### Expert Committee recommendation

1. Application for the addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed. The Expert Committee recognized the importance of age-appropriate formulations of essential medicines to better meet the dosing needs of children. The Committee noted that the 7:1 ratio of amoxicillin to clavulanic acid is associated with similar efficacy to the 4:1 ratio but has a reduced frequency of gastrointestinal adverse effects. The dispersible tablet formulation also offers advantages over oral liquid formulations for ease of administration and heat stability. The Committee therefore recommended the inclusion of the 200 mg + 28.5 mg dispersible tablet formulation of amoxicillin + clavulanic acid as an Access group antibiotic on the core list of the EMLc for treatment of bacterial infections in children – specifically those infections for which amoxicillin + clavulanic acid is already recommended on the EMLc.

2. Review of the age-appropriateness of formulations of essential medicines for children. In consideration of the review of the age appropriateness of formulations of medicines on the EMLc, and the comparison report of the EML versus EMLc, the Expert Committee recommended changes to the EMLc for addition of new, age-appropriate formulations and strengths of existing essential medicines, deletion of unavailable or age-inappropriate formulations and strengths, and other listing modifications as proposed in the application. The Committee also endorsed the proposals for further review of the public health relevance and evidence for specific medicines for use in children for potential future consideration for inclusion on the EMLc. The Committee noted and welcomed the ongoing review being coordinated by the Secretariat for the remaining sections of the EMLc for consideration by the 2025 Expert Committee. As a result of the review of the age-appropriateness of formulations on the EMLc, the Expert Committee recommended: - the addition of a new formulation of amoxicillin + clavulanic acid (dispersible tablet...
Background

1. Application for the addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed. The evidence of benefits presented by the applicants was mostly based on studies from the 1990s when the formulation of amoxicillin + clavulanic acid at a 7:1 ratio was first developed. No specific evidence on the efficacy of the dispersible formulation was included. A randomized, observer-blinded, multicentre study conducted in the 1990s evaluated the efficacy of amoxicillin + clavulanic acid as twice daily dosing at a 7:1 ratio compared with three times daily dosing at a 4:1 ratio in 463 children, aged 2–12 years with acute otitis media (3). The two treatment groups demonstrated similar efficacy with clinical success rates at the end of therapy (10 days) of 91.8% for the twice-daily 7:1 group versus 90.5% for the three-times-daily 4:1 group. No significant difference was seen between treatment groups in the incidence of adverse events, however the incidence of diarrhoea was lower in the twice-daily group (6.7% versus 10.3%) group. Significantly more patients in the twice-daily group than the three-times-daily group were reported to have at least 80% compliance with treatment. Another United States study from the 1990s randomized 868 children aged 2–12 years with acute otitis media to receive amoxicillin (45 mg) + clavulanic acid (6.4 mg) twice daily for 10 days, 40/10 mg three times daily for 10 days or 45/6.4 mg twice daily for 5 days (4). Treatment successes (clinical cure or improvement) were reported as 86.5%, 78.7% and 71.1% in the three treatment groups, respectively. The incidence of diarrhoea was significantly greater in the three-times daily group (26.7%), than in the two twice-daily groups (9.6% and 8.7%). A third randomized study from the 1990s of 415 children aged 2 months to 12 years with acute otitis media compared amoxicillin + clavulanic acid twice daily in a 7:1 ratio with three times daily in a 4:1 ratio given for 7 or 10 days (5). At the end of therapy (days 7–12), clinical success (cure) was achieved by about 94% of patients in both treatment groups. At follow-up (days 38–42), 93.3% of patients in the twice-daily group and 87.9% in the three-times-daily group continued to have a clinically successful response. Both treatment regimens were well tolerated, with most adverse events being of a mild-to-moderate and transient nature. Diarrhoea was reported in 7.2% and 10.7% of the twice-daily and three-times daily groups, respectively. Compliance with treatment was reported as 82.8% in the twice-daily group and 73.3% in the three-times-daily group. Results of the three studies mentioned above were pooled in a subgroup analysis in a 2013 Cochrane systematic review (6). No significant differences were found between once- or twice- daily groups and the three-times daily group for: clinical cure rate at the end of therapy (risk ratio (RR) 1.03, 95% confidence interval (CI) 0.99 to 1.07); clinical cure rate during therapy (RR 1.00, 95% CI 0.70 to 1.42); clinical cure rate at post-treatment (RR 1.04, 95% CI 0.98 to 1.10); recurrent infection after completion of therapy (RR 1.01, 95% CI 0.39 to 2.60); overall adverse reactions (RR 0.92, 95% CI 0.52 to 1.63); diarrhoea

Summary of evidence

250 mg + 62.5 mg) to the EMLc. - the addition of a new strength formulation of nitrofurantoin (solid oral dosage form 50 mg) on the EMLc. - the addition of a new strength formulation of sulfamethoxazole + trimethoprim (dispersible tablet 100 mg + 20 mg) on the EMLc.
Committee considerations

1. Application for the addition of amoxicillin + clavulanic acid 200 mg + 28.5 mg dispersible tablet to the core list of the EMLc for the same indications for which other formulations of amoxicillin + clavulanic acid are currently listed. The WHO AWaRe (Access, Watch, Reserve) antibiotic book (9) provides guidance on the prescribing and use of antibiotics on the WHO Model Lists of Essential Medicines for the empiric treatment of common infections in adults and children. It reflects the recommendations for essential antibiotics made by the WHO Expert Committee on Selection and Use of Essential Medicines, incorporating the principles of the WHO AWaRe classification of antibiotics. 

The Global Coordination and Partnership department within the Antimicrobial Resistance division reviewed and provided comments on the application, indicating its support for the addition of the proposed new dispersible tablet formulation of amoxicillin + clavulanic acid on the EMLc. The EML Antimicrobial Working Group reviewed the application and advised that it supports the inclusion of amoxicillin + clavulanic acid dispersible tablets at a 7:1 ratio (200 mg + 28.5 mg) on the EMLc. The Working Group noted that the 7:1 dispersible tablets proposed in the application offer several advantages over currently listed paediatric formulations such as ease of administration and heat stability at a similar price. The oral liquid formulations currently listed on the Model Lists must be refrigerated after reconstitution which is a challenge in many resource-constrained settings. The Working Group acknowledged that amoxicillin + clavulanic acid was identified as one of the priority antibiotics during the WHO meeting on paediatric drug optimization for antibiotics in November–December 2022. While UNICEF currently procures amoxicillin + clavulanic acid dispersible tablets at a 4:1 ratio (250 mg + 62.5 mg), which is also being proposed for inclusion on the EMLc as part of the EMLc formulation review in the context of the Global Accelerator for Paediatric Formulations project, it was considered that the additional availability of a dispersible tablet at a 7:1 ratio may offer certain advantages. These advantages include allowing higher doses of amoxicillin without dose-related side-effects associated with a higher clavulanic acid dose (e.g. in settings where penicillin non-susceptible pneumococci are prevalent). The Working Group noted that the dispersible tablets proposed in this application did not receive regulatory approval from the European Medicines Agency as they did not meet its requirement of disintegration within 3 minutes, an issue which does not seem to affect hospital or community use or offset the key advantages. Given the public health need for this formulation, the Working Group did not consider this should preclude its addition to the EMLc.
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