Antimicrobial prescribing practices for children hospitalised with respiratory tract illnesses at a tertiary public sector hospital in South Africa

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Background. Antimicrobial prescribing practices for children hospitalised with lower respiratory tract infections (LRTIs) are infrequently reported, particularly in developing countries.
Objectives. We evaluated the antimicrobials prescribed to children with severe respiratory illness hospitalised at Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, South Africa, from 22 July until 22 September 2021.
Methods. Children aged 1 month to 14 years who were hospitalised with severe acute respiratory illness were enrolled. We assessed frequency of antibiotic usage, admission diagnoses and 28-day outcomes.
Results. A total of 183 children were screened and 85 (46.4%) were enrolled. Most of the enrolled children (*n*/*N*=75/85; 88.2%) received antibiotic therapy. The most common diagnoses were bronchiolitis (*n*/*N*=30/85; 35.3%), LRTI (*n*/*N*=21/85; 24.7%), and pneumonia (*n*/*N*=18/85; 21.2%). Twenty-five (83.3%) of the children with bronchiolitis were treated with antibiotic therapy. Of the 122 antibiotics prescribed, 109 (89.3%) were classified in the WHO AWaRe groups of antimicrobials, and 95 (77.9%) were 'Access' antibiotics. Co-amoxiclav, amoxicillin and ampicillin were the most commonly prescribed antimicrobials. The median length of hospitalisation in those who survived to discharge was 3 (1 - 57) days. Three children died, two in-hospital and one post discharge.
Conclusion. Antimicrobials are commonly prescribed to children with severe respiratory illness hospitalised at CHBAH. Children with bronchiolitis were commonly treated with antimicrobials and should be targeted as a major focus group for optimisation of antimicrobial stewardship practice.

Keywords. child; respiratory infection; antibiotics; bronchiolitis; antimicrobial stewardship.

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Lower respiratory tract infections (LRTIs) are a leading cause of death in children less than five years of age globally, although the burden of disease and mortality is declining steadily due to increasing access to vaccines, improvements in the care of immunocompromised children, and increasing access to healthcare facilities.[1] LRTI is a blanket term, which includes a spectrum of infectious syndromes of the lung, spanning from bronchiolitis (which is typically caused by respiratory viruses) and bronchopneumonia, to pneumonia associated with consolidation of the alveolar spaces (which may be caused by respiratory viruses, bacteria, fungi, or a combination of infecting organisms).

In the era before access to the polysaccharide-protein vaccines that target *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, these two pathogens were responsible for over 50% of all childhood pneumonia episodes.[4] With increasing access to highly effective vaccines that reduce the risk of pneumonia caused by these bacteria, respiratory viruses have come into prominence as leading causes of paediatric pneumonia requiring hospitalisation. In the Pneumonia Etiology Research for Child Health (PERCH) Study, respiratory syncytial virus (RSV) was the leading cause of radiologically confirmed pneumonia in HIV-uninfected children less than 5 years of age, and respiratory viruses generally caused 61.4% (95% credible interval 57.3 - 65.6%) pneumonia episodes.[5]

The World Health Organization (WHO) established a classification system of pneumonia in 2005,[2] which was updated in 2013[3] and promotes the use of a highly sensitive but nonspecific case definition of childhood pneumonia. WHO guidelines for treatment of severe childhood pneumonia recommends use of ampicillin (or penicillin) and gentamicin administered intravenously for five days,[24] as there is no established clinical or biochemical marker to differentiate bacterial from viral infection. Over-reliance on antimicrobial therapy drives antimicrobial resistance (AMR), therefore it is important to rationalise antimicrobial prescribing in children hospitalised with pneumonia. Paediatric pneumonia guidelines currently recommend antibiotic therapy as part of the management of children hospitalised with pneumonia, although many pneumonia episodes may be caused by viruses.[6]

We evaluated the antibiotic prescribing practices of clinicians treating children hospitalised with respiratory infections at Chris Hani Baragwanath Academic Hospital (CHBAH), a public sector facility in Johannesburg, South Africa (SA).

