resistant (MDR) \( \text{N. gonorrhoeae} \) isolates comes at a time when STI control programmes are weak and under-resourced, as substantial funds, human resources and technical expertise are being redirected to other public health priorities, such as HIV/AIDS and tuberculosis. To assist ongoing surveillance efforts, new definitions for MDR and extensively drug-resistant (XDR) have recently been published (Table I).\(^{22}\) At present, MDR gonococcal strains are circulating, mainly in the Western Pacific region, characterised by combined resistance to oral cephalosporins, quinolones, penicillins and tetracyclines.\(^{15}\) Although such isolates have yet to be reported from African countries, history suggests that they soon will be. At the present time, there have been no confirmed cases of XDR genital gonorrhoea in terms of either additional ceftriaxone resistance, or the combination of resistance to both oral cephalosporins and spectinomycin. The ultimate threat to gonorrhoea-control programmes remains, as has happened with other Gram-negative bacteria, the acquisition of extended-spectrum β-lactamases and carbapenemases by \( \text{N. gonorrhoeae} \) which will render all cephalosporins, including ceftriaxone, ineffective.
There now exists growing international concern that gonorrhoea may become untreatable within a few decades. The impact of untreated gonorrhoea on HIV transmission could also be significant in those African countries with high prevalence of both infections. As there are no new therapeutic drugs in the drug-delivery pipeline, there is an urgent public health need to reduce the global burden of gonorrhoea, and hence dependence on antimicrobial agents in the longer term. Such an approach, for any given country, would ideally consist of an accurate knowledge of the local epidemiology of gonococcal infection, early detection and treatment of cases, screening of high-risk populations, a continued supply of effective antibiotics at all treatment facilities, efficient partner notification practices, and perhaps most important of all, effective change in terms of increased condom use and reduction of high-risk sexual behaviour.

**Limitations of recent surveillance data regarding gonococcal antimicrobial resistance in Africa**

Most African national departments of health have failed to undertake any gonococcal antimicrobial susceptibility surveys since the introduction of syndromic management in the late 1990s, despite WHO guidance that such periodic surveillance should form an integral part of the syndromic management approach. Additionally, only a few peer-reviewed articles on this topic have been published in the past decade, mainly from South Africa (Table II). Where data do exist, there are important differences in methodology, for example testing strategies for the determination of antimicrobial resistance and type of media used for such testing. Several studies are also limited by small numbers and the lack of use of panels of appropriate *N. gonorrhoeae* control strains which contain gonococci of susceptible, intermediate and resistant phenotypes for the antibiotics under evaluation. In addition, there is an apparent lack of confirmation of potentially important resistance findings by other laboratories with proven experience in antimicrobial susceptibility testing of *N. gonorrhoeae* isolates. This is well demonstrated by the claims of putative ceftriaxone-resistant isolates, when, indeed, no such strains have been shown to exist globally. Several African surveys have also suffered from inadequate storage capacity in terms of access to -70°C freezers, failure to use appropriate cryovials and preservative suspensions for gonococci, and breakdown in viable transfer from primary testing laboratories to regional reference centres.

Surveillance undertaken at South Africa’s University of KwaZulu-Natal clearly demonstrated how quickly antimicrobial resistance can appear, with a reported rise in the prevalence of QRNG from 0% to 22% over a one-year period (Table I). The emergence of antimicrobial-resistant *N. gonorrhoeae* isolates can occur silently and spread rapidly in the absence of ongoing microbiological surveillance. A good example of this is seen in Uganda, a country where ciprofloxacin has been first-line therapy for presumptive gonococcal infections for many years without investment in surveillance activities. Two recently undertaken surveys now report a high prevalence of ciprofloxacin resistance in both commercial sex workers (80%) and men with urethral discharge (95%).

**Renewal of the WHO GASP**

The provision of microbiological and clinical surveillance systems is cited as one of the key support structures in the WHO global strategy for the prevention and control of STIs. Yet, high-quality programmes for the surveillance of antimicrobial-resistant *N. gonorrhoeae* isolates exist in only a handful of countries, for example the US-based Gonococcal Isolate Surveillance Project (GISP), the UK-based Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) and the Australian Gonococcal Surveillance Programme.

