Monitoring gonococcal antimicrobial susceptibility

The rapidly changing antimicrobial susceptibility of Neisseria gonorrhoeae has created an important public health problem. Because of widespread resistance to other antimicrobials, in many countries only cephalosporin-based regimens are recommended. Increasingly, countries use a combination of a cephalosporin and azithromycin for the co-treatment of gonorrhoea and chlamydia. While azithromycin is included primarily to treat chlamydia, it has the added benefit of providing additional coverage for treating gonorrhoea.

Gonococcal resistance to penicillin and tetracycline first emerged in Asia during the 1970s. It became widespread in multiple regions during the early 1980s. Global efforts to establish routine surveillance of the antimicrobial resistance of gonorrhoea began in the early 1990s. High levels of resistance to quinolones (e.g. ciprofloxacin) appears to have developed by the mid-2000s in several regions, leading countries to revise their treatment guidelines to use third generation oral cephalosporins such as cefixime or injectable cephalosporins such as ceftriaxone. Unfortunately, however, data indicate increasing gonococcal resistance to, and treatment failures with, third generation oral cephalosporins. Several of the gonococcal strains associated with failure of cephalosporin treatment have also demonstrated resistance to other antibiotics and have been classified as multi-drug resistant gonococci.

The GASP network

The Gonococcal Antimicrobial Surveillance Programme (GASP) has documented the emergence and spread of antimicrobial resistance in gonorrhoea since 1992 and has provided evidence to inform national, regional, and global treatment guidelines. The GASP is a worldwide laboratory network that is coordinated by focal points and regional coordinating centres. Each designated regional focal point, in partnership with its WHO regional office, collates data on patterns of antimicrobial susceptibility in gonorrhoea in participating countries. The regional focal points provide technical support to countries to strengthen laboratory capacity and external quality assurance programmes, including maintenance and distribution of WHO reference panels (17).

Sustaining this programme is essential but challenging. Antimicrobial resistance surveillance is often lacking or of poor quality in countries with a high burden of gonorrhoea. Also, there is a general lack of reliable antimicrobial resistance data for gonorrhoea globally and thus inadequate knowledge of the extent of the spread of resistant gonococci.

WHO has recently released surveillance standards and updated the WHO reference panels for the external quality assurance programme to enhance global surveillance of multidrug and extended-spectrum cephalosporin drug resistant gonorrhoea (7, 18). The WHO standards describe the microbiological and epidemiologic requirements to ensure the validity of data. In addition, research is underway to develop new molecular technologies and approaches that could be combined with existing methods to improve surveillance data on antimicrobial resistance.

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.

Recommendations for monitoring

WHO recommends monitoring gonococcal antimicrobial susceptibility at least once a year as one of the core components of STI surveillance. Antimicrobial susceptibility is measured by minimum inhibitory concentrations—that is, the lowest concentration of an antibiotic that inhibits visible growth of the bacteria. Gonorrhoea isolates for antimicrobial resistance testing should be sampled from sequential confirmed gonorrhoea cases from participating facilities throughout the course...
of the year. Men with urethral discharge are often selected for sampling because of the relative ease of collection, higher yield of positive cultures, and lower cost than for sampling women. WHO recommends using data from gonococcal antimicrobial resistance surveillance to refine treatment options and that use of an antibiotic for routine treatment be discontinued when the rate of therapeutic failure and/or of antimicrobial resistance reaches or exceeds 5%.

GASP data for 2010 showed that the majority of countries in Asia have a high proportion of penicillinase-producing \textit{N. gonorrhoeae} (PPNG) isolates, which confers resistance to penicillin (Figure 13). High rates of PPNG have also been observed in countries in the Americas. Lower rates of PPNG have been observed in European countries.

### Table 3

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>Regional GASP focal points</th>
<th>Number of countries participating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Formerly, until February 2012, Sexually Transmitted Infections Reference Centre, National Health Laboratory Service, Johannesburg, South Africa</td>
<td>5</td>
</tr>
<tr>
<td>The Americas</td>
<td>Sexually Transmitted Infections Reference Centre, National Institute of Infectious Disease, Buenos Aires, Argentina</td>
<td>13 plus Canada and the USA</td>
</tr>
<tr>
<td></td>
<td>University of Saskatchewan, Saskatoon, Canada</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, USA</td>
<td></td>
</tr>
<tr>
<td>The Eastern Mediterranean</td>
<td>STD Laboratory, Bacterial Department, National Institute of Hygiene, Rabat, Morocco</td>
<td>1</td>
</tr>
<tr>
<td>Europe</td>
<td>Sexually Transmitted Bacteria Reference Laboratory, Health Protection Agency Centre, London, UK</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>WHO Collaborating Centre for Gonorrhoea and Other STIs, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden</td>
<td></td>
</tr>
<tr>
<td>South-East Asia</td>
<td>WHO GASP South-East Asia Regional Reference Laboratory, VMMC and Safdarjang Hospital, New Delhi, India</td>
<td>6</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>WHO Collaborating Centre for STD – South Eastern Area Laboratory Services (SEALS), The Prince of Wales Hospital, Sydney, Australia</td>
<td>15</td>
</tr>
</tbody>
</table>

The most recent published data from GASP participating sites have been collated in this report (Annex 10) (19, 20, 21).
The majority of countries in the Americas, Asia, and Europe reported high rates of resistance to ciprofloxacin or other quinolones. Rates of quinolone resistance were low in only a handful of countries (Figure 14).

