ANTIMICROBIAL RESISTANCE AMONG CHILDREN IN SUB-SAHARAN AFRICA

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ABSTRACT

Background: Antimicrobial resistance (AMR) is an important threat to international health, potentially undermining nearly a century of gains since antibiotics were discovered. Sub-Saharan Africa (sSA) has high paediatric mortality rates due to infectious diseases, and has been identified as a region particularly lacking in diagnostic capacity and AMR surveillance. Therapeutic guidelines for empiric treatment of common life-threatening infections are dependent on the available information regarding microbial aetiology and antimicrobial susceptibility.

Methods: We conducted a review of the current published literature reporting AMR among the general paediatric population in sub-Saharan Africa since 2005, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines.

Findings: 1,075 articles were reviewed, of which 18 met the inclusion criteria. These data included 67,451 invasive bacterial isolates from inconsistently defined populations in predominantly urban tertiary settings. Among neonates, Gram-negative organisms were the predominant cause of early-onset neonatal sepsis with a high reported prevalence of extended-spectrum beta-lactamase producing organisms (up to 76%). Gram-positive bacteria were responsible for a high proportion of infection among older paediatric patients, with high reported prevalences of non-susceptibility to current WHO therapeutic guidelines (*Staphylococcus aureus* exhibits non-susceptibility to ampicillin [IQR 85-100%], gentamicin [IQR 10-60%], and cloxacillin [IQR 10-55%]; while *Streptococcus pneumoniae* exhibits resistance to ampicillin (20-22%) and gentamicin (77-78%). Inherent biases exist, including failure to delineate community-acquired from hospital-acquired infections, or identify pre-treatment with antimicrobials.

Interpretation: There is a striking paucity of recent or population-representative literature given the potential magnitude of the problem, especially with regard to community-acquired infections. What *is* known comes from very few centres where microbiological facilities are available. Although limited in its geographic distribution and with poorly identified denominators, the recent literature reports widespread *in vitro* non-susceptibility to recommended empiric antimicrobials from children in sSA. Improved collaboration and standardised reporting are urgently required to address

increasing AMR among children in sSA. Further research should focus on identifying differential resistance patterns for community- versus hospital-acquired infections, implementing standardised reporting systems such as the WHO Global Antimicrobial Resistance Surveillance System (GLASS), and pragmatic clinical trials to assess the efficacy of alternative treatment regimens.

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INTRODUCTION

Of the pressing threats to international health, antimicrobial resistance (AMR) is of increasing importance. AMR threatens to undermine nearly a century of gains made since the discovery of antibiotics and their contribution to improvements in childhood survival in the developing world, particularly among neonates.[1,2] AMR is reported in both community-acquired (CA) and health-care associated (HA) infections worldwide.[3] However, in low- and middle-income countries (LMICs), surveillance is often inconsistent due to a lack of integration, non-representativeness of localised data, inconsistent laboratory quality, and limited microbiological diagnostic facilities.[3]

Recently, sub-Saharan Africa (sSA; defined as per the boundaries set by the World Bank's World Development Indices)[4] has been identified as the region with the *most* limited implementation of antimicrobial surveillance strategies, alongside limited infection prevention and control programmes. Only 6 (13%) of the 41 World Health Organization (WHO) Africa region member states conduct surveillance for bacterial AMR, and external quality assurance of laboratory procedures is unusual.[5–7]

The problem of AMR in sSA is set against a background of an ongoing high incidence of acute respiratory infections, diarrhoeal diseases, parasitic and invasive bacterial infections as well as chronic conditions such as HIV, tuberculosis and malnutrition,[8–11] which increase the demand for both preventative and therapeutic antimicrobials.[12] Unregulated antibiotics are readily available in most communities through shops and drug stores, and are widely used in domestic and commercial animal husbandry.[13] In clinics and hospitals, limited diagnostic resources and consequent therapy based on clinical syndromes that are sensitive (rather than specific) for serious bacterial infections (are are therefore likely to capture viral, parasitic and/or self-limiting illnesses) also drive antibiotic consumption – a key factor in promoting resistance.[18] Moreover, the spread of *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBL) and other multi-drug resistant (MDR) organisms in both community- and hospital-based populations potentially limits the availability of suitable antimicrobials to treat such infections.[14,15] Escalation of resistance may also occur when therapies normally reserved for second, third or fourth-line treatment in resource-rich settings (such as third-generation cephalosporins, carbapenems and polymyxins) begin to be used widely in sSA without supportive microbiological facilities, expert advice, or adequate prescription controls.[16,17]

Conversely, when higher-level treatment *is* required, it is often unavailable or too expensive for a majority of the population of sSA. Decreased susceptibility to antimicrobials is therefore important, not just due to the health care implications of limited treatment options (especially in resource-poor settings such as sSA) and the potentially poorer clinical outcomes,[3,18,19] but also due to the costs associated with utilising more expensive therapies across a wider spectrum of patients and prolonging hospitalisation.[20]

The WHO recommends penicillin (or ampicillin) plus gentamicin as empiric therapy in suspected neonatal and paediatric sepsis in resource-limited settings (Table 1), and advises tailoring therapy to local resistance patterns.[21] However, in practice, this is usually impossible due to restricted local data secondary to a lack of reliable laboratory facilities with external quality assurance or collaborative surveillance.[3] A high prevalence of non-susceptibility to recommended empiric therapies has previously been reported amongst invasive bacterial isolates throughout sSA,[3,6,7,22] however the vast majority of research has been limited to tertiary settings. Despite urgent calls for updated WHO guidelines to limit avoidable mortality due to AMR, they have remained unchanged for the majority of causes of invasive paediatric bacterial infections.[23,24]

The 2014 ‘Global Report on Antimicrobial Surveillance’ highlights the pressing need to strengthen knowledge and surveillance mechanisms for AMR – reiterating a theme which has resonated in the literature for over a decade.[25,26] Therefore, we aimed to systematically review data published since 2005 on antimicrobial susceptibility for the commonest bacteria causing serious infections amongst children in sSA, with a focus on the current WHO recommendations for empiric treatment among children without specific risk factors (HIV or tuberculosis, TB) to increase the knowledge and evidence base regarding local non-susceptibility patterns among a generalisable paediatric population.

METHODS

After conferring on the search terms, the primary investigator (PW) conducted a review of published and grey literature, originally performed on 12th December 2015 and later updated in December 2016. Included reports were reviewed by JB. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews was followed.[27] Pubmed, Embase, Medline and Cochrane databases were searched, as well as the reference lists of relevant articles. The search strategy is documented in Figure 1. To ensure current susceptibility patterns were investigated, articles were restricted to those reporting data collated since 2005 to ensure emerging threats to susceptibility – such as the spread of ESBL – were captured.

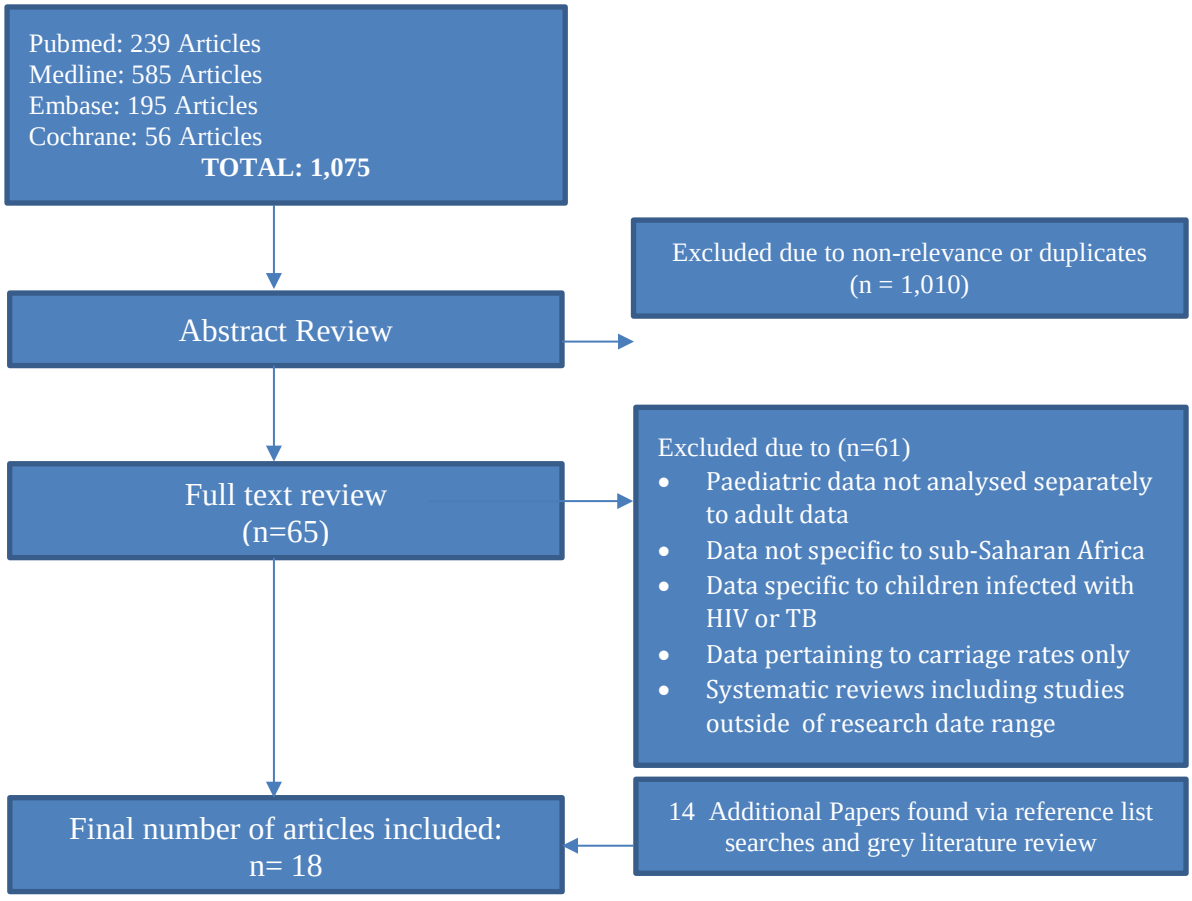

Figure 1: Flow Diagram Summarising the Selection of Publications for Review

Inclusion criteria were pre-defined as: research providing information on bacterial infections (including either aetiology or disease burden / incidence); paediatric data specified (or clearly

delineated from adult data); and information on antimicrobial testing methodologies documented. Pre-defined exclusion criteria were: data aggregated with regions beyond sSA; literature focussed on solely analysing sub-populations with potentially confounding comorbidities (such as HIV or TB); poor methodological study design; data collection occurring significantly prior to search period; and data pertaining to carriage rates only (rather than invasive isolates). After abstracts were screened for these criteria, information was extracted from selected articles and documented into tabulated form (Appendix 1), including study year, location, setting, population age group, study design, microbiological methods (bacterial isolation methods and antibiotic susceptibility testing) and level of evidence, as per the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) methodology; which was utilised to summarise the quality of the evidence for each study by assessing study type, quality, limitations, inconsistency or possibility of bias.[28] Grading was performed by both PW and JB; any disagreements were resolved by consensus.

