Antimicrobial resistance among children in sub-Saharan Africa

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Antimicrobial resistance is an important threat to international health. Therapeutic guidelines for empirical treatment of common life-threatening infections depend on available information regarding microbial aetiology and antimicrobial susceptibility, but sub-Saharan Africa lacks diagnostic capacity and antimicrobial resistance surveillance. We systematically reviewed studies of antimicrobial resistance among children in sub-Saharan Africa since 2005. 18 of 1075 articles reviewed met inclusion criteria, providing data from 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 prevalence of extended-spectrum β-lactamase-producing organisms. Gram-positive bacteria were responsible for a high proportion of infections among children beyond the neon atal period, with high reported prevalence of non-susceptibility to treatment advocated by the WHO therapeutic guidelines. There are few up-to-date or representative studies given the magnitude of the problem of antimicrobial resistance, especially regarding community-acquired infections. Research should focus on differentiating resistance in community-acquired versus hospital-acquired infections, implementation of standardised reporting systems, and pragmatic clinical trials to assess the efficacy of alternative treatment regimens.

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Introduction

As a pressing threat to international health, antimicrobial resistance is of increasing importance. Resistance to antimicrobials threatens to undermine nearly a century of gains made since the discovery of antibiotics and the contribution of these drugs to improvements in childhood survival in the developing world, particularly among neonates.[1,2] Antimicrobial resistance has been reported in both community-acquired and health-care-associated infections worldwide.[3] However, in low-income and middle-income countries, surveillance is often inconsistent because of insufficient integration and non-representativeness of local data, inconsistent laboratory quality, and scarce microbiological diagnostic facilities.[3]

Sub-Saharan Africa (as defined by the World Bank's World Development Indicators[4]) has the least comprehensive antimicrobial surveillance strategies of all world regions, alongside scarce infection prevention and control programmes. Only six (15%) of the 41 WHO Africa region member states carry out surveillance for bacterial antimicrobial resistance, and external quality assurance of laboratory procedures is infrequent.[5–7]

Sub-Saharan Africa has a high incidence of acute respiratory infections, diarrhoeal diseases, parasitic and invasive bacterial infections, and chronic conditions such as HIV, tuberculosis, and malnutrition.[8–11] These conditions increase demand for both preventive 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, scarce diagnostic resources and consequent therapy based on clinical syndromes that are sensitive (rather than specific) for serious bacterial infections (therefore likely to capture viral, parasitic, and self-limiting illnesses) also drive antibiotic consumption, which is a key factor in promotion of resistance.[14] Moreover, the spread of Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs) and other multidrug-resistant (MDR) organisms in both community-based and hospital-based populations potentially limits the availability of suitable antimicrobials to treat such infections.[15,16] Escalation of resistance might also occur when therapies normally reserved for second-line, third-line, or fourth-line treatment in resource-rich settings (such as third-generation cephalosporins, carbapenems, and polymyxins) start to be used widely in sub-Saharan Africa without supportive microbiological facilities, expert advice, or adequate prescription controls.[17,18]

Conversely, higher-level treatment is often unavailable or too expensive for most of the population of sub-Saharan Africa. Decreased susceptibility to antimicrobials is therefore important, not just because of the health-care implications of having few treatment options (especially in resource-poor settings such as sub-Saharan Africa) and potentially poorer clinical outcomes,[3,14,19] but also because of the costs associated with use of more expensive therapies for a wide range of patients and prolonged stays in hospital.[20]

WHO recommends penicillin (or ampicillin) plus gentamicin as empirical therapy in suspected neonatal and paediatric sepsis in resource-limited settings (tables 1, 2), and advises tailoring therapy to local resistance patterns.[21] However, in practice, tailoring of therapy is usually impossible because of a lack of data about local susceptibility due to insufficient reliable laboratory facilities with external quality assurance or collaborative surveillance.[3] High prevalence of non-susceptibility to recommended empirical therapies has previously been reported among invasive bacterial isolates throughout sub-Saharan Africa;[3,6,7,43] however, most research has been limited to tertiary settings. Despite urgent calls for updated WHO guidelines to limit avoidable mortality due to antimicrobial resistance, these guidelines have remained unchanged for almost all causes of invasive paediatric bacterial infections.[21,44]

The 2014 Global Report on Antimicrobial Surveillance[3] highlighted the pressing need to strengthen knowledge

and surveillance mechanisms for antimicrobial resistance, reiterating a theme which has resonated in the literature for more than a decade.[28,45] Therefore, we aimed to systematically review data published since 2005 on antimicrobial susceptibility for the commonest bacteria that cause serious infections in children in sub-Saharan Africa, with a focus on WHO recommendations for empirical treatment among children without specific risk factors (HIV or tuberculosis) to increase the knowledge and evidence base regarding local non-susceptibility patterns among a generalisable paediatric population.

