Antimicrobial resistance in Neisseria gonorrhoeae in South-East Asia

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Abstract
Systematic antimicrobial resistance (AMR) surveillance of Neisseria gonorrhoeae at the local, regional, and global levels is a necessary tool for informing and modifying empirical antimicrobial prescription and for designing and monitoring interventions to control resistance. The accumulation and dissemination of surveillance data require functional and quality-assured laboratories for the pathogen isolation and susceptibility testing, demographic data, databases, and information dissemination channels. Many developing countries in WHO’s South-East Asia (SEA) Region lack more than one of these essential requirements, and thus surveillance data are lacking for N. gonorrhoeae. Comparing resistance trends across different countries is challenged by the lack of continuous surveillance data from many SEAR countries. Establishment of the WHO global Gonococcal Antimicrobial Surveillance Programme (GASP) across all regions assists in generating AMR data, as well as in compiling and disseminating the information. Participation in EQAS programmes and appropriate use of the WHO reference panel by GASP participants is a necessary requirement for the validation of gonococcal AMR data. The currently recommended treatment for gonorrhoea includes the use either of third generation cephalosporins or of spectinomycin. To ensure that the limited resources are used in the best possible ways, gonococcal resistance against these drugs should continuously be surveyed. High dosages and incorrect use of the first-line antibiotics for the treatment of gonorrhoea should be discouraged to delay the emergence of cephalosporin resistance.

Keywords: Antimicrobial resistance, surveillance, Neisseria gonorrhoeae, South-East Asia Region, Gonococcal Antimicrobial Surveillance Programme

Introduction
Antimicrobial resistance (AMR) has become a major public health problem and it contributes to health and economic losses worldwide. AMR to commonly prescribed antibiotics is increasing both in developing as well as developed countries. Resistance has emerged even to newer, more potent antimicrobial agents and some micro-organisms may develop resistance to a single antimicrobial agent (or related class of agent), while others develop resistance to several antimicrobial agents or classes. These organisms are often referred to as multidrug-resistant or MDR strains. In some cases, the microorganisms have become so resistant that no available antibiotics are effective against them.

The growing threat from resistant organisms calls for concerted action to prevent the emergence of new resistant strains and the spread of existing ones. The problem of AMR requires a multi-pronged research approach. There have been several initiatives by the World Health Organization (WHO) and the US Centre for Disease Control (CDC) directed at addressing the problem of antimicrobial resistance such as:

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The most deadly infectious diseases in the world today are also the ones for which AMR has emerged. AMR has rendered care for and treatment of such serious illnesses as diarrhoeal diseases, respiratory tract infections, sexually transmitted infections, meningitis, pneumonia, and hospital-acquired infections more difficult and expensive than ever imagined.

Gonorrhoea, a sexually transmitted infection, remains a significant disease globally and gonococcal AMR severely compromises control of gonococcal disease, preventing effective treatment of individuals, increasing the rate of morbidity and complications and enhancing the transmission of HIV. Effective treatment of gonorrhoea depends to a significant degree on having available data on AMR patterns in Neisseria gonorrhoeae. Over the last decade, N. gonorrhoeae strains have developed a high level of resistance against several antimicrobial agents such as sulfonamides, penicillin, tetracycline and quinolones in different countries, posing an increasing problem in the management of gonorrhoea. The emergence of strains resistant to extended-spectrum cephalosporins, the antibiotics used as the first-line treatment for uncomplicated gonococcal infections, is now a serious concern worldwide as it may lead to untreatable gonorrhoea. This review is aimed at analyzing the problem of antimicrobial resistance in N. gonorrhoeae, particularly in countries of the WHO SEA Region.

