Gonococcal antimicrobial resistance
in the Western Pacific Region

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Introduction

The most recent World Health Organization (WHO) data estimate that 35.2 million new gonorrhoea infections occur in the Western Pacific Region annually, representing approximately 40% of the global burden of new gonorrhoea infections *(1)*.

Gonorrhoea is caused by infection with the bacterium *Neisseria gonorrhoeae*. Therefore, effective antibiotic treatment is a key component of strategies for gonorrhoea disease control and prevention. Over time, *N. gonorrhoeae* has developed antibiotic resistance[a] to each successive therapeutic recommendation, leaving limited options for treatment and raising high-level concerns for the future management of this infection.

WHO has defined criteria for decreased susceptibility to cephalosporin antibiotics and defined *N. gonorrhoeae* treatment failure (Box 1 and 2). The emergence of antimicrobial resistance (AMR)[b] presents a threat to global health security. In 2013, the United States Centers for Disease Control and Prevention (CDC) elevated the threat level of antibiotic-resistant *N. gonorrhoeae* to urgent *(2)*, and in September 2016, global leaders met to address the seriousness of the situation at the United Nations General Assembly. The WHO Gonococcal Antimicrobial Surveillance Programme (GASP) for the Western Pacific Region has been monitoring gonococcal AMR in the Region since 1992.

Gonococcal AMR in the Western Pacific Region – the current situation

Over time, antibiotics from four classes – penicillins, tetracyclines, fluoroquinolones and cephalosporins –have been sequentially recommended as first-line treatment for gonorrhoea, with changes in recommendations driven by the emergence and persistence of resistance.

Resistance to penicillin and tetracycline was first reported in the United States of America and Europe *(3)* and is now highly prevalent worldwide with few exceptions. Resistance to fluoroquinolone was widespread in countries and areas in the Western Pacific Region by the 1990s *(3)*. More recently, ceftriaxone-resistant strains of *N. gonorrhoeae* have been reported in Japan and Australia *(4)*, and globally there have been increasing reports of *N. gonorrhoeae* resistance to azithromycin *(5–7)*. The H041 strain of *N. gonorrhoeae* that is resistant to extended spectrum cephalosporins was isolated in Japan in 2009 *(8, 9)*, and the genetically similar A8806 strain was identified in Australia in 2013. Today, ciprofloxacin and penicillin resistance is widespread in most countries and areas in the Western Pacific Region, with the exception of remote parts of Australia and New Caledonia, and isolates with decreased susceptibility to ceftriaxone and azithromycin (Table 1) are widely reported.

[a] Antibiotic resistance occurs when bacteria change in response to the use of these medicines.

[b] Antimicrobial resistance (AMR) is the ability of a microorganism (like bacteria, viruses, and some parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it. As a result, standard treatments become ineffective, infections persist and may spread to others.

Key messages:

1. Ciprofloxacin, tetracycline and penicillin resistance is highly prevalent in the Western Pacific Region with the exception of remote areas in Australia and New Caledonia.
2. *Neisseria gonorrhoeae* isolates with decreased susceptibility to ceftriaxone and azythromycin are widely reported.
3. Increasing the coverage of antimicrobial resistance (AMR) surveillance in the Western Pacific Region is critical to inform treatment guidelines and to monitor AMR.

Box 1. WHO criteria for decreased susceptibility to cephalosporin antibiotics

Drug	MIC (mg/l)*
Cefixime	≥0.25
Ceftriaxone	≥0.125

MIC, minimum inhibitory concentration.
* The MIC break points for cephalosporins for AMR in *N. gonorrhoeae* have yet to be established. The MIC break-point values used in the case definitions are established by using inputs from expert microbiologists, based on laboratory observations.
Source: Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2012.

Box 2. Case definition of *N. gonorrhoeae* cephalosporin treatment failure

A person who has received appropriate treatment for gonococcal infection with one of the recommended cephalosporin regimens (for example, ceftriaxone or cefixime).

AND

One of the following positive tests for *N. gonorrhoeae*:

- the presence of intracellular Gram-negative cocci on microscopy taken at least 72 hours after completion of treatment; or
- isolation of *N. gonorrhoeae* by culture taken at least 72 hours after completion of treatment; or
- a positive nucleic acid amplification test taken 2–3 weeks after completion of treatment.

AND

No history of sexual contact reported during the post-treatment follow-up period.

Source: Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2012.

