Review of national treatment guidelines for sexually transmitted infections in the Western Pacific Region

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Key facts

- Among 37 countries and areas in the Western Pacific Region, at least 26 have sexually transmitted infection (STI) guidelines. Of those, 11 Pacific island countries have adopted the 2016 WHO STI guidelines.
- For treatment of gonococcal infections, among 26 countries and areas that have developed STI guidelines, 19 recommend dual therapy with either ceftriaxone or cefixime plus azithromycin. Five countries recommend single therapy either with ceftriaxone or cefixime. With regard to dosage of ceftriaxone, seven countries recommend 500 mg or higher dosage.
- Increased coverage of antimicrobial resistance surveillance for *Neisseria gonorrhoeae* in the Region is needed to inform treatment regimens.
- Almost all countries recommend intramuscular benzathine penicillin G as the first-line regimen for treatment of syphilis. However, stock-out of the drug is reported in several countries in the Region.

Introduction

The most recent data produced by the World Health Organization (WHO) show that annually there were 215 million new cases of chlamydia, gonorrhoea and syphilis among people aged 15–49 years *(1)*. In particular, the number of the new cases was estimated to be largest in the Western Pacific Region in 2012 (97 million: i.e. chlamydia 61 million, gonorrhoea 35 million and syphilis 1 million, respectively) *(1)*. The Western Pacific had the second largest burden of herpes simplex virus (HSV)-2 infection after the African Region, both for incidence and prevalence, in 2012 (3.7 million new cases and 81.2 million with infection, respectively) *(2)*.

The *Global Health Sector Strategy on Sexually Transmitted Infections* (STIs) highlights several important public health issues. These include the rising risk of untreatable gonorrhoea with high-level antimicrobial resistance (AMR) and elimination of mother-to-child transmission of syphilis *(3)*. To achieve the goals set in the Global Health Sector Strategy, WHO guidelines for the treatment of four STIs (*Chlamydia trachomatis, Neisseria gonorrhoeae, Treponema pallidum* and genital HSV) were updated in 2016.

The aims of this fact sheet are to review treatment guidelines for these four STI in the Western Pacific Region in accordance with the 2016 WHO STI guidelines and to describe the situation regarding the treatment of STIs in this Region. The most up-to-date STI guidelines for each country were obtained through WHO country offices and through online searches. Ministries of health were contacted to verify the information, where necessary.