**Methods**

A Medline search was conducted using PubMed, for articles published since 1990 under the major headings of “antimicrobial resistance in N. gonorrhoeae in SEA Region countries”, “Surveillance of antimicrobial/drug resistance in N. gonorrhoeae” and “gonorrhea treatment/therapy.”. Data were compiled from relevant articles.
Sources of data on AMR in N. gonorrhoeae

The need to identify and characterize the resistance profile of N. gonorrhoeae has been recognized as a public health priority. This has been addressed by a number of bodies while establishing surveillance programmes for AMR in gonococci so as to address the need for quality control (internal) and quality assurance (external) programmes, increasing difficulties accessing isolates as the use of non-culture based testing increases, and the need to define sample populations and sample sizes for valid data generation. These surveillance programmes include the WHO Gonococcal Antimicrobial Surveillance Programme (GASP); the United States Gonococcal Isolate Surveillance Programme (GISP); the Australian Gonococcal Surveillance Programme (AGSP) and the UK Gonococcal Resistance to Antibiotics Surveillance Programme (GRASP). Some of these systems use intermittent and others use continuous surveillance.

The WHO GASP was established in different regions of the world in 1990. GASP is important in assisting health providers in making recommendations regarding effective antibiotics for treatment. The progress of GASP has been slow in some regions due to a delay in establishing laboratories, networks and infrastructure for activities such as quality assurance. However, programmes have been established in Latin America and the Caribbean, and in the WHO Regions of the Western Pacific (WPR) and South-East Asia (SEAR). Within these regions, a number of national networks are at various stages of development. WHO recently reviewed the standards required for surveillance of antimicrobial resistance in N. gonorrhoeae.

The GASP in WHO-WPR and the GISP in the United States are continuous surveillance programmes with programme-specific quality assurance (QA) and quality control (QC) using published standardised methodology; Data are published annually.

Most of the studies on surveillance have been conducted within hospitals and other closed environments, in more developed countries where gonorrhoea rates are often a fraction of those in less developed countries. Almost all developing countries have been insufficiently studied, but there are some areas from which continuous data and from some countries few or no data are available. Surveillance data from several more developed countries suggest that AMR in gonococci in most developed countries is not as great a problem and often AMR which does exist is primarily imported rather than endogenous.

Status of AMR of N. gonorrhoeae in WHO-SEAR countries

South-East Asia is most likely an origin of drug resistance. Penicillinase-producing strains were first isolated in 1976 in South-East Asia, and resistance to spectinomycin and tetracycline of gonococci emerged in the 1980s. Fluoroquinolone-resistant gonococci were found in several Asian countries during the early 1990s.

GASP became functional in the SEA Region in 1997. Two regional reference laboratories (RRL), one each in India and Thailand, were identified to provide technical and material support to five countries each. The Inter-Regional Reference Laboratory, located at the WHO Collaborating Centre for Sexually Transmitted Diseases, Sydney, Australia, provides technical support, reference panels of gonococci for use in internal quality control and organizes the external quality assurance system (EQAS) for these laboratories. The WHO EQAS programme includes dispatching a set of gonococci each year as unknowns to each participating laboratory. The participating laboratories in this network conduct susceptibility testing and incorporate quality control (e.g. control panels) and participate in the EQAS programme. Participating laboratories send AMR data to
the WHO Collaborating Centre in Sydney where data are analysed. Focal point laboratories from India, Thailand, and Sri Lanka have participated in the programme since its inception. Bangladesh and Nepal participated initially and discontinued later. However, laboratories in Myanmar and Bhutan have started participating for the last few years. Effective surveillance of AMR in these countries is expected to monitor trends in established types of resistance and promptly identify new types of resistance.

India

β-lactamase producing N. gonorrhoeae was observed for the first time in Madras (Chennai), followed by detection from Bombay (Mumbai), Trivandrum (Thiruvananthapuram), Vishakhapatnam and Chandigarh14-18. The regular monitoring of antimicrobial susceptibility is being carried out at the Regional STD Teaching, Training and Research Centre in New Delhi since 1995 and this centre is functioning as a WHO-SEAR GASP Regional Reference Laboratory (RRL) since 200019-21. Surveillance data available from other centres in India (except from Pune where continuous surveillance since 1995 and AIIMS, Delhi since 2007- unpublished) are intermittent23-29. The National AIDS Control Organization along with RRL are trying to establish antimicrobial susceptibility testing for N. gonorrhoeae in all Regional STI Centres and State Reference Centres for STIs so as to monitor the trends in different regions of the country.