There are growing reports of decreased susceptibility of *N. gonorrhoeae* to ceftriaxone and cefixime; in 2010, 36 countries reported elevated minimum inhibitory concentration to third-generation cephalosporins (either cefixime ($\geq 0.25 \mu g/mL$) or ceftriaxone ($\geq 0.125 \mu g/mL$)) (Figure 15). The first reported treatment failure to cefixime occurred in Japan in 2002 (22), followed by treatment failures in Austria, Canada, France, Norway, South Africa, and the United Kingdom (23, 24, 25, 26, 27, 28). In addition, reports of failure to treat pharyngeal gonorrhoea with ceftriaxone have been verified in Australia, Japan, Slovenia, and Sweden (29, 30, 31, 32). The majority of reports are from developed countries; surveillance data from resource-constrained settings are scarce. It can be assumed, however, that the treatment failures in these 10 countries represent only the tip of a silent epidemic of antimicrobial resistance.

Resistance to spectinomycin is monitored in several countries in the Americas (Argentina and Chile), Asia (Bhutan, Brunei, China, Japan, Mongolia, and Sri Lanka), and some European countries. To date, decreased susceptibility to spectinomycin has been reported in Brunei, China, Mongolia, and the Russian Federation.

Some European countries, Chile, and the USA have identified resistance to azithromycin, which is recommended for use with cephalosporins for dual therapy of gonorrhoea as well as for co-treatment of chlamydia. In most of these countries with data, resistance remains well below the 5% threshold. Few countries in the Americas and Asia have been monitoring azithromycin resistance.

Gonococcal antimicrobial resistance could pose a major challenge to efforts to control gonorrhoea and its complications. To facilitate action against the spread of multidrug resistant *N. gonorrhoeae*, WHO has launched the *Global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae* (33). The global action plan should be implemented within the context of enhanced STI surveillance to facilitate early detection of emerging resistant strains, combined with a public health response to prevent and treat gonococcal infections and to mitigate the impact of cephalosporin-resistant *N. gonorrhoeae* on sexual and reproductive health.

Figure 13
Proportion of penicillinase-producing *N. gonorrhoeae* isolates reported in countries, 2010

Source: GASP 2013
Figure 14
Proportion of *N. gonorrhoeae* strains resistant to ciprofloxacin and/or other quinolones reported in countries, 2010

Source: GASP 2013

Figure 15
Countries with documented elevated minimum inhibitory concentrations to cefixime and/or ceftriaxone, 2010

Source: GASP 2013
Summary and next steps

This document provides a baseline report on what STI surveillance data are available and what is currently known at a global level prior to increased efforts to improve STI surveillance. Surveillance data are available online in some countries across the regions, and the number of countries reporting is increasing over time. However, prior to WHO’s establishing a global system, data are not consistently available except in regions with routine collection systems (Europe for general population STI indicators and the Americas for EMTCT of syphilis indicators).

To develop routine collection systems, WHO headquarters, regional offices, and country counterparts will continue collaborating to implement the Road Map for Strengthening STI Surveillance (Annex 1). Priority activities related to the road map at the global level include continuing to increase the STI data available through the WHO Global Health Observatory, improving STI data collection through the GARPR system, supporting regions to offer training in STI surveillance, and developing tools to facilitate assessment of national surveillance systems. It will be important for the regional level to facilitate training for countries and to identify countries in need of technical support. At the country level governments and key partners should work together to review existing national systems and identify priority areas for improvement.

The most widely available data are related to syphilis in pregnancy. These data suggest that many countries are making great progress in eliminating MTCT of syphilis. In fact, several countries may be eligible to begin processes that will lead to validation of elimination. Most likely, data quality will improve as countries make strides towards elimination.

This baseline report also shows that, although gonococcal antimicrobial susceptibility data are available through GASP for 62 countries, there are still many geographic areas where resistance patterns are unknown. In particular, WHO headquarters and the African regional office (AFRO) are working to establish a stronger GASP network in the African region that will collect information to guide countries’ selection of effective gonococcal therapy. Such information is critical, as resistance to third-generation cephalosporins has been noted in at least 36 countries, and treatment failures, in at least 10 countries. WHO also is working with regional reference centres to improve the capacity to collect valid and comparable data monitoring antimicrobial resistance. In addition, distribution and use of WHO reference panels should support laboratory quality assurance systems.

This baseline report and future reports like it will provide information that countries, regions, and global stakeholders can use to strengthen STI surveillance. Investing in these surveillance systems is critical for efforts to reduce the burden of STI and, by preventing HIV infections and reducing the burden of STI sequelae such as stillbirths, neonatal deaths, and infertility, to attain Millennium Development Goals 4, 5, and 6.