Oral step-down, optimal drug, and total duration of antibiotic treatment in African children hospitalised with severe community-acquired pneumonia (PediCAP): a factorial randomised controlled trial

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Summary

Background WHO recommends 5 days of intravenous antibiotics for children hospitalised with severe community-acquired pneumonia (CAP). We aimed to investigate the safety of a step-down to different oral antibiotics and the shortest effective duration.

Methods PediCAP was an open-label, parallel group, 2×5 factorial randomised controlled trial of children aged 2 months to 6 years hospitalised with severe CAP without complicating factors in 13 hospitals across five sub-Saharan African countries. Children weighing 3–30 kg and with point-of-care C-reactive protein of more than 10 mg/L were randomly assigned (5:5:1) to either a step-down from intravenous antibiotics to oral amoxicillin (250 mg) or amoxicillin–clavulanate (co-amoxiclav; 200 mg amoxicillin to 28·5 mg clavulanate) via dispersible tablets twice daily (superiority comparison) for five total (intravenous plus oral) durations (4–8 days; non-inferiority comparison), or a 5-day, fixed-duration, intravenous-only treatment (non-inferiority comparison). Children were stepped down when clinically improved and able to take oral antibiotics. Clinicians could change antibiotics if clinically indicated. The primary outcome was the proportion of readmission or death at day 28 (non-inferiority margin *vs* intravenous only: +10%). The study was registered with the ISRCTN registry (ISRCTN63115131) and is complete.

Findings Between Dec 7, 2020, and Aug 14, 2023, 2248 children were screened for eligibility and 1101 were randomly allocated (480 [43·6%] girls and 621 [56·4%] boys). The primary outcome was available in 1055 (95·8%) children. For children in the step-down groups, the mean total antibiotic exposure was 6·0 days (SD 3·5) in the 4-day group, 6·8 days (4·2) in the 5-day group, 7·4 (3·6) in the 6-day group, 8·3 days (3·4) in the 7-day group, and 9·2 days (2·9) in the 8-day group (p<0·0001), with 140 (68·6%) of 204, 151 (76·3%) of 198, 167 (85·2%) of 196, 179 (89·5%) of 200, and 186 (91·6%) of 203, respectively, stepping down within their randomised duration (p<0·0001). Primary outcomes occurred in 33 (6·9%) of 475 in the co-amoxiclav group, 27 (5·6%) of 484 in the amoxicillin group, and six (6·3%) of 96 in the intravenous-only group, with both oral step-down strategies non-inferior to the intravenous-only strategy (upper 95% CIs of 6·0 for co-amoxiclav and 5·7 for amoxicillin) and no evidence of superiority for co-amoxiclav over amoxicillin (adjusted risk difference 1·3% [95% CI –1·8 to 4·4]; p=0·40). Primary outcomes occurred in eight (4·1%) of 194 in the 4-day group, ten (5·3%) of 190 in the 5-day group, 16 (8·5%) of 188 in the 6-day group, 16 (8·3%) of 193 in the 7-day group, and ten (5·2%) of 194 in the 8-day group; all durations were non-inferior to the 8-day group (all upper 95% CIs ≤6·0%). There was no evidence of consistent differences in adverse events for oral antibiotic or duration comparisons. For antibiotic-related or serious adverse events, there was one (1·0%) in the intravenous-only group and 12 (2·5%) in the amoxicillin group (adjusted risk difference –2·3% [95% CI –4·2 to –0·3]; p=0·025), and 16 (3·4%) in the co-amoxiclav group (+0·8% [–1·2 to 2·8]; p=0·42); rates increased with randomised duration (slope estimate +0·9% [0·1 to 1·7]; p=0·032).

Interpretation For sub-Saharan African children hospitalised with severe CAP without complicating factors, a strategy of stepping down upon clinical improvement to oral amoxicillin after initial intravenous antibiotics, with a total treatment duration of 4–5 days, is non-inferior to WHO-recommended 5-day intravenous treatment.

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See Online for appendix

Research in context

Evidence before this study

We searched the International Clinical Trials Registry Platform on Sept 29, 2025, for ongoing or completed trials of severe pneumonia in children (free-text search combining "pneumonia" AND "child" AND "trial"), with particular interest in studies evaluating intravenous-to-oral antibiotic switch strategies, identifying 140 records of which only 25 investigated antibiotic management. Just three were directly relevant to the questions addressed in this trial. One completed trial in Kenya compared oral amoxicillin with intravenous benzylpenicillin for severe pneumonia in children younger than 5 years, finding oral amoxicillin non-inferior (7% non-inferiority margin) for short-term treatment failure assessed at 48 h, defined as any one of several new danger signs, persistence of tachydyspnoea or fever, or clinician decision to modify antibiotic treatment. Two ongoing or planned trials are evaluating intravenous antibiotic regimens, or early switch to oral treatment, but neither addresses optimal oral step-down choice or total duration. A systematic search of MEDLINE and Embase (from database inception to Sept 29, 2025), using Medical Subject Headings and free-text terms for "antibiotic treatment", "severe or very severe pneumonia", and "child", identified several systematic reviews and meta-analyses since 2022. Across 17 randomised trials and over 15 000 children, shorter antibiotic regimens (ie, 3–5 days) were consistently as effective as longer courses (ie, 7–10 days) for community-acquired pneumonia, with fewer adverse events. However, most of these trials were conducted in mild or moderate pneumonia, often managed in the community. Evidence in hospitalised children with severe pneumonia was scarce; older systematic reviews and meta-analyses of these trials concluded that oral antibiotics were generally as effective as injectable antibiotics, but with little evidence to guide whether, when, and how to switch from intravenous to oral therapy, or how long to continue treatment.

Added value of this study

PediCAP is among the largest and most comprehensive randomised trials to date that addresses antibiotic management of severe childhood community-acquired pneumonia requiring hospital admission in sub-Saharan Africa. Using a novel, multiarm, response over continuous intervention design, our study shows that, after at least 24 h of injectable therapy and clinical improvement, a step-down to oral amoxicillin is non-inferior to the current WHO standard of 5 days of injectable antibiotics in terms of readmission to hospital or mortality, with no benefit from using broader-spectrum oral amoxicillin–clavulanate. Furthermore, total treatment courses of 4–5 days were as effective as 7–8-day regimens.

Implications of all the available evidence

Taken together with existing evidence on antibiotic duration in mild and moderate pneumonia, PediCAP shows that shorter courses and an early switch to oral treatment are also safe and effective for children hospitalised with severe or very severe pneumonia, including in resource-constrained settings. Implementing an intravenous-to-oral step-down strategy with amoxicillin, for a total duration of 4–5 days, would allow earlier discharge, reduce the risk of hospital-acquired infections and antimicrobial resistance, and lessen the financial burden of hospitalisation on families. Furthermore, this strategy reduces unnecessary parenteral antibiotic exposure and supports reliance on amoxicillin as the preferred oral antibiotic given its availability, affordability, and alignment with WHO recommendations. These findings support a revision of WHO guidelines for severe childhood pneumonia and provide a pragmatic, scalable strategy for improving outcomes and reducing costs in low-income and middle-income countries where pneumonia remains a leading cause of child mortality.

Introduction

Pneumonia remains a leading cause of childhood morbidity and mortality worldwide, with most severe cases and hospitalisations occurring in low-income and middle-income countries.[1,2] Although mortality has declined, pneumonia still accounts for millions of hospital admissions and substantial health-care costs globally.[2,3]

Trials in WHO-defined non-severe pneumonia have shown that shorter antibiotic courses are safe and effective compared with longer treatments of 5–10 days.[4–8] Similarly, several meta-analyses, each synthesising data from more than 10 000 children, support that shorter courses are not associated with higher rates of treatment failure, relapse, or mortality, and can reduce adverse events.[9–11] However, most of this evidence comes from outpatient or community-managed pneumonia, with very little trial evidence to guide management of children admitted with WHO-defined severe pneumonia.[12,13]

Older studies in high-income countries suggest that oral antibiotics are effective in hospitalised non-critically ill patients with pneumonia who are able to tolerate oral medication.[14–16] Furthermore, a Kenyan randomised trial found that oral amoxicillin was non-inferior to intravenous benzylpenicillin in children admitted with severe pneumonia.[17] In contrast, there have been no large-scale multicentre trials in Africa evaluating the safety of intravenous-to-oral switch in children not initially able to tolerate oral medication.

For severe childhood pneumonia, current WHO guidelines advise hospital admission and 5 days of injectable antibiotics, typically administered intravenously,[12] and 5 days of oral amoxicillin for mild-to-moderate cases.[13] *The WHO AWaRe (Access, Watch, Reserve) Antibiotic Book* maintains these

recommendations, pending robust trial evidence on intravenous-to-oral step-down and total duration of treatment.[18] Which oral step-down antibiotic to use remains uncertain, particularly given the more than 90% coverage of pneumococcal conjugate vaccine across many African countries.[19] *Streptococcus pneumoniae* remains the leading pathogen associated with childhood community-acquired pneumonia (CAP) mortality globally; yet mixed bacterial aetiology is common, and pathogens such as *Staphylococcus aureus* are frequently detected in hospitalised children and fatal cases.[1,20,21] Broader-spectrum agents, such as amoxicillin–clavulanate (co-amoxiclav) could therefore theoretically offer advantages based on the expected aetiological spectrum.