See Online for appendix

	Dosage
Sepsis in a child aged <2 months	
Ampicillin intravenous	50 mg/kg QID for 7–10 days (21 days for meningitis)
plus gentamicin intravenous	5–7·5 mg/kg daily for 7–10 days (21 days for meningitis)
Second line: ceftriaxone intravenous	50–100 mg/kg once daily for 7–10 days
Sepsis in a child aged <2 months where referral is not possible	
Amoxicillin oral	50 mg/kg BID for 7 days
plus gentamicin intramuscular or intravenous	5–7·5 mg/kg daily for 2–7 days
Sepsis in a child aged <2 months if skin conditions suggest *Staphylococcus aureus*	
Cloxacillin or flucloxacillin intravenous	25–50 mg/kg BID or QID (age dependent) for 7–10 days
plus gentamicin	5–7·5 mg/kg daily for 7–10 days (21 days for meningitis)
Sepsis in a child aged >2 months	
Ampicillin intravenous	50 mg/kg QID for 7–10 days
plus gentamicin intravenous or intramuscular	7·5 mg/kg daily for 7–10 days
Second line: ceftriaxone intravenous or intramuscular	50 mg/kg BID or 100 mg/kg daily for 7–10 days
Sepsis in a child aged >2 months if skin conditions suggest *S aureus*	
Flucloxacillin intravenous	50 mg/kg QID for 7–10 days
plus gentamicin	7·5 mg/kg daily
Typhoid fever	
Ciprofloxacin oral	15 mg/kg BID for 7–10 days
Second line: intravenous ceftriaxone	80–100 mg/kg daily for 5–7 days
or azithromycin oral	20 mg/kg daily for 5–7 days
Pneumonia	
Ampicillin intravenous	50 mg/kg QID for 7–10 days
plus gentamicin intravenous	7·5 mg/kg daily for 7–10 days
Second line: ceftriaxone intravenous	80 mg/kg daily for 7–10 days
Pneumonia (if *S aureus* is suspected)	
Flucloxacillin or cloxacillin intravenous	50 mg/kg QID for 7–10 days
plus gentamicin	7·5 mg/kg intramuscular or intravenous once a day
Dysentery (presumed due to *Shigella* spp)	
Ciprofloxacin oral	15 mg/kg BID for 3 days
Second line: ceftriaxone intravenous	50–80 mg/kg daily for 3 days
Osteomyelitis	
Chloramphenicol	25 mg/kg TID
Second line: cloxacillin or flucloxacillin intravenous	50 mg/kg QID for up to 5 weeks (step down to oral once clinically improving)
or clindamycin or third-generation cephalosporins	No dosages specified; clear circumstances of when such therapy would be appropriate are not outlined
Meningitis in neonates	
Ampicillin	50 mg/kg BID for 3 weeks
plus gentamicin	5–7·5 mg/kg daily for 3 weeks
Ceftriaxone intravenous	50–75 mg/kg daily for 3 weeks
plus gentamicin	5–7·5 mg/kg daily for 3 weeks
Cefotaxime	50 mg/kg BID or TID (age dependent) for 3 weeks
plus gentamicin	5–7·5 mg/kg daily for 3 weeks

(Table 1 continues on next page)

Methods

Search strategy and selection criteria

After conferring on the search terms, the primary investigator (PCMW) reviewed published and grey literature on Dec 12, 2015 and later on Dec 3, 2016. JAB reviewed the included reports. Data for this Review were identified by searches of MEDLINE, PubMed, Embase, and Cochrane, and by identifying references from relevant articles using the search terms "child*", "pediat*", "paediat*", "Africa*", "sub-Sahara*", "antimicrobial" or "antibiotic", "resistance", and "susceptibility" or "sensitivity". Only reports of studies done in human beings published between Dec 12, 2005, and Dec 12, 2015, were included. There were no language restrictions on the search. To ensure current susceptibility patterns were investigated, articles were restricted to those reporting data collated since 2005 to make sure emerging threats to susceptibility—such as the spread of ESBL—were captured.

Inclusion criteria were predefined as research providing information on bacterial infections (including either aetiology, disease burden, or incidence), specified paediatric data (or clearly delineated from adult data), and information on antimicrobial testing methods documented. Predefined exclusion criteria were data aggregated with regions beyond sub-Saharan Africa, literature focused on solely analysing subpopulations with potentially confounding comorbidities (such as HIV or tuberculosis), poor methodological study design (such as retrospective observational studies with small patient numbers or those in which laboratory procedures were poorly defined), data collection that occurred substantially before the search period, and data pertaining to carriage only (rather than invasive isolates).

After abstracts were screened for these criteria, information was extracted from selected articles and converted into tabulated form (appendix), 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) method. The GRADE method was used to summarise the quality of evidence for each study by assessment of study type, quality, limitations, inconsistency, or possibility of bias.[46] Grading was performed by both PCMW and JAB, and any disagreements were resolved by consensus.

Results

The initial search identified 1075 potentially relevant papers. Abstract review excluded 1010 papers that did not meet inclusion criteria or were identified as duplicate studies. Of the 65 papers that underwent full text review, four met the inclusion criteria. 14 further studies were identified from reference lists, resulting in a total of 18 studies for inclusion (figure 1).

The 18 reports included in this Review were from 11 nations throughout sub-Saharan Africa (figure 2). Seven studies[26,31,32,38,39,47,48] were done in rural settings, ten in urban settings,[14,19,28,29,34–38,49] and one was a laboratory-based study collating data across both urban and rural settings.[33] The hospital-based studies were almost exclusively done in tertiary health facilities, whereas one study also included patients presenting at a secondary health facility.[37] There was one cross-sectional study,[27] one case-control study,[36] and six case series;[19,26,28,29,33,35] the remaining ten studies[14,31,32,34,37–40,48,49] were cohort designs. Six studies[33,35,38–40,50] examined only one genus of pathogen, whereas the remaining studies[14,19,25,26,28,29,31,32,34,36,37,48] examined invasive disease. Because of the heterogeneity of the studies (in terms of settings, inclusion criteria, laboratory methods, reported outcomes, and quality of evidence) a formal meta-analysis was not possible; however, where possible, we calculated IQRs for specific pathogen susceptibilities.

Six of the studies[14,31,32,37,38,49] were moderate quality (GRADE level B), seven[19,26,34–36,39,40] were low quality (GRADE level C), and the remaining five[25,28,29,33,48] were classified as very low quality (GRADE level D). All studies described the microbiological techniques used (an inclusion criterion), although culture media, methods for identification of organisms, and definitions of non-susceptibility varied between studies. 12 studies[14,19,26,31,32,35,37–39,47,48,51] used automated culture techniques, whereas the remainder used manual methods. Only three studies[14,30,38] (17%) ascertained recent antimicrobial exposure (and took this into account in the data analysis). Five papers[14,26,35,37,38] (28%) reported external quality control of the laboratory. Most isolates were identified from blood cultures, although one study[34] included induced sputum samples, and four studies[26,35,48,50] investigated both blood and CSF samples in patients with meningitis. Across the studies, a total of 67 451 cultures were collected, of which 5607 (8·3%) were positive for a bacterial pathogen. Further information on non-susceptibility prevalence was obtained from 236 laboratory-stored isolates[33] and 149 diarrhoeal isolates of children infected with *Shigella* spp or *Salmonella* spp.[39] Non-susceptibility medians, ranges, and IQRs (including comparison to international treatment guidelines) are documented in tables 3 and 4.