STI guidelines in the Region

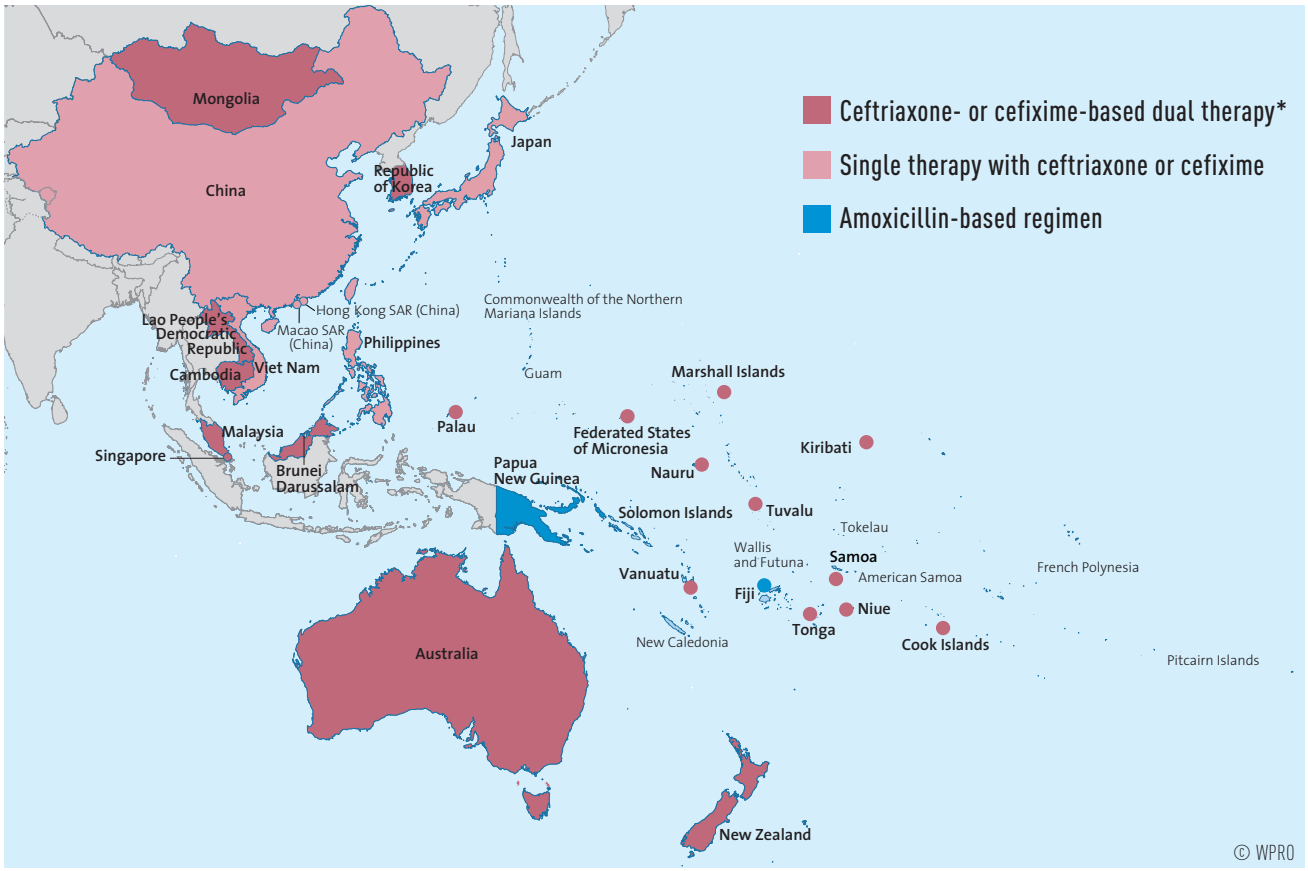
Among 37 countries and areas in the Western Pacific Region, at least 26 have developed STI guidelines. Of those, 11 Pacific island countries and areas (Cook Islands, Kiribati, Marshall Islands, Federated States of Micronesia, Nauru, Niue, Palau, Samoa, Tonga, Tuvalu and Vanuatu) have adopted the 2016 WHO STI guidelines. For all those countries and areas, we reviewed the first-line and alternative regimens for treatment of syphilis (primary/secondary/latent) and uncomplicated genital (cervix and urethra) gonococcal, chlamydial, and HSV infection.

Gonorrhoea

Ciprofloxacin and penicillin resistance is widespread in most countries and areas in the Region. Isolates with decreased susceptibility to ceftriaxone and azithromycin have also been widely reported *(4)*. In early 2018, one case of a gonorrhoea strain with resistance to ceftriaxone (minimum inhibitory concentration, or MIC = 0.5 mg/L) and high-level resistance to azithromycin (MIC > 256 mg/L), as well as to most other antimicrobials, was reported in the United Kingdom of Great Britain and Northern Ireland *(5)*. Two such strains were also reported in Australia *(6)*. Two of the three cases were travel-associated, and both acquired gonorrhoea in the South-East Asia Region. Antimicrobial susceptibility data are lacking in many countries and areas in this Region.

