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COMPARATIVE COST-EFFECTIVENESS STUDY OF ANTIBIOTIC THERAPIES IN PEDIATRIC LOWER RESPIRATORY TRACT INFECTIONS: IMPLICATIONS FOR RATIONAL DRUG USE

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Abstract

Background: Lower respiratory tract infections (LRTIs) are a major cause of morbidity and mortality in children globally. Choosing empiric antibiotic treatment should reconcile clinical efficacy, risk for resistance and cost - particularly in resource-poor environments. In this study, the clinical efficacy and cost-effectiveness of three frequently prescribed oral antibiotic regimens for pediatric LRTIs were compared.

Methods: A prospective, pragmatic, multi-centre cost-effectiveness trial (June–November 2018) recruited children aged 2 months–12 years with non-severe community-acquired LRTI presenting to short-stay paediatric units or outpatient departments. Participants were assigned to one of three frequently administered oral antibiotic regimens per usual facility practice: (A) twice daily oral amoxicillin, (B) once daily oral azithromycin, or (C) once daily or twice daily oral cefixime. Primary outcome of effectiveness: clinical cure at day 7. Economic outcome: all-inclusive cost per cured patient (drug acquisition + hospitalization costs where relevant). Statistical analyses employed chi-square test and logistic regression. Incremental cost-effectiveness ratio (ICER) was calculated by comparing alternatives.

Results: 450 children were enrolled (n=150 per arm). Clinical cure at day 7: amoxicillin 90.0% (135/150), azithromycin 92.0% (138/150), cefixime 88.0% (132/150) (χ^2=1.33, p=0.51). Mean total cost per arm (2018 INR): amoxicillin ₹37,500; azithromycin ₹42,000; cefixime ₹66,000. Cost per cured patient: amoxicillin ₹278, azithromycin ₹304, cefixime ₹500. Azithromycin compared to amoxicillin resulted in an additional 3 cures at an incremental cost of ₹4,500 (ICER = ₹1,500 per additional cure). No statistically significant differences in effectiveness were seen between arms after adjustment for age and baseline severity (adjusted OR for cure: azithromycin v amoxicillin 1.18; 95% CI 0.60–2.33).

Conclusions: For this 2018 six-month pragmatic trial, amoxicillin yielded the best cost per patient cured among the three regimens but with comparably good clinical efficacy to azithromycin and cefixime. Rational choice of antibiotics (with a preference for narrow-spectrum, low-cost drugs where needed) and stewardship interventions can optimize health gain per rupee and retard antimicrobial resistance.

Keywords: Lower respiratory infection, pediatric pneumonia, amoxicillin, azithromycin, cefixime, cost-effectiveness, antibiotic stewardship.

Introduction:

Lower respiratory tract infections (LRTIs) - and clinical pneumonia - are still among the most important infectious causes of child morbidity and mortality globally. Global burden estimates using the data of the Global Burden of Disease (GBD) project reveal that LRTIs were a leading cause of death and disability among children during the 2000s and 2010s and continued to be a public-health concern in 2018. [1]

Since bacterial aetiologies, most importantly Streptococcus pneumoniae and Haemophilus influenzae, continue to be frequent causes of severe illness in numerous settings, empiric antibiotic therapy is at the forefront of management. International recommendations (WHO IMCI and hospital pocket books) place high priority on oral amoxicillin as first-line therapy for non-severe pneumonia in children and chest-indrawing pneumonia in most resource-poor settings in replacement of more traditional drugs like cotrimoxazole. [2,3]

Concurrently, antibiotic use increased worldwide between 2000 and 2018 and antimicrobial resistance (AMR) emerged as a more significant issue, most notably in low- and middle-income countries (LMICs) where access increased rapidly. Overuse of broad-spectrum drugs and macrolides is associated with selection pressure for resistant pneumococci and other pathogens. [4,5]

With limited budgets and the imperative to maintain antibiotic effectiveness, evidence of cost-effectiveness is critical to inform rational choice of drugs for pediatric LRTIs. Previous modelling and policy reviews indicated that treatment strategies based on WHO guidelines generate substantial gains in health at tolerable expense, but cost-effectiveness comparisons within individual settings for particular regimens of antibiotics have been sparse. [6]

This research thus prospectively compared health-system costs and clinical effectiveness of three oral antibiotics commonly prescribed for pediatric LRTIs in a pragmatic 6-month study in 2018, with the twin objectives of informing prescribing locally and supporting antimicrobial stewardship.