Methods

This study was a site-specific sub-study of the PediCAP Trial (https://penta-id.org/severe-infections-and-antimicrobial-resistance/pedicap/), a trial undertaken in SA, Mozambique, Uganda, Zimbabwe and Zambia that investigated the efficacy of oral step-down antibiotic treatment for children aged two months to six years hospitalised with severe pneumonia in preventing death or re-hospitalisation within 28 days of randomisation. PediCAP inclusion criteria were a point-of-care C-reactive protein (CRP) level ≥10 mg/L and an admission diagnosis of severe pneumonia requiring at least 24 hours of intravenous antibiotic therapy (ampicillin, ampicillin and gentamicin, ceftriaxone or cefotaxime). Treatment arms in PediCAP were assigned through a centralised randomisation process, with participants receiving either five days of intravenous antibiotic therapy, or step-down to dispersible amoxicillin or co-amoxiclav tablets for 4 to 8 days of treatment. In PediCAP, study participants were followed for a period of four weeks post randomisation to evaluate the primary outcome of readmission or death.

Children admitted to the general paediatric wards at CHBAH, from 22 July to 22 September 2021 were enrolled into this sub-study if deemed ineligible for PediCAP enrolment. The rationale for including children that were ineligible for inclusion in the PediCAP trial was so that we could evaluate the regular prescribing practices of clinicians when treating children hospitalised with respiratory tract infections. Children with an admission diagnosis predominantly due to asthma were not considered for enrolment, unless they were on antimicrobial therapy.

Participant clinical and demographic details, including antibiotic regimens, were entered into case report forms and captured electronically for data cleaning and analysis. Reasons for not being enrolled into PediCAP, demographic and clinical data, admission and discharge diagnoses, outcome and length of hospitalisation were also recorded. Antimicrobial therapy used during the hospitalisation, and outcome at 28 days after enrolment were evaluated through inpatient follow-up assessments and telephonic follow-up interviews post discharge.

Conventional descriptive statistical methods were used to analyse the data. Additionally, we compared the characteristics of children hospitalised with a diagnosis of bronchiolitis and those of children with other LRTI diagnoses to appraise the differences in clinical characteristics between the groups. Duration of antimicrobial therapy for those discharged home on anti-tuberculosis therapy was censored on 15 November 2021 for the calculation of total antimicrobial administration for the study participants, combined. This cut-off date was arbitrarily chosen to accommodate prolonged therapy in children discharged on anti-tuberculosis therapy. All analyses were done using R version 4.2.2 (R Core Team).[8]

Written informed consent was obtained from caregivers, and assent was obtained from children older than 7 years of age. The Human Research Ethics Committee (Medical) of the University of the Witwatersrand Faculty of Health Sciences approved the study (ref. no. M210606).

Results

In the 2-month study period, there were 934 general paediatric admissions to CHBAH, of which 247 (26.4%) were admitted with respiratory illness. Of these, 183 (74.1%) were screened for inclusion, of which 85 (46.4%) were enrolled. The most common reasons for non-enrolment (n=98) included inability to contact caregivers (n=34; 34.7%), refusal of consent (n=16; 16.3%), and screening failure (n=12; 12.2%). Screening failure occurred when the child was eligible for inclusion but not enrolled erroneously. Among the enrolled children, reasons for non-enrolment into the PediCAP Trial included being age-ineligible (n=11), having low CRP levels (n=17), not having been started on antibiotic treatment for their respiratory illness (n=9) and clinician antibiotic choice (n=48).

Characteristics of the study participants

The most common diagnoses included bronchiolitis, LRTI and pneumonia, which were diagnosed in 69 (81.2%) of the participants (Fig. 1a). There were 67 (78.8%) HIV-negative children, 15 (17.6%) with undetermined HIV infection status and three (3.5%) HIV-positive children. The three HIV-positive children were admitted with diagnoses of pneumonia (n=2) and bronchiolitis (n=1). One of the HIV-positive patients (a 10.4-year-old male) had an undetectable HIV viral load and a CD4 cell count of 128 cells/μL on a dolutegravir-based ART regimen. The other two HIV-positive children (aged 3.0 and 13.3 months, respectively) were ART-naïve, and presented with respiratory infections as part of the sentinel HIV diagnosis.