RESULTS

Search strategy and selection criteria:
Data for this Review were identified by searches of the databases MEDLINE, PubMed, Embase and Cochrane, and references from relevant articles using the search terms "child*", "pediat*", "paediat*". "Africa*", "sub-Sahara*", "antimicrobial" or "antibiotic", "resistance", "susceptibility" or "sensitivity". Only articles conducted in humans published since 2005 were included.

The initial search identified 1,075 potentially relevant papers. Abstract review excluded 1,010 papers not meeting inclusion criteria or the identification of duplicate studies. Of the 65 paperstabl that underwent full text review, four met the inclusion criteria. Fourteen further studies were identified from reference lists, resulting in a total of 18 studies for inclusion.

STUDY CHARACTERISTICS

The 18 reports included were from 11 nations throughout sub-Saharan Africa (represented topographically in Figure 2). Seven studies[29–35] were conducted in rural settings and the remaining 10 in urban settings; while one was a laboratory-based study collating data across both urban and rural settings.[36] The hospital-based studies were almost exclusively conducted in tertiary health facilities, while one study also included patients presenting to a secondary health facility.[37] There was one cross sectional study,[38] one case control study[39] and six case series;[19,34,36,40–42] the remaining ten were cohort designs. Six studies examined only one genus of pathogen,[30,32,36,40,43] while the remaining examined invasive disease. Due

to the heterogeneity of the studies (in terms of settings, inclusion criteria, laboratory methods, reported outcomes and the quality of evidence) a formal meta-analysis was not possible; however, where possible, interquartile ranges were calculated for specific pathogen susceptibilities.

Six of the studies were of moderate-quality evidence (GRADE Level B); seven were low-quality evidence (Grade Level C); and the remaining five were classified as very low-quality evidence (GRADE level D). All studies described the microbiological techniques used (an inclusion criterion), although culture media and methods for identification of organisms and definitions of non-susceptibility varied between studies. Twelve studies utilised automated culture techniques,[18,19,29–35,37,40,45] while the remainder used manual methods. Only three studies (17%) ascertained recent antimicrobial exposure (and took this into account when analysing their data).[18,26,30] Five papers (28%) reported external quality control of their laboratory.[18,30,34,37,40] The majority of isolates were identified from blood cultures, although one study included induced sputum samples,[46] and four studies investigated both blood and CSF samples in patients presenting with meningitis.[34,35,40,43] Across the studies, a total of 67,451 cultures were collected, of which 5,607 (8.3%) were positive for a bacterial pathogen. Further information on non-susceptibility prevalence was obtained from 236 laboratory-stored isolates[36] and 149 diarrhoeal isolates of children infected with *Shigella* spp. or *Salmonella* spp.[32]

AGE RANGE

The studies covered the full paediatric age range of 0-18 years, with a focus on young childhood (0-5 years). Four studies exclusively investigated infections in infants within the first 90 days of life.[34,38,40,41]

COMMUNITY ACQUIRED (CA) & HOSPITAL ACQUIRED (HA) INFECTION

Ten studies specifically examined CA infections only,[29–32,35,37,39,43,44,46] while three others investigated antibiotic susceptibility patterns distinguishing CA and HA infection[18,19,34] (and while the incidence of differing infectious aetiologies may have been clarified within these studies, only two studies analysed the resistance patterns for each subset independently[18,19]). The remaining five studies did not identify whether the infections were community or nosocomial in nature.

Figure 2: Overview of study location by country (attached as .eps file)

KEY PATHOGENS & SUSCEPTIBILITY PATTERNS IN NEONATES

Aetiology-based systematic reviews identify Gram-negative organisms (*E. coli, Klebsiella spp.*) and (less commonly) *S. agalactiae* as the predominant causes of early-onset neonatal sepsis in sSA, which is defined as sepsis occurring <72 hours of age (aside from sepsis due to *S. agalactiae* which was defined as occurring from day 0 to day 6).[47] *S. aureus* is an important cause of late-onset sepsis (with an ongoing burden caused by *E. coli, Klebsiella spp*. and *S. agalactiae*, and other Gram-positive organisms such as *S. pyogenes*).[47–53] Early-onset infections are usually due to vertically transmitted infections, yet they may also be secondary to nosocomial acquisition (in which case resistance is more likely to be an issue); while late-onset infections are due to horizontal (either CA *or* HA) infection.[24] While the understanding of susceptibility patterns according to the time of onset of neonatal infection is important, the majority of included studies investigating invasive neonatal infections failed to clearly delineate whether these were early- or late-onset, and whether the patient population was transferred from the delivery ward or presenting for admission from the community. This is well documented within the literature as a common issue when analysing data pertaining to neonatal infection in sub-Saharan Africa.[47,52]

Four studies specifically investigated neonatal patient populations born within hospital environs and at home.[34,38,40,41] As anticipated, these studies found a predominance of infections caused by Gram-negative bacteria and in particular *Klebsiella* spp., which was responsible for approximately half of all blood stream infections (especially in early-onset illness).[38,41] Other common neonatal pathogens identified included *S. aureus* (range 27%-39%),[38,41,48] *E. coli (*21%),[34] and *S. agalactiae* (6.9%[34]; 20%[48]).

Resistance patterns for these organisms are outlined below. Of note, a high prevalence of MDR organisms was documented in a prospective cross-sectional study of 300 neonates in Tanzania, with 40% (36/91) of Gram-negative organisms exhibiting ESBLs while 30% (9/30) of *S. aureus* samples were methicillin-resistant; however these were not identified as CA or HA.[38] MDR organisms were associated with increased mortality rates for both populations (52% vs 25% in ESBL producing organisms; and 55% vs 21% mortality in MRSA organisms; p=0.0008).

Studies investigating specific pathogens in neonates, isolating *S. agalactiae* from 57 infants in Malawi and 37 in Mozambique, reveal an approximately equal incidence of early-onset (EOD) and late-onset disease (LOD), with a higher case fatality for EOD.[29,40] All isolates were susceptible to β-lactams. Only one study was based in a rural setting, which investigated invasive bacterial infections in infants born outside the hospital, but did not delineate infections as CA or HA. An important finding in this study was diminishing *in vitro* susceptibility of all isolates to the WHO recommended ampicillin and gentamicin over the study period (from 88% susceptibility in 2001 to 66% in 2009; p<0.001).[34]

KEY PATHOGENS & SUSCEPTIBILITY PATTERNS IN PAEDIATRIC PATIENTS

A. Gram-Negative Organisms

i. Salmonella spp.

Salmonella spp. are the most frequently isolated Gram-negative pathogen in children greater than 1 month of age in sSA, with a predominance in the wet season.[9,23,29,37,54] The majority of studies did not analyse *S. typhi* and non-typhoidal species independently for susceptibility patterns against individual antibiotics. Nine of the included papers investigated susceptibility patterns to *Salmonella* spp.,[18,19,29–32,37,42,44] revealing non-susceptibility to penicillin/ampicillin (IQR 39-73%; median 66), gentamicin (IQR 23-32%; median 28), co-trimoxazole (IQR 48-67%; median 60); amoxicillin-clavulanate (20%[42]; 38%[29]; 74%[30]); and chloramphenicol (IQR 15-54%; median 27). Only one paper delineated CA and HA infections, with a slightly higher prevalence of non-susceptibility amongst HA isolates.[18] MDR organisms are of increasing concern, with up to 65% of *S. typhi* and up to 98% of non-typhoidal isolates exhibiting combined resistance to ampicillin, co-trimoxazole and chloramphenicol.[30,31,44]

ii. Klebsiella spp.:

Klebsiella spp. causes a significant amount of morbidity among paediatric patients in sSA, accounting for almost half of all Gram-negative infections in neonates and a significant overall burden of HA infection.[9,23,54,55] Nine studies assessed *Klebsiella* spp. susceptibility patterns,[18,19,26,34,38,39,41,42,45] of which two delineated HA and CA acquisition[18,19] while other research specifically evaluated HA strains,[39] CA strains,[45] or did not clarify the mode of acquisition. This research revealed a consistently high prevalence of non-susceptibility to commonly used antimicrobial therapies, including gentamicin (IQR 48-58%; median 49) and ceftriaxone (range 33-50%[34,38,46]). Non-susceptibility was similar between CA and HA strains,

and high frequencies of ESBL-producing *Klebsiella* spp. were documented (from 76% for CA isolates to 82% among HA isolates[26,39]).

iii. Escherichia coli:

E. coli causes a significant burden of disease in sSA, responsible for approximately 11% of all paediatric blood stream infections[19] and predominating as a cause of CA sepsis.[54,56] Eight papers assessed non-susceptibility of *E. coli,* documenting non-susceptibility to penicillin/ampicillin of 50-100% (IQR 78-96%; median 93); gentamicin (IQR 20-46%; median 29); and ceftriaxone (IQR 12-34%; median 16).[34,38,41,42,46] One paper delineated CA and HA acquisition, revealing a higher frequency of non-susceptibility among HA isolates (gentamicin non-susceptibility of 29% among CA isolates compared to 46% among HA isolates).[18] ESBL-producing *E. coli* infections were also more frequent among HA isolates (22%[19], 58%[39]) compared to CA isolates (12%[19]).

iv. Shigella spp.

Although *Shigella spp.* are an important cause of CA bacteraemia[25,37,57] only one paper assessed susceptibility of *Shigella* spp. to commonly available antimicrobials, documenting resistance to co-trimoxazole (87%), ampicillin (56%) and chloramphenicol (52%) alongside high levels of MDR (non-susceptibility to >2 antimicrobials from different classes).[32] However, when analysed together with other *Enterobacteriaceae*, there was evidence of sensitivity to ciprofloxacin.[18]

v. Haemophilus influenzae type b:

While the advent of the conjugate vaccine has considerably diminished the burden of *Haemophilus influenzae* type b,[58] its case fatality rate has the potential to remain high due to significant antimicrobial resistance to first-line therapies. Three papers assessed resistance among *Haemophilus* isolates, documenting non-susceptibility to ampicillin and chloramphenicol ranging from 50% to 100%, rendering these antimicrobials as largely ineffective in treating *Haemophilus influenzae* meningitis.[29,35,46]

vi. Acinetobacter spp.