The 2016 WHO STI guidelines recommend dual therapy with either ceftriaxone or cefixime plus azithromycin as the first-line regimen (Table 1). This dual therapy has been adopted as the first-line regimen in 19 countries, while single therapy with ceftriaxone or cefixime has been recommended in five countries and areas. Ceftriaxone is used as the first-line regimen in all countries except Fiji and Papua New Guinea, which recommend an amoxicillin-based regimen as the first line (Figure 1). Whereas the 2016 WHO STI guidelines recommend a single dose of 250 mg intramuscular ceftriaxone injection, seven countries recommend 500 mg or higher dosage of ceftriaxone. Spectinomycin is adopted as the first-line or alternative regimen in 19 countries and areas.

FIGURE 1. Recommended regimens for uncomplicated genital gonococcal infection in countries and areas in the Western Pacific Region



Nineteen countries and areas (Australia, Cambodia, Lao People's Democratic Republic, Malaysia, Mongolia, New Zealand, Republic of Korea, Singapore, plus Cook Islands, Kiribati, Marshall Islands, Federated States of Micronesia, Nauru, Niue, Palau, Samoa, Tonga, Tuvalu, Vanuatu) recommend ceftriaxone- or cefixime-based dual therapy as the first-line regimen.

Five countries and areas [China, Hong Kong SAR (China), Japan, Philippines, Viet Nam] recommend single therapy with ceftriaxone or cefixime.

Fiji and Papua New Guinea recommend amoxicillin-based regimens.

* 11 Pacific island countries have adopted the 2016 WHO STI guidelines.

In practice, many countries lack access to diagnostic methods such as culture, antimicrobial susceptibility testing or nucleic acid amplification tests (NAATs). Hence presumptive treatment based on syndromic management is commonly practised. More data on AMR for *N. gonorrhoeae* in the Western Pacific Region are required to inform treatment and contain the emergence of further antimicrobial-resistant strains. Considering that drug-resistant strains for ceftriaxone and azithromycin, as well as other antimicrobials, have emerged, the development of new antimicrobials effective for *N. gonorrhoeae* is also a priority.

Syphilis

Surveillance data for syphilis are not always available in all countries in this Region. However, the reported number of syphilis cases is increasing in several countries, including Australia, Japan, New Zealand and the Republic of Korea *(7,8,9)*. Particularly in Japan, the number of reported syphilis cases in 2017 was nine times higher than that in 2010 *(7)*.

The 2016 WHO STI guidelines recommend intramuscular benzathine penicillin G (BPG) as the first-line regimen and procaine penicillin, doxycycline, ceftriaxone, azithromycin and erythromycin as the alternative regimens (Table 2). BPG is used as the first-line regimen in all countries and areas except Japan. BPG is also the only WHO-recommended regimen for pregnant women to prevent mother-to-child transmission of syphilis. However, many countries in this Region, including Australia, Cambodia, New Zealand and the Philippines, experienced stock-outs of BPG between 2014 and 2016 *(10)*. To avoid stock-outs of BPG, stable supply and procurement need to be ensured *(10)*.

Doxycycline is the most common alternative regimen, followed by erythromycin and ceftriaxone, which are recommended in 23, 21 and 19 countries and areas, respectively. Azithromycin is recommended in 16 countries. The duration of treatment for regimens other than BPG is approximately two weeks for early syphilis and four weeks for late syphilis.

Treatment for syphilis can be challenging for patients with penicillin allergy, and particularly for pregnant women. Evidence is limited for treatment efficacy of alternative regimens such as ceftriaxone, erythromycin and doxycycline *(11)*. Also, doxycycline is contraindicated for pregnant women because of possible teratogenicity, and resistance to azithromycin has been reported in some strains of *T. pallidum (11)*.

Chlamydia

Since chlamydia infection is asymptomatic in most cases (male 50%; female 70%) and is related to serious complications in reproductive health, such as infertility, ectopic pregnancy, preterm birth and low birthweight *(12)*, proper diagnosis and treatment are critical.