RRL has been conducting a country-based GASP EQAS programme in India since 2000 to evaluate the quality of the AMR testing data and assess the network capability to detect newly emerging AMR30. AMR surveillance data from RRL is based on N. gonorrhoeae isolates obtained from patients attending male and female Sexually Transmitted Diseases (STD) clinics. Data of the first 14 years (Fig. 1), have documented the pattern of AMR in N. gonorrhoeae, highlighting the alarming increase in ciprofloxacin and penicillin resistance from 1995 to 20089,19-21. Ciprofloxacin resistance increased from 3.4% in 1996 to 83.3% in 2008. In 2004, it was 97.2%. Penicillinase-producing N. gonorrhoeae (PPNG) strains varied from 3.4% to 35.1% between 1996 to 2008. A rising trend was observed in the isolation of tetracycline-resistant N. gonorrhoeae (TRNG), from 1.7% in 1996 to 19.3% in 2008. Ceftriaxone less-susceptible strains were detected for the first time in 2001 from RRL20. Only nine strains (2.4%) were found to be less sensitive to ceftriaxone from 2002 to 200621. Ceftriaxone

![Fig. 1: Trend of Antimicrobial Resistance from 1996-2008 at New Delhi, India](image-url)
less-sensitive strains varied from 1.3% to 1.7% between 2002 to 2004 but an insignificant rise to 5.5% was observed in 2006. These strains almost always exhibited resistance to quinolones or quinolones and penicillin. All the strains were found to be sensitive to spectinomycin except one strain in 2002. The frequency of multiresistant isolates found (23.3%) in RRL was quite high.

The continued high prevalence of penicillin resistance up to 2003 followed by the decrease up to 2006 may reflect the loss of selective pressure from the disuse of penicillin as treatment for gonorrhoea. From 2002 to 2006, 21.2% of isolates were found to be PPNG and the results compared well with another study from north India. In contrast, Bhalla et al. and Khaki et al. in Delhi from the same STD clinic reported 8%, 11.1% and 17.3% of isolates to be PPNG in 1998, 2002 and 2007, respectively.

The increasing trend of TRNG observed in RRL may reflect ongoing selective pressure produced by the use of tetracyclines to treat other infections and its use as adjunct therapy in the syndromic management of STDs. Tetracycline resistance was observed to be 51% in another Indian city without any mention of TRNG. In contrast, Bhalla et al. and Khaki et al. from Delhi reported 28%, 2.8% and 20% of isolates as TRNG in 1998, 2002 and 2007, respectively.

The use of the quinolone group of antibiotics for the treatment of gonorrhoea has been discontinued in India for quite some time because of reported high levels of resistance. However, there were considerable differences in rates of quinolone resistance in different studies in India. All isolates were found to be susceptible to ceftriaxone, spectinomycin, cefixime and azithromycin in a study from Delhi. It is fortunate that, except for one strain, spectinomycin resistance has not been reported from RRL and other STD clinics as it is an alternative drug of choice for cases having hypersensitivity to cephalosporins. Spectinomycin is not easily available in India and this may explain the retention of efficacy of this antibiotic.

Reduced susceptibility towards ceftriaxone was also reported by some laboratories in India. However, two strains isolated from a focal point laboratory in India, showing reduced susceptibility towards ceftriaxone, could not be confirmed at the RRL, New Delhi. Ceftriaxone less-susceptible strains (unconfirmed by MIC) from other focal point laboratories were not received at the RRL for confirmation. All ten cases from RRL, having strains less susceptible to ceftriaxone, responded to treatment with ceftriaxone or cefixime. Treatment failures are documented with oral third-generation cephalosporins such as cefixime, cefdinir and cefditoren from some countries but not as yet with ceftriaxone.