The studies covered the full paediatric age range of 0–18 years, with a focus on young childhood (0–5 years). Four studies[30,45,46,48] exclusively investigated infections in infants within the first 90 days of life.

Ten studies[31,32,34,36–40,48,50] specifically examined community-acquired infections only, and three studies[14,19,26] investigated antibiotic susceptibility patterns that distinguished community-acquired and hospital-acquired infection (and although the incidence of different infectious aetiologies could have been clarified within these studies, only two studies[14,19] analysed the resistance patterns for each subset independently). The remaining five studies[27–29,33,35] did not identify whether the infections were community-acquired or nosocomial in nature.

Gram-negative organisms (*Escherichia coli, Klebsiella* spp) and (less commonly) *Streptococcus agalactiae* were the predominant causes of early-onset neonatal sepsis in sub-Saharan Africa, which is defined as sepsis occurring at younger than 72 h of age (aside from sepsis due to *S agalactiae*, which was defined as occurring from 0–6 days).[52] *S aureus* is an important cause of late-onset sepsis (with an ongoing burden caused by *E coli, Klebsiella* spp, *S agalactiae*, and other Gram-positive organisms such as *Streptococcus pyogenes*).[52–58] Early-onset infections are usually vertically transmitted, yet they might also be secondary to nosocomial acquisition (in which case resistance is more likely to be an issue), whereas late-onset infections are due to horizontal infection (either community-acquired or hospital-acquired).[44] Although the understanding of susceptibility patterns according to the time of onset of neonatal infection is important, most of the included studies that investigated invasive neonatal infections did not clearly delineate whether these were early-onset or late-onset, and whether the patient population was transferred from the delivery ward or presenting for admission from the community.[52,57]

Four studies[26–28,35] specifically investigated neonatal patient populations born within hospital environments and at home. 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 bloodstream infections (especially in early-onset illness).[27,28] Other common

	Dosage
(Continued from previous page)	
Meningitis in children older than 28 days	
Ceftriaxone intravenous	50 mg/kg intramuscular or intravenous BID for 7–10 days
Second line: cefotaxime intravenous	50 mg/kg intramuscular or intravenous QID for 7–10 days
Meningitis in children older than 28 days with no known resistance to chloramphenicol or β-lactams locally	
Chloramphenicol intravenous	25 mg/kg QID for 10 days
plus ampicillin intramuscular or intravenous	50 mg/kg QID for 10 days
or benzylpenicillin intravenous	60 mg/kg QID for 10 days
Urinary tract infection	
Co-trimoxazole oral	4 mg/kg plus 20 mg/kg BID for 5 days
Second line: ampicillin	50 mg/kg intramuscular or intravenous every 6 h
plus gentamicin	5–7·5 mg/kg daily

First-line and second-line treatment guidelines for common paediatric infective illnesses. Data are from WHO pocket book of hospital care for children[23] and WHO guideline for managing possible serious bacterial infection in young infants when referral is not feasible.[22] BID=twice daily. TID=three times daily. QID=four times daily.

***Table 1*: Choices of antibiotic recommendations for various diagnoses**

	Reported non-susceptibility
Sepsis in a child aged <2 months[8,23-25]	
Klebsiella spp	
Ampicillin	100% (71–100)[14,26-29]
Gentamicin	49% (48–58)[14,26,27,29,30]
Ceftriaxone	43% (NA);[26] 50% (NA)[27]
Staphylococcus aureus	
Ampicillin	90% (85–100)[14,27,28,31,32]
Gentamicin	29% (10–60)[14,32-34]
Cloxacilllin	20% (10–55)[14,27,28]
Streptococcus agalactiae	
Ampicillin	0% (NA)[31,35]
Gentamicin	Not reported
Ceftriaxone	0% (NA)[35]
Escherichia coli	
Ampicillin	93% (78–96)[14,26-29,36]
Gentamicin	29% (20–46)[14,26-29,31]
Ceftriaxone	16% (12–34)[26-29]
Sepsis in a child aged >2 months[9,23,24,31,37]	
Salmonella spp	
Ampicillin	66% (39–73)[14,29,31,37-40]
Gentamicin	28% (23–32)[14,29,38]
Ceftriaxone	0% (NA);[32] 0% (NA)[38]
E coli	
Ampicillin	93% (78–96)[14,26-29,36]
Gentamicin	29% (20–46)[14,26-29,31]
Ceftriaxone	16% (12–34)[26-29]
Streptococcus pneumoniae	
Ampicillin	20% (NA)[38] or 22% (NA)[32]
Gentamicin	77% (NA)[32] or 78% (NA)[38]
Ceftriaxone	0% (NA)[38]
Klebsiella spp	
Ampicillin	100% (71–100)[14,26-29]
Gentamicin	49% (48–58)[14,26,27,29,34]
Ceftriaxone	43% (NA);[26] 50% (NA)[27]
S aureus	
Ampicillin	90% (85–100)[14,27,28,31,32]
Gentamicin	29% (10–60)[14,32,33,34]
Cloxacilllin	20% (10–55)[14,27,28]
Typhoid fever	
Salmonella enterica serotype Typhi	
Ciprofloxacin	0% (NA)[32,38]
Ceftriaxone	0% (NA)[32,38]
Azithromycin	Not reported
Pneumonia[9,24,41]	
S pneumoniae	
Ampicillin	20% (NA)[38] or 22% (NA)[32]
Gentamicin	77% (NA)[32] or 78% (NA)[38]
Ceftriaxone	0% (NA)[38]
S aureus	
Ampicillin	90% (85–100)[14,27,28,31,32]
Gentamicin	29% (10–60)[14,32-34]
Cloxacilllin	20% (10–55)[14,27,28]

(Table 2 continues in next column)