The 2016 WHO STI guidelines recommend azithromycin or doxycycline as the first-line regimens (Table 3). All 26 countries and areas have adopted azithromycin as the first-line regimen, and in 24 countries doxycycline is the first-line or alternative regimen. There is a wide variety of alternative regimens. Erythromycin (including erythromycin ethyl succinate) and ofloxacin are alternative regimens in 19 countries. With regard to regimens not recommended in the 2016 WHO STI guidelines, some quinolones (levofloxacin, spalfloxacin, moxifloxacin, tosfloxacin, sitafloxacin) and macrolides (clarithromycin, erythromycin ethyl succinate, roxythromycin, josamycin) are recommended as alternative regimens in some countries.

Genital herpes simplex virus

HSV-2 is the most common cause of genital ulcers. This infection is of particular concern due to its epidemiological synergy with HIV infection and transmission. People infected with HSV-2 are approximately three times more likely to be infected with HIV, and people with both HIV and genital HSV are more likely to transmit HIV to others *(14)*. Although rare, neonatal HSV infection has high morbidity and mortality *(15,16)*.

There are only three drugs (aciclovir, valaciclovir and famciclovir) recommended in the 2016 WHO STI guidelines for treatment of genital herpes (Table 4) *(17)*. Although the benefits of these medicines are probably similar, WHO guidelines recommend aciclovir over valaciclovir and famciclovir, due to its low cost. Aciclovir is recommended as the first-line regimen in all countries and areas except Australia and New Zealand, where valaciclovir is the only first-line regimen. However, all countries have adopted regimens that are included in the 2016 WHO STI guidelines as the first-line or alternative regimen, and only slight differences in treatment duration are observed among these countries and areas.

Conclusion

STI treatment guidelines in countries in the Region are generally in line with the 2016 WHO STI guidelines. However, continued efforts are needed to collect local resistance data and adopt optimal regimens based on the updated surveillance data in each country. This especially applies to gonococcal infection, highly resistant strains of which are reported in this Region. There is also a need for an effective alternative regimen for syphilis in people with penicillin allergy, and especially for pregnant women. Strengthening of the existing surveillance system, including collaboration and integration of surveillance data across the Region, is needed to understand more fully the epidemiology of STIs to inform treatment guidelines in this Region.

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TABLE 1. Recommended regimens for treatment of **uncomplicated genital gonococcal infection** in 26 countries and areas in the Western Pacific Region

COUNTRY	FIRST-LINE TREATMENT	ALTERNATIVE TREATMENT	YEAR
WHO [18] # and 11 PICs	**Ceftriaxone 250 mg IM once / Cefixime 400 mg PO once + Azithromycin 1 g PO once**	**Ceftriaxone 250 mg IM once Cefixime 400 mg PO once Spectinomycin 2 g IM once**	**2016**
Australia [19]	Ceftriaxone 500 mg IM once + Azithromycin 1 g PO once	NA	2018
Cambodia [20]	Ceftriaxone 250 mg IM once / Cefixime 400 mg PO once + Azithromycin 1 g PO once	Ceftriaxone 500 mg IM once / Cefixime 800 mg PO once + Azithromycin 2 g PO once	2018 §
China [21]	Ceftriaxone 500 mg IM once / Spectinomycin 2–4 g IM once	Cefixime 400 mg PO once / Cefotaxime 1 g IM once	2014
Fiji [22]	Amoxicillin 2.5 g PO once + Amoxicillin-Clavulanate 625 mg PO once + Probenecid 1 g PO once	Ceftriaxone 250 mg IM once	2011
Hong Kong SAR (China) [23]	Ceftriaxone 250 mg IM once	Spectinomycin 2–4 g IM once	2017
Japan [24]	Ceftriaxone 1 g IV once	Spectinomycin 2 g IM once	2016
Lao People's Democratic Republic [25]	Ceftriaxone 250 mg IM once / Cefixime 400 mg PO once + Azithromycin 1 g PO once / Doxycycline 100 mg bid 7 d	NA	2018 §
Malaysia [26]	Ceftriaxone 500 mg IM once + Azithromycin 1 g PO once	Cefixime 400 mg PO once Cefotaxime 500 mg IM once Spectinomycin 2 g IM once	2015
Mongolia [27]	Ceftriaxone 250 mg IM once / Cefixime 400 mg PO once / Spectinomycin 2 g IM once / Cephalosporins group antibiotics injection once + Azithromycin 1 g PO once / Doxycycline 100 mg PO bid 7 d	NA	2017
New Zealand [28]	Ceftriaxone 500 mg IM once + Azithromycin 1 g PO once	NA	2017
Papua New Guinea* [29]	Amoxicillin 2 g PO once + Amoxicillin-Clavulanate 1250 mg PO once + Probenecid 1 g PO once + Azithromycin 1 g PO once	NA	2018 §
Philippines [30]	Ceftriaxone 250 mg IM once / Cefixime 400 mg PO once	Spectinomycin 2 g IM once	2018 §
Republic of Korea [31]	Ceftriaxone 500 mg/1 g IV/IM once / Spectinomycin 2 g IM once + Azithromycin 1 g PO once	NA	2016
Singapore [32]	Ceftriaxone 500 mg IM once + Azithromycin 1–2 g PO once / Doxycycline 100 mg PO bid 7–14 d	Cefotaxime 1 g IM once / Spectinomycin 2 g IM once / Aztreonam 1 g IM once + Azithromycin 1–2 g PO once / Doxycycline 100 mg PO bid 7–14 d / Azithromycin 2 g PO once (not as monotherapy)	2013
Viet Nam [33]	Ceftriaxone 250 mg IM once Cefixime 400 mg PO once	NA	2015