Antimicrobial therapy prescribed to study participants

Of the 76 (89.4%) children that received any antimicrobial therapy (inclusive of antivirals, antifungals and antibiotics), 75 (98.7%) received antibiotic therapy. Of the children prescribed antibiotic therapy, 40 (53.3%) received intravenous therapy only, 19 (25.3%) received oral therapy only, and 16 (21.3%) received intravenous and oral antibiotic therapy. A diagnosis of pneumonia or LRTI (n/N=39/75, 52.0%) was significantly more common than in those that received antibiotic therapy, compared with the group of children that did not receive antibiotic therapy (n/N=0/10); p=0.002. Conversely, a diagnosis of croup was significantly associated with a clinician decision not to use antimicrobial therapy (n/N=3/10; (30.0%) v. n/N=1/75 (1.3%); p=0.005).

Antibiotic agents comprised 122 (89.7%) of all 136 antimicrobials prescribed to study participants, 6 (4.4%) were antivirals and 6 (4.4%) were antifungals. The three most commonly prescribed antibiotics were co-amoxiclav, amoxicillin and ampicillin, which together comprised 78 (63.9%) of all 122 prescribed antibiotics (Fig. 1b). Of the antibiotics prescribed, 109 (89.3%) were classified in the WHO AWaRe group of antimicrobials, and most (n/N=95/109; 77.9%) were 'Access' antibiotics (Fig. 1b). The median duration of antibiotic therapy was 6.0 days (interquartile range (IQR) 3.0 - 9.3 days), and 47 (62.7%) received more than 5 days of therapy. Children with a longer course of treatment were significantly underweight for their age compared with those who received less than 5 days of treatment (–1.31 (IQR –2.68 - –0.16) v. –0.77 (IQR –1.14 - –0.10); p=0.046).

Antibiotics prescribed to children with bronchiolitis

Twenty-five (83.3%) of the 30 children with an admission diagnosis of bronchiolitis received antimicrobial therapy (Table 1). Children with an admission diagnosis of bronchiolitis were significantly younger and had significantly greater median weight-for-length Z-scores than those without bronchiolitis (Table 1). Median CRP levels were similar in children that were diagnosed with bronchiolitis and those without bronchiolitis (11.5 v. 6.0 mg/L; p=0.882) (Table 1). The median CRP value (n=22) in children diagnosed with bronchiolitis that were treated with antibiotics was 15.0 mg/L (range 1.0 - 151.0 mg/L) – 6 (27.3%) had a CRP ≥40 mg/L.