To address three crucial evidence gaps, the PediCAP trial used a novel multiarm response over continuous intervention (ROCI)[22] factorial design in African children hospitalised with severe pneumonia to evaluate effectiveness and safety of (1) a step-down from intravenous to oral antibiotics after clinical improvement compared with 5 days of intravenous-only treatment (hypothesising the non-inferiority of step-down); (2) oral amoxicillin versus co-amoxiclav for step-down (hypothesising the superiority of co-amoxiclav); and (3) total treatment durations of 4, 5, 6, 7, or 8 days of sequential intravenous and oral antibiotics (hypothesising the non-inferiority of shorter durations compared with 8 days), with 28-day all-cause hospital readmission or death as the primary outcome. The major advantage of the ROCI design is that it avoids the arbitrary comparison of a single shorter duration with a single longer duration; in reality, neither might be optimal, with the risk that shorter durations are not found to be non-inferior to longer durations, even if the longer duration is too long compared with a non-tested shorter duration. Randomising to multiple arms spread across a range of durations of clinical interest by use of the ROCI design allows the relationship between treatment duration and response to be estimated and the shortest non-inferior duration to be identified.

Methods

Study design

PediCAP used a novel ROCI design[22] in an open-label, multicentre, international, randomised, parallel-group, 2×5 factorial trial, with one additional arm, conducted in 13 secondary and tertiary hospitals in five African countries (Mozambique, South Africa, Uganda, Zambia, and Zimbabwe). Further methodological detail on the design assumptions and rationale is provided in the appendix (pp 5–6), which describes the rationale for the intravenous-to-oral step-down strategy, the choice of multiple total antibiotic durations, and the inclusion of a benchmark intravenous-only arm.

Ethical and regulatory approval was obtained from local and national ethics committees and regulatory agencies in each country, and from University College London (London, UK; appendix p 6). There were no material changes to the protocol beyond the inclusion of additional sites to increase recruitment rates. Each centre had a Community Advisory Board providing input into the conduct of the trial and the reporting of the results. Patients and the public were not directly involved in the trial design. An independent Trial Steering Committee and Data Monitoring Committee provided oversight (appendix p 6). The trial was registered with the ISRCTN registry (ISRCTN63115131) and the protocol and statistical analysis plan are available online.

For the **protocol and statistical analysis plan** see https://www.isrctn.com/ISRCTN63115131

Participants

Eligible children were aged 2 months to 6 years, weighing 3–30 kg, who were admitted to hospital with severe CAP without complicating factors (eg, immediate admission to an intensive care unit) and were judged by the treating clinician to require at least 24 h of WHO-recommended intravenous antibiotics, as specified in the trial protocol (see appendix p 7 for full eligibility criteria). Eligibility further required that protocol-defined intravenous antibiotic therapy was about to be or had already been initiated, and that no more than 24 h of such treatment had been received at the point of randomisation to ensure inclusion of children with severe pneumonia who were not already ready for oral step-down.

Severe pneumonia was defined as difficulty breathing, with or without cough reported by a parent or carer, plus one or more of: (1) central cyanosis or hypoxaemia (room air pulse oximetry <90%); (2) any sign of severe respiratory distress (eg, severe chest indrawing, grunting, nasal flaring, and head nodding); or (3) signs of pneumonia (eg, fast breathing [respiratory rate ≥50 breaths per min at age 2–11 months and ≥40 breaths per min at age ≥1 years] or chest indrawing) plus a general danger sign (eg, inability to breastfeed or drink, lethargy or reduced consciousness, convulsions, or moderate or severe malnutrition).[12,13]

Children with point-of-care C-reactive protein (CRP) less than 10 mg/L were excluded to enrich the trial population with children more likely to have bacterial pneumonia and more likely to benefit from antibiotics, thereby reducing bias to the null in this non-inferiority trial from including children unlikely to benefit from treatment regardless of drug or duration. This exclusion was not intended to imply that children with low CRP do not require antibiotics in routine clinical practice. Further exclusion criteria are available in the appendix (p 7).

Sex data were reported by parents or guardians with the options of male or female. Ethnicity information was not collected. Parents and guardians provided written informed consent before randomisation.

Randomisation and masking

Children were randomly assigned (5:5:1) to one of three antibiotic strategies: oral step-down to either

amoxicillin 250 mg or co-amoxiclav (200 mg amoxicillin, 28·5 mg clavulanate) dispersible tablets administered twice daily with doses according to weight bands (appendix p 22), or to remain on WHO-recommended intravenous-only antibiotics for 5 days (appendix p 14). In each oral step-down arm, children were randomly assigned (1:1:1:1:1) to 4, 5, 6, 7, or 8 days total of intravenous plus oral antibiotic therapy (counting the time from the start of intravenous antibiotics, not from randomisation). Randomisation, stratified by site, used a computer-generated sequential list with variably sized permuted blocks (sizes 11 and 22) prepared by the trial statistician, incorporated within a secure online system and concealed from site staff until enrolment. The trial statistician had other roles in trial preparation, data management, and trial analysis. Trial procedures were not masked because treatment allocation established the route and duration of antibiotic therapy and the timing of oral step-down, which was assessed by the same teams delivering care. Masking was therefore not feasible, and there was insufficient funding for additional staff solely to collect outcome data.

Procedures

Children allocated to oral step-down were switched after at least 24 h of intravenous antibiotics when the treating clinician judged them clinically improved (appendix pp 8, 22). If sufficient clinical improvement did not occur before their randomly assigned total intravenous plus oral duration, the child stayed on intravenous treatment throughout and stopped treatment when clinically appropriate. Children were discharged when clinically recovered (ie, not receiving oxygen) and tolerating oral medicines, with any remaining step-down treatment completed at home. Children randomly assigned to intravenous only had 5 days intravenous treatment. If clinically required, clinicians could change antibiotics (eg, to broader spectrum), reinitiate intravenous or oral antibiotics, or prescribe concomitant medication at any time. The clinical management of participating children was overseen by treating physicians; study procedures were overseen by study clinicians in consultation.

Children were assessed daily during initial hospitalisation, recording clinical condition, antibiotic doses, concomitant medication, any standard-of-care test results, and adverse events (appendix p 15). Discharged children were followed up at days 7, 14, and 21 by telephone, and face to face or by telephone at day 28.

Outcomes

All outcomes were assessed up to day 28 from randomisation. The primary outcome was the proportion of all randomly assigned children with hospital readmission or all-cause death, ignoring intercurrent events of change from randomised treatment (treatment policy) and restricted to children with known day-28 status (principal stratum). Secondary effectiveness outcomes were assessed in all children and included pneumonia-related readmission or death (adjudicated by a masked committee; appendix p 9), all-cause mortality, length of hospitalisation (initial and up to day 28), days of supplemental oxygen during initial hospitalisation, total days of antibiotic exposure, and modification of antibiotics from randomised allocation. Secondary safety outcomes, systematically assessed in all children during hospitalisation and at follow-up visits, included the proportion of serious adverse events, antibiotic-related adverse events (identified by the treating clinician), and key events reflecting common antibiotic toxicities (eg, diarrhoea; appendix p 9).

Statistical analysis

For the superiority comparison between the co-amoxiclav and amoxicillin step-down, 1000 children randomly assigned 1:1 provided 81% power to detect a 6% absolute reduction in the primary outcome from 15% (amoxicillin) to 9% (co-amoxiclav), assuming a 5% loss to follow-up (two-sided α of 0·05; superiority). The assumed control-group event rate of 15% was informed by observational data from sub-Saharan Africa reporting approximately 10% 1-month mortality[23] and site estimates of approximately 10% readmission after severe childhood pneumonia (similar to subsequent studies[24]), conservatively adjusted to 15% because lower rates are generally observed in trials than in observational studies. For the non-inferiority comparison between co-amoxiclav step-down and 5-day intravenous only, randomly assigning 500 versus 100 children, respectively, provided 89% power to show non-inferiority with a conservative 10% non-inferiority margin (two-sided α of 0·05) in line with US Food and Drug Administration recommendations for adult bacterial CAP (appendix pp 10–11).[25,26] No interaction was assumed between drug and duration because an additional day of β-lactam therapy was expected to have a similar incremental effect regardless of whether amoxicillin or co-amoxiclav was used. In simulations, 500 children in five duration groups for each step-down antibiotic estimated the duration–response association within a 5% error margin in more than 95% of simulation (details and full simulation results have been published previously[22]).