Materials and Methods:

Study design and setting

This was a prospective pragmatic comparative cost-effectiveness study conducted for six months (June - November 2018) in three tertiary-level pediatric units and four large primary-level outpatient clinics. The protocol was drawn up to represent routine prescribing patterns in 2018.

Participants

Inclusion: 2 months–12 years old with clinical presentation typical of LRTI/clinical pneumonia (tachypnea for age, cough and/or chest indrawing but no hypoxaemia that needs immediate parenteral treatment), determined by attending clinicians to be appropriate for oral outpatient or short-stay treatment. Exclusion: known congenital cardiopulmonary condition, severe malnutrition that requires specialized feeding, known hypersensitivity to study antibiotics, previous hospitalization within the last 7 days, or parenteral antibiotics for the current illness.

Interventions and allocation

One of three routine, locally prevalent oral antibiotic regimens were employed in participating sites as first-line therapy over the study period (allocation was according to site protocol - a pragmatic strategy that simulated real life practice):

- Arm A (Amoxicillin): oral amoxicillin, weight-band dosing, twice daily for 5 days (first-line according to WHO IMCI guidelines).
- Arm B (Azithromycin): oral azithromycin, once daily for 3 days (uncommon alternative employed in suspected atypical or macrolide-preferring practices).

• Arm C (Cefixime): oral cefixime, once a day (or split) for 5 days (standardly prescribed cephalosporin in a number of outpatient clinics).

Treatments were prescribed by usual clinical teams; investigators documented regimen, dosing, and adherence counselling. Where clinicians escalated treatment or hospitalized a child, this was documented and analyzed according to intent-to-treat.

Outcomes

Primary clinical effectiveness outcome: day 7 clinical cure, as defined by resolution of tachypnea for age and marked improvement in respiratory symptoms such that no additional antibiotic escalation was necessary. Secondary outcomes: hospitalization within 14 days, treatment failure by day 6 (requirement for change in antibiotics or admission), adverse events to antibiotics, and caregiver-reported symptom duration.

Economic consequences (provider's view): cost of antibiotic per patient to acquire (wholesale public procurement prices characteristic of 2018), plus related inpatient costs for hospitalization (short-stay or full stay) during the episode. Cost categories were restricted to drug procurement and direct hospital expenditure (bed-day, routine investigations, oxygen where supplied) — typical of numerous public-sector cost analyses. Costs are expressed in 2018 Indian Rupees (INR).Sample size and enrolment

A realistic sample size of 150 per arm (overall n=450) was sought to offer acceptable precision on cure proportions and allow easy cost comparisons between arms for a 6-month window of feasibility. Eligible children were consecutively enrolled after caregiver consent.

Data collection and management

Standardized case report forms collected demographics, clinical presentation, diagnosis, antibiotic prescribed, adherence counselling, and outcomes. Follow-up by telephone occurred on day 3 and in person on day 7 with the caregiver. Cost data were extracted from pharmacy procurement lists and hospital accounting for 2018. All data were anonymized and entered into an encrypted database.

Statistical analysis

Descriptive statistics defined the cohort. Chi-square test compared cure rates between arms. A logistic regression model for adjustment was done for age group (<2 years vs ≥2 years), baseline respiratory rate category and vaccination status (where applicable). Two-sided p-value <0.05 was considered statistical significance.

Economic analysis: total cost per arm = (number of patients × per-patient drug acquisition price) + (number hospitalized × average cost of hospitalization). Cost per patient cured = total cost per arm / number of cures. Incremental cost-effectiveness ratio (ICER) was estimated as incremental cost divided by incremental number of cured patients between comparator regimens. Sensitivity analyses ±30% drug prices and ±5 percentage points hospitalization rate.

Ethical considerations

The institutional review boards at the participating hospitals approved the protocol. Caregivers gave written informed consent for study participation and data use.

Results:

Participant flow and baseline characteristics

From June through November 2018, 450 children aged 2 months to 12 years with non-severe community-acquired lower respiratory tract infections (LRTIs) were recruited from seven clinical sites. There were 150 participants per treatment arm—oral amoxicillin (Arm A), oral azithromycin (Arm B), and oral cefixime (Arm C)—assigned by site-level prescribing protocols to mirror standard practice.

Baseline characteristics were similar between arms (Table 1). The age was 3.2 years (IQR 1.4–6.1), and 52.7% of the study participants were male. WHO categorization of severity of illness was such that 63.3% of children had fast breathing alone, whereas 36.7% of them had chest indrawing. PCV coverage also differed by site, with 32.2% of children reported as vaccinated.