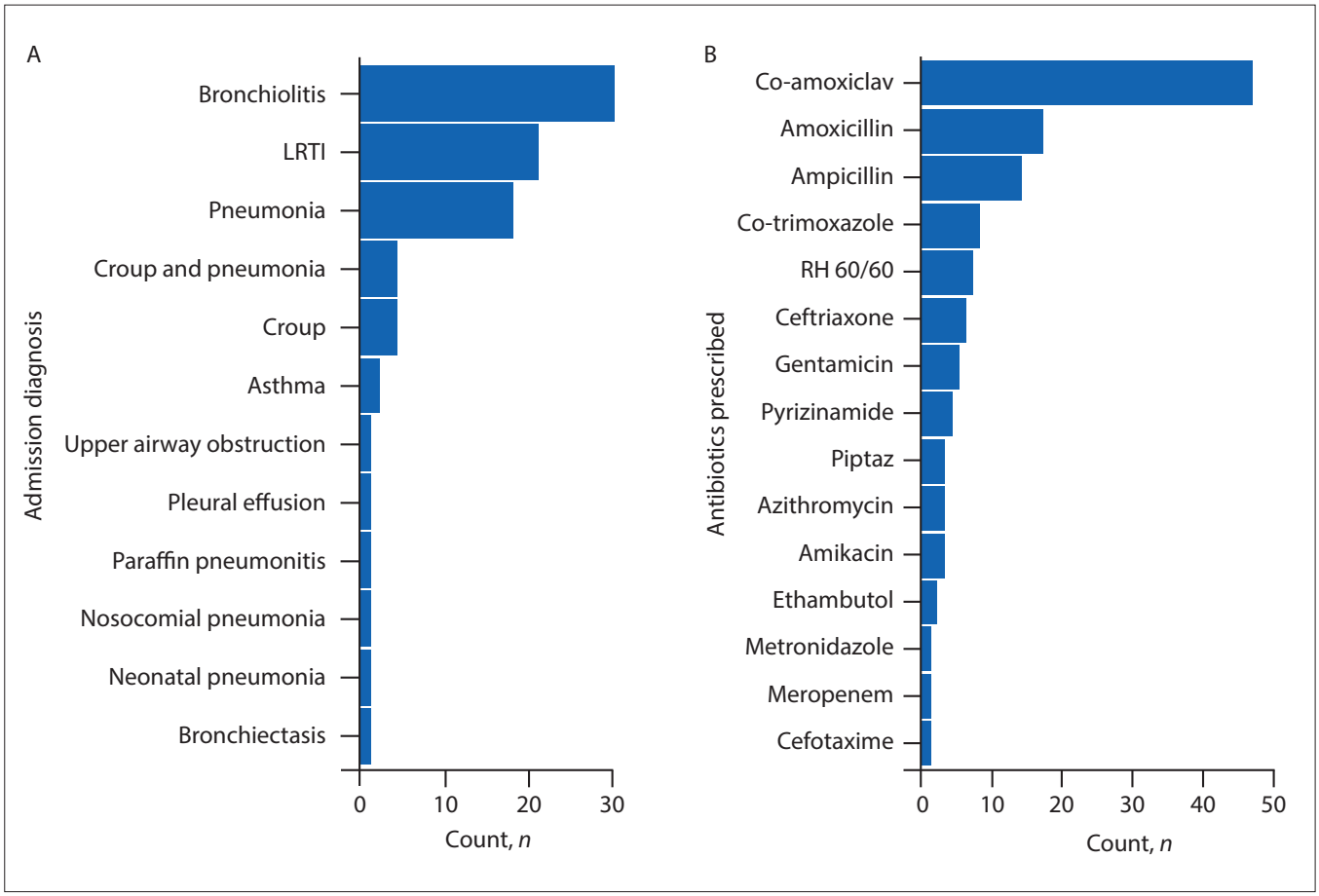

Fig. 1. Admission diagnoses (A) and antibiotic prescribed (B) to study participants. (co-amoxiclav = amoxicillin and clavulanate; LRTI = lower respiratory tract infection; co-trimoxazole = trimethoprim-sulphamethoxazole; RH 60/60 = combination tablet of rifampicin (60 mg) and isoniazid (60 mg); Piptaz = piperacillin-tazobactam.)

Table 1. Characteristics of study children, stratified by diagnosis of bronchiolitis

	Overall (*N*=85), *n* (%)*	Not bronchiolitis (*N*=55), *n* (%)*	Bronchiolitis (*N*=30), *n* (%)*	*p*-value
Sex male (%)	49 (57.6)	31 (56.4)	18 (60.0)	0.925
Age category, months				0.580
<2	8 (9.4)	5 (9.1)	3 (10.0)	
2 - 11	29 (34.1)	14 (25.5)	15 (50.0)	
12 - 72	37 (43.5)	28 (50.9)	9 (30.0)	
>72	11 (12.9)	8 (14.5)	3 (10.0)	
Median (IQR) CRP, mg/L	6.50 (3.00 - 40.00)	6.00 (3.00 - 40.00)	11.50 (2.50 -27.25)	0.882
CRP ≥10 mg/L	31 (45.6)	19 (43.2)	12 (50.0)	0.776
HIV status (%)				0.981
Unknown	15 (17.6)	10 (18.2)	5 (16.7)	
Negative	67 (78.8)	43 (78.2)	24 (80.0)	
Positive	3 (3.5)	2 (3.6)	1 (3.3)	
Median (IQR) LAZ	–1.27 (–2.87 - –0.04)	–1.23 (–2.12 - 0.16)	–1.60 (–3.84 - –0.66)	0.130
Median (IQR) WAZ	–0.88 (–1.75 - 0.05)	-0.94 (–1.90 - –0.21)	–0.77 (–1.71 - 0.14)	0.348
Median (SD) WLZ	0.15 (1.84)	0.67 (1.56)	1.30 (1.58)	<0.001
Antimicrobials given	76 (89.4)	51 (92.7)	25 (83.3)	0.329
Number of antimicrobials (IQR)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	1.00 (1.00 - 2.00)	0.801
Median (IQR) duration of antimicrobial therapy, days	6.00 (3.00 - 9.25)	7.00 (3.25 - 10.00)	5.00 (2.00 - 8.00)	0.154