The primary analysis population included all randomly assigned children with outcomes observed, regardless of treatment received. The primary analysis used binomial regression (logistic link function), adjusted for randomisation stratification factors (ie, site and other factorial randomisations; two centres with fewer than five randomly assigned children were grouped with the geographically nearest centre within the same country), and marginalised on the risk difference scale. Duration–response associations were estimated separately for oral amoxicillin and co-amoxiclav groups with fractional polynomials in the dani R package, allowing non-linear associations.[22] A combined model tested whether these

duration–response associations varied between co-amoxiclav and amoxicillin using main effects and interactions, which were also used to investigate prespecified subgroup effects. Secondary outcomes were analysed similarly by use of binomial regression and exact tests for binary outcomes, linear regression for continuous outcomes, and Cox regression for time-to-event outcomes (further details are in the appendix [pp 10–11]). As well as analysing presence or absence as binary outcomes, adverse events were summarised by body system. Because rates of missing data were below the prespecified 5% cutoff, multiple imputation for missing primary outcomes was not initially performed but was added as an exploratory analysis at the request of a reviewer, together with an exploratory analysis of predictors of loss to follow-up for the primary outcome (last seen alive before day 28; appendix pp 11–12). An independent Data Monitoring Committee oversaw the trial and reviewed interim data on four occasions as part of routine oversight without prescribed stopping rules (appendix p 6). All analyses were performed using R (version 4.3.2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Sandoz provided oral amoxicillin and co-amoxiclav fixed-dose combination dispersible tablets, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 7, 2020, and Aug 14, 2023, 2248 children were screened and 1101 were randomly assigned to

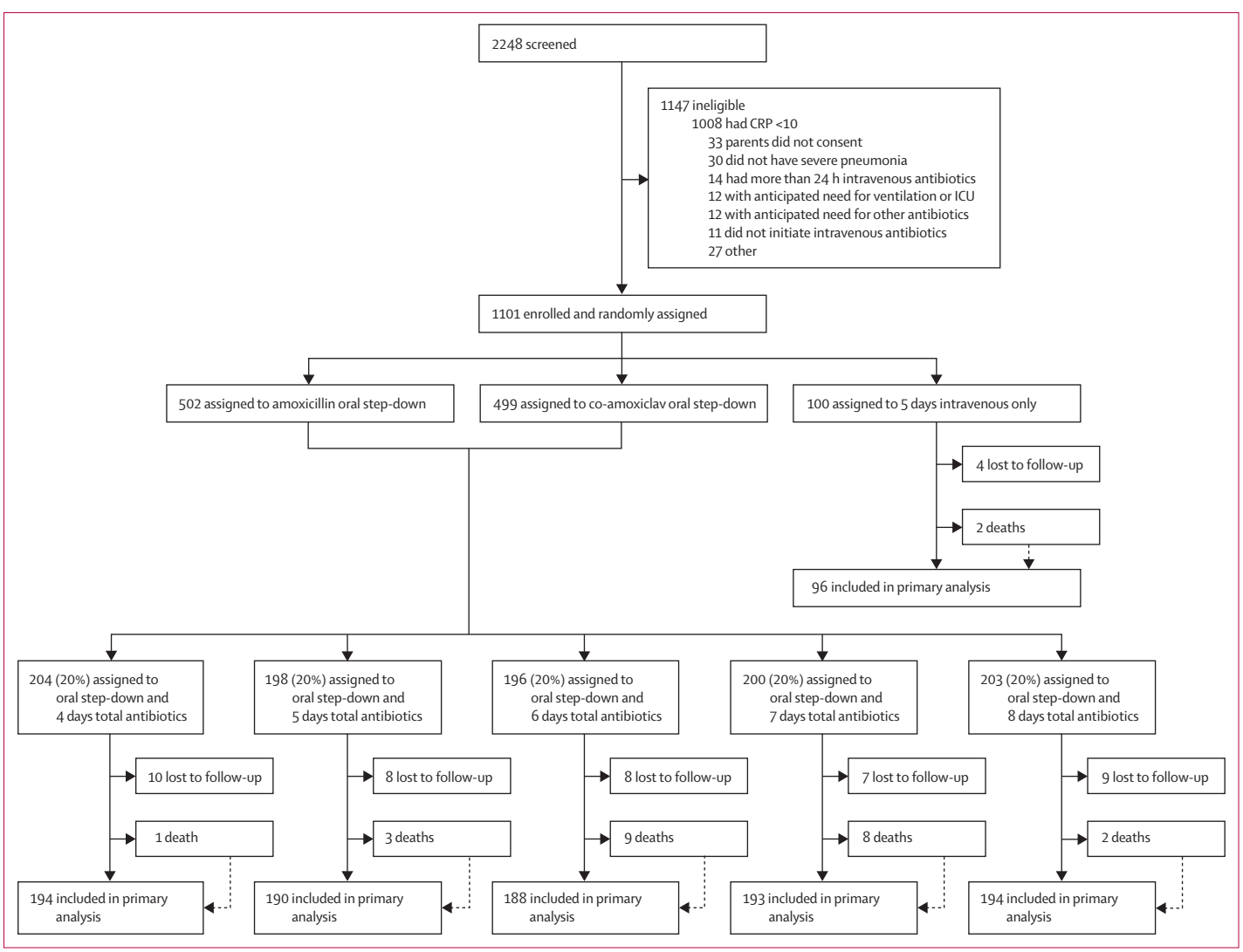

Figure 1: **PediCAP trial profile**
Children randomly assigned to the 5 days intravenous-only group were not randomly assigned to duration groups. CRP=C-reactive protein. ICU=intensive care unit.

the amoxicillin group (n=502), the co-amoxiclav group (n=499), or the intravenous-only group (n=100). 1055 (95·8%) children had day-28 outcomes (figure 1).

At baseline, 490 (44·5%) children were younger than 12 months (median 13 months [IQR 6–25]) and 697 (63·3%) weighed less than 10 kg (median 9 kg [IQR 7–11]; table 1; appendix pp 23–28). 1002 (91·0%) had at least one dose of pneumococcal conjugate vaccine. 685 (62·2%) needed oxygen, 639 (58·0%) had central cyanosis or hypoxaemia, 986 (89·6%) had signs of severe respiratory distress, and 738 (67·0%) had signs of CAP and a general danger sign (appendix pp 16, 23–28). Parents commonly reported cough, fast breathing, and fever (appendix p 16). 893 (81·1%) children had

	Overall (N=1101)	Amoxicillin (n=502)	Co-amoxiclav (n=499)	Intravenous only (n=100)	4 days (n=204)	5 days (n=198)	6 days (n=196)	7 days (n=200)	8 days (n=203)
Country									
Mozambique	204 (18·5%)	95 (18·9%)	90 (18·0%)	19 (19·0%)	37 (18·1%)	37 (18·7%)	36 (18·4%)	36 (18·0%)	39 (19·2%)
South Africa	280 (25·4%)	128 (25·5%)	127 (25·5%)	25 (25·0%)	53 (26·0%)	51 (25·8%)	50 (25·5%)	50 (25·0%)	51 (25·1%)
Uganda	287 (26·1%)	131 (26·1%)	131 (26·3%)	25 (25·0%)	53 (26·0%)	52 (26·3%)	51 (26·0%)	54 (27·0%)	52 (25·6%)
Zambia	183 (16·6%)	83 (16·5%)	83 (16·6%)	17 (17·0%)	34 (16·7%)	32 (16·2%)	32 (16·3%)	34 (17·0%)	34 (16·7%)
Zimbabwe	147 (13·4%)	65 (12·9%)	68 (13·6%)	14 (14·0%)	27 (13·2%)	26 (13·1%)	27 (13·8%)	26 (13·0%)	27 (13·3%)
Median age, months	13 (6–25)	13 (6–24)	13 (7–26)	14 (7–22)	14 (7–25)	13 (7–23)	13 (6–29)	13 (6–27)	13 (7–24)
Sex									
Female	480 (43·6%)	212 (42·2%)	217 (43·5%)	51 (51·0%)	90 (44·1%)	78 (39·4%)	82 (41·8%)	99 (49·5%)	80 (39·4%)
Male	621 (56·4%)	290 (57·8%)	282 (56·5%)	49 (49·0%)	114 (55·9%)	120 (60·6%)	114 (58·2%)	101 (50·5%)	123 (60·6%)
Weight band									
≥3 kg to <6 kg	162 (14·7%)	78 (15·5%)	73 (14·6%)	11 (11·0%)	17 (8·3%)	29 (14·6%)	37 (18·9%)	32 (16·0%)	36 (17·7%)
≥6 kg to <10 kg	535 (48·6%)	248 (49·4%)	240 (48·1%)	47 (47·0%)	115 (56·4%)	102 (51·5%)	81 (41·3%)	98 (49·0%)	92 (45·3%)
≥10 kg to <14 kg	274 (24·9%)	124 (24·7%)	119 (23·8%)	31 (31·0%)	48 (23·5%)	48 (24·2%)	48 (24·5%)	46 (23·0%)	53 (26·1%)
≥14 kg to <20 kg	115 (10·4%)	46 (9·2%)	60 (12·0%)	9 (9·0%)	21 (10·3%)	18 (9·1%)	27 (13·8%)	20 (10·0%)	20 (9·9%)
≥20 kg to <25 kg	15 (1·4%)	6 (1·2%)	7 (1·4%)	2 (2·0%)	3 (1·5%)	1 (0·5%)	3 (1·5%)	4 (2·0%)	2 (1·0%)
Weight-for-age Z score									
–3 or less	96 (8·7%)	47 (9·4%)	44 (8·8%)	5 (5·0%)	10 (4·9%)	21 (10·6%)	23 (11·7%)	16 (8·0%)	21 (10·3%)
–3 to –2 or less	139 (12·6%)	65 (12·9%)	61 (12·2%)	13 (13·0%)	30 (14·7%)	22 (11·1%)	20 (10·2%)	34 (17·0%)	20 (9·9%)
–2 to <2	831 (75·5%)	374 (74·5%)	383 (76·8%)	74 (74·0%)	162 (79·4%)	146 (73·7%)	150 (76·5%)	141 (70·5%)	158 (77·8%)
2 to <3	24 (2·2%)	12 (2·4%)	8 (1·6%)	4 (4·0%)	2 (1·0%)	7 (3·5%)	2 (1·0%)	7 (3·5%)	2 (1·0%)
>3	11 (1·0%)	4 (0·8%)	3 (0·6%)	4 (4·0%)	0	2 (1·0%)	1 (0·5%)	2 (1·0%)	2 (1·0%)
Height-for-age Z score									
–3 or less	173 (15·7%)	87 (17·3%)	79 (15·8%)	7 (7·0%)	34 (16·7%)	32 (16·2%)	29 (14·8%)	33 (16·5%)	38 (18·7%)
–3 to –2 or less	152 (13·8%)	81 (16·1%)	57 (11·4%)	14 (14·0%)	25 (12·3%)	26 (13·1%)	28 (14·3%)	26 (13·0%)	33 (16·3%)
–2 to <2	713 (64·8%)	311 (62·0%)	333 (66·7%)	69 (69·0%)	139 (68·1%)	122 (61·6%)	131 (66·8%)	131 (65·5%)	121 (59·6%)
2 to <3	24 (2·2%)	8 (1·6%)	12 (2·4%)	4 (4·0%)	2 (1·0%)	6 (3·0%)	4 (2·0%)	5 (2·5%)	3 (1·5%)
>3	37 (3·4%)	14 (2·8%)	17 (3·4%)	6 (6·0%)	3 (1·5%)	12 (6·1%)	4 (2·0%)	4 (2·0%)	8 (3·9%)
Unknown	2 (0·2%)	1 (0·2%)	1 (0·2%)	0	1 (0·5%)	0	0	1 (0·5%)	0
HIV status									
Infected	9 (0·8%)	7 (1·4%)	2 (0·4%)	0	1 (0·5%)	3 (1·5%)	3 (1·5%)	1 (0·5%)	1 (0·5%)
Exposed, uninfected	73 (6·6%)	29 (5·8%)	39 (7·8%)	5 (5·0%)	10 (4·9%)	20 (10·1%)	13 (6·6%)	12 (6·0%)	13 (6·4%)
Uninfected	586 (53·2%)	262 (52·2%)	267 (53·5%)	57 (57·0%)	107 (52·5%)	98 (49·5%)	99 (50·5%)	113 (56·5%)	112 (55·2%)
Mother negative, assumed uninfected	270 (24·5%)	122 (24·3%)	126 (25·3%)	22 (22·0%)	51 (25·0%)	45 (22·7%)	53 (27·0%)	50 (25·0%)	49 (24·1%)
Unknown	163 (14·8%)	82 (16·3%)	65 (13·0%)	16 (16·0%)	35 (17·2%)	32 (16·2%)	28 (14·3%)	24 (12·0%)	28 (13·8%)
Any pneumococcal conjugate vaccine dose									
Yes	1002 (91·0%)	450 (89·6%)	463 (92·8%)	89 (89·0%)	187 (91·7%)	178 (89·9%)	179 (91·3%)	189 (94·5%)	180 (88·7%)
No	61 (5·5%)	30 (6·0%)	24 (4·8%)	7 (7·0%)	15 (7·4%)	10 (5·1%)	6 (3·1%)	8 (4·0%)	15 (7·4%)
Not known	38 (3·5%)	22 (4·4%)	12 (2·4%)	4 (4·0%)	2 (1·0%)	10 (5·1%)	11 (5·6%)	3 (1·5%)	8 (3·9%)
CRP result									
10–40 mg/L	208 (18·9%)	101 (20·1%)	89 (17·8%)	18 (18·0%)	31 (15·2%)	34 (17·2%)	34 (17·3%)	54 (27·0%)	37 (18·2%)
40–80 mg/L	402 (36·5%)	179 (35·7%)	183 (36·7%)	40 (40·0%)	72 (35·3%)	67 (33·8%)	84 (42·9%)	63 (31·5%)	76 (37·4%)
>80 mg/L	491 (44·6%)	222 (44·2%)	227 (45·5%)	42 (42·0%)	101 (49·5%)	97 (49·0%)	78 (39·8%)	83 (41·5%)	90 (44·3%)

