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Antibiotic resistance compromises treatment of pneumonia in Ugandan children

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Introduction

The 2006 Uganda Demographic and Health Survey (DHS) found that 21% of deaths in children under 5 were caused by acute respiratory infections, despite the fact that 73% of children with symptoms had been taken to a health facility, and 47% of those had received an antibiotic (UBOS 2007). A study of Ugandan children who died of pneumonia found that most were given antimalarials at home, but 11 children who had been given cotrimoxazole at home died despite this treatment (Källander et al 2008). The aim of this project is to document the impact of antibiotic resistance (ABR) on the treatment of pneumonia in Ugandan children under 6 seen in outpatient settings.

Methods

Data from outpatient registers were abstracted by medical, dental and pharmacy students for 10,172 visits, including 2,347 visits of children under 6, to hospital OPDs and health centers at 10 sites in Uganda in 2008-2009. Antibiotic resistance data were derived through collection and analysis of available published and unpublished Ugandan data on ABR of *S. pneumoniae* and *H. influenzae* and literature review. Analysis was performed using Epidata, Epidata Analysis, Stata v. 9, and Excel.

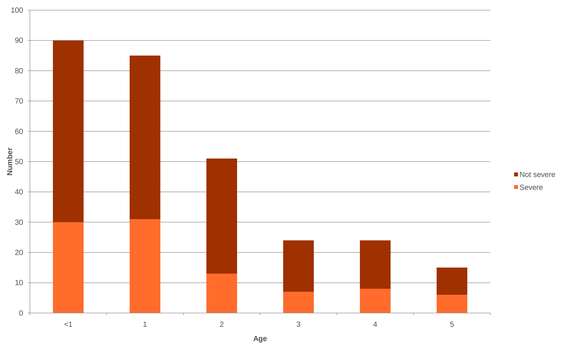
This research was approved by the Tufts University Medical Campus Institutional Review Board, the Ethical Review Committee of Makerere University, the National Council for Science and Technology of Uganda, and the Office of the President of Uganda.

Figure 1. Map of Uganda

Results

Diagnoses of pneumonia
288 of 2347 (12.3%) children under 6 had a recorded clinical diagnosis of pneumonia, of which 95 (33%) were judged to be "severe" and 193 (66%) "not severe." Figure 2 shows the ages of the children with pneumonia, by severity.

Figure 2. Ages of children with pneumonia diagnosis.



Overlap with malaria
A clinical diagnosis of malaria was also recorded for 186 (64.6%) of the children diagnosed with pneumonia, and 177 (61.5%) received at least one antimalarial. Of those children receiving an antimalarial, however, 9 (5%) received an antimalarial judged to be ineffective, e.g. either chloroquine (CQ) or sulfadoxine / pyrimethamine (S/P). Approximately 65% of malaria cases also received one or more antibiotic, of which 55% was cotrimoxazole.

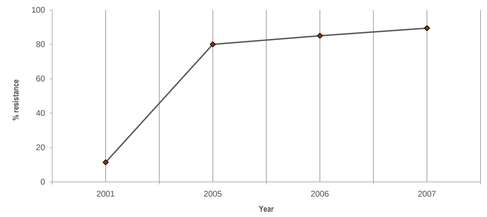
Most commonly used antibiotics and resistance patterns
The most commonly prescribed antibiotic was cotrimoxazole (38.7%), to which ABR approaches or exceeds 80% in Uganda, followed by benzyl penicillin (25.1%), amoxicillin (22.1%), and other antibiotics including chloramphenicol, erythromycin, PPF, and cephalosporins (14.2%). 89 (31%) of children received multiple antibiotics, of which 55 (19%) received cotrimoxazole plus a second antibiotic. However, 88 children (30.5%) received cotrimoxazole alone, and no antibiotic was recorded for 19 children (7%).

Thus, approximately 37% of children with pneumonia seen at health facilities received potentially ineffective antibiotic therapy for pneumonia.

