I.7	Inclusion of ampicillin and gentamicin on the EMLc for complicated intra-abdominal infections in neonates and children
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Community-acquired intra-abdominal infections occur in children worldwide and are caused by a variety of conditions most frequently acute appendicitis and in endemic settings intestinal perforation occurring as a complication of enteric fever. Acute appendicitis is particularly frequent in children and most cases (70%) are uncomplicated and with a very low short-term post appendectomy mortality (1%).
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Aminoglycoside-based regimens (usually gentamicin-based) and **ampicillin, in combination with gentamicin** are recommended as one of anti-infective options equally as other antibiotic regimes in the international guidelines of intra-abdominal infections and in the 2017 WHO guideline for the empiric antibiotic treatment of necrotizing enterocolitis in neonates.
Have all important studies and all relevant evidence been included in the application?	☒ Yes ☐ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included:
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). The review of systematic reviews on antibiotic treatment of complicated intra-abdominal infections yielded indeterminate results, therefore recommendations for the EMLs is based on the review of national and international guidelines. **Aminoglycoside-based regimens (usually gentamicin-based) are equally recommended as one of anti-infective options as other antibiotic regimes.** For community-acquired complicated intra-abdominal infections in children, **the 2010 IDSA recommended aminoglycoside-based regimens (gentamicin or tobramycin in combination with metronidazole or clindamycin with or without ampicillin),** a carbapenem (ertapenem, meropenem, imipenem), a beta-lactam/beta-lactamase inhibitor combination (piperacillin-tazobactam, ticarcillin-clavulanate), or advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, cefepime) plus metronidazole. With severe beta-lactam allergies, either an aminoglycoside or ciprofloxacin plus metronidazole are recommended. Additionally, 2017 the Surgical Infection Society revised the 2010 guidelines and confirmed aminoglycosides-based regimens for neonates, in particular the guidelines say "**Use ampicillin, gentamicin, and either metronidazole** or clindamycin **in pediatric patients less than one month** of age (45 weeks post-conceptional age)

	In the 2017 WHO recommendations on newborn health, the guideline specifically addresses the empiric antibiotic treatment of **necrotizing enterocolitis** in neonates and recommends the use of **ampicillin in combination with gentamicin (without metronidazole)** for 10 days which is the same empiric treatment recommended in the same guideline for neonatal sepsis. Therefore, the actual magnitude and clinical relevance of benefit associated with use of **ampicillin and gentamicin for** community-acquired complicated intra-abdominal infections in children are **evident.** Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Yes.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The harms and toxicities of gentamicin are well known and have been reviewed extensively by the Expert Committee on previous occasions. Gentamicin has been included on the EML since 1977 and on the EMLc since 2007. These antibiotics are commonly used in neonates and children and are already listed in the EMLc for other indications and the evidence of benefits (and harms and toxicity) has already been extensively revised by the EML Working Group and Expert Committee. In particular ampicillin is already listed in the EMLc as first choice for the treatment of severe community-acquired pneumonia, complicated severe acute malnutrition and sepsis (in neonates and children). Ampicillin is also listed as second choice for the treatment of acute bacterial meningitis. Gentamicin is already listed in the EMLc as first choice for the treatment of severe-community acquired pneumonia, complicated severe acute malnutrition and sepsis (in neonates and children). Gentamicin is also listed as second choice for surgical prophylaxis. Therefore, the evidence of the safety and adverse effects associated with ampicillin and gentamicin is adequate.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Gentamicin has a potential damage to renal function and hearing. Therefore, monitoring renal serum peak and trough concentration is necessary for certain group of neonatal patients. Gentamicin is contraindicated to be used in pediatric patients with significant renal dysfunction and requiring dialysis and in neonates post conceptional age <44 weeks. Use of gentamicin should be very precautious in pediatric patients with chronic ascites or serious liver disease, with known auditory or vestibular disease and with a family history of possible aminoglycoside-associated hearing impairment or loss.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The overall benefit to risk ratio of gentamicin and ampicillin treatment for the complicated intra-abdominal infections in neonates and children is favourable.

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	High.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Serum peak and trough concentrations should be monitored in patients: 1) receiving >5 days of gentamicin therapy; 2) with impaired renal function; 3) altered large volume of distribution.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Gentamicin has regulatory approval globally and is widely available.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: In Pocket book of hospital care for children: Guidelines for the management of common childhood illnesses 2013, the first-line antibiotics for treatment of meningitis are ampicillin and gentamicin for 3 weeks. In WHO recommendations on newborn health (2017): guideline for suspected neonatal sepsis and to possible serious bacterial infections, neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first line antibiotic treatment for at least 10 days. (Strong recommendation).
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Gentamicin has regulatory approval globally and is widely available. Gentamicin is a frequently prescribed antibiotics for use in neonates globally. As gentamicin is already included on the Model Lists and in many national essential medicine lists, a review of the comparative costs and cost-effectiveness has not been undertaken.
Any additional comments	None
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Aminoglycoside-based regimens (usually gentamicin-based) and ampicillin in combination with gentamicin regimen are recommended as one of anti-infective options equally as other antibiotic regimes in the international guidelines of intra-abdominal infections and in the 2017 WHO guideline for the empiric antibiotic treatment of necrotizing enterocolitis in neonates. Thus, I recommend to include ampicillin and gentamicin on the EMLc for the new indication of complicated intra-abdominal infections in neonates and children based on local resistance data.

References (if required)	