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	Reported non-susceptibility
Dysentery (presumed due to *Shigella* spp)	
Shigella spp	
Ciprafloxacin	0% (community-acquired) and 11% (hospital-acquired) when analysed in conjunction with other Enterobacteriaceae[14]
Ceftriaxone	Not documented
Osteomyelitis	
S aureus	
Chloramphenicol	47% (21–81)[14,32,34]
Cloxacillin	20% (9–68)[15,27,28]
Clindamycin	21% (NA)[33] or 44% (NA)[27]
Third-generation cephalosporins	Not reported
Flucloxacillin	17% (NA)[32]
Meningitis in a child aged <28 days	
Klebsiella spp	
Ampicillin	100% (71–100)[14,26-29]
Gentamicin	49% (48–58)[14,26,27,29,30]
Ceftriaxone	43% (NA);[26] 50% (NA)[27]
S agalactiae	
Ampicillin	0% (NA)[31,35]
Gentamicin	Not reported
Ceftriaxone	0% (NA)[35]
E coli	
Ampicillin	93% (78–96)[14,26-29,36]
Gentamicin	29% (20–46)[14,26-29,31]
Ceftriaxone	16% (12–34)[26-29]
Haemophilus influenzae type b	
Penicillin and ampicillin	5–100%*
S pneumoniae	
Ampicillin	20% (NA)[38] or 22% (NA)[32]
Gentamicin	77% (NA)[32] or 78% (NA)[38]
Ceftriaxone	0% (NA)[38]
Urinary tract infection[19,24,42]	
E coli	
Co-trimoxazole	87–90%* (community-acquired)[14,31] or 77% (NA) (hospital-acquired)[14]
Ampicillin	93% (78–96)[14,26-29,36]
Gentamicin	29% (20–46)[14,26-29,31]
Klebsiella spp	
Co-trimoxazole	63% (community-acquired) or 94% (hospital-acquired)[14]
Ampicillin	100% (71–100)[14,26-29]
Gentamicin	49% (48–58)[14,26,27,29,34]

Data are presented as median (IQR) where available. NA=not available.
*Data are presented as the range where indicated.

***Table 2*: Reported non-susceptibility in most likely causative organisms to drugs documented in this Review**

neonatal pathogens identified included *S aureus* (range 27–39%),[27,28,53] *E coli* (21%),[26] and *S agalactiae* (6·9%[26] and 20%[53]). A high prevalence of MDR organisms was documented in a prospective cross-sectional study[27] of 300 neonates in Tanzania, with 40% (36 of 91 isolates) of

Gram-negative organisms showing ESBLs, and 30% (nine of 30 isolates) of *S aureus* classified as meticillin resistant. However, these isolates were not identified as community-acquired or hospital-acquired.[27] MDR organisms were associated with increased mortality for both populations (52% *vs* 25% in ESBL-producing organisms, p=0·0008; and 55% *vs* 21% mortality in meticillin-resistant *S aureus* organisms; p=0·0008).

Studies[31,35] that isolated *S agalactiae* from 57 neonates in Malawi and 37 in Mozambique revealed an approximately equal incidence of early-onset and late-onset disease, with a higher case fatality rate for early-onset disease. All isolates were susceptible to β-lactams. One further study[26] based in a rural setting investigated invasive bacterial infections in infants born outside hospital, but did not delineate infections as community-acquired or hospital-acquired. An important finding in this study[26] was diminishing in-vitro susceptibility of all isolates to WHO recommended ampicillin and gentamicin over the study period (from 88% susceptibility in 2001 to 66% in 2009; p<0·001).

Gram-negative bacteria

Salmonella spp are the most frequently isolated Gram-negative pathogens in children older than 1 month in sub-Saharan Africa, with a predominance in the wet season.[9,23,24,31,37] Few studies analysed *Salmonella enterica* serotype Typhi (*S typhi*) and non-typhoidal species independently for susceptibility patterns against individual antibiotics. Nine of the included papers[14,19,29,31,32,37–40] investigated susceptibility patterns to *Salmonella* spp, revealing non-susceptibility to penicillin and ampicillin (median 66%, IQR 39–73), gentamicin (28%, 23–32), co-trimoxazole (60%, 48–67), amoxicillin-clavulanate (20%,[29] 38%,[31] and 74%[32]), and chloramphenicol (27%, 15–54). Only one paper[14] delineated community-acquired and hospital-acquired infections, with a slightly higher prevalence of non-susceptibility in hospital-acquired isolates. MDR organisms are of increasing concern, with up to 65% of *S typhi* and up to 98% of non-typhoidal salmonella isolates showing combined resistance to ampicillin, co-trimoxazole, and chloramphenicol.[32,33,45]

Klebsiella spp cause a substantial amount of morbidity among paediatric patients in sub-Saharan Africa, accounting for almost half of all Gram-negative infections in neonates and a substantial overall burden of hospital-acquired infection.[9,25,55,56] Nine studies[18,19,21,28,36,40,41,43,46] assessed *Klebsiella* spp susceptibility patterns, of which two delineated hospital-acquired and community-acquired acquisition,[18,19] whereas other research specifically evaluated hospital-acquired strains,[41] community-acquired strains,[46] or did not clarify the place of acquisition. This research revealed a consistently high prevalence of non-susceptibility to commonly used antimicrobial therapies, including gentamicin (median 49%, IQR 48–58%) and ceftriaxone (range 33–50%[36,40,47]). Non-susceptibility was similar between community-acquired and hospital-acquired