For years, cotrimoxazole has been the first line of treatment against *S.pneumoniae* in Uganda. Cotrimoxazole resistance has increased rapidly in Uganda. In 2000, *S. pneumoniae* resistance to cotrimoxazole was 11.7 % in Kampala, but by 2007 rates of 89.4% were noted in Kampala. Elsewhere in Uganda, cotrimoxazole resistance also increased significantly to 77-80% over a period of 6 years. Use of cotrimoxazole prophylaxis in HIV-positive patients is thought to be largely responsible for the increasing resistance.

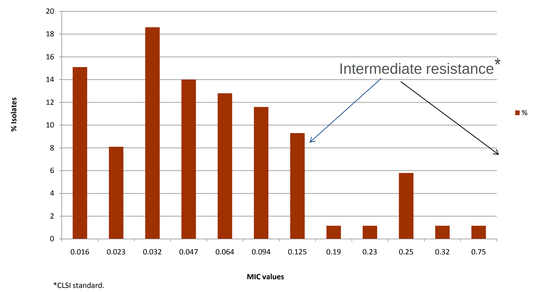
Results (continued)

Figure 3. Rise in resistance to cotrimoxazole, 2001-2007.



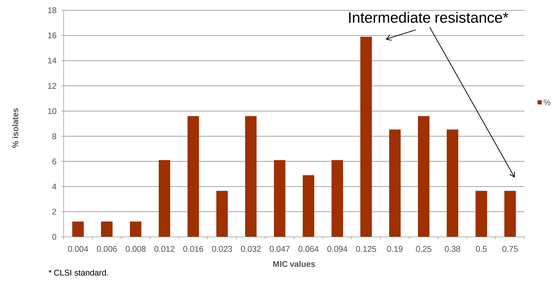
The Network for Surveillance of Pneumococcal Diseases in the East African Regions (NETSPEAR), examined *S.pneumoniae* isolates from 4 regions in Uganda. Their data showed that none of the isolates were fully resistant to benzyl penicillin. Intermediate resistance to benzyl penicillin was however observed for 20% of the isolates.

Figure 4. MIC values of benzyl penicillin.



Amoxicillin resistance is also increasing, with 50% of the isolates showing intermediate resistance to amoxicillin. Efforts to conserve it are essential. Concerns about stability of amoxicillin in tropical conditions have also been raised, however (Naidoo et al, 2009).

Figure 5. MIC values of amoxicillin.



Some centers in Uganda have now started using ceftriaxone, but the high cost of ceftriaxone is problematic. Resistance of *S. pneumoniae* to ceftriaxone was reported to be 1.8-5.7% between 2003-2005 in Lacor (northern Uganda) and 5.2% in Kampala. Resistance to ceftriaxone is still low, but surveillance systems should be put in place to monitor resistance to this key antibiotic.

Conclusions

Although febrile children with pneumonia are frequently seen in outpatient settings, and antibiotic therapy is almost always prescribed, many received either cotrimoxazole (approximately 80% rate of antibiotic resistance) or no antibiotic at all, thus antibiotic therapy was potentially ineffective or absent in about 37% of cases. This may contribute to high mortality from pneumonia despite empirical treatment. However, little is known about the clinical impact of *in vitro* resistance and its relationship with treatment failure. Additional research in this area is needed.

Children with a pneumonia diagnosis were almost as likely to receive an antimalarial (58%) as an effective antibiotic (63%).

Until recently, Uganda's standard treatment for pneumonia was cotrimoxazole but this has recently been changed to amoxicillin. The new treatment guidelines had not yet been widely disseminated at the time of the study. Prescribers need to be made more aware of high levels of ABR to cotrimoxazole, and alternative antibiotics should be provided in Uganda. However, resistance to amoxicillin is increasing and must be closely monitored.

Standard treatment guidelines for conditions requiring antibiotics need to be updated more frequently than other standard treatment guidelines, so a mechanism for informing prescribers on a more frequent basis needs to be found. Furthermore, data on antibiotic resistance are scarce and not collected on a systematic basis, so more investment in equipping laboratories to collect and transmit relevant antibiotic resistance data is urgently required.

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