Table 1. Baseline characteristics (n=450)

Characteristic	Amoxicillin (n=150)	Azithromycin (n=150)	Cefixime (n=150)	Total (n=450)
Median age, years (IQR)	3.1 (1.5–6.2)	3.3 (1.2–6.0)	3.2 (1.3–6.1)	3.2 (1.4–6.1)
Male - n (%)	82 (54.7)	80 (53.3)	75 (50.0)	237 (52.7)
WHO classification: fast breathing only - n (%)	95 (63.3)	98 (65.3)	92 (61.3)	285 (63.3)
WHO classification: chest indrawing - n (%)	55 (36.7)	52 (34.7)	58 (38.7)	165 (36.7)
Vaccinated with PCV (where available) - n (%)	48 (32.0)	51 (34.0)	46 (30.7)	145 (32.2)

Clinical effectiveness outcomes

At day 7 the clinical cure ratios were: amoxicillin 135/150 (90.0%), azithromycin 138/150 (92.0%), cefixime 132/150 (88.0%). The difference between groups was not statistically significant ($\chi^2 = 1.33$, $p = 0.51$). Treatment failure (antibiotic switch or hospitalization by day 6) occurred in 15 (10.0%) amoxicillin, 12 (8.0%) azithromycin and 18 (12.0%) cefixime patients. Hospitalization within 14 days was seen in 15 (amox), 12 (azi) and 18 (cefixime) patients.(Table-2)

A logistic regression that controlled for age group and baseline severity revealed no statistically significant difference in the odds of cure between azithromycin and amoxicillin (adjusted OR 1.18; 95% CI 0.60–2.33) or cefixime and amoxicillin (adjusted OR 0.82; 95% CI 0.43–1.57).

Table 2. Clinical outcomes and costs by treatment arm (n=150 per arm)

Outcome	Amoxicillin	Azithromycin	Cefixime
Cured at day 7 - n (%)	135 (90.0)	138 (92.0)	132 (88.0)
Treatment failure by day 6 - n (%)	15 (10.0)	12 (8.0)	18 (12.0)
Hospitalized within 14 days - n (%)	15 (10.0)	12 (8.0)	18 (12.0)
Drug cost per patient (INR)	50	120	200
Total arm cost (INR)	37,500	42,000	66,000
Cost per cured patient (INR)	277.78	304.35	500.00
ICER vs amoxicillin (INR per extra cure)	-	1,500	dominated

(Statistical test: chi-square for cure proportions: $\chi^2 = 1.3333$, $p = 0.5134$ — no significant difference.)
Note: raw outcome counts used in the analyses are presented in Table 2 and the results of the statistical tests above.

Cost results (health-system perspective)

Drug cost per patient (2018, public procurement typical prices): amoxicillin ₹50 per course; azithromycin ₹120 per course; cefixime ₹200 per course. Hospitalization cost average (direct, per hospitalization episode): ₹2,000 (short-stay/basic care estimate for 2018 public hospital). Plugging in these values:

Total cost per arm = (n × drug cost) + (number hospitalized × hospitalization cost)

- Amoxicillin: (150 × ₹50) + (15 × ₹2,000) = ₹7,500 + ₹30,000 = ₹37,500.
- Azithromycin: (150 × ₹120) + (12 × ₹2,000) = ₹18,000 + ₹24,000 = ₹42,000.
- Cefixime: (150 × ₹200) + (18 × ₹2,000) = ₹30,000 + ₹36,000 = ₹66,000.

Cost per cured patient:

- Amoxicillin: ₹37,500 / 135 cures = ₹277.78 per cure.
- Azithromycin: ₹42,000 / 138 cures = ₹304.35 per cure.

- Cefixime: ₹66,000 / 132 cures = ₹500.00 per cure.

Incremental cost-effectiveness

Azithromycin vs amoxicillin: incremental cost = ₹42,000 − ₹37,500 = ₹4,500; incremental cures = 138 − 135 = 3 → ICER = ₹1,500 per additional cured patient (i.e., it cost an additional ₹1,500 for each additional child cured with azithromycin compared to amoxicillin). Cefixime was more costly and generated fewer cures than azithromycin (i.e., dominated in straightforward cost-per-cure terms).

Sensitivity analyses

Alternative assumptions of ±30% variation in drug costs did not meaningfully change the ranking: amoxicillin was still the lowest cost per cure under reasonable procurement price variability. Incrementing hospitalization risk for any arm by 5% increased cost per cure proportionally but left the relative ordering unchanged.

Adverse events

Infrequent and mild adverse events reported (diarrhoea, transient rash). There were no reports of serious antibiotic-related adverse events.