(Table 1 continues on next page)

	Overall (N=1101)	Amoxicillin (n=502)	Co-amoxiclav (n=499)	Intravenous only (n=100)	4 days (n=204)	5 days (n=198)	6 days (n=196)	7 days (n=200)	8 days (n=203)
(Continued from previous page)									
Mean heart rate, bpm	140 (19)	140 (19)	141 (18)	139 (21)	139 (20)	141 (18)	140 (19)	142 (17)	140 (20)
Mean respiratory rate, brpm	51 (12)	50 (12)	52 (12)	51 (12)	51 (12)	51 (12)	51 (13)	51 (12)	50 (12)
Mean oxygen saturation, SaO_2	92 (7)	92 (8)	92 (7)	93 (7)	93 (6)	92 (8)	92 (8)	92 (8)	92 (8)
Oxygen saturation <90%	343 (31·2%)	156 (31·1%)	157 (31·5%)	30 (30·0%)	66 (32·4%)	62 (31·3%)	58 (29·6%)	67 (33·5%)	60 (29·6%)
Mean temperature, °C	37·0 (0·9)	37·0 (0·9)	37·0 (0·8)	37·0 (0·9)	37·0 (0·8)	37 (1)	37·0 (0·9)	37·0 (0·9)	37·0 (0·9)

Data are n (%), median (IQR), or mean (SD). Children assigned to oral step-down groups appear twice in the table: once in randomised drug columns (ie, amoxicillin or co-amoxiclav) and once in the randomised duration columns (ie, 4, 5, 6, 7, or 8 days). See the appendix for additional baseline characteristics (pp 23–28); these characteristics are across the 11 factorially randomised individual arms (pp 29–31), community-acquired pneumonia signs (p 16), and parent-reported symptoms (p 16). bpm=beats per min. brpm=breaths per min. CRP=C-reactive protein. SaO_2=transcutaneous oxygen saturation.

Table 1: **Participant characteristics**

point-of-care CRP above 40 mg/L (table 1). Only nine (0·8%) had an HIV infection. Only 454 (41·2%) children had a chest x-ray, which was not required for trial entry; of the 451 with available x-ray results, 434 (96·2%) had findings suggestive of pneumonia (appendix pp 23–28).

Before initiating intravenous antibiotics in hospital, 176 (16·0%) children had received oral or intramuscular antibiotics in the community (appendix pp 23–28), with 130 (73·9%) of these children receiving oral or intramuscular antibiotics for 24 h or less. Initial WHO-recommended intravenous antibiotics were penicillin alone (222 [20·2%] of 1101), penicillin and gentamicin (532 [48·3%]), and ceftriaxone or cefotaxime (347 [31·5%]).

Children received a median of 2·0 days (IQR 1·5–3·4) of intravenous antibiotics in the amoxicillin group, 2·0 days (1·5–3·5) in the co-amoxiclav group, and 5·0 days (5·0–5·5) in the intravenous-only group (figure 2A; appendix pp 32–37); 1087 (98·7%) received at least 24 h of intravenous antibiotics. There was no evidence that time to step-down differed between antibiotics (p=0·69; appendix p 38). The proportion of children who stepped down each day were similar between the duration groups (figure 2B; appendix pp 18, 39), with, for example, 1·5–4·1% children stepping down on the day of randomisation across the different duration groups, 37·9–45·9% stepping down on day 2, and 20·4–27·1% stepping down on day 3 (appendix p 39). Expectedly, fewer children in total stepped down within their randomised duration in the shorter groups (140 [68·6%] of 204 in the 4-days group, 151 [76·3%] of 198 in the 5-days group, 167 [85·2%] of 196 in the 6-days group, 179 [89·5%] of 200 in the 7-days group, and 186 [91·6%] of 203 in the 8-days group), instead completing their course intravenously. 55 (6·7%) of the 823 children who stepped down in the oral step-down groups received intravenous antibiotics at some point after step-down (including in subsequent readmissions), with no evidence of variation by randomised total duration (p=0·19); 611 (74·2%) were discharged before the end of their oral course (range 44–90%; p<0·0001 across randomised durations;

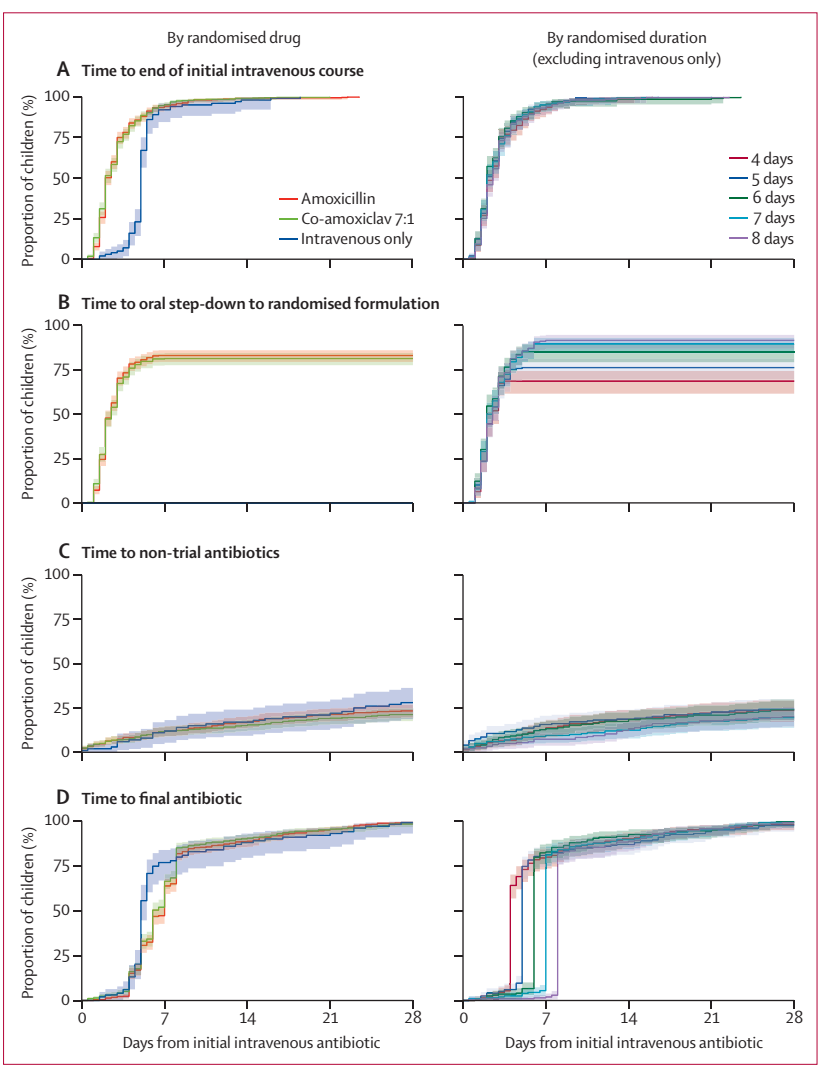

Figure 2: **Antibiotic treatment over time by randomised drug and by randomised duration in the oral step-down groups only**

