| I.6 | Proposal to extend the indications for gentamicin on the EMLc to include bacterial meningitis in neonates |
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| Does the application adequately address the issue of the public health need for the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Neonatal meningitis is found worldwide. The Global Burden of Disease (GBD) study estimated in 2016 that almost 20.000 neonates died of meningitis globally. Risk factors include among others pre-term birth, low birth weight but also maternal peripartum infections or delivery-associated risk factors such as prolonged rupture of membranes or traumatic delivery. Causative pathogens differ from those commonly found in older children and adults with infectious meningitis. In particular, Streptococcus agalactiae (group B streptococci) and Escherichia coli are those pathogens most frequently responsible for meningitis in this age group along with Listeria monocytogenes and Streptococcus pneumoniae. Streptococcus agalactiae remains the most frequent cause of neonatal meningitis despite a decline in new cases over the years in settings where maternal screening and intrapartum antibiotic prophylaxis of mothers with a positive screening test is performed as part of prenatal care. The incidence and mortality of meningitis are higher in countries with limited resources.<br>Treating neonates with suspected meningitis can prevent morbidity (high rates of neurological disabilities) and mortality at the individual level. The Global Burden of Disease study also indicates that the peak age of incident meningitis is during the neonatal period and that rates of disabilities are also highest in the youngest. In particular 5.8% of total (all ages) meningitis DALYs were attributable to low birthweight and short gestation in 2016 with the highest rates of attributable DALYs occurring in the meningitis belt countries, Burundi, Malawi, Somalia, Zambia, and Afghanistan. All attributable burden was in neonates younger than 28 days. Benefits of treating suspected meningitis overlap with the benefits of treating sepsis (or a possible serious bacterial infection). Published data show that neonatal possible serious bacterial infections remain a major cause of morbidity and mortality especially in the first days of life and in low-and middle-income countries. |
| 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. | The treatment options for neonatal meningitis of ampicillin in combination with gentamicin, and the use of ceftriaxone or cefotaxime as alternatives to ampicillin are recommended by several WHO guidelines. Ampicillin, ceftriaxone and cefotaxime are currently included on the EMLc for the treatment of acute bacterial meningitis related to their good CSF penetration, safety profile and coverage of the most common pathogens.<br>The 2017 WHO EML/EMLc guideline suggests a penicillin (ampicillin, penicillin, or intravenous benzylpenicillin) along with gentamicin as the empirical core antibiotics for treatment of neonatal sepsis, which usually overlaps with neonatal bacterial meningitis. |
| Have all important studies and all relevant evidence been included in the application? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>If no, please provide brief comments on any relevant studies or evidence that have not been included: |

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| Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>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).<br>Of the two reviews considered in the application from the McMaster Group, one (2 RCTs, 127 participants) compared single to combination regimens for suspected early neonatal sepsis, but had indeterminant results on mortality within 28 days (RR 0.75, 0.19 to 2.9) because of the limited sample size. A review which examined antibiotic regimens for late onset sepsis in neonates (1 RCT, 24 participants), comparing beta-lactams to beta-lactams and aminoglycosides also was indeterminant (RR 0.17, 0.01 to 0.2) because it was severely underpowered.<br>The evidence of efficacy/effectiveness were based on the review of national and WHO guidelines.<br>The WHO handbook recommends, for newborns with any signs of serious bacterial infection or sepsis, to give ampicillin or penicillin and gentamicin as first-line antibiotic. The 2017 WHO EML/EMLc guideline suggests a penicillin (ampicillin, penicillin, or intravenous benzylpenicillin) along with gentamicin as the empirical core antibiotics for treatment of neonatal sepsis, which usually overlaps with neonatal bacterial meningitis.<br>The NICE guideline recommends benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless local bacterial resistance patterns suggest using a different antibiotic. The American Academy of Pediatrics recommends ampicillin and an aminoglycoside, typically gentamicin, for treatment of infants with suspected early onset sepsis in neonates.<br>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?<br>Yes. |
| Does the application provide adequate evidence of the safety and adverse effects associated with the medicine? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>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. |

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| Are there any adverse effects of concern, or that may require special monitoring? | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>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: 1) receiving >5 days of gentamicin therapy; 2) with impaired renal function; 3) altered large volume of distribution.<br>Gentamicin is contraindicated to use in neonates post conceptional age <44 weeks. Use of gentamicin should be precautious in neonatal patients 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 treatment for neonate bacterial meningitis 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)**?**<br>(e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments: Ideally, it is necessary to monitor serum TDM to adjust the optimal dosage to provide the effective treatment and avoid the potential harm to renal function and hearing. |
| Are you aware of any issues regarding the registration of the medicine by national regulatory authorities?<br>(e.g. accelerated approval, lack of regulatory approval, off-label indication) | ☐ Yes<br>☒ No<br>☐ Not applicable<br>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?<br>(refer to: https://www.who.int/publications/who-guidelines) | ☒ Yes<br>☐ No<br>☐ Not applicable<br>Comments:<br>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.<br>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). |

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| 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. | Based on the treatment options of ampicillin in combination with gentamicin for neonatal meningitis and sepsis recommended by several WHO guidelines, I recommend to extend the indications for gentamicin on the EMLc to include bacterial meningitis in neonates. |
| References<br>(if required) | |