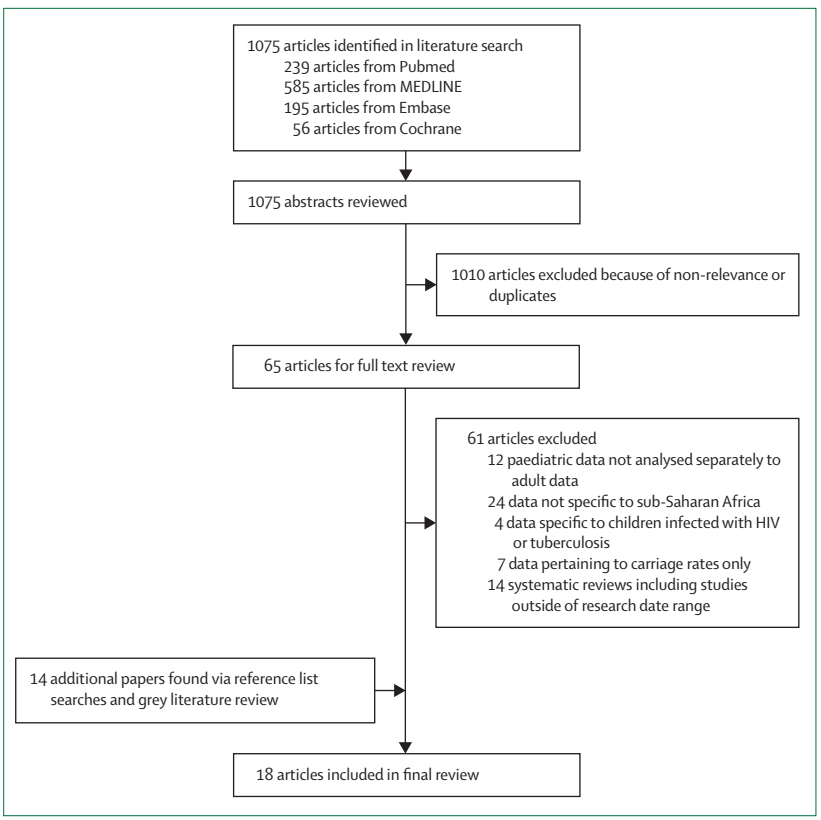

***Figure 1*: Search strategy**

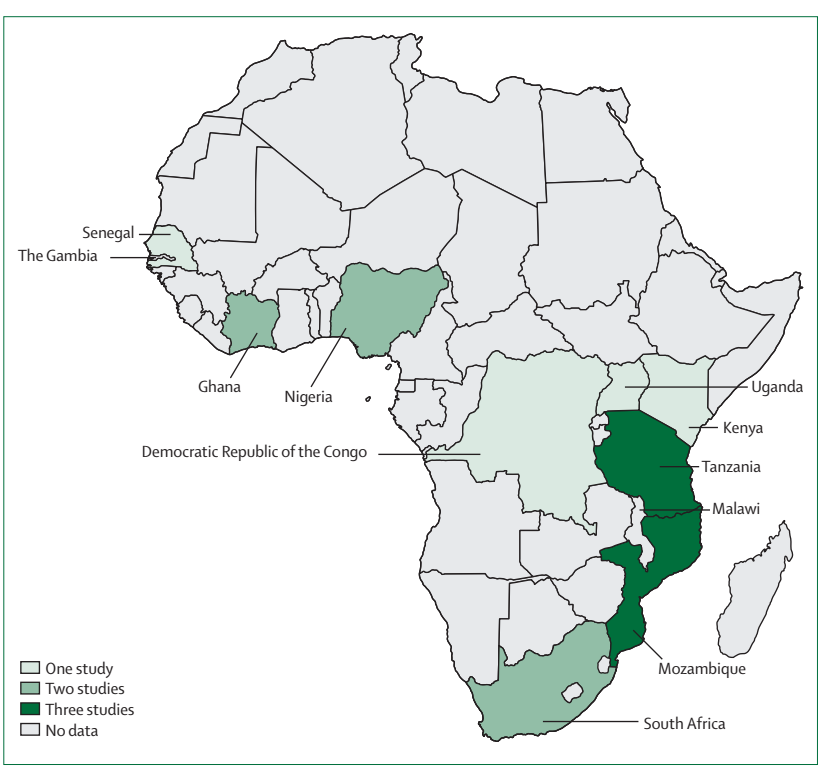

***Figure 2*: Study locations**

	Number of isolates not susceptible (n)/number tested (N)	Median non-susceptibility rate (IQR)
***Klebsiella* spp**		
Penicillin and ampicillin	45/100 (45%);[29] 55/57 (96%);[26] 17/17 (100%; CA and HA);[28] 53/53 (100%; CA and HA);[14] 50/50 (100%; CA)[27]	100% (71–100)
Gentamicin	49/100 (49%);[29] 28/57 (49%);[26] 25/53 (47%; CA and HA);[14] 33/50 (66%)[27]	49% (48–58)
Ceftriaxone	25/57 (43%);[26] 25/50 (50%);[27] 1/3 (33%)[34]	..
Cefotaxime	24/50 (48%);[26] 12/53 (22%; CA);[14] 8/53 (15%; HA)[14]	..
Ceftazidime	28/57 (49%);[26] 11/53 (21%; CA);[14] 8/53 (15%; HA)[14]	..
Ciprofloxacin	4/50 (8%);[27] 0/3 (0%)[34]	..
Chloramphenicol	10/19 (53%; CA);[14] 15/34 (44%; HA)[14]	..
Co-trimoxazole	12/19 (63%; CA);[14] 32/34 (94%; HA)[14]	..
ESBL-producing proportion	27/35 (76%; CA);[19] 93/119 (78%; HA);[19] 33/40 (83%; HA)[36]	..
Escherichia coli		
Penicillin and ampicillin	155/310 (50%);[29] 32/41 (78%);[26] 11/13 (85%; HA);[14] 13/14 (93%);[28] 148/154 (96%; CA);[31] 23/24 (96%; CA);[14] 22/22 (100%)[27]	93% (78–96)
Amoxicillin-clavulanate	6/24 (25%; CA);[14] 9/13 (69%; HA)[14]	..
Gentamicin	4/41 (10%);[26] 62/310 (20%);[29] 40/142 (28%);[31] 7/24 (29%; CA);[14] 6/14 (43%);[28] 6/13 (46%; HA);[14] 15/22 (68%)[27]	29% (20–46)
Ceftriaxone	31/310 (10%);[29] 2/14 (14%);[28] 7/41 (17%);[26] 11/22 (50%)[27]	16% (12–34)
Cefotaxime	11/22 (50%)[27]	..
Ceftazidime	11/22 (50%)[27]	..
Chloramphenicol	120/155 (78%; CA)[31]	..
Co-trimoxazole	21/24 (87%; CA);[14] 10/13 (77%; HA);[14] 128/142 (90%; CA)[31]	..
ESBL-producing proportion	9/76 (12%; CA);[19] 4/19 (22%; HA);[19] 11/22 (50%);[27] 23/40 (58%; HA)[36]	36% (17–54)
***Salmonella* spp**		
Penicillin and ampicillin	10/40 (25%);[39] 10/30 (30%);[29] 13/27 (48%; CA);[14] 60/92 (65%);[37] 8/12 (67%; HA);[14] 74/103 (72%);[40] 296/401 (74%);[31] 107/128 (84%; CA)[38]	66% (39–73)
Amoxicillin-clavulanate	6/30 (20%);[29] 152/401 (38%);[31] 95/128 (74%; CA)[38]	..
Gentamicin	6/30 (20%);[29] 7/27 (26%; CA);[14] 38/128 (30%; CA);[38] 4/12 (33%; HA)[14]	28% (23–32)
Co-trimoxazole	7/40 (18%);[39] 17/30 (55%);[29] 13/27 (48%; CA);[14] 8/12 (67%; HA);[14] 55/92 (60%);[37] 264/401 (66%);[31] 98/128 (77%; CA)[38]	60% (48–67)
Tetracycline	14/128 (11%; CA);[38] 6/40 (15%)[39]	..
Chloramphenicol	6/40 (15%);[39] 6/30 (20%);[29] 4/27 (15%; CA);[14] 4/12 (33%; HA);[14] 216/401 (54%);[31] 105/128 (82%; CA)[38]	27% (15–54)
Ciprofloxacin	0/128 (0%; CA);[38] 0/129 (0%)[32]	..
Ceftriaxone	0/128 (0%; CA);[38] 0/129 (0%)[32]	..
Multidrug-resistant proportion	*Salmonella enterica* serotype Typhi: 34/133 (33%);[40] 84/129 (65%);[32] non-typhoidal salmonella: 99/129 (77%);[32] 97/128 (76%);[38] 101/103 (98%)[40]	..
***Shigella* spp**		
Penicillin and ampicillin	61/109 (56%)[39]	..
Co-trimoxazole	92/109 (84%)[39]	..
Tetracycline	72/109 (66%)[39]	..
Chloramphenicol	57/109 (52%)[39]	..
Multidrug-resistant proportion	71/109 (65%)[39]	..
***Haemophilus influenzae* type b**		
Penicillin and ampicillin	7/14 (50%);[48] 61/113 (54%);[31] 6/6 (100%; CA)[34]	..
Chloramphenicol	56/113 (50%);[31] 9/10 (90%);[48] 6/6 (100%; CA)[34]	..
Co-trimoxazole	26/113 (23%)[31]	..
***Acinetobacter* spp**		
Penicillin and ampicillin	37/66 (56%);[26] 0/3 (0%; CA);[14] 0/9 (0%; HA)[14]	..
Gentamicin	18/66 (27%);[26] 2/3 (67%; CA);[14] 4/9 (44%; HA)[14]	..
Ceftriaxone	23/66 (35%)[26]	..
Ceftazidime	2/9 (22%; HA);[14] 1/3 (33%; CA)[14]	..
Multidrug-resistant proportion	4/16 (25%; CA);[19] 49/68 (72%; HA)[19]	..