The shaded areas represent 95% CIs. Times are measured from the initiation of intravenous treatment because treatment duration within randomised groups was based on the total duration of intravenous and oral antibiotics. Randomisation was within 24 h of initiation of intravenous antibiotics for all participants, with very similar durations across all groups (appendix pp 23–28). The time to oral step-down per oral antibiotic and per duration are available in the appendix (p 19).

	Amoxicillin	Co-amoxiclav	Intravenous only	Difference co-amoxiclav *vs* amoxicillin: average adjusted marginal effects (95% CI)	p value (co-amoxiclav *vs* amoxicillin)	Difference amoxicillin *vs* intravenous only: mean adjusted marginal effects (95% CI)	p value (amoxicillin *vs* intravenous only)
Readmission to hospital or death	27/484 (5·6%)	33/475 (6·9%)	6/96 (6·3%)	+1·3% (–1·8 to 4·4)	0·40	–2·3% (–10·2 to 5·7)	0·58
Death	11/484 (2·3%)	12/473 (2·5%)	2/96 (2·1%)	+0·3% (–1·6 to 2·1)	0·79	–2·4% (–10·3 to 5·5)	0·55
Length of stay during index hospitalisation, days	5·5 (4·1; n=502)	5·2 (3·6; n=499)	6·5 (3·0; n=100)	–0·3 (–0·7 to 0·2)	0·22	–0·9 (–1·8 to –0·0)	0·049
Total length of stay up to 28 days, days	5·7 (4·3; n=484)	5·4 (3·8; n=475)	6·9 (3·6; n=96)	–0·2 (–0·7 to 0·3)	0·36	–1·1 (–2·1 to –0·1)	0·025
Days of supplemental oxygen during index hospitalisation	2·4 (3·7; n=502)	2·1 (3·3; n=499)	2·2 (2·7; n=100)	–0·3 (–0·7 to 0·1)	0·14	+0·4 (–0·4 to 1·1)	0·34
Days on antibiotics up to 28 days	7·8 (4·0; n=484)	7·4 (3·4; n=473)	7·3 (5·2; n=96)	–0·5 (–0·9 to 0·0)	0·050	+2·2 (1·3 to 3·1)	<0·0001
Modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days	117/485 (24·1%)	111/479 (23·2%)	30/97 (30·9%)	–0·9% (–6·2 to 4·5)	0·74	–10·2% (–22·3 to 2·0)	0·10
Modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse	22/485 (4·5%)	18/473 (3·8%)	6/96 (6·3%)	–0·7% (–3·2 to 1·8)	0·57	–4·5% (–12·7 to 3·7)	0·28
Grade 3 or 4 adverse events or serious adverse events	44/484 (9·1%; 59 events)	45/474 (9·5%; 56 events)	9/96 (9·4%; 12 events)	+0·3% (–3·3 to 3·9)	0·86	–1·0% (–8·7 to 6·8)	0·81
Antibiotic-related adverse events or serious adverse events	12/484 (2·5%; 14 events)	16/475 (3·4%; 21 events)	1/96 (1·0%; 1 events)	+0·8% (–1·2 to 2·8)	0·42	+2·3% (0·3 to 4·2)	0·025
Line complications	21/484 (4·3%)	26/475 (5·5%)	11/96 (11·5%)	+1·3% (–1·7 to 4·4)	0·39	–12·9% (–24·8 to –0·1)	0·048

Data are n/N (%), n/N (%; n events) for adverse events, or mean (SD; n). The n/N data for adverse events represent the number of children who had at least one adverse event per the total number of children with available data. Estimates of differences between drugs are outputs from models with fixed effects of drug, duration, and site. Estimates of linear effect of duration are outputs from models including only children in oral step-down arms with fixed effects of drug, duration, and site. See the appendix for other secondary outcomes including key solicited events and specific complications (pp 44–45), details of serious adverse events and reactions (p 51), and more analyses of mortality (pp 13, 21, 48–50). CAP=community-acquired pneumonia.

Table 2: **Effect of randomised drug on primary and key secondary and safety outcomes**

appendix p 39). Overall, by day 28, 232 (21·1%) of 1101 children received antibiotics other than WHO-recommended intravenous antibiotics or oral antibiotics to which they were allocated (125 [11·4%] within their initial antibiotic course), with no strong evidence of differences between groups (29 [29·0%] of 100 in the intravenous-only group, 103 [20·5%] of 502 in the amoxicillin group, and 100 [20·0%] of 499 in the co-amoxiclav group; p=0·91 for amoxicillin *vs* co-amoxiclav, p=0·063 for co-amoxiclav *vs* intravenous only; appendix pp 32–34) or durations (41 [20·1%] of 204 in the 4-day group, 44 [22·2%] of 198 in the 5-day group, 44 [22·4%] of 196 in the 6-day group, 38 [19·0%] of 200 in the 7-day group, and 36 [17·7%] of 203 in the 8-day group; p=0·73; figure 2C; appendix pp 35–37). Most deviations in the intravenous-only group (25 [86·2%] of 29) were unplanned step-downs to oral antibiotics (appendix pp 32–34). Similar proportions of children randomly assigned to different drugs and durations remained on any antibiotics after their randomised duration (figure 2D; appendix pp 32–37); 387 (35·1%) received steroids or bronchodilators (per drug p=0·48, per duration p=0·97) and 31 (2·8%) received antituberculosis antibiotics (per drug p=1·00, per duration p=0·032). Pathogens were rarely isolated: of 258 children with a blood culture taken at baseline, only 11 (4·3%) had any pathogen (*S aureus* [n=3], *S aureus* plus *Salmonella* spp [n=1], *Acinetobacter baumanii* [n=2], *Escherichia coli* [n=1], *Salmonella* spp [n=1], *Enterococcus faecium* [n=1], and *Candida* spp [n=1]).

Data for the primary outcome (ie, death or readmission by day 28) were ascertainable in 1055 (95·8%) children. There was no evidence of association between having the primary outcome ascertained and any randomised allocation (all p>0·30) or other key baseline characteristics (all p>0·14), although there was small variation across centres (p=0·039 to p=0·90; appendix pp 40–41). In children with ascertainable primary outcomes, readmission or death occurred by day 28 in 27 (5·6%) of 484 in the amoxicillin group, 33 (6·9%) of 475 in the co-amoxiclav group, and six (6·3%) of 96 in the intravenous-only group (table 2; figure 3A; appendix p 20). There was no evidence that co-amoxiclav was superior to amoxicillin (adjusted risk difference [ARD] 1·3% [95% CI –1·8 to 4·4; p=0·40). Both amoxicillin (–2·3% [–10·2 to 5·7]; p=0·58) and co-amoxiclav (–0·7% [–7·4 to 6·0]; p=0·83) were non-inferior to intravenous only (non-inferiority margin +10%; figure 3B). Of the 66 events, 42 (64%) were readmissions, occurring a median of 17 days (IQR 12–21) after randomisation, and 24 (36%) were deaths, occurring a median of 5 days (2–11) after randomisation. There was one death after

readmission. Of the 60 events occurring in children randomised to step-down, 31 (52%) occurred after step-down.

In the oral step-down groups, all durations were non-inferior to 8 days (figure 3C; all upper 95% CI ≤6·0). There was no evidence of association between randomised duration and primary outcome (0·5% [95% CI –0·6 to 1·6] higher readmission or death for each additional day's antibiotics; p=0·34; table 3; figure 3A). Results by use of multiple imputation in all randomly assigned children were very similar for both randomised comparisons (appendix p 42). There was no evidence of interaction between the effects of drug and duration ($p_{interaction}$ =0·85; appendix p 43), or of different effects of step-down drug or randomised duration across the 13 prespecified subgroups, including age, CRP, or oxygen at baseline, and stepped down within 3 days of randomisation (all $p_{interaction}$ >0·16; appendix pp 44–47). Causes of readmission and death were primarily related to pneumonia or respiratory tract infections (appendix pp 48–49).