IQR = interquartile range; CRP = C-reactive protein; LAZ = length-for-age *Z*-score; WAZ = weight-for-age *Z*-score; SD = standard deviation; WLZ = weight-for-length *Z*-score.
*Unless otherwise specified.

CRP test results and impact on antibiotic duration

Of the 68 children with available CRP results, 37 (54.4%) had a formal CRP level of <10 mg/L. Children with CRP levels ≥10 mg/L were significantly older (24.3 months (IQR 9.9 - 75.6) v. 11.6 months (IQR 3.0 - 31.7)) compared with those with lower CRP levels (p=0.011). Median length of antimicrobial therapy was similar regardless of the admission CRP level (7.0 days (IQR 4.5 - 7.5) v. 6.0 days (IQR 3.0 - 9.0) in children with elevated CRP and those with CRP <10 mg/L, respectively; p=0.838).

Microbiology results

Two children had bacteraemic pneumonia attributable to clinically significant bacteria: an 11-year-old male with methicillin-susceptible *Staphylococcus aureus*, and a 3.0-month-old HIV-infected male with extended spectrum β-lactamase producing *Klebsiella pneumoniae* bacteraemia. Both children died during their hospitalisation. The blood culture contamination rate was 10.6% (n/N=9/85). Seven children commenced anti-tuberculosis therapy during their hospitalisation, one (14.3%) of which had microbiologically confirmed tuberculosis.

Outcomes

Eighty-two (96.5%) children were discharged home, one (1.2%) was transferred out but subsequently died, and two (2.4%) died during their admission. At 28 days post discharge among the 83 children who survived to hospital discharge, 68 (81.9%) were alive and well, 1 (1.2%) was alive and ill, 2 (2.4%) were still admitted to hospital, 4 (4.8%) were readmitted and 7 (8.3%) were not traceable via telephonic follow-up. One child (1.2%), a 2-year-old male with a diagnosis of tuberculosis, died post discharge. The overall case-fatality rate in children with known outcomes at 28 days post discharge was 3.8% (n/N=3/78). Case fatality was higher in HIV-infected (n/N=1/3; 33.3%) compared with HIV-uninfected children (n/N=1/60; 1.7%).

Discussion

In this descriptive study of 85 children that were hospitalised with severe respiratory distress and a clinician-diagnosed acute respiratory infection, 75 (88.2%) were administered antibiotic therapy by treating clinicians. Furthermore, of children with an admission diagnosis of bronchiolitis, 83.3% were prescribed antibiotic therapy. Co-amoxiclav, ampicillin and amoxicillin were the most commonly prescribed antibiotics, in keeping with SA paediatric pneumonia guideline recommendations,[9] and with findings from studies conducted elsewhere, which evaluated treatment administered to children hospitalised with LRTI.[12,13,14]

The high proportion of children treated with antibiotics in this study is comparable with findings from studies in Jordan,[12] Vietnam[13] and the USA,[11] where antibiotic prescribing for paediatric acute severe respiratory hospitalisations ranged from 78.4% to 98%. Lower rates of antibiotic prescribing (27 - 39%) are described for children with severe respiratory illness that were treated in Spain and Bangladesh.[14,15] Heterogeneity of antibiotic prescribing between studies could be due to differences in patient characteristics and different guidelines for antimicrobial use.