#: WHO STI guideline recommends that local resistance data should determine the choice of therapy (both for dual and single therapy). In settings where local resistance data are not available, the WHO STI guideline suggests dual therapy over single therapy for people with genital gonorrhoea.

NA: not available

bid: twice daily – **d:** day – **IM:** intramuscularly – **IV:** intravenously – **PO:** orally

PICs: Pacific island countries and areas – ***:** for urethral discharge syndrome – **§:** ongoing revision

TABLE 2. Recommended regimens for treatment of syphilis in 26 countries and areas in the Western Pacific Region

COUNTRY	FIRST-LINE TREATMENT			ALTERNATIVE TREATMENT			YEAR
	REGIMENS	EARLY §1	LATE §1	REGIMENS	EARLY §1	LATE §1	
WHO [11] and 11 PICs	**Benzathine penicillin G 2.4 MU IM**	**Once**	**/w 3 w**	**Procaine penicillin G 1.2 MU IM** **Doxycycline 100 mg PO bid** **Ceftriaxone 1 g IM qd** **Azithromycin 2 g PO** **Erythromycin 500 mg PO qid**	**10–14 d** **14 d** **10–14 d** **Once** **14 d**	**20 d** **30 d** **NA** **NA** **30 d**	**2016**
Australia [19]	Benzathine penicillin G 1.8 g IM	Once	/w 3 w	Procaine penicillin G 1.5 g IM Doxycycline 100 mg PO bid	10 d 14 d	15 d 28 d	2018
Cambodia [20]	Benzathine penicillin G 2.4 MU IM Procaine penicillin G 1.2 MU IM	Once 10–14 d	/w 3 w NA	Doxycycline 100 mg PO bid Ceftriaxone 1 g IM qd Erythromycin 500 mg PO qid	14 d 10–14 d 14 d	30 d NA 30 d	2018 §3
China [21]	Benzathine penicillin G 2.4 MU IM Procaine penicillin G 0.8 MU IM	/w 2 w 15 d	/w 3 w 20 d	Doxycycline 100 mg PO bid Tetracycline 500 mg PO qid Ceftriaxone 0.25–0.5 g IM qd Erythromycin 500 mg PO qid	15 d 15 d 10 d 15 d	30 d 30 d NA 30 d	2014
Fiji [22]	Benzathine penicillin G 2.4 MU IM	Once	/w 3 w	Doxycycline 100 mg PO bid Erythromycin 500 mg PO qid	14 d 14 d	30 d 14 d	2011
Hong Kong SAR (China) [23]	Benzathine penicillin G 2.4 MU IM	/w 2 w	/w 3 w	Doxycycline 100 mg PO bid	2–4 w	NA	2017
Japan [24]	Benzylpenicillin benzathine 0.4 MU PO tid Amoxicillin 500 mg PO tid	2–4 w* 4–8 w**	8–12 w	Doxycycline/minocycline 100 mg PO bid Acetylspiramycin 200 mg PO 6 times/d	2–4 w* 4–8 w**	8–12 w	2016