Median and IQR could not be calculated if there were fewer than three papers assessing non-susceptibility rates. CA=community-acquired, where specified in the literature (blank=not specified). HA=hospital-acquired, where specified in the literature (blank=not specified). ESBL=extended-spectrum β-lactamases.

***Table 3*: Non-susceptibility patterns of key Gram-negative pathogens**

	Number of isolates not susceptible (n)/number tested (N)	Median non-susceptibility rate (IQR)
Streptococcus pneumoniae		
Penicillin and ampicillin	4/20 (20%; CA);[38] 5/22 (23%)[32]	..
Amoxicillin-clavulanate	2/18 (11%; CA)[38]	..
Gentamicin	17/22 (77%);[32] 16/20 (78%; CA)[38]	..
Chloramphenicol	2/18 (11%; CA);[38] 5/20 (25%)[32]	..
Co-trimoxazole	20/116 (17%; CA);[37] 19/20 (95%; CA);[32] 17/17 (100%; CA);[38] 11/11 (100%);[50] 29//29 (100%)[31]	100% (56–100)
Ciprofloxacin	9/21 (43%)[32]	..
Tetracycline	14/19 (74%);[32] 15/20 (75%; CA)[38]	..
Ceftriaxone	0/20 (0%; CA)[38]	..
Streptococcus agalactae		
Penicillin and ampicillin	0/35 (0%);[31] 0/57 (0%)[35]	..
Chloramphenicol	10/35 (29%);[31] 11/57 (19%)[31]	..
Erythromycin	12/57 (21%)[35]	..
Co-trimoxazole	5/34 (15%)[31]	..
Ceftriaxone	0/57 (0%)[35]	..
Staphylococcus aureus		
Penicillin and ampicillin	17/32 (52%);[31] 23/27 (85%);[28] 170/189 (90%);[31] 29/32 (90%);[27] 13/13 (100%; CA);[14] 17/17 (100%; HA)[14]	90% (85–100)
Flucloxacillin	5/30 (17%)[32]	..
Oxacillin	17/189 (9%)[31]	..
Cloxacillin	1/13 (8%; CA);[14] 2/17 (12%; HA);[14] 9/32 (28%);[27] 22/27 (81%)[28]	20% (10–55)
Co-trimoxazole	11/24 (54%);[32] 19/32 (60%)[27]	..
Gentamicin	0/13 (0%; CA);[14] 3/17 (19%; HA);[14] 9/32 (29%);[32] 3/9 (33%; CA);[34] 210/248 (85%)[33]	29% (10–60)
Nitrofurantoin	94/248 (38%)[33]	..
Clindamycin	52/248 (21%);[33] 14/32 (44%)[27]	..
Erythromycin	0/13 (0%; CA);[14] 2/9 (23%; CA);[34] 5/17 (29%; HA);[14] 144/248 (58%);[33] 21/32 (66%)[27]	29% (12–62)
Ciprofloxacin	NA/32 (14%);[27] 10/31 (32%)[32]	..
Chloramphenicol	2/13 (15%; CA);[14] 5/17 (29%; HA);[14] 6/9 (67%; CA);[17] 30/32 (94%)[32]	47% (21–81)
Meticillin	58/131 (44%)[19]	..
Meticillin-resistant *S aureus*		
Oxacillin plus cefoxitin	9/32 (28%);[27] 14/95 (15%; CA);[19] 23/36 (65%; HA)[19]	..

Median and IQR could not be calculated if there were fewer than three papers assessing non-susceptibility rates. CA=community-acquired, where specified in the literature (blank=not specified). HA=hospital-acquired, where specified in the literature (blank=not specified). NA=not available.

