efficacy, a properly designed study will be required to answer this question definitively. Animal studies of experimental aspergillosis where voriconazole was given once or twice daily showed similar efficacy for the same doses.\textsuperscript{9,10} In children, because of the high clearance, voriconazole exposure is lower than in adults with the same doses. Thus, higher doses are recommended in order to achieve exposure similar to that in adults. A similar observation has been made for fluconazole.\textsuperscript{11} As shown in this letter, splitting the daily dose into three or four doses over the same period may not increase antifungal efficacy if the $fAUC/MIC$ target is not attained.

**Transparency declarations**

None to declare.

**References**


**Comment on: Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: a randomized controlled trial**

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Sir,

We welcome the study by Vilas-Boas et al.\textsuperscript{1} comparing amoxicillin dosing schedules for children with community-acquired pneumonia (CAP). A large number of patients were randomized and it adds to an evolving evidence base from disparate international settings favouring twice-daily oral amoxicillin for CAP to improve adherence, including in scenarios where intravenous therapy has traditionally been used. There is also relevance for intravenous-to-oral switch decision-making and antimicrobial stewardship. However, we believe that some aspects of the study design and consequently the interpretation of the results are flawed, potentially leading to erroneous conclusions and/or the findings being deemed non-applicable to other settings.

First, the inclusion criteria were not specific for bacterial infection. A large proportion of children presenting with CAP have viral infection,\textsuperscript{2} and efficacy studies of the treatment of bacterial pneumonia can be limited by the inclusion of these patients.\textsuperscript{3} While a pragmatic approach may be justifiable, criticism of other pragmatic studies has focused on a lack of supportive radiological and/or microbiological evidence of bacterial infection to define a group likely to benefit from antibiotic therapy. In this study, despite the inclusion criteria being clinical features of lower respiratory tract infection ‘plus presence of pulmonary infiltrate/consolidation on the chest radiograph’, 86% of chest X-rays were concordantly reported as normal. The efficacy results of different antibiotic dosing regimens must therefore be interpreted with caution due to the likely inclusion of many patients without bacterial pneumonia.
Second, the dose of amoxicillin is low at 50 mg/kg/day. Although international guidelines support twice-daily dosing, the WHO and IDSA guidelines recommend 80–90 mg/kg/day. Inadequately treated pneumococcal pneumonia may have serious sequelae. The key pharmacodynamic parameter determining the efficacy of amoxicillin is length of time over the MIC (T>MIC), and for pneumococci the target is at least 40%–50% of the dosing interval. A pharmacokinetic study comparing thrice-daily and twice-daily dosing found that fewer than half of children receiving 50 mg/kg/day divided into twice daily had amoxicillin concentrations above 2 mg/L the CLSI MIC cut-off for penicillin resistance in non-meningeal infection for >50% of the dosing interval. The authors recommended at least 60–80 mg/kg/day for twice-daily dosing. While lower doses may be adequate for the most susceptible pneumococcal isolates, pneumococci with reduced penicillin susceptibility may require higher doses of amoxicillin to optimize T>MIC to avoid unnecessary recourse to broader spectrum agents. In addition, although the authors state that their region currently has a low prevalence of pneumococcal resistance, administering too low a dose has been found to be a risk factor for the carriage of resistant pneumococci.

Third, the goal of improved adherence may have been affected by the intervention. Patients were randomized to receive twice-daily or thrice-daily antibiotics and, to enable blinding, received placebo for the other arm. Although this is a neat idea, it resulted in dosing five times a day. Study participants are often more compliant than patients in real life but there was no attempt to assess adherence and this frequent administration regimen could have affected results by contributing to underdosing in both arms.

Viruses and pneumococci are responsible for the vast majority of CAP cases. Amoxicillin should be the first-choice oral antibiotic for CAP including for intravenous-to-oral switch where clinical improvement has occurred on narrow-spectrum parenteral agents (benzylpenicillin or an aminopenicillin). Compared with amoxicillin, many paediatric prescribers in our setting have greater familiarity with and trust in twice-daily dosing with amoxicillin/clavulanate formulations. This is despite the fact that effective twice-daily dosing of these formulations is obtained through an increased dosage of amoxicillin relative to clavulanate. Broader spectrum agents should not be chosen over amoxicillin for CAP in the spurious belief that amoxicillin may not be dosed twice daily. To effect the maximal change in prescribing practices, future studies of twice-daily amoxicillin dosing for CAP in children should concentrate on defining a group of participants most likely to benefit from antibiotic therapy and focus on the attainment of adequate T>MIC for common bacterial causes of CAP.

Transparency declarations
None to declare.

References