Lao People's Democratic Republic [25]	Benzathine penicillin G 2.4 MU IM Procaine penicillin G 1.2 MU IM	Once 10–14 d	/w 3 w 20 d	Doxycycline 100 mg PO bid Ceftriaxone 1 g IM qd Azithromycin 2 g PO Erythromycin 500 mg PO qid	14 d 10–14 d Once 14 d	30 d NA NA 30 d	2018 §3
Malaysia [26]	Benzathine penicillin G 2.4 MU IM Procaine penicillin G 0.6 MU IM	Once 10 d	/w 3 w 17 d	Doxycycline 100 mg PO bid Ceftriaxone 0.5 g IM qd Azithromycin 2 g PO Erythromycin 500 mg PO qid Erythromycin ethylsuccinate 800 mg PO qid	14 d 10 d Once 14 d 14 d	28 d NA NA 28 d 28 d	2015
Mongolia [27]	Benzathine penicillin G 2.4 MU IM	Once*	/w 3 w***	Doxycycline 100 mg PO bid Ceftriaxone 1 g IV/IM qd Erythromycin 500 mg PO qid	14 d 10–14 d 14 d	28 d 10–14 d 30 d	2017
New Zealand [28]	Benzathine penicillin G 1.8 g IM	Once	/w 3 w	NA	NA	NA	2017
Papua New Guinea [29]	Benzathine penicillin G 2.4 MU IM	Once* /w 3 w**	NA	NA	NA	NA	2018 §3
Philippines [30]	Benzathine penicillin G 2.4 MU IM	Once	/w 3 w	Doxycycline 100 mg PO bid Ceftriaxone 1 g IM qd Azithromycin 2 g PO Erythromycin 500 mg PO qid	14 d 10–14 d Once 14 d	30 d NA NA 30 d	2018 §3
Republic of Korea §2 [31]	Benzathine penicillin G 2.4 MU IM	Once	/w 3 w	Doxycycline 100 mg PO bid Ceftriaxone 1 g IV/IM qd Azithromycin 2 g PO Erythromycin 500 mg PO qid	14 d 10–14 d Once 14 d	28 d NA NA 28 d	2016
Singapore §2 [32]	Benzathine penicillin G 2.4 MU IM Procaine penicillin G 0.6 MU IM	Once 10 d	/w 3 w 17–21 d	Doxycycline 100 mg PO bid Tetracycline 500 mg PO qid Ceftriaxone 0.5 g IM qd Azithromycin 0.5 g PO qd Erythromycin 500 mg PO qid	14 d 14 d 10 d 10 d 14 d	28 d 28 d NA NA 28 d	2013
Viet Nam [33]	Benzathine penicillin G 2.4 MU IM	Once* /w 2–4 w**	/w 4 w	Procaine penicillin G 1MU IM Benzyl penicillin G 1MU IM Tetracycline 2 g/d PO Erythromycin 2 g/d PO	15 d*/** 30 d*/** 15 d** 15 d**	15 d 30 d 15–20 d 15–20 d	2015

MU: million units – **qd:** once daily – **qid:** four times daily – **tid:** three times daily

/w 2 w: once weekly for two weeks – **/w 3 w:** once weekly for three weeks – **/w 4 w:** once weekly for four weeks – See Table 1 for other abbreviations in this table.