Given the global nature of the problem, it is important that gonococcal antimicrobial resistance surveillance is regionally based and involves a network of national reference laboratories, that countries agree to share their data with each other at regional level, and that permission is obtained for regional data sets to be submitted to a central database in order to present a global picture at the WHO headquarters. The WHO is currently renewing its efforts to strengthen global gonococcal antimicrobial resistance surveillance networks based on the success of the WHO Western Pacific Region’s GASP, which has been in operation since 1992 and currently involves approximately 20 countries. The WHO’s enhanced GASP activities have four main objectives: firstly, to collect good quality data on gonococcal infections and the magnitude of resistant strains; secondly, to improve current knowledge of the potential mechanisms of cephalosporin resistance in *N. gonorrhoeae* through laboratory studies; thirdly, to enhance an early warning system to detect the emergence of cephalosporin-resistant gonococci; and lastly, to share experiences with other agencies monitoring emergence of resistance and to plan for containment of the spread of antimicrobial-resistant *N. gonorrhoeae*.

The WHO Global GASP team has identified regional focal institutions/individuals to carry out varying activities to achieve the GASP objectives. These GASP collaborating institutions include the WHO Collaborating Centre for Sexually Transmitted Diseases (STD) and HIV at the Prince of Wales Hospital, Sydney, Australia (WPRO-linked GASP); the Regional...
Table II: Published gonococcal antimicrobial resistance surveys from Africa (2001-2010)

<table>
<thead>
<tr>
<th>Country (year)</th>
<th>Population</th>
<th>Method</th>
<th>No. of isolates</th>
<th>Resistance (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Penicillins</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>Ethiopia 2001*</td>
<td>Men with MUS attending PHC clinic</td>
<td>Disc diffusion</td>
<td>142</td>
<td>86.6 (86.6)</td>
<td>29.6</td>
</tr>
<tr>
<td>South Africa 2003*</td>
<td>Men with MUS attending STI clinic, Durban</td>
<td>Agar dilution</td>
<td>139</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>South Africa 2004#</td>
<td>Men with MUS, attending STI clinic, Durban</td>
<td>Agar dilution</td>
<td>259</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>South Africa 2004-2005*</td>
<td>Men with MUS, attending 2 PHC clinics and private GP, Pretoria</td>
<td>Agar dilution</td>
<td>141</td>
<td>29.1 (15.6)</td>
<td>53.9 (36.2)</td>
</tr>
<tr>
<td>South Africa 2004-2008*</td>
<td>Men with MUS, attending PHC clinic, Johannesburg</td>
<td>Etest</td>
<td>172</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>South Africa 2005*</td>
<td>Men with MUS, attending STI clinic, Durban</td>
<td>Agar dilution</td>
<td>248</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Mozambique 2005*</td>
<td>Men with MUS and women with VDS attending PHC clinic, Maputo</td>
<td>Agar dilution</td>
<td>55</td>
<td>63.8 (61.8)</td>
<td>80.0 (76.4)</td>
</tr>
<tr>
<td>South Africa 2007*</td>
<td>Men with MUS, attending PHC clinic, Cape Town and Johannesburg</td>
<td>Etest</td>
<td>288</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Malawi 2007*</td>
<td>Men with MUS attending STI clinic at main hospital, Lilongwe</td>
<td>Agar dilution</td>
<td>100</td>
<td>19</td>
<td>77</td>
</tr>
<tr>
<td>South Africa 2008*</td>
<td>Men with MUS, attending PHC clinic, Johannesburg</td>
<td>Etest</td>
<td>209</td>
<td>25.8 (25.8)</td>
<td>75.1 (73.7)</td>
</tr>
<tr>
<td>Kenya 2009*</td>
<td>Men with MUS, attending PHC clinic, Kisumu</td>
<td>Disc diffusion</td>
<td>90</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

Note: papers were excluded if they reported susceptibility data on less than 50 isolates or if they repeated data reported in one of the papers already included on the table; *= date of publication, # = date of survey, NT = not tested
Reference Laboratory of the Regional STD Teaching, Training and Research Centre at Safdarjang Hospital, New Delhi, India (SEARO-linked GASP); the University of Saskatchewan, Saskatoon, Canada, which will assist with GASP activities in Latin American and Caribbean countries (AMRO-linked GASP); the National Reference Laboratory for Pathogenic Neisseria, Örebro University Hospital, Örebro, Sweden (EURO-linked GASP); and the STI Reference Centre, NICD/NHLS, Johannesburg, South Africa (AFRO-linked GASP). In addition, three GASP partners will be involved in providing expertise and sharing data, namely the CDC (GISP), the Health Protection Agency (GRASP) and the International Collaborative Group on Gonococci.