For most secondary effectiveness outcomes, there was little evidence of differences between drugs or durations (tables 2, 3; appendix pp 20, 50–51). Results were similar in the 51 (77%) of the 66 primary outcomes (ie, deaths and readmissions) adjudicated as being pneumonia related. There was no evidence of a linear association between randomised duration and death (+0·3% [95% CI –0·3 to 1·0] per additional antibiotic day; p=0·33), but there were slightly more deaths with 6-day treatment duration than the 8-day treatment duration (ARD +4·0% [0·1 to 7·9]). This finding likely reflects chance because, of the 23 deaths occurring in those randomised to step-down, 21 (91%) did not step down before death, 14 (61%) deaths occurred before their total randomised treatment duration, and 11 (48%) died up to and including day 4 (ie, the shortest duration tested; appendix pp 13, 21, 52). Both of the deaths that occurred after step-down were in the amoxicillin 7 days group, occurring on days 17 and 24 and having received antibiotics for 9 days and 8 days, respectively; one child was discharged on day 4 and died on day 17 after becoming ill at home 2 days before, and one child died after readmission to hospital on day 24 after diagnoses of HIV, rectovaginal fistula, patent ductus arteriosus, and a positive *Candida* spp blood culture.

Hospital stays were longer in the 5-day intravenous-only group than in the oral step-down groups for both the initial hospitalisation (mean 0·9 days [95% CI 0·0–1·8]; p=0·049) and in total up to day 28 (1·1 [0·1–2·1]; p=0·025; table 2), but there was no evidence of differences across durations (p=0·42 for index hospitalisation, p=0·34 for total length of stay up to 28 days; table 3) or between amoxicillin and co-amoxiclav step-down (p=0·22 for index hospitalisation, p=0·36 for total length of stay up to 28 days; table 2). There was no evidence of differences between the randomised drug

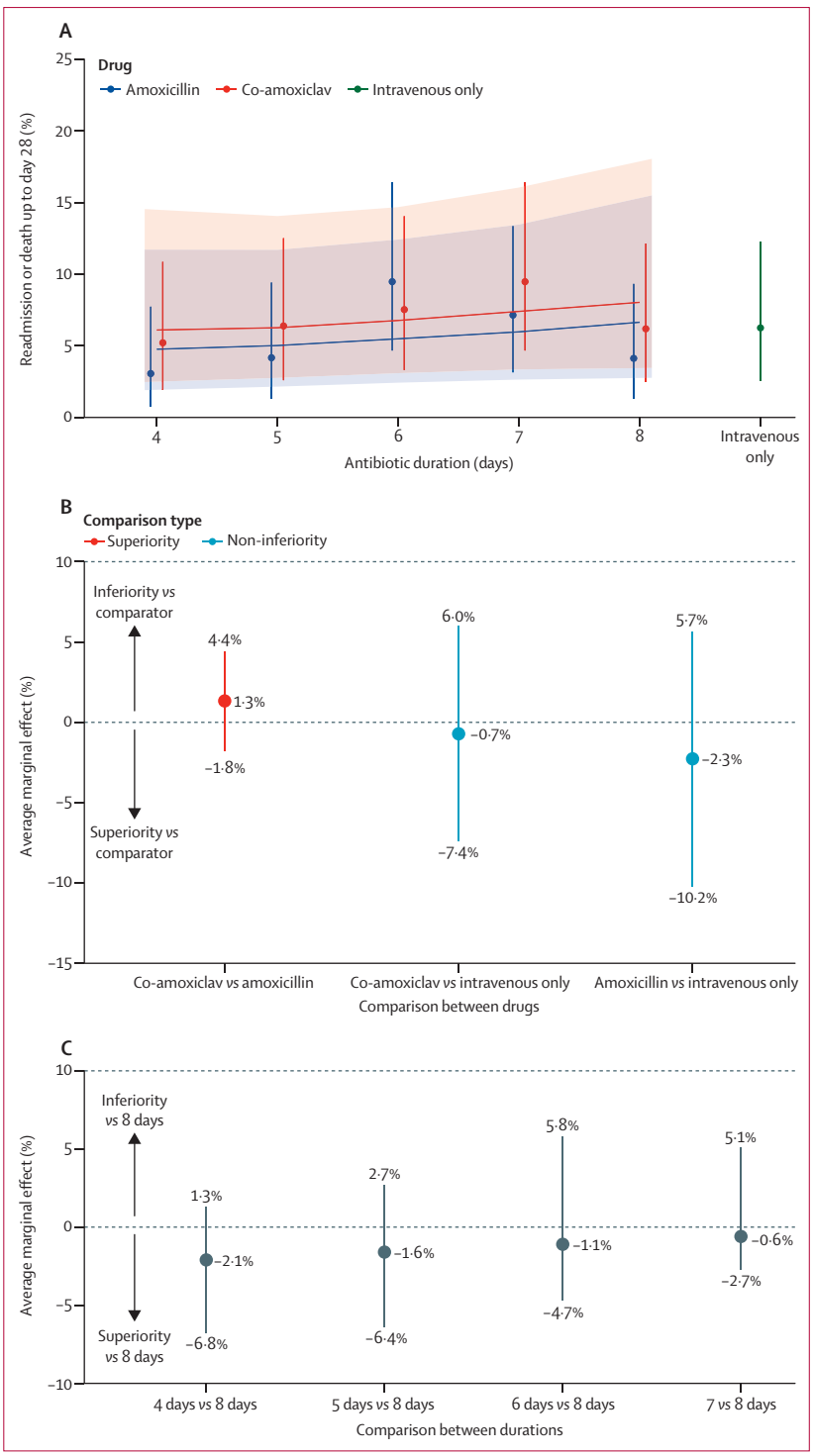

***Figure 3*: Readmission or death by day 28 (primary outcome)**
(A) By antibiotic duration, showing fitted lines. Vertical lines show 95% CIs. Shaded areas show the 95% CIs for the fitted lines. Higher values correspond to worse outcomes. (B) By drug comparisons. Vertical lines show 95% CIs. The dotted horizontal line at 10% represents the non-inferiority margin. (C) By duration comparisons for oral step-down groups only. Vertical lines show 95% CIs. The dotted horizontal line at 10% represents the non-inferiority margin.

	4 days	5 days	6 days	7 days	8 days	Mean adjusted marginal linear effect per additional day (95% CI)	p value
Readmission to hospital or death	8/194 (4·1%)	10/190 (5·3%)	16/188 (8·5%)	16/193 (8·3%)	10/194 (5·2%)	+0·5% (–0·6 to 1·6)	0·34
Death	1/194 (0·5%)	3/190 (1·6%)	9/188 (4·8%)	8/193 (4·1%)	2/192 (1·0%)	+0·3% (–0·3 to 1·0)	0·33
Length of stay during index hospitalisation, days	5·0 (2·8; n=204)	5·6 (4·7; n=198)	5·2 (4·0; n=196)	5·4 (3·9; n=200)	5·4 (3·8; n=203)	+0·1 (–0·1 to 0·2)	0·42
Total length of stay up to 28 days, days	5·1 (3·0; n=194)	5·8 (4·7; n=190)	5·4 (4·1; n=188)	5·8 (4·4; n=193)	5·6 (4·0; n=194)	+0·1 (–0·1 to 0·3)	0·34
Days of supplemental oxygen during index hospitalisation	2·0 (2·3; n=204)	2·5 (4·3; n=198)	2·2 (2·9; n=196)	2·3 (3·6; n=200)	2·4 (4·0; n=203)	+0·1 (–0·1 to 0·2)	0·43
Days on antibiotics up to 28 days	6·0 (3·5; n=194)	6·8 (4·2; n=190)	7·4 (3·6; n=188)	8·3 (3·4; n=193)	9·2 (2·9; n=192)	+0·8 (0·6 to 0·9)	<0·0001
Modification of randomised antibiotics for any reason other than early stopping, or requiring a subsequent course of antibiotics for any reason up to 28 days	46/194 (23·7%)	47/192 (24·5%)	47/188 (25·0%)	46/194 (23·7%)	42/196 (21·4%)	–0·6% (–2·4 to 1·3)	0·54
Modification of randomised antibiotics for inadequate response, or additional courses in the index hospitalisation for CAP relapse	7/194 (3·6%)	7/190 (3·7%)	12/188 (6·4%)	9/194 (4·6%)	5/192 (2·6%)	–0·2% (–1·0 to 0·7)	0·71
Grade 3 or 4 adverse events or serious adverse events	12/194 (6·2%; n=15 events)	16/190 (8·4%; n=20 events)	20/188 (10·6%; n=28 events)	24/193 (12·4%; n=30 events)	17/193 (8·8%; n=22 events)	+1·0% (–0·3 to 2·2)	0·14
Antibiotic-related adverse events or serious adverse events	1/194 (0·5%; n=1 events)	5/190 (2·6%; n=6 events)	7/189 (3·7%; n=11 events)	6/193 (3·1%; n=6 events)	9/193 (4·7%; n=11 events)	+0·9% (0·1 to 1·7)	0·032
Line complications	10/194 (5·2%)	13/190 (6·8%)	8/189 (4·2%)	10/193 (5·2%)	6/193 (3·1%)	–0·6% (–1·6 to 0·4)	0·22

Data are n/N (%), n/N (%; n events) for adverse events, or mean (SD; n). The n/N data for adverse events represent the number of children who had at least one adverse event per the total number of children with available data. Estimates of differences between drugs are outputs from models with fixed effects of drug, duration, and site. Estimates of linear effect of duration are outputs from models including only children in oral step-down groups with fixed effects of drug, duration, and site. See the appendix for other secondary outcomes including key solicited events and specific complications (pp 46–47), details of serious adverse events and reactions (p 52), and more analyses of mortality (pp 13, 21, 48–50). CAP=community-acquired pneumonia.

Table 3: **Effect of randomised duration on primary and key secondary and safety outcomes**

groups or the randomised duration groups in the number of days of oxygen during initial hospitalisation (all p>0·14). As expected, children randomly assigned to an oral treatment group and longer treatment durations received more total days of antibiotics (intravenous and oral) than those randomly assigned to shorter durations and intravenous-only treatment (both p<0·0001; tables 2, 3).

