

## ABSTRACT

**BACKGROUND:** There are concerns that the evidence from studies showing non-inferiority of oral amoxicillin to benzyl penicillin for severe pneumonia may not be generalizable to high mortality settings. **METHODS:** An open-label multicenter randomized controlled non-inferiority trial was conducted at six Kenyan hospitals. Eligible children aged 2 - 59 months were randomized to receive amoxicillin or benzyl penicillin and followed up for the primary outcome of treatment failure at 48 hours. A non-inferiority margin of risk difference between amoxicillin and benzyl penicillin groups was pre-specified at 7%. **RESULTS:** We recruited 527 children including 302 (57.3%) with co-morbidity. Treatment failure was observed in 20/260 (7.7%) and 21/261 (8.0%) of patients in the amoxicillin and benzyl penicillin arms respectively (risk difference -0.3%, 95% confidence interval (CI) -5.0 to 4.3) in per protocol analyses. These findings were supported by the results of intention to treat analyses. Treatment failure by day 5 post-enrolment was 11.4% and 11.0% and rising to 13.5% and 16.8% by day 14 in the amoxicillin versus benzyl penicillin groups respectively. The most frequent cause of cumulative treatment failure at day 14 was clinical deterioration within 48 hours of enrolment (33/59; 55.9%). Four patients died (overall mortality 0.8%) during the study, three of whom were allocated to the benzyl penicillin group. The presence of wheeze was independently associated with less frequent treatment failure. **CONCLUSIONS:** Our findings confirm non-inferiority of amoxicillin to benzyl penicillin, provide estimates of risk of treatment failure in Kenya and offer important additional evidence for policy making in sub-Saharan