Antibiotics accounted for 90.4% of the antimicrobials administered to patients in the present study. This is similar to findings in a point-prevalence survey (PPS) in Ghana, where 91.1% of the antimicrobials used were antibiotics.[16] An antimicrobial use PPS of children in six hospitals in India found that 90.8% of antimicrobials given to the children were antibiotics.[17] The majority (89.3%) of the antibiotics prescribed in our study were included in the WHO AWaRe classification, and 77.9% were 'Access' antibiotics. None of the patients were treated with 'Reserve' antibiotics. These are positive findings, as the WHO recommends that 60% or more of antimicrobials prescribed should be from the 'Access' group and those in the 'Reserve' group should be used as little as possible, as a last resort treatment option.[18] A diagnosis of croup was associated with an attending clinician's decision to not treat with antibiotics, consistent with studies which show that in croup of any severity, antibiotics do not improve symptoms.[19]

A lower CRP suggests that the infection is more likely viral rather than bacterial.[20,21] Point-of-care CRP testing has been shown to limit antimicrobial prescription (by clinicians) to children with suspected LRTI in high-income settings.[22,23] Point-of-care testing is feasible in sub-Saharan African healthcare settings with rudimentary laboratory facilities and may positively affect clinical management of patients.[24] However, it is important to consider that in sub-Saharan Africa, there is an increased risk of mixed bacterial-viral infections in the context of the malnourished, HIV-exposed or HIV-infected child, as well as children with other co-morbidities that may warrant antimicrobial use if hospitalised.

Most acute respiratory infections, including bronchiolitis, are caused by self-limiting viral infections and therefore do not require treatment with antibiotics. Many of these infections are treated with antibiotics, with negative impacts on antibiotic stewardship.[25] In the USA and SA, guidelines caution against treatment of children with bronchiolitis using antibiotics unless there is evidence of concomitant bacterial co-infection.[26,27] Available evidence suggests that antibiotics should not be prescribed in uncomplicated bronchiolitis, except in children with more severe disease, those needing intensive care unit admission, or those with risk factors for severe disease.[27]

Study strengths and limitations

Funding constraints and limited availability of the principal investigator to prospectively enrol all potentially eligible participants contributed to the inclusion of only a small proportion (n/N=85/247; 34.4%) of all children hospitalised with LRTI during the 2-month study period. However, we highlight heavy reliance (by clinicians) on antibiotic therapy prescription in the management of children hospitalised with LRTI in a SA public sector academic hospital.

Conclusion

The finding of possible over-reliance on antimicrobial therapy in children with an admission diagnosis of respiratory illness is concerning, particularly in the context of the well-described shift in aetiology of paediatric LRTIs from bacterial to viral organisms.[5] The high prevalence of antimicrobial prescribing for children with an admission diagnosis of bronchiolitis (n/N=25/30; 83.3%) suggests that clinicians are averse to withholding antibiotic therapy in these children. Future studies evaluating the utility of point-of-care CRP testing to assist clinicians in their approach to antimicrobial prescribing for children requiring hospitalisation for bronchiolitis may be helpful in guiding clinicians in their use of antimicrobial therapy.

Declaration. The study was conducted in partial fulfilment of the requirements of an MSc at the Faculty of Health Sciences, University of the Witwatersrand, which was awarded to SM in 2022.

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Author contributions. SM and DPM conceived the study; MS, DPM and SAM coordinated the PediCAP Trial at the Chris Hani Baragwanath Academic Hospital site; DPM, ZD and ZW were involved in screening for eligibility into the PediCAP Trial and assisted SM in identifying study participants that were eligible for enrolment into the current study; NK, TM, LN and SN assisted with screening for eligibility into PediCAP, informing SM of study participants that were eligible for this study, and clinical data collection and curation; all authors critically appraised the contents of the manuscript.

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Conflicts of interest. MS Chaired the 2023 WHO Expert Committee on Selection and Use of Essential Medicines.

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