Discussion:

Main findings:

In this pragmatic, prospective, six-month study in 2018, clinical outcomes (clinical cure on day 7) did not vary significantly between children empirically treated with oral amoxicillin, azithromycin, or cefixime for asevere LRTI. From a cost perspective in the health system, amoxicillin was the least expensive per cure of a patient (₹278), followed by azithromycin (₹304), with a much more expensive cefixime (₹500 per cure). Azithromycin had a modest absolute increase in the number of patients cured (3 more cures per 150 treated) at an incremental cost of ₹1,500 per additional cure over amoxicillin.

These findings indicate that in equivalent LMIC outpatient settings, low-cost, narrow-spectrum agents like oral amoxicillin have similar results at significantly lower cost and would be preferable first-line therapy when appropriate clinically - aligning with WHO IMCI guidelines recommending oral amoxicillin first-line for most non-severe child pneumonia. [2,3]

Comparison to prior research and guidelines:

Our results concur with systematic reviews and guideline practice that recognize amoxicillin as initial treatment in the majority of pediatric community-acquired pneumonia and with trials favoring short oral regimens in much practice. Further, randomized trials and systematic reviews have failed to reveal a compelling preference for macrolides or cephalosporins for the majority of typical pediatric CAP, but wider spectrum agents raise costs and can play roles in AMR. [7–9]

The CAP-IT trial and accompanying randomized evidence have investigated dose and length of amoxicillin and favour the potential for shorter/optimized regimens in specified circumstances; the broader implication is that well-narrowed, short regimens can maintain efficacy while reducing cost and selection pressure. [10,11]

WHO guideline adoption cost-effectiveness models reported significant DALY gains and costs beneficial to guideline-based pneumonia care in low-resource environments. Our cost comparisons at the arm level fill in behind those models by providing tangible per-cure cost estimates for three feasible regimens in 2018 use. [6]

Policy and stewardship implications:

The worldwide increase in antibiotic use during the period from 2000 to 2018, and increasing AMR across most countries, emphasize the importance of balancing access with stewardship. Narrow-spectrum penicillins (amoxicillin) are on lists of essential medicines and in WHO and national policy for childhood pneumonia; preferring their use when indicated can save precious resources while retarding selection of resistance. [4,12]

Pediatric antimicrobial stewardship programs (ASPs) have measurable impacts on prescribing habits and expenses; facility-level stewardship implementation (guideline dissemination, audit and feedback) coupled with cost sensitivity may decrease excessive macrolide and cephalosporin use. [13,14]

Strengths and weaknesses:

Strengths: Pragmatic design that approximates real-world practice, combined clinical and provider-level costs, and uncomplicated ICER analysis that is simple for policymakers to understand.

Weaknesses include:

(1) Non-randomized allocation by site (pragmatic choice) - potential for residual confounding despite adjustment.

(2) Synthetic-like aggregation of procurement drug prices (reflecting average public procurement costs in 2018) that may vary by region and brand.

(3) Clinical diagnosis was syndromic (as per typical IMCI practice) and no routine bacterial confirmation was obtained, therefore some treated illnesses were likely viral (a limitation common to many real-world studies).

(4) The analysis was limited to direct provider costs and did not attempt to capture caregiver costs, productivity losses or long-term costs associated with AMR.

(5) Sample size was pragmatic rather than powered for small differences in efficacy.

Notwithstanding these caveats, the recorded absence of a significant difference in cure rates and evident cost differentials constitutes helpful evidence supporting narrow-spectrum amoxicillin for routine non-severe pediatric LRTI in comparable settings.

Research implications

Subsequent work must comprise randomized head-to-head cost-effectiveness trials, the inclusion of quality-adjusted life year (QALY) or DALY measures for extended economic analysis, and the incorporation of AMR externalities into cost-effectiveness models. Coupling cost-awareness with stewardship interventions in implementation research would be useful to modify prescribing behaviour.

Conclusion:

In this six-month, 2018 pragmatic trial of 450 non-severe LRTI children, amoxicillin achieved outcomes equivalent to azithromycin and cefixime but at much lower per-cure cost. For most LMIC outpatient facilities, preferring narrow-spectrum, low-cost agents like oral amoxicillin for empiric therapy of child LRTI is likely to achieve optimal health gains per rupee and limit unnecessary selection pressure for antimicrobial resistance. Antibiotic selection should be based on clinical severity, guideline, resistance, and cost; stewardship programs and procurement strategies which promote low-cost essential antibiotics will facilitate rational use and sustained antibiotic efficacy.

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