***Table 4*: Non-susceptibility patterns of key Gram-positive pathogens**

strains, and high frequencies of ESBL-producing *Klebsiella* spp were documented (from 76% for community-acquired isolates to 82% among hospital-acquired isolates[30,36]).

E coli causes a substantial burden of disease in sub-Saharan Africa; it is responsible for approximately 11% of all paediatric bloodstream infections[19] and is a predominant cause of community-acquired sepsis.[24,42] Eight papers[19,25,26,28,29,34,36,40] assessed non-susceptibility of *E coli*, documenting non-susceptibility to penicillin and ampicillin of 50–100% (median 93%, IQR 78–96), gentamicin (29%, 20–46), and ceftriaxone (16%, 12–34). One paper[14] delineated community-acquired and hospital-acquired infection, revealing a higher frequency of non-susceptibility among hospital-acquired isolates (gentamicin non-susceptibility of 29% among community-acquired isolates compared with 46% among hospital-acquired isolates). ESBL-producing *E coli* infections were also more common among hospital-acquired isolates (22%[19] and 58%[36]) compared with community-acquired isolates (12%[19]).

Although *Shigella* spp are an important cause of community-acquired bacteraemia,[37,45,59] only one paper[37] 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 more than two antimicrobials from different classes). However, when analysed together with other Enterobacteriaceae, there was evidence of sensitivity to ciprofloxacin.[14]

Although the advent of the conjugate vaccine has considerably diminished the burden of *Haemophilus influenzae* type b,[41] its case fatality rate has the potential to remain high because of substantial antimicrobial resistance to first-line therapies. Three papers[31,34,48] assessed resistance among *Haemophilus* spp isolates, documenting non-susceptibility to ampicillin and chloramphenicol ranging from 50% to 100%, rendering these antimicrobials largely ineffective in treating *H influenzae* meningitis.

Although a rare cause of sepsis, *Acinetobacter* spp are nonetheless clinically significant because of their high mortality when causing bacteraemia (up to 25%), with 78% of hospital-acquired *Acinetobacter* spp isolates (and 25% of community-acquired isolates) being MDR in a large study[19] of paediatric bloodstream 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). A large case series[26] of 4849 neonates in rural Kenya identified *Acinetobacter* spp as a cause of 10% of positive blood cultures in infants not born in hospital, with resistance to penicillin and ampicillin (56%, 95% CI 42–70), gentamicin (27%, 14–39), and ceftriaxone (35%, 22–48). A further review[14] of 1787 paediatric patients in Tanzania reported increased non-susceptibility to ampicillin (100% for both community-acquired and hospital-acquired isolates), gentamicin (44% for hospital-acquired isolates and 67% for community-acquired isolates), and ceftazidime (22% among hospital-acquired isolates and 33% among community-acquired isolates; susceptibility profiles tested for three community-acquired invasive isolates and nine hospital-acquired isolates).

Gram-positive bacteria

S pneumoniae is the most common Gram-positive organism isolated in positive blood cultures in children in sub-Saharan Africa[9,24,53] and is responsible for up to 35% of clinical episodes of sepsis, with a predominance in the dry season.[9] Although the burden of disease caused by this pathogen is declining as the pneumococcal conjugate vaccine is introduced, it nevertheless continues to cause substantial morbidity and mortality.[60,61] Three papers[32,34,38] analysed susceptibility patterns of *S pneumoniae,* documenting non-susceptibility (which was not classified into intermediate-level *vs* high-level resistance) to penicillin and ampicillin (range 6–24%) and chloramphenicol (11–25%); however, two studies showed full susceptibility to ceftriaxone.[32,38] Although no longer part of WHO treatment guidelines, co-trimoxazole and macrolide antibiotics are still often prescribed in low-income and middle-income countries to treat pneumonia (and as prophylaxis for children with HIV). A median prevalence of 100% (IQR 56–100) non-susceptibility to co-trimoxazole was documented,[31,32,37,38,50] although susceptibility to erythromycin remains adequate.[34,49]

S aureus causes a substantial burden of bloodstream infections in paediatric patients in sub-Saharan Africa.[19,23,31,32,37,40,47] WHO's recommendation is for first-line treatment with cloxacillin, for which median non-susceptibility was 20% (IQR 10–55%), with similar susceptibility patterns between community-acquired and hospital-acquired isolates.[14,25,28] Chloramphenicol and flucloxacillin are the treatment of choice for osteomyelitis, with median reported non-susceptibility of 47% (21–81) for chloramphenicol and 17% for flucloxacillin (based on a sample of 32 positive blood cultures in children aged <5 years in rural Ghana).[14,32,34]

Alongside its effect within the community, *S aureus* is the most common hospital-acquired infection,[14] and there is an increased propensity for these strains to be multiresistant (defined as having both oxacillin and cefoxitin resistance; identified among 20 [15%] of 131 community-acquired isolates and 85 [65%] of 131 hospital-acquired isolates from a study[19] of invasive infection in children in South Africa; however, this research did not identify if previous antibiotic exposure confounded these blood culture results). A laboratory review[33] of 248 meticillin-resistant isolates (not differentiated by community-acquired *vs* hospital-acquired) collected throughout South Africa revealed high frequencies of non-susceptibility to gentamicin (85%), erythromycin (58%), nitrofurantoin (38%), and clindamycin (21%); however, isolates were fully sensitive to vancomycin.