Table 1. Gonococcal AMR in selected countries and areas in the Western Pacific Region, 2015

GASP participating countries and areas	Ceftriaxone % (range)	Azithromycin % (range)	Penicillin % (range)	Ciprofloxacin % (range)
Australia - Urban	0.1–5	0.1–5	16–30	16-30
Australia - Remote	0	0	0.1–5	0.1–5
China	6-15	16-30	71-100	71-100
China, Hong Kong SAR	0.1–5	6-15	31–70	71–100
Japan	16–30	16–30	31–70	71–100
Mongolia	N/A	6–15	31–70	31–70
New Caledonia	N/A	NA	0.1–5	6–15
New Zealand	0.1–5	0.1–5	16–30	31–70
Philippines	0	0	71–100	71–100
Republic of Korea	16–30	0	71–100	71–100
Singapore	0	0.1–5	31–70	71–100
Viet Nam	NA	0	31–70	71–100

NA, not available

Source: WHO Collaborating Centre for Sexually Transmitted Diseases, New South Wales Health Pathology East, The Prince of Wales Hospital, Sydney, Australia. Data reported by 23 laboratories from 11 countries which are listed under Acknowledgements.

Responses to gonococcal AMR in the Western Pacific Region

AMR surveillance is the key strategy used to monitor the impact and spread of gonococcal resistance. The WHO GASP in the Western Pacific Region has documented the emergence and spread of gonococcal AMR since 1992. In 2015, the network, from which the WHO Collaborating Centre for Sexually Transmitted Diseases in Sydney, Australia collated and reported antimicrobial susceptibility testing data, included 23 laboratories in 11 Western Pacific Region countries: Australia, China, Hong Kong SAR (China), Japan, Mongolia, New Caledonia, New Zealand, the Philippines, the Republic of Korea, Singapore and Viet Nam (Table 1). A total of 9298 clinical *N. gonorrhoeae* isolates were collected and tested for AMR.

The WHO Collaborating Centre in Sydney provides GASP laboratories in the Western Pacific and South-East Asia regions with technical support and advice, consumables for antimicrobial susceptibility testing and the WHO *N. gonorrhoeae* control strain panel for quality control. It also coordinates the external quality assurance programme of WHO GASP in the Western Pacific Region. The WHO Collaborating Centre in Sydney welcomes new laboratories to participate in GASP, which is also a component of the WHO Global Antimicrobial Resistance Surveillance System (GLASS)[c].

From 2012 to 2015, as part of the WHO Global GASP objective to obtain more and better-quality regionally derived data on AMR of *N. gonorrhoeae* from all WHO regions, the WHO Collaborating Centre in Sydney conducted a study to collect minimum inhibitory concentration (MIC) data for ceftriaxone, which remains the primary treatment recommended in most countries in this Region.

[c] Global Antimicrobial Resistance Surveillance System (GLASS) at http://www.who.int/antimicrobial-resistance/global-action-plan/surveillance/glass/en/

WHO in the Western Pacific Region monitors and supports the implementation of the new WHO gonorrhoea treatment guidelines released in 2016 (Table 2) *(10)*. Only a few countries have updated their national sexually transmitted infection (STI) treatment guidelines in line with WHO recommendations.

Challenges and next steps

The threat of emergence of resistance to cephalosporins is of great concern as there are limited alternative treatment options for gonorrhoea. Gaps in surveillance data limit the understanding of the epidemiology of gonococcal AMR. There are limited or no AMR data available from some countries for manifold reasons including syndromic management (therefore no antibiotic susceptibility testing), lack of capacity and/or resourcing for antibiotic susceptibility testing, limited access to laboratories and services, and the use nucleic acid amplification tests by preference or necessity in place of culture for detection of gonorrhoea. Further, with regard to management, many Member States are lower middle-income countries, and the supply of antibiotics, and adherence to recommended guidelines, are subject to challenges in resourcing and national policy. Only a few countries are on track in adopting new WHO treatment recommendations.

As comprehensive data on gonococcal AMR are necessary for planning and resource allocation, both materially and technologically, increasing the coverage of WHO GASP in the Western Pacific Region is a priority. In addition to expanding culture and MIC capability, there is a need to look to newer tests to enhance AMR surveillance. Molecular assays have been developed to detect *N. gonorrhoeae* AMR markers and implementing these can increase the evidence base for treatment guidelines, particularly in settings where culture is limited. Recent work in Australia has demonstrated the efficacy and impact of these assays in remote settings *(11, 12)*.