While a rarer cause of sepsis, *Acinetobacter* is nonetheless clinically significant due to its high mortality rate when causing bacteraemia (up to 25%), with 78% of HA *Acinetobacter* isolates (and 25% of CA isolates) displaying MDR in a large study of paediatric blood stream

infections in South Africa (which included a small cohort of patients [13%] who were HIV-positive, in whom there was no statistically significant difference in the likelihood of bloodstream infections).[19] A large case series of 4,849 neonates in rural Kenya identified *Acinetobacter* as a cause of 10% of positive blood cultures in outborn infants, with documented resistance to penicillin/ampicillin (56%; 95% CI 42 to 70), gentamicin (27%; 95% CI 14 to 39) and ceftriaxone (35%; 95% CI 22 to 48).[34] A further review of 1,787 paediatric patients in Tanzania reported higher rates of non-susceptibility to ampicillin (100% for both CA and HA), gentamicin (44% and 67% for HA and CA, respectively), and ceftazidime (22% among HA isolates and 33% among CA isolates; susceptibility profiles revealed by three CA invasive isolates and nine HA isolates).[18]

B. Gram-Positive Bacteria:

i. Streptococcus pneumoniae

S. pneumoniae is the most common Gram-positive organism isolated in positive blood cultures in children in sSA,[9,48,54] responsible for up to 35% of clinical episodes of sepsis with a predominance in the dry season.[9] While the burden of disease caused by this pathogen is declining as the pneumococcal conjugate vaccine is introduced, it nevertheless continues to cause significant morbidity and mortality.[59,60] Three papers analysed susceptibility patterns of *S. pneumoniae,* documenting non-susceptibility (which was not classified into intermediate- versus high-level resistance) to penicillin/ampicillin (range 6% to 24%) and chloramphenicol (range 11% to 25%);[30,31,46] yet full susceptibility to ceftriaxone was revealed by 2 studies.[30,31] Although no longer part of the WHO treatment guidelines, co-trimoxazole and macrolide antibiotics are still often prescribed in LMICs to treat pneumonia (and as prophylaxis for children infected with HIV). A high prevalence of non-susceptibility to co-trimoxazole was documented (IQR 56-100%; median 100);[29–31,37,43] although susceptibility to erythromycin remains adequate.[46,61]

ii. Staphylococcus aureus

S. aureus causes a significant burden of bloodstream infections in paediatric patients in sSA.[19,23,29,31,33,37,44] The WHO recommendation is for first-line treatment with cloxacillin which was found to exhibit non-susceptibility rates of (IQR) 10-55% (median 20); with similar susceptibility patterns between CA and HA isolates.[18,38,41] Chloramphenicol and flucloxacilin are listed as the treatment of choice for osteomyelitis, with reported non-susceptibility rates

of (IQR)21-81% (chloramphenicol; median 47) and 17% (flucloxacillin; based on a sample of 32 positive blood cultures in children aged <5 years in rural Ghana).[18,31,46]

Alongside its impact within the community, *S. aureus* has been identified as the most common HA infection,[18] and there is an increased propensity for these strains be multi-resistant (defined as exhibiting both oxacillin and cefoxitin resistance – identified among 15% (20/131) of CA and 65% (85/131) of HA isolates from a study of invasive infection in children in South Africa; however, this research did not identify if prior antibiotic exposure confounded these blood culture results).[19] A laboratory review of 248 methicillin-resistant isolates (not differentiated by CA versus HA) collected throughout South Africa revealed high frequencies of non-susceptibility to gentamicin (85%), erythromycin (58%), nitrofurantoin (38%), clindamycin (21%), yet isolates were fully sensitive to vancomycin.[36]

iii. Enterococci

Research which arose from a Tanzanian cohort study of 1,828 blood stream infections assessed susceptibility patterns of *Enterococci*, revealing these organisms were responsible for 15% of culture-confirmed causes of bacteraemia and resulted in case fatalities rates of 29% and 7% for *Enterococcus faecalis* and *Enterococcus faecium* (respectively). A small number of invasive isolates (n=21 for *E. faecium* and n=15 for *E. faecalis)* suggested more frequent non-susceptibility in HA infection to ampicillin (89% HA, 75% CA) and gentamicin (67% HA, 33% CA) for *E. faecium*; while *E. faecalis* exhibited ampicillin susceptibility.[18]

DISCUSSION

Our results, summarised in Table 2, highlight a dramatic lack of data on antimicrobial non-susceptibility patterns in the general paediatric population of sSA, particularly in the area of CA infection. Based on the estimated prevalence of non-susceptibility amongst positive cultures, current empirical treatment guidelines – relying heavily on commonly-available antibiotics such as penicillin and gentamicin – need review, as highlighted and summarised in Table 1. Considering that the paediatric population in sSA constitutes approximately 429 million children[62] the 67,451 cultures tested in the literature identified in this review (of which approximately 8% were culture-positive) reveal the paucity of investigations (particularly for CA infections) documented for such a large population at risk. Furthermore, a large proportion of research fails to clearly delineate the denominator of their study population,

making the attribution of the prevalence of non-susceptible pathogens difficult. Whilst our review focussed on a generalised paediatric population, estimates of non-susceptibility are likely to be higher in specific populations at risk (such as children living with HIV and TB) and warrant further reviews to identify non-susceptibility rates in these high-risk groups; as children with immunocompromising conditions have been identified as a unique population in their acquisition of antimicrobial resistant infections due to their exposure to empiric antimicrobials, frequent encounters with health care settings, and overall immune dysfunction.[63–66]

Increasing evidence highlighting a lack of sensitivity to the current WHO antibiotic guidelines has been a recurring theme in the international literature,[23,55] and together with the data presented here (Table 1), a review of currently-recommended empirical therapies in warranted. In the 2013 WHO guideline revisions, updated antibiotic therapy in relation to susceptibility were instituted for some organisms (for example, from chloramphenicol[67] to ciprofloxacin[21] to treat *Shigella* and *Salmonella* spp. infections); yet many common organisms continue to be treated with regimens with reportedly high frequencies of *in vitro* non-susceptibility due to a lack of an evidence base (or local data) to support further changes. Such an evidence base needs to comprise antimicrobial susceptibility patterns (identified from standardised reporting of defined populations) and the results of clinical trials that include safety data and patient outcomes.

Our review has several limitations, including heterogeneity among the included studies and a possible sampling bias, with the majority of studies arising from tertiary centres in urban settings, underestimating the significant burden of CA infections. This would likely overestimate the burden of morbidity caused by Gram-negative bacteria, which have a higher propensity to result in hospital presentation due to the more severe clinical presentation and failure of oral therapy in the community; and introduces the possibility of a non-representative population selection, as increased population density may be independently associated with AMR.[68] The majority of research failed to identify whether isolates were secondary to CA or HA infections, an issue previously highlighted in analysing resistance patterns in paediatric patients in Africa;[49,51,69] and while documentation of prior exposure to antimicrobials was minimal, it is uncertain how pre-treatment (a common practice prior to tertiary presentation in sSA) affects the validity of the findings of these studies.

Publication bias is also likely to be an issue, and although our search generated a large number of results, papers published in regard to individual pathogens may have not been captured by our search terms – for example, while susceptibility for *Shigella* spp. to ciprofloxacin was revealed, the possibility of increasing non-susceptibility should be considered in light of the increasing burden of the *S. typhi* MDR haplotype H58, which is widely evident throughout Asia and with reports of this species arising in parts of sSA.[70] There is also likely to be an element of geographical publication bias, as although eleven nations were represented in the results, one third of these arose from Southern Africa and despite their large population base, Central and West African nations were under-represented – an issue previously revealed by other reviews on antimicrobial data in Africa.[9,55] Finally, non-susceptibility estimates were calculated based on a small number of isolates, which is representative of the proportions documented through the cascade of hospital-based admissions – that is, of the large number of hospital presentations, a very small proportion will have positive blood cultures, of which an even smaller proportion will be positive for a particular pathogen for which non-susceptibility to antimicrobials can be tested. This may result in imprecision of results, and has been documented in recent publications.[71] The tension between high prevalence of non-susceptibility amongst a few isolates and a low overall incidence amongst all seriously ill children poses a further challenge for interpretation.

Nevertheless, the data available is conclusive that AMR is an increasing and real threat among children admitted to hospital in sSA, and prevalent MDR organisms are likely to become progressively pathogenic due to their well-documented swift spread within both CA and HA infections.[19,26,30–32,38,39,44,45] Recent research has documented frequent (up to 45%) community carriage of ESBLs, as well as nosocomial acquisition occurring at a rate of 20% for every 48 hours spent in hospital.[26] In light of the increasing prevalence of MDR organisms in hospital environs, simple improvements in local hospital-based infection control measures are important.[18,45] To this end, our findings support a recently published systematic review and meta-analysis assessing the most effective strategies for implementing antimicrobial stewardship policies in local settings identified strategies which could be extrapolated to LMICs to tackle antimicrobial resistance.[72] These include (i) the more rigorous use of empirical therapy that follows appropriately formulated local antimicrobial guidelines; (ii) consistently taking blood cultures (where possible) prior to the commencement of antimicrobial therapy (to allow earlier cessation of antibiotics if negative), and (iii) de-escalation of therapy (from intravenous to oral) as soon as clinical improvement occurs.[72]

Within sSA there are few AMR awareness programmes, with limited national and regional coordination.[7] These considerations should be incorporated into revisions of international treatment guidelines and monitoring of antimicrobial usage; while at the community-level, infection control requires addressing more pervasive and challenging issues inextricably linked with under-development, such as poor sanitation and hygiene, overcrowding, and strategies aimed at limiting the availability of freely available over-the-counter antibiotics. Historically, several effective surveillance systems have successfully been instituted for high profile diseases (such as malaria, HIV and MDR-tuberculosis), providing evidence that a paediatric-focussed AMR-surveillance programme *could* be achieved with adequate commitment.[72]

How increasing AMR contributes to neonatal and child mortality is a difficult association to currently draw firm conclusions upon in light of the challenges of attributing mortality to AMR versus the underlying condition (which may be nosocomial in nature or a more severe illness), or a lack of access to appropriate antibiotics; and it is interesting to note that increasing AMR has occurred over the last two decades concurrent with substantial progress in child mortality rates in LMICs. Furthermore, *in vitro* non-susceptibility does not necessarily correlate with a lack of clinical therapeutic effect. Nevertheless, excessive mortality rates attributable to AMR have been reported,[73,74] highlighting the importance of enhanced research in this area.