Analysis of data from a Tanzanian cohort study of 1828 bloodstream infections showed that enterococci were responsible for 15% of culture-confirmed causes of bacteraemia and resulted in case fatality rates of 29% for *Enterococcus faecalis* and 7% for *Enterococcus faecium*. A small number of invasive isolates (21 for *E faecium* and 15 for *E faecalis)* suggested more frequent non-susceptibility in hospital-acquired infection to ampicillin (89% hospital-acquired, 75% community-acquired) and gentamicin (67% hospital-acquired, 33% community-acquired) for *E faecium*, although *E faecalis* showed ampicillin susceptibility.[14]

Discussion

Our results highlight a dramatic lack of data on antimicrobial non-susceptibility patterns in the general paediatric population of sub-Saharan Africa, particularly for community-acquired infection. Based on the estimated prevalence of non-susceptibility among positive cultures, empirical treatment guidelines—which rely heavily on commonly available antibiotics such as penicillin and gentamicin—need review (tables 1, 2). Considering that about 429 million children live in sub-Saharan Africa,[62] the 67 451 cultures tested in the studies identified in this Review (of which approximately 8% were culture-positive) reveal the paucity of investigations (particularly for community-acquired infections) for such a large population at risk. Furthermore, a large proportion of research does not clearly delineate the denominator of the study population, making attribution of the prevalence of non-susceptible pathogens difficult. Although our Review focused on a generalised paediatric population, estimates of non-susceptibility are likely to be higher in specific populations at risk (such as children with HIV or tuberculosis) and warrant further reviews. Children with immunocompromising conditions are a unique population in their acquisition of antimicrobial-resistant infections because of their exposure to empirical antimicrobials, frequent encounters with health-care settings, and overall immune dysfunction.[63–66]

There is increasing evidence of antimicrobial resistance to drugs recommended in WHO antibiotic guidelines,[23,25] and together with the data presented here (tables 1, 2), a review of recommended empirical therapies is warranted. In the 2013 WHO guideline revisions, recommendations for some organisms were changed on the basis of susceptibility (eg, from chloramphenicol to ciprofloxacin[23] to treat *Shigella* spp and *Salmonella* spp infections); however, many common organisms continue to be treated with regimens with reportedly high frequencies of in-vitro non-susceptibility because of insufficient evidence (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 most studies arising from tertiary centres in urban settings, and underestimating the substantial burden of community-acquired infections. This sampling bias could overestimate the burden of morbidity caused by Gram-negative bacteria, which have a higher propensity to result in hospital presentation because of more severe clinical features and failure of oral therapy in the community, which introduces the possibility of non-representative population selection, as increased population density might be independently associated with antimicrobial resistance.[67] Most research did not identify whether isolates were secondary to community-acquired or hospital-acquired infections, an issue previously highlighted in analysis of resistance patterns in paediatric patients in Africa,[54,56,68] and although previous exposure to antimicrobials was rarely documented, it is uncertain how pretreatment (a common practice before tertiary presentation in sub-Saharan Africa) 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 about individual pathogens might 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 is reported to be present in parts of sub-Saharan Africa.[69] An element of geographical publication bias is also likely since a third of countries were in southern Africa and, despite their large populations, central and west African nations were underrepresented, an issue previously noted by other reviews of antimicrobial data in Africa.[9,25] Finally, non-susceptibility estimates were calculated from a small number of isolates, which are 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 cascade might result in imprecise results, and has been documented previously.[70] The tension between high prevalence of non-susceptibility in a few isolates and a low overall incidence among all seriously ill children poses a further challenge for interpretation.

Nevertheless, the available data are conclusive that antimicrobial resistance is an increasing and real threat among children admitted to hospital in sub-Saharan Africa, and prevalent MDR organisms are likely to become progressively pathogenic because of their swift spread within both the community and in hospital.[19,25,30,32,36,38–40,51] Community carriage of ESBLs is common (up to 45%), and nosocomial acquisition occurs at a rate of 20% for every 48 h spent in hospital.[30] In light of the increasing prevalence of MDR organisms in hospitals, simple improvements in local hospital-based infection control measures are important.[14,51] Our findings support a systematic review and meta-analysis[71] that assessed the most effective strategies for implementing antimicrobial stewardship policies in local settings, which identified strategies that could be extrapolated to low-income and middle-income countries to tackle antimicrobial resistance. These strategies include more rigorous use of empirical therapy that follows appropriately formulated local antimicrobial guidelines, consistently taking blood cultures (where possible) before the start of antimicrobial therapy (to allow earlier cessation of antibiotics if negative), and de-escalation of therapy (from intravenous to oral) as soon as clinical improvement occurs.[71]

There are few antimicrobial resistance awareness programmes in sub-Saharan Africa, with low frequencies of national and regional coordination.[7] These considerations should be incorporated into revisions of international treatment guidelines and monitoring of antimicrobial use. At the community level, infection control requires addressing of more pervasive and challenging issues that are inextricably linked with underdevelopment, such as poor sanitation and hygiene, overcrowding, and strategies aimed at limiting the availability of freely available over-the-counter antibiotics. Several effective surveillance systems have successfully been instituted for high-profile diseases (such as malaria, HIV, and MDR tuberculosis), providing evidence that a paediatric-focused antimicrobial resistance surveillance programme could be achieved with adequate commitment.[71]

It is difficult to draw firm conclusions about how increasing antimicrobial resistance contributes to neonatal and child mortality in light of the challenges of attributing mortality to antimicrobial resistance versus the underlying condition (which might be nosocomial in nature or a more

severe illness), or due to insufficient access to appropriate antibiotics. Additionally, antimicrobial resistance has been increasing over the past two decades while child mortality has fallen greatly in low-income and middle-income countries. Furthermore, in-vitro non-susceptibility does not necessarily correlate with a lack of clinical therapeutic effect. Nevertheless, excessive mortality rates attributable to antimicrobial resistance have been reported,[72,73] 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, education of physicians on prescribing practices, improvement of laboratory infrastructure, and promotion of collaboration between regional sites. Future research should focus on identification of appropriate local empirical therapies with improved susceptibility profiles, provision of clear clinical indications for timely second-line therapy when empirical therapy fails, establishment of guidelines for the de-escalation and cessation of antibiotic therapy, and regular surveillance of antimicrobial use within integrated, coordinated, international surveillance programmes. Standardised research methods adhering to WHO's Global Antimicrobial Resistance Surveillance System[74] should be used, clearly delineating resistance patterns for community-acquired versus hospital-acquired 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 strategy will allow non-susceptibility patterns and antimicrobial use to be monitored on a continental scale, and will ensure this issue of utmost public health concern is effectively addressed.

Contributors

PCMW did the literature search, designed figure 1, and wrote the first draft of the paper. PCMW and JAB carried out data analysis and interpretation. DI and JAB reviewed and helped revise the report. JAB conceptualised the paper, the study, and figure 2.

Declaration of interests

We declare no competing interests.

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