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Review

Antibiotic non-susceptibility among *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates identified in African cohorts: a meta-analysis of three decades of published studies

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ABSTRACT

Management of community-acquired pneumonia caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* type B (Hib) can be complicated by emerging antimicrobial non-susceptibility. We conducted a meta-analysis to examine the antibiotic susceptibility of community-acquired invasive infections with *S. pneumoniae* and Hib in Africa from 1978 to 2011. With the notable exceptions of widespread trimethoprim/sulfamethoxazole (SXT) and tetracycline non-susceptibility, the majority of pneumococci remain susceptible to ampicillin/amoxicillin. However, 23.8% of pneumococcal meningitis isolates are non-susceptible to penicillin. Similarly, Hib isolates show non-susceptibility to SXT, tetracycline, erythromycin and chloramphenicol. β-Lactamase production among Hib isolates is increasing, a new observation for Africa, but is mitigated somewhat by Hib vaccination scale-up. In summary, pneumococcal susceptibility to amoxicillin remains high throughout Africa, and amoxicillin can be effectively and safely used as first-line treatment for childhood pneumonia. Data support first-line treatment of bacterial meningitis with ceftriaxone or cefotaxime.

1. Introduction

Globally, community-acquired pneumonia (CAP) is the leading cause of death among children <5 years of age and continues to have a major public health impact both in adults and children. Aetiological data for CAP come primarily from studies of inpatients with severe pneumonia, with the most common bacterial pathogens being *Streptococcus pneumoniae* (17–37%) and *Haemophilus influenzae* (0–31%) [1]. In addition to being the most common cause of CAP among children and adults, *S. pneumoniae* is also the most common cause of community-acquired meningitis and bacteraemia [2]. Bacteraemia is present in ca. 20% of pneumococcal pneumonias in adults, with case fatality rates of 10–30%. Pneumococcal disease primarily affects young children, adults >65 years of age and immunocompromised individuals, with 1.5 million people dying annually.

Given that there are limited data regarding the aetiology of non-severe pneumonia, antibiotics have been targeted at the pathogens known to cause severe pneumonia. Management can be complicated by emerging non-susceptibility among pathogens causing CAP to the different classes of antibiotics that are typically prescribed [3]. Following the initial detection of penicillin-non-susceptible *S. pneumoniae* in a few geographic regions, including South Africa, in the 1970s, non-susceptibility spread rapidly worldwide [4,5]. Despite concerns about reported in vitro non-susceptibility of pneumococci to penicillin, there are no reports of microbiologically confirmed clinical failure following intravenous penicillin therapy [6]. However, a multilevel, cross-sectional study among 4888 children with CAP presenting to 33 children's hospitals in the USA found that every 10% increase in penicillin-non-susceptible pneumococcal isolates was associated with a 39% increase in broad-spectrum antibiotic prescribing [7].

Among oral agents, there are data showing in vitro non-susceptibility to trimethoprim/sulfamethoxazole (SXT) correlating with poor clinical outcome in acute otitis media [8]. Although a higher failure rate for children with severe pneumonia receiving

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SXT compared with amoxicillin has been demonstrated [9], it is not clear whether this was due to non-susceptibility to SXT. Of note, in a study with careful matching of patients infected with the same organism, antibiotic non-susceptibility was associated with higher medical costs, longer length of hospital stay and higher death rates [10].

In Africa, where insufficiently trained human resources can be a limiting factor to appropriate management of CAP and less than one-third of children with suspected pneumonia receive antibiotics [11], the perceived threat of reduced antibiotic susceptibility is often cited as a reason community health workers should not prescribe antibiotics. However, the actual extent of antibiotic non-susceptibility among respiratory pathogens in Africa is unclear. This meta-analysis examines antibiotic susceptibility among *S. pneumoniae* and *H. influenzae*, the most common causes of CAP globally and in Africa. For community-acquired infections with *S. pneumoniae* and *H. influenzae*, we reviewed antibiotic susceptibility profiles for invasive isolates in African cohorts from 1978 to 2011, looking for patterns over time and across regions. In addition to providing a historical record of non-susceptibility patterns, this meta-analysis also allows a current snapshot of antibiotic non-susceptibility in Africa and can be used to establish a baseline to track antibiotic non-susceptibility trends.

2. Methods

2.1. Search strategy and selection criteria

PubMed, EMBASE and the 'Africa-Wide Information' databases were searched for studies reporting on antibiotic non-susceptibility/resistance of *H. influenzae* type B (Hib) or *S. pneumoniae* from isolates collected in Africa (search terms listed in Appendix A). All initial searches were conducted by Boolean phrase and were not limited by publication date (results ranging from 1969 to 2011). Publications written in English, French, Spanish and Portuguese were included.