Until new antimicrobial strategies are discovered and tested, the focus must remain on adherence to tailored local guidelines, educating physicians on prescribing practices, improving laboratory infrastructure, and promoting collaboration between regional sites. Future research should focus on identifying appropriate local empirical therapies with improved susceptibility profiles, providing clear clinical indications for timely second-line therapy when empirical therapy fails, establishing guidelines for the de-escalation and cessation of antibiotic therapy and regular surveillance of antimicrobial usage within integrated, coordinated international surveillance programmes. Standardised research methods adhering to the WHO's Global Antimicrobial Resistance Surveillance System (GLASS)[75] must be pursued, clearly delineating resistance patterns for CA versus HA infections, while assessing for possible biases such as prior antibiotic exposure and ensuring systematic selection of patients for inclusion, with clearly identified population denominators. This will allow non-susceptibility patterns and antimicrobial usage to be monitored on a

continental scale, and ensure this issue of utmost public health concern is effectively addressed.

AUTHORS' CONTRIBUTIONS:

PW: Literature search, Figures (excluding Figure 2), data analysis and interpretation, writing of the first draft of the paper.

DI: Regular review of multiple drafts, with significant contributions to each draft as comments and suggestions for improvement.

JB: Original concept, study design, data analysis, data interpretation, significant reviews of multiple drafts, design of Figure 2.

DECLARATION OF INTERESTS:

We declare that we have no conflicts of interest.

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Diagnosis	**Antibiotic**	**Dosage**	**Reported non-susceptibility for most likely organisms (IQR% where available); Median**
Sepsis in a child aged <2 months	Ampicillin IV *plus* Gentamicin IV *or* Ceftriaxone IV Or If skin conditions suggest *S. aureus*: Cloxacillin IV *plus* Gentamicin ***Where referral is not possible*** Amoxicillin PO Gentamicin IM	50mg/kg QID for 7-10 days (21 days for meningitis) 5-7.5mg/kg daily 7-10 days (21 days for meningitis) 50mg/kg BD (<7 days) or QID (>7 days) for 21 days 25-50mg/kg BD-QID (age dependent) for 7-10 days 5-7.5mg/kg daily 7-10 days (21 days for meningitis) 50mg/kg BD for 7 days 5-7.5mg/kg daily for 2 - 7 days	Most likely organisms:[8,23,54,55] *1.* ***Klebsiella* spp.***:* -Ampicillin IQR 71-100%; 100[18,34,38,41,42] -Gentamicin IQR 48-58%; 49[18,34,38,42,46] -Ceftriaxone 43%[34]; 50%[38] **2. *Staphylococcus aureus*:** -Ampicillin IQR 85-100%; 90[18,29,31,38,41] -Gentamicin IQR 10-60%; 29[18,31,36,46] -Cloxacillin IQR 10-55%; 20[18,38,41] **3. *Streptococcus agalactiae*:** -Ampicillin: 0%[29,40] -Gentamicin: Not reported -Ceftriaxone: 0%[40] **4. *Escherichia coli:*** -Ampicillin: IQR 78-96%; 93[18,34,38,39,41,42] -Gentamicin: IQR 20-46%; 29[18,29,34,38,41,42] -Ceftriaxone: IQR 12-34%; 16[34,38,41,42]
Sepsis in a child aged >2 months	Ampicillin IV *plus* Gentamicin IV *or* Ceftriaxone IV If skin conditions suggest *Staphylococcus aureus*: Flucloxacillin IV *plus* Gentamicin	50mg/kg QID for 7-10 days 7.5mg/kg daily for 7-10 days 50mg/kg BD; or 100mg/kg daily for 7-10 days 50mg/kg QID for 7-10 days 7.5mg/kg daily	Most likely organisms:[9,23,29,37,54] 1. ***Salmonella* spp.**: -Ampicillin IQR 39-73%; 66[18,29,30,32,37,42,44] -Gentamicin: 23-32%; 28[18,30,42] -Ceftriaxone: 0%[31]; 0%[30] **2. *Escherichia coli:*** Non-susceptibility as documented above **3. *Streptococcus pneumoniae*:**

Diagnosis	Antibiotic	Dosage	Reported non-susceptibility for most likely organisms (IQR% where available); Median
			See 'Pneumonia' guidelines below **4. *Klebsiella* spp.:** Non-susceptibility as documented above **5. *Staphylococcus aureus*:** Non-susceptibility as documented above
Typhoid Fever	Ciprofloxacin PO 2nd line: IV Ceftriaxone *or* Azithromycin PO	15mg/kg BD for 7-10 days 80-100mg/kg/day for 5-7 days 20mg/kg/day for 5-7 days	***1. Salmonella typhi:*** Non-susceptibility to: -Ciprofloxacin:0%[30,31] -Ceftriaxone: 0%[31];0%[30] -Azithromycin: Not reported
Pneumonia	Ampicillin IV *plus* Gentamicin IV *or* Ceftriaxone IV *or* If *S. aureus* pneumonia is suggested: Cloxacillin IV *plus* Gentamicin	50mg/kg QID for 7-10 days 7.5mg/kg daily for 7-10 days 80mg/kg daily for 7-10 days; if Amp/Gent fails 50mg/kg QID for 7-10 days As above	Most commonly due to:[9,54,58] 1. ***Streptococcus pneumoniae:*** -Ampicillin Resistance 20%[30]; 22%[31] -Gentamicin Resistance 77%;[31] 78%[30] -Ceftriaxone resistance: 0%[30] **2. *Staphylococcus aureus:*** Non-susceptibility as documented above
Dysentery (presumed due to *Shigella* spp.)	Ciprofloxacin PO 2nd line: Ceftriaxone IV	15mg/kg BD for 3 days 50-80mg/kg daily for 3 days	**1. *Shigella* spp**.: -Ciprofloxacin resistance: 0% (CA); 11% (HA), when analysed in conjunction with other *Enterobacteriaceae*[18] -Ceftriaxone resistance: not documented
Osteomyelitis	Chloramphenicol *or* Cloxaxcillin / Flucloxacillin IV	25mg/kg TDS 50mg/kg QID for up to 5 weeks (step down to PO once clinically improving)	Most likely due to: 1. ***Staphylococcus aureus*:** Non-susceptibility to: -Chloramphenicol: 18-87%[18,31,46]

Diagnosis	Antibiotic	Dosage	Reported non-susceptibility for most likely organisms (IQR% where available); Median
	Additionally - "Clindamycin or 3rd generation cephalosporins may be given" (Clear circumstances of when such therapy would be appropriate are not outlined)	No dosages given	-Cloxacillin: 9-68%[18,38,41] -Clindamycin: 21%[36]; 44%[38] -3rd generation cephalosporins: Not reported
Meningitis	**Neonates:** Ampicillin and Gentamicin for 3 weeks *or* Ceftriaxone IV *or* Cefotaxime IV With gentamicin **Older Children:** Ceftriaxone IV *or* Cefotaxime IV **Or:** if no known resistance to Chloramphenicol or β-lactams locally: Chloramphenicol IV *plus* Ampicillin IM/IV **Or:** Chloramphenicol IV *plus* Benzylpenicillin IV	(Doses as above) 50mg-75mg/kg daily for 3 weeks 50mg/kg BD-QID (age dependent) for 3 weeks For 3 weeks 50mg/kg IM or IV bd for 7-10 days 50mg/kg IM or IV qid for 7-10 days 25mg/kg QID for 10 days 50mg/kg QID for 10 days 25mg/kg QID for 10 days 60mg/kg QID for 10 days	As above

Diagnosis	Antibiotic	Dosage	Reported non-susceptibility for most likely organisms (IQR% where available); Median
Urinary Tract Infection	Co-trimoxazole PO (2nd line: Ampicillin plus Gentamicin)	4mg/kg plus 20mg/kg BD for 5 days Dosages as above	Most likely organisms:[19,54,56] **1. *Escherichia coli*:** -Co-trimoxazole Resistance: 87-90%(CA);[18,29] 77% (HA)[18] -Ampicillin and Gentamicin resistance: as above **2. *Klebsiella* spp.:** -Co-trimoxazole Resistance: 63% (CA); 94% (HA)[18] -Ampicillin and Gentamicin resistance: as above

Table 1: Antibiotic Recommendations from the WHO Pocket Book of Hospital Care for Children, 2013 (2nd) Edition and WHO Guideline for Managing Possible Serious Bacterial Infection in Young Infants When Referral is Not Feasible (2015), with efficacy based on non-susceptibility patterns documented by this review [21,76]

BD = twice daily; TDS = three times daily; QID = four times daily; IV = intravenous; IM = intramuscular; PO = *per os* (by mouth)

GRAM-NEGATIVE ORGANISMS		***Number of isolates not susceptible (n) / Number tested (N)***	***(Non-Susceptibility Rate; %)***	***Interquartile Range (IQR;%); Median***
Klebsiella *spp.*	Penicillin/Ampicillin	45/100 55/57 17/17 53/53 50/50	45%[42] 96%[34] 100%[41] 100%[18] (CA & HA) 100%[38] (CA)	71-100%; 100
	Gentamicin	49/100 28/57 25/53 33/50	49%[42] 49%[34] 47%[18] (CA & HA) 66%[38]	48-58%; 49
	Ceftriaxone	25/57 25/50 1/3	43%[34] 50%[38] 33%[46]	
	Cefotaxime	24/50 12/53 8/53	48%[34] 22%[18] (CA) 15%[18] (HA)	
	Ceftazidime	28/57 11/53 8/53	49%[34] 21%[18] (CA) 15%[18] (HA)	
	Ciprofloxacin	4/50 0/3	8%[38] 0%[46]	
	Chloramphenicol	10/19 15/34	53%[18] (CA) 44%[18] (HA)	
	Co-trimoxazole	12/19 32/34	63%[18] (CA) 94%[18] (HA)	
	ESBL producing (Proportion; %)	*27/35* *93/119* *33/40*	*76%[19] (CA)* *78%[19] (HA)* *83%[39] (HA)*	
Escherichia coli	Penicillin/Ampicillin	155/310 32/41 11/13 13/14 148/154 23/24 22/22	50%[42] 78%[34] 85%[18] (HA) 93%[41] 96%[29] (CA) 96%[18] (CA) 100%[38]	78-96%; 93
	Amoxicillin-Clavulanate	6/24 9/13	25%(CA)[18] 69% (HA)[18]	
	Gentamicin	4/41	10%[34]	20-46%;

