Have all important studies/evidence of which you are aware been included in the application?

Yes  [ ]  No  [x]

Please provide brief comments on any relevant studies that have not been included:

Antimicrobial resistance data are important to recommend the antibiotic therapy for STIs. Antimicrobial resistance among Neisseria gonorrhoeae and Treponema pallidum is increasingly reported and challenges to the current recommended antibiotic regimens. Thus, the existing studies relevant to antimicrobial resistance should be fully cited and the latest literatures should be included in the reference. Below are the recent relevant studies not be included:

For Neisseria gonorrhoeae, these recent studied should be considered to be included:


For Treponema pallidum, these recent studies should be considered to be included:


(2) For each of the STIs reviewed in the application, and noting the corresponding updated WHO treatment guidelines, please comment in the table below on the application’s proposal for antibiotics to be included on the EML:

(Note that some proposed antibiotics may already be included on the current EML).

<table>
<thead>
<tr>
<th>STI</th>
<th>COMMENTS (use as much space as you need)</th>
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<tbody>
<tr>
<td>Chlamydia trachomatis</td>
<td>1. Regarding azithromycin dosing, dosing for neonate chlamydial conjunctivitis is not consistent with the dosing recommendation for children 2 months to 12 years. The WHO STI guideline recommends azithromycin 20 mg/kg/day orally, one dose daily for 3 days for the treatment of neonates with chlamydial conjunctivitis. However, <strong>dosing recommendation for azithromycin is 10 mg/kg/day PO given once daily in the chapter of Antibiotic Dosing for Children: Expert Recommendations.</strong> Question arises about why neonates receive higher dose of azithromycin for the treatment of chlamydial conjunctivitis? A higher dose recommendation is based on which consideration: pharmacokinetics or better adherence of single high dose?</td>
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| Neisseria gonorrhoeae      | 1. Antimicrobial resistance in Neisseria gonorrhoeae is a public health and clinical issue. Overall, resistance to cefixime, ceftriaxone and azithromycin is at low level currently in most of regions, rates of resistance to ciprofloxacin, tetracycline and penicillin has been at high level globally. The Dual therapy with cefixime/ceftriaxone plus azithromycin is preferred over single therapy to achieve the clinical and microbiological cure.  
2. As high rate of resistance to tetracycline in Neisseria gonorrhoeae, the effectiveness of tetracycline hydrochloride 1% eye ointment for prophylaxis of gonococcal ophthalmia neonatorum could be a problem and recommendation should be reconsidered.  
3. In the section of Antimicrobial Resistance in Neisseria gonorrhoeae of page 2, the data on resistance status are general. It is better to supplement the latest global or regional data on resistance patterns in this section.  
4. In **Ceftriaxone and cefixime resistance** Unemo M of page 27, reference 2 (Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime and ceftriaxone-resistant Neisseria gonorrhoeae in France: novel penA mosaic allele in a successful international clone causes treatment failure. Antimicrob Agents Chemother. 56(3):1273-80) did not show which year the literature was published (in 2012). |
| **Treponema pallidum (syphilis)** | 1. Azithromycin and erythromycin recommendation for treatment of syphilis should be cautious due to the following facts: (1) A high prevalence of the A2058G mutation in circulating strains of T. pallidum has been reported in several areas of the USA, Canada, Europe, Sydney (84%) and China (91.9%), with an increasing frequency of the mutation over time. [Stamm LV. Syphilis: antibiotic treatment and resistance. Epidemiol Infect. 2015;143(8):1567-74.]. (2) Azithromycin treatment failures were identified in San Francisco, and samples from these individuals contained the 23S A2058G mutation [CDC. Azithromycin treatment failures in syphilis infections—San Francisco, California, 2002–2003. MMWR Morb Mortal Wkly Rep. 2004.53 (9): 197–198.]. (3) A recent study showed that azithromycin uniformly failed to cure rabbits infected with strains harboring either 23S rDNA A2058G mutation [Molini BJ, Tantalo LC, Sahi SK, et al. Macrolide Resistance in Treponema pallidum Correlates With 23S rDNA Mutations in Recently Isolated Clinical Strains. Sex Transm Dis. 2016;43(9):579-83.].  
2. Trials investigating appropriate dosages and effectiveness of ceftriaxone use for early and late syphilis are desirable because ceftriaxone is an alternative option for pregnant women and patients allergic to penicillin.  
3. The outcomes of macrolide-treated patients with syphilis should be assessed from the clinical and serological aspects. |

(3) Please frame the decisions and recommendations that the Expert Committee could make.  
a) WHO recommendations for the treatment of Chlamydia trachomatis are rational and fully accepted.  
b) The Dual therapy with cefixime/ceftriaxone plus azithromycin is preferred over single therapy to achieve the clinical and microbiological cure considering the emergence of resistance of cefixime, ceftriaxone and azithromycin among Neisseria gonorrhoeae. Recommendation of tetracycline hydrochloride 1% eye ointment for prophylaxis of gonococcal ophthalmia neonatorum should be reconsidered in terms of the high rate of resistance to tetracycline in Neisseria gonorrhoeae.  
c) Azithromycin and erythromycin recommendation for treatment of syphilis should be cautious due to a high prevalence of the A2058G mutation mediating macrolides resistance in T. pallidum and Azithromycin treatment failures identified in mutant strains in human and rats. The outcomes of macrolide-treated patients with syphilis should be assessed from the clinical and serological aspects.  

(4) References (if required)  
See above mentioned.