- PubMed: The searches included the medical subject heading (MeSH) terms with all fields and subheading groups to pull the greatest number of potentially relevant publications.
- EMBASE: We excluded the optional Medline search from the EMBASE search and maximised the power of the database by using the synonym function [to capture multiple spellings and related terms (/syn)] and Emtree terms.
- Africa-Wide Information: The Africa-Wide database incorporates South African Studies, African Studies and African HealthLine databases.

All search results were exported into EndNote X5 (Thomson Reuters, Carlsbad, CA) to sort the results and to eliminate duplicate publications.

Studies were screened for relevance to the analysis based on sequential review of study titles and then study abstracts. This was done in parallel by two members of the team and discrepancies were resolved by consensus of the group.

Inclusion criteria were the following: data on antibiotic resistance or non-susceptibility among *S. pneumoniae* and/or Hib as determined by Kirby–Bauer disc diffusion, broth microdilution, agar dilution or Etest; data presented that enable determination of a numerator and denominator (needed for the calculation of antibiotic non-susceptibility rates); invasive isolates from community-acquired disease; for invasive isolates, source from a normally sterile site [e.g. cerebrospinal fluid (CSF), blood, pleural fluid]; and for carriage isolates, source must be nasopharyngeal (NP)/oropharyngeal (OP) specimens and obtained from subjects without acute respiratory infections.

Exclusion criteria were the following: not primary data; nosocomially acquired invasive infections; single case reports or very small (≤10 isolates) case series; data from outside Africa; data reported in publications in languages other than English, French, Spanish or Portuguese; publications where antibiotic non-susceptibility data for invasive and non-invasive sources could not be disaggregated; failure to specify the method used for determining antibiotic susceptibility; for studies using disc diffusion, failure to use oxacillin discs to screen for penicillin non-susceptibility (data for other antibiotics could still be included, however); for carriage studies only, patients presenting with clinical illness; for Hib studies only, data pertaining to non-serotype B isolates; and the inability to locate the article despite all reasonable attempts (defined as the article not found in the collections at Boston University, University of Washington or Harvard University Medical Schools and not available via intralibrary loans or via online collections; we did not attempt to locate articles by writing to study authors).

2.2. Data collection and analysis

The following were extracted into a Microsoft Excel (Microsoft Corp., Redmond, WA) spreadsheet: author; title; date of publication; country/countries of study; community setting; population studied; type of study; source of isolates; time period of study; antibiotic susceptibility testing method; and antibiotic non-susceptibility rates. Susceptibility data were extracted for the following antibiotics as available: ampicillin/amoxicillin; penicillin; ceftriaxone/cefotaxime; erythromycin; SXT; clindamycin; chloramphenicol; tetracycline; and, in the case of Hib, β-lactamase production. Given their overlapping spectrum of activity and breakpoints, results for amoxicillin and ampicillin and for ceftriaxone and cefotaxime were combined. For penicillin, ampicillin/amoxicillin and ceftriaxone/cefotaxime, non-susceptibility rates were interpreted as pertaining to central nervous system infections only, since non-susceptibility breakpoints for pneumonia or bloodstream infections require minimum inhibitory concentration (MIC) data, which were only collected in a very few studies.

Non-susceptibility was defined as the union of intermediate- and high-level non-susceptibility. Weighted averages were calculated across studies for the proportion of non-susceptible isolates using the Freeman–Tukey (FT) arcsine transformation method [12]. This method generates weighted averages in a meta-analysis of proportions with robust standard errors and 95% confidence intervals (CIs) and is optimal for the analysis of events that occur with low (or zero) frequencies, as with a Poisson distribution [13]. Since this approach is not asymptotic, the upper and lower confidence bounds were truncated at 0% and 100%, respectively. Where appropriate, risk ratios (RRs) and 95% CIs were calculated based on the FT-adjusted proportions.

Studies were organised for analysis primarily based on whether they pertained to invasive isolates of *S. pneumoniae* or Hib or whether they reported on isolates identified in carriage surveys of otherwise healthy patients. Within the set of studies of invasive isolates, the subset of studies that specifically provided data on non-susceptibility among CSF isolates was identified. In addition, the following analyses within the full set of studies of invasive isolates were conducted stratifying by the following features:

- geography, with countries grouped by southern, western, eastern/central combined, and northern regions;
- time, clustered by earliest through to 1995, 1996–2000, 2001–2005 and 2006–2011;

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