		62/310 40/142 7/24 6/14 6/13 15/22	20%[42] 28%[29] 29%[18] (CA) 43%[41] 46%[18] (HA) 68%[38]	29
	Ceftriaxone	31/310 2/14 7/41 11/22	10%[42] 14%[41] 17%[34] 50%[38]	12-34%; 16
	Cefotaxime	11/22	50%[38]	
	Ceftazidime	11/22	50%[38]	
	Chloramphenicol	120/155	78%[29] (CA)	
	Co-trimoxazole	21/24 10/13 128/142	87%[18] (CA) 77%[18] (HA) 90%[29] (CA)	
	ESBL producing (Proportion; %)	*9/76* *4/19* *11/22* *23/40*	*12%[19] (CA)* *22%[19] (HA)* *50%[38]* *58%[39] (HA)*	*17-54%;* *36*
Salmonella *spp.*	Penicillin/Ampicillin	10/40 10/30 13/27 60/92 8/12 74/103 296/401 107/128	25%[32] 30%[42] 48%[18] (CA) 65%[37] 67%[18] (HA) 72%[44] 74%[29] 84%[30] (CA)	39-73%; 66
	Amoxicillin-Clavulanate	6/30 152/401 95/128	20%[42] 38%[29] 74%[30] (CA)	
	Gentamicin	6/30 7/27 38/128 4/12	20%[42] 26%[18] (CA) 30%[30] (CA) 33%[18] (HA)	23-32%; 28
	Co-trimoxazole	7/40 17/30 13/27 8/12 55/92 264/401 98/128	18%[32] 55%[42] 48%[18] (CA) 67%[18] (HA) 60%[37] 66%[29] 77%[30] (CA)	48-67%; 60
	Tetracycline	14/128	11%[30] (CA)	

		6/40	15%[32]	
	Chloramphenicol	6/40	15%[32]	15-54%; 27
		6/30	20%[42]	
		4/27	15%[18] (CA)	
		4/12	33%[18] (HA)	
		216/401	54%[29]	
		105/128	82%[30] (CA)	
	Ciprofloxacin	0/128	0%[30] (CA)	
		0/129	0%[31]	
	Ceftriaxone	0/128	0%[30] (CA)	
		0/129	0%[31]	
	Multi-drug Resistant *(Proportion; %)*	*34/133*	***S. Typhi:*** *33%[44]*	
		84/129	*65%[31]*	
			Non-Typhoidal Salmonella:	
		99/129	*77%[31]*	
		97/128	*76%[30]*	
		101/103	*98%[44]*	
Shigella *spp.*	Ampicillin/Penicillin	61/109	56%[32]	
	Co-trimoxazole	92/109	84%[32]	
	Tetracycline	72/109	66%[32]	
	Chloramphenicol	57/109	52%[32]	
	Multi-drug Resistant *(Proportion; %)*	*71/109*	*65%[32]*	
Haemophilus Influenzae *type b*	Penicillin/Ampicillin	7/14	50%[35]	
		61/113	54%[29]	
		6/6	100%[46] (CA)	
	Chloramphenicol	56/113	50%[29]	
		9/10	90%[35]	
		6/6	100%[46] (CA)	
	Co-trimoxazole	26/113	23%[29]	
Acinetobacter *spp.*	Penicillin/Ampicillin	37/66	56%[34]	
		0/3	0%[18] (CA)	
		0/9	0%[18] (HA)	
	Gentamicin	18/66	27%[34]	
		2/3	67%[18] (CA)	
		4/9	44%[18] (HA)	
	Ceftriaxone	23/66	35%[34]	
	Ceftazidime	2/9	22%[18] (HA)	
		1/3	33%[18] (CA)	
	Multi-drug Resistant	*4/16*	*25%[19] (CA)*	

	(Proportion; %)	*49/68*	*72%[19] (HA)*	
GRAM-POSITIVE ORGANISMS		***Number of isolates not susceptible (n) / Number tested (N)***	***Non-Susceptibility Rate (%)***	***Interquartile Ranges (IQR; %); Median***
Streptococcus pneumoniae	Penicillin/Ampicillin	4/20 5/22	20%[30] (CA) 23%[31]	
	Amoxicillin-Clavulanate	2/18	11%[30] (CA)	
	Gentamicin	17/22 16/20	77%[31] 78%[30] (CA)	
	Chloramphenicol	2/18 5/20	11%[30] (CA) 25%[31]	
	Co-trimoxazole	20/116 19/20 17/17 11/11 29//29	17%[37] (CA) 95%[31] (CA) 100%[30] (CA) 100%[43] 100%[29]	56-100%; 100
	Ciprofloxacin	9/21	43%[31]	
	Tetracycline	14/19 15/20	74%[31] 75%[30] (CA)	
	Ceftriaxone	0/20	0%[30] (CA)	
Streptococcus agalactae	Penicillin/Ampicillin	0/35 0/57	0%[29] 0%[40]	
	Chloramphenicol	10/35 11/57	29%[29] 19%[29]	
	Erythromycin	12/57	21%[40]	
	Co-trimoxazole	5/34	15%[29]	
	Ceftriaxone	0/57	0%[40]	
Staphylococcus aureus	Ampicillin/Penicillin	17/32 23/27 170/189 29/32 13/13 17/17	52%[31] 85%[41] 90%[29] 90%[38] 100%[18] (CA) 100%[18] (HA)	85-100%; 90
	Flucloxacillin	5/30	17%[31]	
	Oxacillin	17/189	9%[29]	
	Cloxacillin	1/13 2/17 9/32 22/27	8%[18] (CA) 12%[18] (HA) 28%[38] 81%[41]	10-55%; 20

	Co-trimoxazole	11/24 19/32	54%[31] 60%[38]	
	Gentamicin	0/13 3/17 9/32 3/9 210/248	0%[18] (CA) 19%[18] (HA) 29%[31] 33%[46] (CA) 85%[36]	10-60%; 29
	Nitrofurantoin	94/248	38%[36]	
	Clindamycin	52/248 14/32	21%[36] 44%[38]	
	Erythromycin	0/13 2/9 5/17 144/248 21/32	0%[18] (CA) 23%[46] (CA) 29%[18] (HA) 58%[36] 66%[38]	12-62%; 29
	Ciprofloxacin	NA/32 10/31	14%[38] 32%[31]	
	Chloramphenicol	2/13 5/17 6/9 30/32	15%[18] (CA) 29%[18] (HA) 67%[46] (CA) 94%[31]	21-81%; 47
	Methicillin	58/131	44%[19]	
Methicillin-Resistant Staphylococcus aureus	Oxacillin + cefoxitin resistance	9/32 14/95 23/36	28%[38] 15%[19] (CA) 65%[19] (HA)	

Table 2 ***Non-susceptibility Patterns of Key Pathogens;***
CA = Community-acquired; HA = Hospital-acquired, where specified in the literature (blank=not specified); NA = Not Available.

Appendix 1: Characteristics of Included Studies

	Author	Year Published; Years Data Collected	Study Design	Title	Setting (primary / secondary / tertiary); Community v's Hospital Acquired Infections	Location	Age Range (Neonate / Paediatric)	Microbiology Techniques / Quality	Findings	GRADE Level of Evidence (Comments)
1	Blomberg et al.[18]	2007; patients presenting 2001-2002.	Cohort	**Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: A prospective cohort study**	Urban tertiary setting; Both community- and hospital-acquired infections	Tanzania	0-7 years (average age 8.5 months); n=1,787 of n=1,828 admissions presenting with signs of sepsis were included in the study to have blood cultures collected	1-5ml of Blood inoculated in BACTEC blood-culturing vials were incubated for 6 weeks, then subcultured in agar and isolates identified by AEI20E/API20NE/API20AUX systems (aerobic cultures only). Susceptibilities against antimicrobial agents were tested by disk diffusion methods according to the CLSI guidelines. Gram-negative bacteria were investigated for extended-spectrum beta-lactamases with E-test, PCR and DNA sequencing. *Enterococcal* isolates were investigated by PCR to affirm identity and vancomycin resistance.	• At least 2/3 of the included patients had received antimicrobial therapy prior to blood cultures being collected • The incidence of laboratory-confirmed bloodstream infection was 13.9% (255 of 1,828 admissions) • A single pathogen was identified in 224 children (12.3%); 31 children (1.7%) had polymicrobial infection with 2-4 isolates identified • Half of all laboratory-confirmed bloodstream infections were identified as potentially hospital-acquired • *Salmonella* and *E Coli* were the most common isolates in **community-acquired** infections; and *Klebsiella* and *Staphylococcus Aureus* were the most common **hospital-acquired** infections • *Klebsiella* was the most common cause of neonatal bloodstream infection (54%) • In children >1 month *Salmonella* spp. were the most frequently isolated pathogen • Children with laboratory-confirmed bloodstream infection had a 3-fold increased risk of mortality; with Gram-negative blood stream infection being twice as fatal as malaria (45.6% vs 20.2%) and Gram-positive sepsis being the least common cause of mortality (16.7%) • *Enterobacteriaceae* displayed high frequency of resistance to commonly-used antimicrobials:	B (Large sample size; prospective design; identification of prior treatment with antibiotics)

									80% resistance to Ampicillin 33% resistance to gentamicin - However, there was almost universal sensitivity to Ciprofloxacin *Salmonella* spp. Non-suscpetibility: 33% to Chloramphenicol 50% to ampicillin and co-trimoxazole - ESBL was found in 18% of *Enterobacteriacaeae* phenotypes; and these isolates were resistant to almost all tested antimicrobials aside from Ciprofloxacin and Meropenem - The majority of *Staphylococcus aureus* isolates were sensitive to commonly used anti-staphylococcal agents (including cloxacillin and gentamicin) - Antimicrobial treatment prior to blood culture collection was significantly associated with resistance to co-trimoxazole and chloramphenicol in Gram-negative isolates; with resistance to erythromycin (36% vs 0%) and chloramphenicol (46% vs 0%) identified in *Staphylococcus aureus* isolates - Hospital-acquired infections were significantly associated with resistance to amoxicillin-clavulanate and Cephalosporins in *E Coli* infection; and with co-trimoxazole resistance in *Klebsiella* infection 53% of all *Klebsiella* isolates were resistant to gentamicin (as well as inherent resistance to ampicillin), rendering empiric therapy of limited utility; subsequently there was a high incidence of case-fatality of *Klebsiella* bloodstream infections	