§ 1: Except for the Republic of Korea and Singapore, primary, secondary and early latent syphilis (< 2 years after infection) were categorized as early syphilis and late latent (> 2 years after infection) and syphilis with unknown duration was categorized as late syphilis.

§ 2: Early and late latent syphilis are defined as asymptomatic syphilis < 1 year and > 1year after syphilis infection.

§ 3: Ongoing revision.

* Treatment duration for primary syphilis – ** Treatment duration for secondary syphilis – *** Treatment duration for secondary and latent syphilis.

TABLE 3. Recommended regimens for treatment of **uncomplicated genital chlamydial infection** in 26 countries and areas in the Western Pacific Region

COUNTRY	FIRST-LINE TREATMENT	ALTERNATIVE TREATMENT	YEAR
WHO [12] and 11 PICs	**Azithromycin 1 g PO once** **Doxycycline 100 mg PO bid 7 d**	**Tetracycline 500 mg PO qid 7 d** **Erythromycin 500 mg PO bid 7 d** **Ofloxacin 200–400 mg PO bid 7 d**	**2016**
Australia [19]	Azithromycin 1 g PO once Doxycycline 100 mg PO bid 7 d	NA	2018
Cambodia [20]	Azithromycin 1 g PO once Doxycycline 100 mg PO bid 7 d Erythromycin 500 mg PO qid 7 d Ofloxacin 200–400 mg PO bid 7 d	NA	2018 §
China [21]	Azithromycin 1 g PO once Doxycycline 100 mg PO bid 7 d	Minocycline 100 mg PO bid 10 d Tetracycline 500 mg PO qid 2–3 w Erythromycin base 500 mg PO qid 7 d Roxythromycin 150 mg PO bid 10 d Clarithromycin 250 mg PO bid 10 d Ofloxacin 300 mg PO bid 7 d Levofloxacin 500 mg PO qd 7 d Spalfloxacin 200 mg PO qd 10 d Moxyfloxacin 400 mg PO qd 7 d	2014
Fiji [22]	Azithromycin 1 g PO once	NA	2011
Hong Kong SAR (China) [23]	Azithromycin 1 g PO once	Doxycycline 100 mg PO bid 7 d	2017
Japan [24]	Azithromycin 1 g PO once	Doxycycline / Minocycline 100 mg PO bid 7 d Clarithromycin 200 mg PO bid 7 d Levofloxacin 500 mg PO qd 7 d Tosfloxacin 150 mg PO bid 7 d Sitafloxacin 100 mg PO bid 7 d	2016
Lao People's Democratic Republic [25]	Azithromycin 1 g PO once / Doxycycline 100 mg PO bid 7 d + Ceftriaxone 250 mg IM once	Tetracycline 500 mg PO qid 7 d / Erythromycin 500 mg PO qid 7 d / Ofloxacin 200–400 mg PO bid 7 d + Ceftriaxone 250 mg IM once	2018 §
Malaysia [26]	Azithromycin 1 g PO once Doxycycline 100 mg PO bid 7 d	Erythromycin 500 mg PO qid 7 d Erythromycin ethyl succinate 800 mg qid PO 7d Ofloxacin 200 mg bid / 400 mg PO qd 7 d	2015
Mongolia [27]	Azithromycin 1 g PO once Doxycycline 100 mg PO bid 7 d	Erythromycin 500 mg PO qid 7 d Erythromycin ethyl succinate 800 mg qid PO 7d Josamycin 500 mg PO tid 7–10 d Levofloxacin 500 mg PO qd 7 d Ofloxacin 300 mg PO bid 7 d	2017
New Zealand [28]	Azithromycin 1 g PO once Doxycycline 100 mg PO bid 7 d	NA	2017
	Amoxicillin 2 g		