Sri Lanka

PPNG strain was first detected in Sri Lanka in 1980 and routine testing of gonococcal isolates obtained from patients attending the Central STD Clinic, Colombo for PPNG was started the following year. In 1997, a systematic monitoring system for other antibiotics was established with the introduction of GASP. PPNG isolates increased from 3.4% in 1981 to 26% in 1989. However, since 1992, there was a sharp decline in PPNG with none detected in 1995. PPNG isolates were reported to be 61.5% and 52.9% in 2007 and 2008 respectively. A highly significant rise in the percentage of chromosomally mediated resistance to penicillin from 37% in 1996 to 96.8% was observed in 2000. The rest of the strains were less sensitive. Penicillin was withdrawn from use as first-line therapy for gonorrhoea and single dose quinolone therapy introduced in 1993. Occasional clinical resistance to quinolones was first detected in late 1994. Antibiotic susceptibility testing facilities for quinolones were not available routinely in the Central Laboratory of the STD/AIDS Control Programme at that time. As increasing clinical resistance began to
surface during the second quarter of 1995, antibiotic susceptibility testing for quinolones was started in June the same year. The quinolone resistance varied between 14%-50% in the third and fourth quarters of 1995\(^3\). Resistance to ciprofloxacin varied from 10.3% to 13.7% from 1996 to 1998 and showed a declining trend to 8.2% in 2000 followed by a rise to 76.5% in 2008\(^9\)\(^2\). This rapid emergence of quinolone resistance indicated that 4-fluroquinolones were no longer useful as first-line therapy for gonorrhoea in Sri Lanka. Cefuroxime axetil 1 gm orally is the recommended treatment since 1996. No ceftriaxone less-susceptible and spectinomycin-resistant strains were isolated till 2008\(^9\)\(^2\). TRNG isolates were 13.5% in 1997, which decreased to 0% in 2000\(^9\)\(^2\).

**Bangladesh**

In Bangladesh, there was no established systematic antimicrobial susceptibility surveillance for N. gonorrhoeae. The national STI management guidelines recommended the use of ciprofloxacin as the first-line therapy for the treatment of uncomplicated gonococcal infection during 1997-2006. The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) had initiated antimicrobial susceptibility monitoring for N. gonorrhoeae in Dhaka, the capital of Bangladesh, since 1997, and it was subsequently (1999-2003) extended to three major cities (Chittagong, Jessore, and Sylhet), in the southeast, southwest and northeast parts of Bangladesh respectively and later to Faridpur, Barisal and Mymensingh in 2005\(^3\)\(^4\)\(^5\)\(^6\)\(^7\). The programme was part of the STI service-delivery programme established by ICDDR,B. In total, 1,767 N. gonorrhoeae isolates were tested from males and females (population with high-risk behaviour i.e. street-based, brothel-based, hotel-based female sex workers, male having sex with male (MSM) population, male truckers, STI patients and the general population) during 1997-2006.