There was no evidence of consistent differences in adverse events for either step-down or duration comparisons (tables 2, 3; appendix pp 50–51, 53). For antibiotic-related adverse events or serious adverse events, there was one (1·0%) in the intravenous-only group and 12 (2·5%) in the amoxicillin group (ARD –2·3% [95% CI –4·2 to –0·3]; p=0·025; table 2) and rates increased with randomised duration (slope estimate +0·9% [0·1 to 1·7]; p=0·032; table 3). There was no robust evidence of differences in solicited safety outcomes between drugs or durations (appendix pp 50–51), although a higher proportion of children had line complications in the intravenous-only group (11 [11·5%] of 96) than in the amoxicillin group (21 [4·3%] of 484; ARD +12·9% [–0·1 to 24·8]; p=0·048).

Discussion

The PediCAP trial shows that, in terms of all-cause readmission and death within 28 days, a strategy of stepping down from intravenous treatment (given for at least 24 h) to oral amoxicillin, after clinical improvement and when oral medicines are tolerated, and treating for a total of 4–5 days is non-inferior to the WHO-recommended 5-day injectable antibiotics in children with severe CAP without complicating factors admitted in Africa. Although incidence and case fatality of childhood pneumonia are decreasing globally, pneumonia-related admissions have increased, with 12 million hospitalisations worldwide annually,[27] mostly in low-income and middle-income countries. In contrast, most CAP trials in these settings have focused on children managed in the community. Despite ongoing uncertainty in the microbiological attribution of childhood CAP, including frequent bacterial–viral co-detection, reliance on culture-negative syndromic diagnoses, and concerns about antimicrobial resistance influencing empirical treatment choices, we found no evidence to suggest oral step-down to co-amoxiclav was superior to amoxicillin. WHO recommends amoxicillin as the primary oral antibiotic for treating mild-to-moderate CAP,[18] which should therefore also be preferred for intravenous-to-oral step-down given its availability and affordability.[28]

With an intravenous to oral step-down strategy, 4–5 days of total treatment (ie, intravenous plus oral) were non-inferior to 8 days and fixed-duration, 5-day, intravenous-only antibiotics in terms of readmission and mortality. PediCAP tested a pragmatic strategy of stepping down to oral treatment when children had

improved clinically; the need for some children to continue intravenous antibiotics was anticipated within the protocol. Most deaths in children randomly assigned to step-down occurred before the switch to oral treatment, supporting its safety as a strategy. Although emerging evidence suggests that progressively shorter antibiotic courses might be effective when guided by clinical response,[10,11] further trials would be required to establish whether antibiotic treatment can safely be discontinued entirely at the point of clinical improvement. Two-thirds of children allocated oral step-down had changed to oral antibiotics after 3 days, and consequently the mean hospital stay was around 1 day shorter than the 5-day intravenous-only group. Following current guidance to treat for 5 days, implementing an intravenous-to-oral step-down strategy would result in many more children leaving hospital earlier and completing their treatment at home.

Earlier hospital discharge likely has two main benefits. First, longer inpatient stays increase risks of acquiring multidrug-resistant bacteria from hospital environments,[29] which make future infections more difficult to treat with recommended first-choice regimens.[30] Sub-Saharan Africa has a persistently high mortality burden of lower respiratory tract infections, including among children younger than 5 years (615 deaths per 100 000 population; estimated 335 000 deaths in 2021), predominantly driven by *S pneumoniae* (3 750 000 episodes and 69 000 deaths in 2021).[1] This region also has the highest rate of deaths associated with antimicrobial resistance from any infection type, with *S pneumoniae* (estimated deaths 132 700 in 2019) and *Klebsiella pneumoniae* (106 700 deaths) most implicated in children younger than 5 years.[31] Strategies are needed that will adequately treat CAP and minimise exposure to the hospital environment,[32] such as intravenous-to-oral step-down in patients showing clinical improvement after short intravenous treatment. We have shown this strategy to be safe and effective in children presenting with WHO-defined signs and symptoms of severe or very severe CAP.

Second, at family and societal levels, hospital-based treatment of severe acute childhood illness is associated with catastrophic health expenditures in 40–50% of affected households and represents a substantial financial burden for most.[33,34] Length of stay increases the financial burden on families of children requiring hospital treatment in Africa.[34] A safe intravenous-to-oral step-down to an affordable antibiotic that is widely available in high-quality, child-appropriate formulations to complete treatment at home could therefore reduce the economic effects of childhood CAP admissions.

One strength of our study is that the trial eligibility criteria aligned with WHO guidance and were primarily defined by clinical criteria for severe CAP and the decision to admit children to hospital for intravenous antibiotics. To enrich the trial population with children likely to benefit from antibiotics and to guard against bias towards non-inferiority in this open-label trial, children without evidence of clinically relevant inflammation—for example, due to isolated viral aetiology without bacterial co-infection—were excluded with point-of-care, semiquantitative CRP testing if CRP was below 10 mg/L. CRP values of more than 40 mg/L in 81·1% of participants and more than 80 mg/L in 44·6% suggest that the trial cohort predominantly comprised children likely to benefit from antibiotics.[35,36] Other exclusion criteria covered children in whom the strategies investigated might be inappropriate (eg, HIV-positive patients requiring specific antibiotic treatment or prophylaxis).

Although this pragmatic trial did not aim to identify pneumonia aetiology through systematic diagnostic testing, a microbiology substudy identified predominantly bacterial organisms in nasopharyngeal samples, with *S pneumoniae* and *Haemophilus influenzae* detected most frequently, whereas no individual respiratory virus predominated.[37] Co-detection of bacteria and viruses was common, consistent with mixed aetiology in hospitalised childhood pneumonia. These findings support the rationale for antibiotic treatment in this population. Although organisms such as *H influenzae* and *Moraxella catarrhalis*, which typically show reduced in-vitro susceptibility to amoxicillin, were also commonly detected, this finding did not translate into poorer clinical outcomes with amoxicillin in the trial, suggesting that antimicrobial resistance did not meaningfully compromise treatment effectiveness in this population. A key limitation of this substudy[37] is the inability to distinguish between carried and infecting organisms.

Our trial findings are generalisable to settings where CRP testing is not available given that intravenous-to-oral step-down and shorter treatments are likely to be safe even when used with a greater proportion of children who are not likely to benefit from antibiotics than in our study population. Our findings are further strengthened by the diversity of countries and sites included, with probable variability in pathogens and health-care resources. Although recruitment was dominated by southern African countries, we found no evidence of heterogeneity in treatment effects across countries or centres, supporting extrapolation to other sub-Saharan African hospital settings.

Our study has several limitations. PediCAP started before the COVID-19 pandemic, but most recruitment coincided with the pandemic. A small proportion of participants were tested and a negligible proportion were positive for SARS-CoV-2, consistent with rates of COVID-19 among hospitalised children reported for South Africa.[38] However, we cannot exclude the possibility that the microbiological epidemiology of acute respiratory infections was disturbed by the pandemic and national countermeasures. Other limitations include the fact that the primary outcome occurred in fewer children (6%)

than expected (9%) and our non-inferiority margin was prespecified at 10%. However, all upper 95% CIs were 6% or lower, making conclusions reasonably robust. We also only followed children up to 28 days and did not assess the persistence of symptoms, which might be important in long-term lung function and health.[39,40] However, a longer antibiotic treatment has not been shown to be associated with improved long-term respiratory outcomes, consistent with our short-term findings.[30]

PediCAP focused on children admitted to district and tertiary hospitals, and rates of severe malnutrition (12%) and HIV (1%) among enrolled children were low. Critically ill children and children on long-term antibiotics for prophylaxis or treatment (eg, tuberculosis or HIV) were not eligible and further trials of optimal drug, dose, and duration in these populations are required. Conversely, children with moderate illness without complicating factors could potentially be initially managed by oral antibiotics, further shortening hospital admissions or avoiding it altogether; this strategy warrants further evaluation. The low HIV prevalence likely relates to the exclusion of participants with previous antibiotic prophylaxis use. However, vertical transmission prevention programmes have successfully decreased HIV prevalence from 7% of South African paediatric inpatients in 2008 to 1% in 2021,[41] which could also help to explain these low prevalence values.

In summary, the results of PediCAP support a strategy of oral step-down to amoxicillin after 24 h or more of intravenous antibiotics and clinical improvement for most young children admitted to African hospitals with severe CAP. This strategy can be applied without extending total treatment beyond 5 days, in line with current WHO recommendations, and will enable earlier discharge for many children, with probable infection prevention and control and economic benefits.

Contributors

JAB, MC, VMus, DPM, VMul, DN, CC, MB-D, ZD, HAM, CG, SAM, ASW and MSh conceived and designed the study. MC carried out the analysis. MC and ASW directly accessed and verified the underlying data reported in the manuscript. JAB, MC, ASW, and MSh wrote the first draft of the manuscript. VMus, DPM, MSi, VMul, CM, DN, ZW, JC, CC, MB-D, BS, MA, AK, ZD, MK, AT, CJ, JS, WCB, SC, and HAM contributed to data acquisition and editing of the manuscript. JAB, SAM, and MSh provided oversight of the project. All authors read and approved the final draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MC and ASW were supported by core support to the MRC Clinical Trials Unit at UCL (MC_UU_00004/04 and MC_UU_00004/05). ASW is a National Institutes of Health and Care Research Senior Investigator. DPM was partly funded by a grant awarded by the Carnegie Corporation of New York. MSh chaired the 2023 WHO Expert Committee on the Selection and Use of Essential Medicines involved in the development of the 2023 WHO Essential Medicines List for Children, in which the amoxicillin 200 mg and clavulanic acid 28·5 mg (7:1) novel dispersible tablet used in this trial were included. All other authors declare no competing interests.