									• Malnutrition: 1/6 (243/1,603) of the patients were malnourished, and this was a risk factor for death; while in those who survived, it was associated with a prolonged hospital stay • *E. Faecium* and *E.Faecalis* isolates commonly displayed high-level gentamicin resistance (overall 44%) and ampicillin resistance (overall 47%)	
2	Enwere et al.[37]	2006; Recruited 2000-2003	Cohort	**Epidemiologic and Clinical Characteristics of Community-Acquired Invasive Bacterial Infections in children 2-29 months in The Gambia**	Urban secondary and tertiary Settings; Community-acquired infections	The Gambia	2-29 months (7,369 specimens were cultured); infants presenting to a government vaccination post with signs of an acute lower respiratory tract infection who were investigated for invasive bacterial infection.	Bacteria were isolated from blood using automated blood-culture system (Bactec 9050) and inoculated under aerobic and 5% CO2 conditions for 18-24 hours. Identification of *S. Pneumoniae* and *Salmonella* species was by cultural morphology, & susceptibility to analytical profile indices. Resistance to antimicrobials was assessed by disk diffusion for all bacteria and was investigated further by measuring MICs for *Pnuemococci* and *n*on-typhoidal *Salmonella*, but not for other bacteria.	• The most **community-acquired** common organism isolated was *Streptococcus Pneumonia* (35% of episodes) • Non-Typhoidal *Salmonella* was cultured in 28% of isolates • In order of decreasing frequency, the most common other organisms (frequency not specified) were: *-E Coli* *-S. Aureus* *-Meningococcus* *-Streptococcus spp.* *-Shigella spp.* *-Pseudomonas spp.* *-Klebsiella spp*. • Among isolates of non-typhoidal *Salmonella*, resistance was high to ampicillin (65%), co-trimoxazole (60%) and chloramphenicol (24%); yet all isolates were susceptible to cefotaxime • Among *Pneumococcal* isolates, resistance was found to chloramphenicol (9.6%), co-trimoxazole (16.5%) and tetracycline (44.3%) but no isolates were resistant to penicillin, ampicillin or cefotaxime	B (Data collected as part of a randomised, double-blinded, placebo-controlled trial; prospective design; systematic patient recruitment; external quality assurance)

3	Sigauque et al.[29]	2009; patients presenting 2001-2006.	Cohort	**Community-acquired bacteraemia among children admitted to a rural hospital in Mozambique**	Rural tertiary setting; Community-acquired infections	Mozambique	0-15yrs n=19,896 admitted children underwent blood culture investigation of which n=1,592 were bacteraemic	Blood cultures were collected for children with axillary temperatures >39 on admission, inoculated into paediatric culture bottles and incubated in an automated BACTEC 9050 system for 4 days. Positive cultures were examined by Gram stain and subcultured on agar plates then identified according to standard microbiologic procedures. Antibiotic susceptibility was determined by disk diffusion according to CLSI guidelines; and MICs were estimated for *Pneumococcus* using E-strips.	• Bloodstream infections were identified in 8% of paediatric hospital admissions. Non-typhoidal *Salmonella* (26%) and *Pseudomonas* (25%) were the most prevalent pathogens isolated overall • In neonates, *Staphylococcus aureus* (39%) and *Group B Streptococcus* (20%) predominated • Community-acquired bacteraemia associated mortality accounted for 21% of all hospital deaths • Resistance to antibiotics commonly used in Mozambique was high: Pneumococcal isolates were predominantly susceptible to penicillin (89%) and chloramphenicol (93%) but resistant to trimethoprim-sulfamethoxazole • Among non-typhoidal *Salmonella* isolates, 74% were resistant to ampicillin, 66% to trimethoprim-sulfamethoxazole and 54% to chloramphenicol; while 38% were resistant to amoxicillin-clavulanic acid • *Staphylococcus aureus* isolates were 90% resistant to ampicillin and 9% resistant to Oxacillin • *Haemophilus Influenzae* exhibited high resistance to chloramphenicol (50%), penicillin/ampicillin (54%) and co-trimoxazole (23%) • *Group B Streptococcus* isolates exhibited 100% susceptibility to penicillin/ampicillin; 71% susceptibility to chloramphenicol, and 85% susceptibility to co-trimoxazole.	B (Large patient cohort, systematic patient recruitment, prospective study design)

4	Falade et al[43]	2009; patients presenting 2005-2006	Cohort	**Invasive Pneumococcal disease in Children aged <5 years admitted to 3 Urban hospitals in Ibadan, Nigeria.**	Tertiary Urban; Community-acquired infections	Nigeria	Age 2-59 months; n=1,210 cases of suspected community-acquired pneumococcal disease investigated with blood and/or CSF cultures	Inoculated blood culture bottles were incubated in the laboratory for 24-48 hours and then until day 7 if there was no initial growth. Subcultures were performed twice (on days 2 and 3). Further identification of bacterial cultures was conducted by morphological and biochemical methods. Serotyping of Pneumococcal isolates was performed with capsular and factor-typing sera. MIC susceptibility testing was performed using E-strips	• 1,210 children with suspected bacterial disease were investigated over a 24-month period. There were 481 cases of meningitis clinical syndrome, 299 cases of pneumonia and 200 cases of septicaemia; 21 children had invasive *pneumococcal* disease. • 11 *S. pneumoniae* serotype isolates from CSF and blood specimens were susceptible to penicillin, chloramphenicol, cefotaxime, erythromycin and ciprofloxacin; they all showed intermediate resistance to tetracycline and were fully resistant to trimethoprim-sulfamethoxazole	B (Prospective multi-centre study; systematic patient recruitment; external quality control of laboratory procedures)

5	Schwarz et al[30]	2010; patients presenting 2007-2009	Prospective cohort	**Systemic bacteraemia in children presenting with clinical pneumonia and the impact of non-typhoid salmonella (NTS)**	Rural Tertiary; Community-acquired infections	Ghana	n=1,032 blood cultures were collected between children 2 months – 5 years of age presenting with clinical pneumonia; of which n=90 (9%) were positive with presumed contaminants and n=209 (20%) were positive with presumed pathogenic bacteria.	BC incubated in a BACTEC automated BC system for 5/7 or until positive. Broth from positive bottles was directly examined by Gram stain and 20 µl were cultured further on agar Identification of *S. pneumoniae* was based on morphology of colonies and the optochin test. Oxacillin discs were used to determine sensitivity to penicillin. Antibiotic susceptibility testing was performed using the disc diffusion method with the susceptibility breakpoints suggested by CLSI. Lab undertakes external quality assurance programme.	o The most common isolates were non-typhoidal *Salmonella* (n=16, 9.3%); *S.pneumoniae* (n=8, 4.6%); *S.aureus* (n=5, 2.9%); *S. Typhi* (n=4, 2.3%); *Klebsiella* spp. (n=2, 1.2%) **<u>Non-typhoidal *Salmonella* Susceptibility:</u>** • Amoxicillin/Ampicillin 15.5%; • Co-amoxiclav 25.7%; • Cefuroxime 46.5%; • Ceftriaxone 100%; • Co-trimoxazole 23.5%; • Ciprofloxacin 100%; • Gentamicin 70.9%; • Tetracycline 89%; • Chloramphenicol 18% • **Multi-drug resistance** against the three standard drugs amoxicillin, chloramphenicol and co-trimoxazole was 75.5% ***<u>Streptococcal pneumoniae</u>* Susceptibility:** • Amoxicillin/Ampicillin: 80% • Augmentin 88.9%; • Cefuroxime 100%; • Ceftriaxone 100%; • Co-trimoxazole 0%; • Ciprofloxacin 52.6^; • Gentamicin 22.2%; • Tetracycline 25%; • Chloramphenicol 88.9%	B (Prospective study design; systematic patient recruitment; external quality control of laboratory procedures)
6	Nielsen et al.[31]	2012 patients presenting 2007-2009	Prospective Cohort	**Incidence and Characteristics of Bacteremia among Children in Rural Ghana**	Rural Tertiary; Community-acquired infections	Ghana	n=1,196 children aged 0-5 years admitted to a rural hospital in Ghana had blood cultures collected; of which n=238 (20%) were culture positive	Blood cultures were incubated using automated BACTEC for 5/7 or until positive; then examined directly by Gram stain microscopy and sub-cultured on standard media plates. Identification of the organisms was obtained by biochemical and serological tests. Isolates of non-pathogenic microorganisms or skin flora were considered to be contaminants. Susceptibility to penicillin, amoxicillin/ampicillin, amoxicillin & clavulanic acid, flucloxacillin, cefuroxime, ceftriaxone, erythromycin/azithromycin,	The most frequently (**community-acquired)** isolated pathogens were: • Non-typhoidal Salmonella (n=129; 53.3%) • *S. aureus* (n=32; 13.2%) • *S. pneumoniae* (n=22; 9.1%) • *S. Typhi* (n=17; 7%) • Yearly cumulative incidences per 1,000 was 46.6 cases per 1,000 (CI 40.9-52.2) • Wasting was positively associated with bacteraemia and systemic non-typhoidal Salmonellae infection **NON-SUSCEPTIBILTY:** • ***Salmonella Typhi**:* 65% multidrug resistant; yet	B (Systematic patient recruitment although ~10% had missing data and were excluded. Relatively large sample size; prospective study design).