Approximately 9% of the isolates in 1997 were observed to be resistant to ciprofloxacin compared to 87% in 2006 with the highest (92%) resistance in 2003. All the isolates were susceptible to ceftriaxone except that 1.0% strains in 1997 and 1.5% in 2000 were having reduced susceptibility to ceftriaxone\(^9\)\(^2\). All the isolates were also susceptible to azithromycin (MIC of \(\leq 1\) \(\mu\)g/mL), and spectinomycin, except that one isolate (0.2%) in 2002 and one each isolate in 2003, 2005, and 2006 were resistant to azithromycin and spectinomycin respectively\(^9\)\(^2\). Although most isolates were susceptible to azithromycin, a gradual increase in MIC of azithromycin was observed during 2003-2006. While none of the isolates had an MIC of \(\geq 0.25\) \(\mu\)g/mL in 1997, approximately 25% of the isolates from 2003 had an MIC of \(\geq 0.25\) \(\mu\)g/mL for azithromycin. No significant difference in resistance was observed among isolates collected from different populations and cities in a given year. Approximately 14% of the isolates were PPNG in 1997 compared to 44% in 2006. Of the isolates from 1997, 20% were TRNG compared to 86% in 2006. None of the isolates was both PPNG and TRNG in 1997 and 1998 compared to 42% in 2006. Multidrug-resistant N. gonorrhoeae emerged in 1997, and 44% of the strains isolated during 2006 were multidrug-resistant. Of the multidrug-resistant isolates, none was both PPNG and TRNG in 1997 and 1998, and 83% of the isolates were both PPNG and TRNG in 2006\(^9\)\(^2\).

Based on the above surveillance data, the National AIDS and STD Programme, Ministry of Health and Family Welfare, Government of Bangladesh, revised the national guidelines for the management of STIs in 2007 and recommended cefixime as the first-line therapy for gonorrhoea\(^9\)\(^2\).

**Thailand**

Spectinomycin became the primary therapeutic drug for the treatment of gonorrhoea in Thailand in 1983 following a
series of studies which documented PPNG rates of up to 71%. Five years later (1987 and 1988), in a survey of patients with STDs in Bangkok, Cholburi, Chiangmai, and Songkhla, none of 3,200 N. gonorrhoeae isolates was spectinomycin resistant. However, in a study on the 333 isolates from STD patients attending public health clinics in Bangkok and Cholburi in 1990, 8.9% were reported to be spectinomycin resistant. A total of 70% of isolates were resistant to tetracycline and 28.2% were PPNG. Fewer than 1.5% of isolates were resistant to the extended-spectrum cephalosporins tested. Some 0.3% or fewer isolates were resistant to broad-spectrum cephalosporins, fluoroquinolones, or the monobactam aztreonam. Therefore, norfloxacin, ciprofloxacin, ofloxacin, spectinomycin, ceftriaxone, and ceftaxime were recommended for the treatment of uncomplicated gonorrhoea in 1994.

In 1994, out of 101 isolates from patients attending the Bangrak STD clinic in Bangkok, 89.1% were resistant to penicillin or tetracycline. A total of 7.9%, 17.8%, and 7.9% were reported to be TRNG, PPNG and PPNG/TRNG respectively. More than one half (52.3%) of strains were chloramphenicol resistant N. gonorrhoeae (CMRNG). All strains were susceptible to spectinomycin. Approximately, one fifth (21.8%) of all strains exhibited decreased susceptibility to fluoroquinolones and resistance to norfloxacin; these strains included strains exhibiting chromosomally mediated resistance to tetracycline (TetR), CMRNG, and PPNG strains. More than 75% of strains exhibited decreased susceptibility to kanamycin and thiamphenicol; 21% were resistant to kanamycin.

The prevalence of ciprofloxacin-resistant (CipR) strains in Bangkok increased substantially in the 1990s. Trees et al. reported in 1998 and 1999, that CipR strains increased from 13.8% in 1998 to 25.4% in 1999. Because of the high level of CipR isolates at Bangrak Hospital, in 2000, the Thai Ministry of Public Health issued recommendations against the use of fluoroquinolones for the treatment of gonococcal infection in Thailand. Third generation cephalosporins and spectinomycin are recommended for treatment since then.

Lawung et al. reported the elevated trend of antimicrobial resistance from Bangrak hospital, Bangkok (National Centre for Sexually Transmitted Infections) during 2000-2002. The PPNG isolates increased significantly from 50.7% in 2000 to 87.9% in 2002. The ciprofloxacin resistance also increased from 28% during 2000 to 56% during 2002. In addition, there was a positive correlation between the susceptibility to ciprofloxacin and ofloxacin in all strains tested. All isolates were susceptible to ceftriaxone. The incidence of double resistance determinants, penicillin and quinolone resistance, were significantly increased from 34.3% in 2000 up to 77.3% in 2002. In addition, a PPNG and norfloxacin resistant isolate obtained in 2002 was resistant to spectinomycin with a high MIC (>1.024 g/L).