Initial steps taken by the NICD/NHLS to assist in the establish the AFRO-linked GASP

Within South Africa, the STI Reference Centre at the NICD/NHLS developed and has co-ordinated the National Microbiological Surveillance Programme for STIs since 2005. To date, antimicrobial resistance surveys have been completed in Gauteng (annually since 2007), the Northern Cape (2006), Mpu malanga (2006), the Western Cape (2006-07), the Free State (2009), the Eastern Cape (2010), the North West Province (2010-11) and Limpopo (2010-11). These surveys have confirmed widespread ciprofloxacin resistance among gonococci but, to date, no evidence of resistance to either cefixime or ceftriaxone (DA Lewis, unpublished data).

In 2007, in partnership with the Namibian Ministry of Health and Social Services and WHO Country Office for Namibia, the STI Reference Centre participated in STI microbiological surveys at Windhoek and Oshakati. The reported prevalence of ciprofloxacin resistance was 24% overall (Oshakati 48%; Windhoek 5%). As a result of this survey, the Ministry of Health and Social Services revised the national STI treatment guidelines in 2008 and replaced ciprofloxacin with cefixime for the treatment of presumptive gonococcal infection.

Renewed operational efforts from both the WHO and NICD/NHLS to develop the African GASP commenced in early 2010. That same year, the STI Reference Centre designed and implemented a protocol to determine the prevalence of gonococcal resistance to kanamycin, ciprofloxacin, cefixime and ceftriaxone in gonococci isolated from men with urethral discharge attending 12 polyclinics in Harare, Zimbabwe. Following training of both laboratory and clinical staff regarding operational aspects of the protocol, recruitment began in December 2010 and the survey is currently ongoing (Figure 1). Mutare, Bulawayo, Beitbridge and Hurungwe were added as extra sites in 2011, to improve national representativeness.

Towards the end of 2010, staff from the STI Reference Centre also undertook site visits, in collaboration with WHO staff, to the National Reference Laboratory in Anatananarivo, Madagascar and the National Institute for Medical Research in Mwanza, Tanzania in order to discuss survey protocol issues and training needs. Laboratory staff from both these institutions came for training on antimicrobial susceptibility testing for *N. gonorrhoeae* at the NICD/NHLS in early 2011 (Figure 2).

In March 2011, a WHO workshop was held in Harare to review progress of GASP activities in the WHO-AFRO region (Figure 3). The workshop was attended by representatives from national health departments and key laboratories in Bénin, Botswana, Cameroon, Ethiopia, Ghana, Kenya, Madagascar, Nigeria, Tanzania, South Africa, Uganda and Zimbabwe. Technical
experts was provided by staff from the NICD/NHLS, the Centers for Disease Control and Prevention (CDC) and the National Reference Laboratory for Pathogenic Neisseria at Örebro University Hospital, Sweden. Presentations covered completed gonococcal antimicrobial resistance surveys in Botswana and Uganda, ongoing surveys in Zimbabwe and planned surveys in Kenya, Madagascar and Tanzania.

Future challenges to the roll out of GASP in Africa

The recent WHO workshop in Zimbabwe highlighted the fact that most African countries do not possess recent gonococcal survey data. Whilst there have been undoubted public health gains from the introduction of syndromic management in terms of facilitating standardised provision of care at all clinical entry points for the lowest cost, there has been a loss of laboratory expertise in terms of ability to culture gonococci and perform antimicrobial susceptibility testing. A major challenge for the future will thus be to develop laboratory capacity within the region. An international laboratory network needs to be created, where regional centres of excellence will assist with confirmation of putative cephalosporin-resistant gonococci, the coordination of external quality-assurance programmes and the distribution of WHO control N. gonorrhoeae strains. Another key challenge identified was how best to motivate nurses to take on the extra work needed to enrol patients and to take the clinical specimens for surveys, particular when this public health surveys are still viewed as “research”. The development of standardised protocols and the subsequent sharing of data between countries involved in the GASP network, and ultimately dissemination of data at the global level, were additional challenges. However, perhaps the most difficult challenges remain the prioritisation of gonococcal antimicrobial surveillance by national health departments and the allocation of resources to undertake gonococcal antimicrobial susceptibility surveys in a sustainable manner.

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References

2. Lewis DA. The Gonococcus fights back: is this a knock out? Sex Transm Infect 2010; 86: 415-421