AMR data are urgently needed to respond to changes in resistance patterns and to inform the management guidelines. In line with GLASS, WHO has embarked on the development of standardized drug resistance surveillance protocols in selected countries. Exploring substitutes for the extended spectrum cephalosporin antibiotics as first-line treatment for this infection is on the global health and research agenda. Increasing the coverage of AMR surveillance in the Western Pacific Region is critical to inform treatment guidelines and to monitor AMR. Strengthening coverage and reach of primary prevention strategies continues to be an essential public health priority.

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Table 2. Recommendations for treatment of uncomplicated gonorrhoea in 12 Western Pacific Region countries (Last update September 2017)

Country	First-line treatment	Alternative treatments	Year
Australia *(13)*	Ceftriaxone 500 mg, IM single dose plus azithromycin 1 g, PO single dose	Alternative treatments are not recommended because of high levels of resistance EXCEPT for some remote Australian locations and severe allergic reactions. Clinicians are advised to seek local specialist advice.	2014
Cambodia *(14)*	Cefixime 400 mg, PO single dose plus azithromycin 1 g single dose Ceftriaxone 250 mg, IM single dose plus azithromycin 1 g, PO single dose		Ongoing revision in 2017
China *(15)*	Ceftriaxone 250 mg, IM single dose Spectinomycin 2 g, IM single dose	Cefotaxime 1 g, IM single dose	2013
China, Hong Kong SAR *(16)*	Ceftriaxone 250 mg, IM single dose	Spectinomycin 2-4 g[a], IM single dose Azithromycin 2 g[b], PO single dose	2011
Fiji *(17)*	Amoxicillin 2.5 g plus amoxicillin/clavulanic acid 625 mg plus probenecid 1 g, PO single dose		2011
Japan *(18)*	Ceftriaxone 1 g, IV single dose	Spectinomycin 2 g, IM single dose	2016
Lao People's Democratic Republic *(19)*	Ceftriaxone 250 mg, IM single dose plus azithromycin 1 g, PO single dose	Cefixime 400 mg, PO single dose plus azythromycin 1 g, PO single dose	Ongoing revision in 2017
Malaysia *(20)*	Ceftriaxone 250 mg, IM single dose Cefixime 400 mg, PO single dose	Cefotaxime 500 mg, IM single dose Spectinomycin 2 g, IM single dose	2008
New Zealand *(21)*	Ceftriaxone 500 mg, IM single dose plus azithromycin 1 g, PO single dose		2017
Philippines *(22)*	Ceftriaxone 250 mg, IM single dose	Cefixime 400 mg, PO single dose	2010
Singapore *(23)*	Ceftriaxone 500 mg, IM single dose plus azithromycin 1-2 g, stat or doxycycline 100 mg, BID x 1-2 weeks	Cefotaxime 1 g, IM single dose plus azithromycin 1-2 g single dose or doxycycline 100 mg, PO BID x 1-2 weeks Spectinomycin 2 g, IM single dose plus azithromycin 1-2 g single dose or doxycycline 100 mg, PO BID x1-2 weeks Azithromycin 2 g single dose (not as monotherapy) Aztreonam 1 g, IM single dose plus azithromycin 1-2 g single dose or doxycycline 100 mg, PO BID x 1-2 weeks	2013
Tonga *(24)*	Ciprofloxacin 500 mg, PO single dose plus azithromycin 1 g, PO single dose	Ciprofloxacin 500 mg, PO single dose plus doxycycline 100 mg, PO BID x 7 days Amoxicillin 2.5 g, PO single dose plus augmentin 500 mg, PO single dose	2008
Tuvalu *(25)*	Amoxycillin 2-3 g plus/minus amoxicillin/clavulanic acid 500 mg–1 g Amoxycillin 2-3 g plus probenecid 1 g, PO single dose	Ciprofloxacin 500 mg, PO single dose	2010

IM, intramuscular; IV, intravenous; PO, per os (orally); OD, once daily; BID, twice daily; stat, immediately; g, gram; mg, milligram

Notes: [a] Spectinomycin is NOT registered in Hong Kong SAR (China) but can be accessed via a local system of "named patient base". [b] Treatment depends on culture and sensitivity result given that ~ 10% and 20% of the local strains are resistant to azithromycin in Hong Kong SAR (China) respectively. [c] Ciprofloxacin was recommended when resistance testing was available in New Zealand.

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