								co-trimoxazole, ciprofloxacin, gentamicin, tetracycline and chloramphenicol was tested using the Kirby-Bauer disc diffusion method. Multi-drug resistance of Salmonella enterica was defined as simultaneous resistance to amoxicillin, co-trimoxazole and chloramphenicol. S. enterica were screened for resistance to fluoroquinolones (FQ) by nalidixic acid disc diffusion following the CLSI guidelines. Nalidixic acid resistant strains were further tested by ciprofloxacin E test.	sensitive to Ciprofloxacin and Ceftriaxone (100% sensitivity) • **NTS**: 98% susceptible to Ciprofloxacin, 100% sensitive to Ceftriaxone; yet 77% of isolates were multi-drug resistant • ***Staphylococcus aureus***: 48% susceptible to penicillin; 83% to flucloxacillin; 54% to co-trimoxazole; 68% to ciprofloxacin; 71% to gentamicin; 35% to tetracycline; 6% to chloramphenicol • ***Strep pneumoniae***: 76% susceptible to penicillin; 77% to amoxicillin/ampicillin; 100% to cefuroxime, ceftriaxone and 5% to co-trimoxazole (Multi-drug resistance of *Salmonella enterica* was defined as simultaneous resistance to amoxicillin, co-trimoxazole and chloramphenicol)	
7	Mando-mando et al.[32]	2009; patients presenting 2001-2003.	Cohort	**Antimicrobial Susceptibility and Mechanisms of resistance to *Shigella* and *Salmonella* isolates from children under five years of age with diarrhea in rural Mozambique**	Tertiary; Community-acquired	Rural Mozambique	n=109 *Shigella* spp. isolates and n=49 *Salmonella spp.* isolates children <5 years who presented to the outpatient department with diarrhea. Number who attended (denominator) and number with bloody diarrhea not given;	PCR detection of genes encoding beta-lactamases associated in *Shigella* and *Salmonella* isolates presenting with full resistance.	• Very high levels of resistance in *Shigella* isolates to trimethoprim-sulfamethoxazole (84%), tetracycline (66%), ampicillin (56%) and chloramphenicol (52%) • *Salmonella* exhibited resistance to ampicillin (25%) and trimethoprim-sulfamethoxazole (18%), tetracycline (15%), and chloramphenicol (15%) Multi-drug resistance was detected within 65% of *Shigella* isolates and 23% of *Salmonella* isolates	C (Limitations in study design; no denominator identifying number of patients sampled or proportion presenting with bloody diarrhoea)
8	Phoba et al[44]	2014 patients presenting 2008-2012	Retro-spective cohort study	**Epidemic increase in Salmonella bloodstream infection in children, Bwamanda, the Democratic Republic of Congo**	Rural Tertiary; Community-acquired infections	Democratic Republic of Congo	Between 2008-2012; 3,311 children <5 years old were admitted, n=626 blood cultures were collected of which n=168 were positive More than three-quarters (169 out	Children >28/7 with axillary temperature ≥ 38 °C or ≤ 35.5 °C, with suspected septic shock, or signs of invasive bacterial infection. BC samples were cultured via BacT and shipped to Kinshassa INRB, where they were incubated at 35 °C and checked daily for growth by visual inspection of the chromogenic growth indicator	The most common causes of **community-acquired** bacteraemia were (in order of frequency): -NTS -*Salmonella Typhi* -*Klebsiella* spp. -*Staphylococcus Aureus* -*Escherichia Coli* -Enterobacter **NON-SUSCEPTIBILTY:**	C (Retrospective study design; evidence of prior antibiotic use which biases towards non-susceptibility; infections not delineated as

							of 216, 78.2 %) were on antibiotics ≤ 48 h prior to sampling (mostly ampicillin, chloramphenicol or TMP-SMX), but yield of CSO in this group did not significantly differ from those who were not on antibiotics (70 out of 169 [41.4 %] versus 18/47 [38.3 %] respectively	at the bottom of the vials. Skin or environmental bacteria were categorised as contaminants; the other bacteria were considered as clinically significant organisms (CSO). Isolates were further identified to the species level using standard biochemical methods.	• 72.2% of *Salmonella typhi* were co-resistant to ampicililn and co-trimoxazole; with 33% of these showing additional resistance to chloramphenicol (Classified as MDR) • NTS: 95% MDR (resistant to ampicillin, chloramphenicol and co-trimoxazole) • 96.7% of NTS isolates were MDR	CA vs HA; referral pathways unclear)
9	Ndir et al.[39] patients admitted 2012-2013	2016;	Case Control	**Epidemiology and Burden of Bloodstream Infections caused by Extended-Spectrum Beta-Lactamase Producing *Enterobacteriaceae* in a Paediatric Hospital in Senegal**	Urban tertiary setting; Both community- and hospital-acquired infections	Senegal	Ages 0-16yrs; n=1,800 suspected patients with bloodstream infections yielded n=84 cases of patients with ESBL-E positive infections and n=26 ESBL negative *Enterobacteriaceae* infections	Blood samples were drawn from all inpatients with suspected bloodstream infections (n=1,800) and considered hospital acquired if this occurred 48h after admission (72h for neonates). The BSI were defined as ESBL-positive when the blood sample yielded ESBL-producing *Enterobacteriaceae* and ESBL-negative when the strain was *Enterobacteriaceae* susceptible to beta-lactams; identified with API 20E strips and double disc diffusion method using antibiotic discs of cefepime, cefotaxime and ceftazidime	• The overall incidence rate of **hospital-acquired**-BSI caused by ESBL-E strains was 1.52 cases/1,000 patient-days (95% CI 1.2-5.6) • ESBLs were produced by 88% of *Enterobacteriaceae*. isolates, 82% of *Klebsiella* spp. isolates and 58.3% of *E Coli* isolates • Patients with ESBL-positive BSI were significantly younger than patients with ESBL-negative BSI (2.5 yrs vs 4.4 yrs, p=0.021) and were more likely to suffer from sickle cell disease (33.3% vs 11.5%, p=0.044) and be malnourished (38.1% vs 15.4%, p=0.034) • Initial antibiotic therapy (with a third generation cephalosporin in 90% of cases) was inadequate to treat 79.1% of BSI infections (n=87) • 50 patients with a BSI caused by *Enterobacteriaceae* died during the study period (45.5%). The case fatality rate was significantly higher in ESBL-positive patients (54.8%) than in ESBL-negative patients (15.4%, p<0.001). • Rates of ESBL (at 1.52 cases/1,000 patient days) were much higher than recently documented in developed world settings, such as France (0.054/1,000 patient days in 2012)	C (Retrospective study design – case-case-control nested in a cohort; however systematic patient recruitment; prior antibiotic use evident which biases towards increased non-susceptibility)

									• This raises the question as to the choice of third generation cephalosporins as systemic empirical treatment, which is inadequate to treat ESBL-positive BSIs	
10	Gray et al.[40]	2007; patients presenting 2004-2005.	Case Series	**Invasive *Group B Streptococcal* Infection in Infants, Malawi**	Urban tertiary centre; Hospital- v's community-acquired not clearly specified	Blantyre District, Malawi	0-90 days; n=57 neonates with blood and CSF cultures isolating *Group B Streptococcus*	Disc diffusion antimicrobial susceptibility testing performed in accordance with the British Society for Antimicrobial Chemotherapy Guidelines on *Isosensitest* agar; in a laboratory enrolled in the UK National External Quality Assessment Service for Microbiology	Of neonates presenting with invasive group B *Streptococcus* infection, cultures exhibited: • 100% sensitivity to penicillin • 100% sensitivitity to ceftriaxone • 81% sensitivity to chloramphenicol • 79% sensitivity to erythromycin • 4% sensitivity to tetracycline	C (Prospective case series yet external quality control of laboratory; noted issues in clarifying numerator and denominator)

11	Talbert et al.[34]	2010; patients admitted 2001-2009	Case Series	**Invasive bacterial infections in neonates and young infants born outside hospital admitted to a rural hospital in Kenya.**	Rural tertiary centre; Both community- and hospital-acquired (neonates born in hospital and at home)	Kilifi District, Kenya	0-60 days; n=4,849 blood cultures (systematic, all outborn admissions) and 2,140 CSF cultures	Antibiotic sensitivity was assessed using British Society for Antimicrobial Chemotherapy methods; with external quality monitoring via the UK National External Quality Assessment Service.	Non-susceptibility of *Acinetobacter* spp. (with 95% CI) were: • Penicillin/Ampicillin: 56% (42-70) • Gentamicin 27% (14-39) • Ceftriaxone 35% (22-48) Non-susceptibility of *Klebsiella Pneumoniae* were: • Penicillin/Ampicillin: 96% (91-100) • Gentamicin 49% (35-63) • Ceftriaxone 43% (29-57) Non-susceptibility of *E. Coli* were: • Penicillin/Ampicillin: 78 %(65-91) • Gentamicin 10% (1-19) • Ceftriaxone 17% (5-29) There was a reduction in the sensitivity of isolates to ampicillin/gentamicin (WHO Guidelines) over the study period from 88% susceptibility in 2001 to 66% susceptibility in 2009 (p<0.001)	C (Case series of prospectively collected data on a large number of systematically collected participants over prolonged study period; internal and external quality control of laboratory procedures)

12	Nantanda et al.[46]	2008 Patients presenting 2005-2006	Cohort;	**Bacterial aetiology and outcome in children with severe pneumonia in Uganda.**	Urban Tertiary; Community-acquired infections only	Uganda	n=157 children 2-59 months with clinically severe pneumonia; of which n=25 (15.9%) had positive blood cultures and n=79 had positive sputum cultures	157 children aged 2-59 months with symptoms of severe pneumonia (according to WHO guidelines) were recruited over a 4-month period in 2005-2006. Blood and induced sputum were obtained for culture after premedication with Salbutamol and hypertonic saline. Culture and sensitivity for blood and sputum was via manual disk diffusion methods after inoculation on agar plates and incubation for >24/24.	• The mortality rate was 15.3% (n=24) • The most common organisms causing clinically severe pneumonia were: *Strep Pneumoniae* (46%), *Staphylococcus Aureus* (36%), *Haemophilus Influenzae* (24%) and *Klebsiella* species (22%). • ***Staphylococcus Aureus*** was positive on 36% of blood cultures and was positively associated with severe malnutrition. SENSITIVITY PATTERNS: o Erythromycin: 77% o Chloramphenicol (1st line therapy in the unit): 33% o Gentamicin: 66% • ***Streptococcal Pneumoniae*** SENSITIVITY PATTERNS: o Chloramphenicol: 87% o Erythromycin: fully sensitive o Ampicillin: 94% • ***Haemophilus Influenzae*** isolates were completely resistant to Ampicillin and Chloramphenicol • ***Klebsiella*** spp. SENSITIVITY PATTERNS: o Ampicillin: 0% o Chloramphenicol: 40% o Ceftriaxone: 100% o Gentamicin: 50% • ***Escherichia Coli* SENSITIVITY PATTERNS** o Chloramphenicol: 10% o Erythromycin: 75% o Ceftriaxone: 100%	C (Prospective study design, patients systematically recruited yet small sample size, analysed CA infections)
13	Dramowski et al.[19]	2015; patients presenting 2008-2013	Case Series	Trends in Paediatric Bloodstream Infections at a South African referral hospital	Urban tertiary; Both hospital (defined as >72 hours) - and community-acquired	Cape Town, South Africa	0-14 years; n=17,001 cultures of which n=935 were positive and n=864 corresponded with n=864 episodes of bacteraemia. Blood cultures were obtained from all	Bactec / BacT/Alert system utilized to analyse paediatric blood culture bottles; with susceptibility testing performed with the automated Vitek II system using CLSI breakpoints. (935 culture-positive specimens yielded 979 pathogens)	• 94.7% of blood stream infections were monomicrobial and 5% were polymicrobial (2-3 pathogens) • The median age of affected patients was 7.5 months • Blood culture contamination rates were high (6.6%), most commonly with *coagulase negative staphylococci*	C (Retrospective review of patients presenting over extended [5 year] period; yet large sample