In a study on 122 gonococcal isolates from HIV-positive male and female STD patients (including CSWs 22.1%), during June 2005 to May 2007, none of the isolates was susceptible to penicillin or tetracycline. Among the 122 isolates, 83.6% were PPNG, and most (79.5%) of these 122 isolates were further identified as PPNG plus TRNG, with only 4.1% being PPNG alone. With respect to fluoroquinolones, 90.2% and 91% of the isolates were resistant to ciprofloxacin and ofloxacin respectively, much higher than previously reported. No gonococcal isolate with resistance to cefotaxime and ceftriaxone was detected. Recently, 66.9% and 75.6% of strains were reported to be quinolone resistant and 86% and 80.8% as PPNG in 2007 and 2008 respectively.
Nepal

Specific data on the incidence of gonorrhoea and AMR of *N. gonorrhoeae* in Nepal is lacking. A report based only on nine isolates in 2001 showed four as PPNGs, four TRNGs, and only one isolate resistant to ciprofloxacin. No resistance was reported to ceftriaxone and spectinomycin.

In 2001, National STI case management guidelines in Nepal recommended a single oral dose of 500 mg ciprofloxacin as first-line therapy for the management of uncomplicated gonococcal infection. A pilot study was conducted to assess the effectiveness of this recommendation. In this pilot study, a total of 16 gonococcal isolates isolated from symptomatic and asymptomatic males and females attending an STI service delivery clinic in Eastern Nepal were tested for antimicrobial susceptibility testing between May and September 2003. Among the isolates, two (12.5%) were resistant to penicillin, including one PPNG isolate; eight (50%) were resistant to tetracycline, including one TRNG; 14 (87.5%) were resistant to ciprofloxacin; and three (19%) exhibited reduced susceptibility to azithromycin. All isolates were susceptible to ceftriaxone, cefixime, and spectinomycin. Six ciprofloxacin-resistant isolates had chromosomally mediated resistance to tetracycline and one had chromosomally mediated resistance to penicillin.

Limited data from these two studies demonstrate the need for continuous monitoring of antimicrobial susceptibility of *N. gonorrhoeae* in Nepal to revise the national STI case management guidelines for treatment of *N. gonorrhoeae*.

Bhutan and Myanmar

Antimicrobial resistance data from Myanmar are available from one recent report on antibiotic surveillance in WHO-WPR and SEAR countries. Data for Myanmar are based on only 12 isolates in 2008. Out of 12 isolates, 10 were reported to be penicillin resistant, including two PPNG strains. Four and six strains were observed to be resistant and less susceptible to quinolones respectively.

In Bhutan, JDW National Referral Hospital started surveillance of AMR in 2008 in a systematic way. All the 161 isolates were found to be resistant to penicillin and 95% resistant to quinolones in 2008. Susceptibility testing for spectinomycin and tetracycline is also being carried out at this centre. However, data are not mentioned in the above report.

Conclusion

The present review indicates that high rates of penicillin, tetracycline and quinolone resistance have been detected in all countries of the SEA Region. Reduced susceptibility to third-generation cephalosporins used at present as first-line therapy, although rare, has been reported from some SEAR countries. Therefore, AMR surveillance should be continuous in order to reveal the emergence of new resistant strains, to monitor the changing patterns of resistance, and to be able to update treatment recommendations so as to assist in disease control. The factors such as unregulated drug availability, antimicrobial misuse, inadequate antimicrobial drug quality assurance and inadequate surveillance must be addressed to permit a holistic strategy for resistance control. WHO has already started making elaborate plans for a response to the threat of untreatable gonococcal infections.
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