Data sharing

De-identified individual participant baseline characteristics and primary and secondary outcome data are openly available as supplementary material to this manuscript. The protocol and statistical analysis plan are also available at https://www.isrctn.com/ISRCTN63115131. Access to all other de-identified individual participant data will follow a controlled access approach immediately after publication, with no end date. Anyone wishing to access the underlying raw data should contact the corresponding author; data requestors will need to complete a short data access request form, which will be reviewed and approved by the trial investigators, and sign a data access agreement.

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References

1 GBD 2021 Lower Respiratory Infections and Antimicrobial Resistance Collaborators. Global, regional, and national incidence and mortality burden of non-COVID-19 lower respiratory infections and aetiologies, 1990–2021: a systematic analysis from the Global Burden of Disease Study 2021. *Lancet Infect Dis* 2024; **24:** 974–1002.

2 McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *Lancet Glob Health* 2019; **7:** e47–57.

3 Zhang S, Sammon PM, King I, et al. Cost of management of severe pneumonia in young children: systematic analysis. *J Glob Health* 2016; **6:** 010408.

4 Bielicki JA, Stöhr W, Barratt S, et al. Effect of amoxicillin dose and treatment duration on the need for antibiotic re-treatment in children with community-acquired pneumonia: the CAP-IT randomized clinical trial. *JAMA* 2021; **326:** 1713–24.

5 Dinh A, Ropers J, Duran C, et al. Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. *Lancet* 2021; **397:** 1195–203.

6 Ginsburg AS, Mvalo T, Nkwopara E, et al. Amoxicillin for 3 or 5 days for chest-indrawing pneumonia in Malawian children. *N Engl J Med* 2020; **383:** 13–23.

7 Pernica JM, Harman S, Kam AJ, et al. Short-course antimicrobial therapy for pediatric community-acquired pneumonia: the SAFER randomized clinical trial. *JAMA Pediatr* 2021; **175:** 475–82.

8 Williams DJ, Creech CB, Walter EB, et al. Short- *vs* standard-course outpatient antibiotic therapy for community-acquired pneumonia in children: the SCOUT-CAP randomized clinical trial. *JAMA Pediatr* 2022; **176:** 253–61.

9 Kuitunen I, Jääskeläinen J, Korppi M, Renko M. Antibiotic treatment duration for community-acquired pneumonia in outpatient children in high-income countries-a systematic review and meta-analysis. *Clin Infect Dis* 2023; **76:** e1123–28.

10 Gao Y, Liu M, Yang K, et al. Shorter versus longer-term antibiotic treatments for community-acquired pneumonia in children: a meta-analysis. *Pediatrics* 2023; **151:** e2022060097.

11 Bolormaa E, Kang CR, Choe YJ, et al. Evaluating short-course antibiotic therapy for pediatric community-acquired pneumonia: a systematic review and meta-analysis. *Pediatr Infect Dis J* 2025; **44:** 637–44.

12 WHO. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. 2nd edn ed. World Health Organization, 2013.

13 WHO. Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. World Health Organization, 2014.

14 Atkinson M, Lakhanpaul M, Smyth A, et al. Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. *Thorax* 2007; **62:** 1102–06.

15 Rojas-Reyes MX, Granados Rugeles C. Oral antibiotics versus parenteral antibiotics for severe pneumonia in children. *Cochrane Database Syst Rev* 2006; **2006:** CD004979.

16 Teng G-L, Chi J-Y, Zhang H-M, Li X-P, Jin F. Oral *vs* parenteral antibiotic therapy in adult patients with community-acquired pneumonia: a systematic review and meta-analysis of randomized controlled trials. *J Glob Antimicrob Resist* 2023; **32:** 88–97.

17 Agweyu A, Gathara D, Oliwa J, et al. Oral amoxicillin versus benzyl penicillin for severe pneumonia among kenyan children: a pragmatic randomized controlled noninferiority trial. *Clin Infect Dis* 2015; **60:** 1216–24.

18 WHO. The WHO AWaRe (access, watch, reserve) antibiotic book. World Health Organization, 2022.

19 Ikilezi G, Augusto OJ, Dieleman JL, Sherr K, Lim SS. Effect of donor funding for immunization from Gavi and other development assistance channels on vaccine coverage: evidence from 120 low and middle income recipient countries. *Vaccine* 2020; **38:** 588–96.

20 Johnstone SL, Moore DP, Klugman KP, Madhi SA, Groome MJ. Epidemiology of invasive bacterial infections in pneumococcal conjugate vaccine-vaccinated and -unvaccinated children under 5 years of age in Soweto, South Africa: a cohort study from a high-HIV burden setting. *Paediatr Int Child Health* 2020; **40:** 50–57.

21 Mahtab S, Blau DM, Madewell ZJ, et al. Post-mortem investigation of deaths due to pneumonia in children aged 1–59 months in sub-Saharan Africa and South Asia from 2016 to 2022: an observational study. *Lancet Child Adolesc Health* 2024; **8:** 201–13.

22 Quartagno M, Carpenter JR, Walker AS, Clements M, Parmar MK. The DURATIONS randomised trial design: estimation targets, analysis methods and operating characteristics. *Clin Trials* 2020; **17:** 644–53.

23 Ngari MM, Fegan G, Mwangome MK, et al. Mortality after inpatient treatment for severe pneumonia in children: a cohort study. *Paediatr Perinat Epidemiol* 2017; **31:** 233–42.

24 Marangu-Boore D, Mwaniki P, Isaaka L, et al. Characteristics of children readmitted with severe pneumonia in Kenyan hospitals. *BMC Public Health* 2024; **24:** 1324.

25 US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research. Community-acquired bacterial pneumonia: developing drugs for treatment: guidance for industry. June 24, 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/community-acquired-bacterial-pneumonia-developing-drugs-treatment (accessed April 6, 2026).

26 US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Non-inferiority clinical trials to establish effectiveness: guidance for industry. November, 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials (accessed April 6, 2026).

27 McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *Lancet Glob Health* 2019; **7:** e47–57.

28 Dharmapalan D, Bielicki J, Sharland M. Harmonization of amoxicillin dose, duration, and formulation for acute childhood respiratory infections. *Antibiotics* 2023; **12:** 1138.

29 Magwenzi MT, Gudza-Mugabe M, Mujuru HA, Dangarembizi-Bwakura M, Robertson V, Aiken AM. Carriage of antibiotic-resistant *Enterobacteriaceae* in hospitalised children in tertiary hospitals in Harare, Zimbabwe. *Antimicrob Resist Infect Control* 2017; **6:** 10.

30 Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340:** c2096.

31 Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399:** 629–55.

32 Sartorius B, Gray AP, Davis Weaver N, et al. The burden of bacterial antimicrobial resistance in the WHO African region in 2019: a cross-country systematic analysis. *Lancet Glob Health* 2024; **12:** e201–16.

33 Ilunga-Ilunga F, Levêque A, Laokri S, Dramaix M. Incidence of catastrophic health expenditures for households: an example of medical attention for the treatment of severe childhood malaria in Kinshasa reference hospitals, Democratic Republic of Congo. *J Infect Public Health* 2015; **8:** 136–44.

34 Yap A, Olatunji BT, Negash S, et al. Out-of-pocket costs and catastrophic healthcare expenditure for families of children requiring surgery in sub-Saharan Africa. *Surgery* 2023; **174:** 567–73.

35 Van den Bruel A, Thompson MJ, Haj-Hassan T, et al. Diagnostic value of laboratory tests in identifying serious infections in febrile children: systematic review. *BMJ* 2011; **342:** d3082.

36 Higdon MM, Le T, O'Brien KL, et al. Association of C-reactive protein with bacterial and respiratory syncytial virus-associated pneumonia among children aged <5 years in the PERCH study. *Clin Infect Dis* 2017; **64** (suppl 3)**:** S378–86.

37 Rodriguez-Ruiz JP, Loens K, Musiime V, et al. Detection of respiratory pathogens in the nasopharynx of children hospitalised with severe pneumonia in sub-Saharan Africa (P0954). ESCMID Global; April 11–15, 2025.

38 Kufa T, Jassat W, Cohen C, et al. Epidemiology of SARS-CoV-2 infection and SARS-CoV-2 positive hospital admissions among children in South Africa. *Influenza Other Respir Viruses* 2022; **16:** 34–47.

39 Collaro AJ, McElrea MS, Marchant JM, et al. The effect of early childhood respiratory infections and pneumonia on lifelong lung function: a systematic review. *Lancet Child Adolesc Health* 2023; **7:** 429–40.

40 Kok HC, McCallum GB, Yerkovich ST, et al. Twenty-four month outcomes of extended-versus standard-course antibiotic therapy in children hospitalized with pneumonia in high-risk settings: a randomized controlled trial. *Pediatr Infect Dis J* 2024; **43:** 872–79.

41 de Beer ST, Slogrove AL, Eley B, et al. Change in HIV-related characteristics of children hospitalised with infectious diseases in Western Cape, South Africa, 2008–2021: a time trend analysis. *J Int AIDS Soc* 2023; **26** (suppl 4)**:** e26151.