					infections (analysed separately)		children with suspected sepsis or severe infection with a focal site.		• Nearly half of all infectious were hospital-acquired (46.8%; classified as positive >72 hours post hospitalization) • Gram-negative organisms predominated (60%) followed by Gram-positives (32.4%) and fungi (7.4%) • The most common organisms were *Klebsiella* (17%), *Staphylococcus Aureus (14%)* and *Escherichia coli (11%)* • Overall mortality for blood stream infections was 20.4% (176/864); patients with HA BSI experienced **higher mortality than CA BSI** (25% [101/404] vs 16.3% [75/460]; p=0.002) • *Acinetobacter* spp. were associated with the highest BSI mortality • No carbapenem resistant *Enterobacteriaceae* (CRE) or Vancomycin-resistant *Enterococci* (VRE) were isolated • Overall, the prevalence of antimicrobial resistance was much higher in hospital-acquired infections (65.8%) than community acquired isolates (25%) p<0.0001. This was an overall figure based on a subset of four pathogens: **MRSA, multi-drug resistant *Acinetobacter baumannii* and ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae***. • There was not a significant increase in antimicrobial resistance between 2008 and 2013 • <u>ESBL Resistance Rates:</u> -*Klebsiella*: CA: 75.7%; HA 78.3% (p=0.82) -*Escherichia coli*: CA:11.7%; HA 21.7% (p=0.3) • 78% of *Acinetobacter Baumannii* samples were multi-drug resistant • 44% of *Staphylococcus Aureus* samples were methicillin resistant	size; CA vs HA clearly delineated; ICU vs ward-based patient population analysed)

14	Mhada et al.[41]	2012; patients admitted between 2009-2010	Case Series	**Neonatal sepsis at Muhimbili National Hospital, Dar es Salaam, Tanzania: Aetiology, Antimicrobial sensitivity pattern and clinical outcome**	Urban tertiary centre; Did not clearly specify hospital- v's community-acquired patient population (or location of neonatal birth)	Dar es Salaam, Tanzania	0-30 days; n=330 neonates admitted with a clinical diagnosis of sepsis; of which 302 had a culture proven bacterial infection (228 isolates from swabs, 5 isolates from blood, and 69 isolates positive from both swabs and blood; resulting in a total positive blood culture proportion of n=74). Swabs included those taken from cord stump (66.6%) and skin pustules (33.3%).	Culture positive infection of which 69% were bacteria isolated from swabs (umbilical cord stump and skin pustules), 1.5% from blood and 20.9% from both swabs and blood. Details as to antimicrobial susceptibility testing was not provided.	Resistance patterns of *Klebsiella* spp. (based on blood culture isolates): • Penicillin/Ampicillin 100% • Gentamicin 77% (57-90) • Ceftriaxone 18% (7-39) Resistance patterns for *Escherichia Coli* (based on blood culture isolates): • Penicillin/ampicillin 93% (69-99) • Gentamicin: 43% (1-19) • Ceftriaxone 14% (4-40) Resistance patterns for *Staphylococcus Aureus*: • Cloxacillin 81.5% (blood culture); 80.3% (skin swab) • Ampicillin 85% (blood); 88% (swab) Only single cases of *Group B Streptococcus* and *Pseudomonas* infections were found; these data were not included due to sample size	D (Case series which did not delineate HA vs CA infections in data analysis; location of birth unknown; details as to antimicrobial susceptibility testing not provided)
15	Marais et al.[36]	2009; samples collected 2005-2006	Case series	**Antimicrobial susceptibility of methicillin-resistant *Staphylococcus Aureus* isolates from South Africa**	Laboratory-based study (did not present clinical cases)	South Africa	<18yrs; n=248 samples of laboratory-confirmed *mec*A-positive MRSA isolates (142 from NHLS laboratories, 106 from private laboratories; 236 samples had complete data available for specimen source).	23 National Health Laboratory Services and Private Diagnostic Laboratories from 9 provinces in South Africa collected consecutive MRSA isolates, identified by genomic DNA for PCR using the 'rapid lysis' procedure to identify the *mecA* gene. Antibiotic susceptibility was performed using the Kirby-Bauer disc diffusion method according to CLSI guidelines.	Non-susceptibility for *Staphylococcus aureus* to: • Nitrofurantoin (38%) • Gentamicin (85%) • Clindamycin (21%) • Erythromycin (58%) were found. • Non-susceptibility was higher in NHLS laboratories than private laboratories	D (Laboratory-based study which did not correlate with clinical outcomes; multitude of clinical settings investigated relationship between private vs public systems yet CA vs HA and rural vs urban settings not identified)

16	Kayange et al.[38]	2010; Neonates admitted in 2009	Cross-Sectional	**Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza- Tanzania**	Urban Tertiary; Did not specify community-v's hospital-acquired infections	Tanzania	n=300 neonates admitted with clinical sepsis; of which n=57 and n=92 had positive blood cultures due to early and late onset sepsis (respectively).	Blood cultures were inoculated agar and incubated for 7 days or until positive. Antimicrobial susceptibility of isolates was determined by disk diffusion methods according to the CLSI. Isolates were screened for ESBL production using MacConkey agar with 30ug/ml Cefotaxime and confirmed using disc approximation methods.	• Gram-negative bacteria were more frequently isolated than gram positive bacteria (n=91; 61.1%) • Gram-negative sepsis had higher mortality than gram positive sepsis (36.3% case fatality vs 19% case fatality ; p<0.0001), with increased mortality seen in ESBL (52% case fatality vs 25% case fatality , p=0.008) and MRSA isolates (55% vs 21% case fatality , p=0.008) • The most common isolates were *Klebsiella pneumoniae*, *Staphylococcus aureus* and Escherichia coli. • Most *Klebsiella pneumoniae* and *Escherichia coli* were resistant to ampicillin and gentamicin: • ***Klebsiella***: Ampicillin resistance 100%; Gentamicin resistance 67%; Ceftriaxone resistance 50%; Cefotaxime 49%; Ceftazidime 49%; Ciprofloxacin 8% • ***Escherichia Coli*:** Ampicillin resistance 100%; gentamicin resistance 68%; Ceftriaxone resistance 50%; Cefotaxime 50%; Ceftazidime 50%; Ciprofloxacin 4.5% • The majority of *Klebsiella* spp. and *Escherichia coli* species were ESBL producers (49% and 50% respectively) • The majority of Gram-negative isolates were sensitive to ciprofloxacin and meropenem • Among 32 ***Staphylococcus aureus*** isolates, 9 (28%) were found to be **Methicillin Resistant Staphylococcus aureus (MRSA**) (i.e resistant to oxacillin and cefoxitin) Penicillin resistance 90%; Erythromycin resistance 66%; Clindamycin resistance 44%; Cloxacillin resistance 28%; Bactrim resistance: 60%; Ciprofloxacin resistance 14%	D (Prospective cross-sectional study; systematic patient recruitment yet small sample size; EOS vs LOS and location of delivery taken into account in analysis yet CA vs HA infections not specified)

17	Roca et al.[35]	2009; patients presenting 2006-2007	Cohort	**Surveillance of Acute Bacterial Meningitis among Children Admitted to a District Hospital in Rural Mozambique**	Rural Tertiary; Community-acquired infections only	Maputo, Mozam-bique	n=642 children aged 0-15 years with suspected meningitis, of whom n=43 (7%) had positive CSF cultures.	CSF analysis using two sterile tubes to assess CSF glucose, Gram staining, bacterial culture, cell count, protein measurement and latex agglutination for detection of pneumococcus; Hib; meningococcus A, B, C, and W135; and streptococcus B antigens. Blood samples were cultured using an automated blood culture system (Bactec 9050; Becton Dickinson) while the CSF samples were cultured using manual (conventional) methods) and bacterial isolates were identified by colony morphologic analysis and growth requirements. Antibiotic susceptibility testing was performed by disk diffusion or E test	• The most common causes of bacterial meningitis were *Haemophilus Influenzae* Type B (n=14); *Pneumococcus* (n=9); *Meningococcus* (n=7) • All 9 pneumococci isolates were susceptible to chloramphenicol, and 8 were susceptible to penicillin (1 had intermediate resistance) • Of the 10 HiB isolates tested, only 1 was susceptible to chloramphenicol (90% resistance); and 5 were susceptible to ampicillin (50% resistance) • *Neisseria meningitidis* exhibited 50% resistance to Ampicillin and 90% resistance to Chloramphenicol	D (Systematic collection of LPs on all children presenting with defined symptoms of meningitis; yet large proportion had concurrent malaria parasitaemia; HIV status of children unclear; data collated over a short period which may affect variations of disease occurrence for specific pathogens)

18	Nwadioha et al.[42]	2011; patients presenting 2006-2008	Retrospective blood culture analysis (laboratory-based)	**Bacterial isolates in blood cultures of children with suspected septicaemia in urban Kano: a two-year study.**	Tertiary; Did not specify community- vs hospital acquired infections	Nigeria	n=3840 blood cultures were collected in children presenting with clinical signs of sepsis, of which n=700 were positive	Blood culture samples were incubated for 7 days on MacConkey, blood and chocolate agar media. Organisms were isolated by conventional methods. Antibiotic susceptibility tests were done against locally available antibiotics by using disk diffusion method in accordance with the NCCLS / CLSI criteria.	• Out of a total of 3840 blood culture samples, only 18.2% (n=700) were culture positive. • Gram-negative and Gram-positive bacteria constituted 69.3% (n=2661) and 30.7% (n=1179) respectively. • The most prevalent bacterial isolates were ***Escherichia coli*** with 44.3% (n=310/700) and ***Staphylococcus aureus*** 30.7% (n=215/700). • *Escherichia coli* were sensitive to ceftriaxone ***Escherichia coli* SENSITIVITY:** o Ampicillin 50%, o Gentamicin 80%, o Ceftriaxone 90% ***Klebsiella* spp. NON-SUSCEPTIBILITY:** • Ampicillin 45% • Gentamicin 49%	D (Retrospective design; CA vs HA not delineated; laboratory based data not lined to clinical outcome)