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Review

Antibiotic use and resistance in children with severe acute malnutrition and human immunodeficiency virus infection

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ABSTRACT

Severe acute malnutrition (SAM) and human immunodeficiency virus (HIV) infection underlie a major proportion of the childhood disease burden in low- and middle-income countries. These diseases commonly co-occur and lead to higher risk of other endemic infectious diseases, thereby compounding the risk of mortality and morbidity. The widespread use of antibiotics as treatment and prophylaxis in childhood SAM and HIV infections, respectively, has reduced mortality and morbidity but canlead to increasing antibiotic resistance. Development of antibiotic resistance could render future infections untreatable. This review summarises the endemic co-occurrence of undernutrition, particularly SAM, and HIV in children, and current treatment practices, specifically WHO-recommended antibiotic usage. The risks and benefits of antibiotic treatment, prophylaxis and resistance are reviewed in the context of patients with SAM and HIV and associated sub-populations. Finally, the review highlights possible research areas and populations where antibiotic resistance progression can be studied to best address concerns associated with the future impact of resistance. Current antibiotic usage is lifesaving in complicated SAM and HIV-infected populations; nevertheless, increasing baseline resistance and infection remain a significant concern. In conclusion, antibiotic usage currently addresses the immediate needs of children in SAM and HIV endemic regions; however, it is prudent to evaluate the impact of antibiotic use on resistance dynamics and long-term child health.

1. Introduction

Childhood undernutrition contributes to more than 45% of worldwide mortality in children aged under 5 years [1,2], the burden of which is concentrated in low- and middle-income countries (LMICs). Childhood undernutrition presents in two major forms: wasting, which is characterised by loss of tissue mass leading to low weight-for-height, with or without oedema; and stunting, which is characterised by impaired linear growth, leading to low height-for-age. All forms of child undernutrition are commonly complicated by infectious diseases, which compromise growth recovery and increase the risk of mortality. Infants living in poor sanitary conditions develop an idiopathic chronic inflammatory enteropathy of the intestine, termed environmental enteropathy, soon after birth, which leads to intestinal leakage of microbial products, and chronic immune activation [3]. These factors contribute to a cascade of negative effects, including muscle wasting, gastrointestinal malabsorption, and infectious disease, which result in severe acute malnutrition (SAM) [4].

SAM is an extreme form of undernutrition characterised by a low weight-for-height z-score (WHZ) of less than -3 standard deviations below the World Health Organization (WHO) normal growth curve standard [5] or mid-upper arm circumference (MUAC) less

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than 115 mm, and/or oedema. SAM affects 49 million children under the age of 5 years globally (2019 UNICEF Census), with more than two-thirds of these children living in Africa and Asia [6]. SAM is further classified upon diagnosis as complicated or uncomplicated, with management occurring in in-patient and out-patient settings, respectively. Complicated SAM requires hospitalisation and treatment in alignment with the WHO 10-step guidelines for management of malnutrition, addressing hypothermia, hypoglycaemia and dehydration prior to treating for infection and weight recovery with antibiotics [7]. In contrast, uncomplicated SAM can be managed in community-based acute malnutrition programmes with ready-to-use therapeutic food and antibiotics. Even with current management strategies, wasting remains at high levels [8]. Death amongst children with SAM is commonly attributed to infections; however, the diagnosis of infection is difficult because of altered clinical presentations, limited resources, and the lack of routine check-ups in children with uncomplicated SAM [9]. The usual signs of a bacterial infection, such as fever, may be absent due to an altered immune state [9,10]. Complicated SAM is associated with high mortality and children often present with infections. Therefore, as per WHO recommendations, any child hospitalised with complicated SAM is assumed to have an underlying infection and is treated with broad-spectrum antibiotics.

Human immunodeficiency virus (HIV) infection, another big contributor to childhood mortality in LMICs, is common in SAM-endemic regions. The 2019 UNICEF estimates show that there are ~1 million children under the age of 9 years living with HIV in sub-Saharan Africa and ~100,000 children in East Asia and the Pacific [11,12]. Antibiotic prophylaxis is an integral part of HIV management in children. The WHO recommends that any child exposed to HIV should receive cotrimoxazole antibiotic prophylaxis starting at 4-6 weeks of age, until after the cessation of breastfeeding once HIV infection has effectively been ruled out [13]. Children with HIV infection receive long-term cotrimoxazole prophylaxis together with antiretroviral therapy (ART), because daily antibiotics have been shown to reduce morbidity and mortality even in the context of long-term ART [14].

With an increase in antibiotic use in food and agriculture in addition to necessary antibiotic-dependent management practices for SAM and HIV children, antibiotic resistance is an immediate concern. Described in this review are the parallels in antibiotic treatment and prophylaxis in SAM and HIV, and the important role of antibiotics in reducing morbidity and mortality in children with complicated and uncomplicated SAM and in children living with HIV exposure and infection. Differences in direct antibiotic activity to prevent or treat infections, and the indirect effects through immunomodulation are highlighted. Also reviewed is the current evidence for the impact of these therapies on carriage of antibiotic resistance genes (ARGs), infections with antibiotic resistant organisms (AROs), particularly enteric pathogen dynamics, and child health. Finally, the need to understand the dynamics of antibiotic resistance acquisition and development in children, and potential areas of future research are discussed.

2. Intersection of severe acute malnutrition and human immunodeficiency virus infection

Infants with undiagnosed HIV infection have rapid disease progression in the absence of ART, and have a high risk of developing malnutrition. Population-level studies have shown that approximately 20% of children with SAM in LMICs are also living with HIV [15,16]. The co-occurrence of HIV with SAM increases the immunometabolic burden, HIV disease progression and, in turn, the probability that an infant will be exposed to broad-spectrum antibiotics in early life. The endemicity of SAM and HIV in these regions with other infectious diseases, such as malaria and tuberculosis (TB), further drives the need for antibiotics for prophylaxis and treatment [17].

Given that more than 80% of the world's undernourished children and more than 95% of HIV-positive/exposed children live in LMICs, the non-specific administration of antibiotics due to these conditions, in addition to rising antibiotic use in food and agriculture, may increase the risk of widespread selection and amplification of ARGs and AROs. However, as the immediate focus is on decreasing morbidity and mortality in children with SAM and HIV, antibiotic resistance is currently overlooked.

Antibiotics that effectively decrease morbidity and possibly contribute to recovery and growth have become a part of regular therapeutic regimens in SAM and HIV. Antibiotic treatment is administered to all children with SAM upon diagnosis, even without an overt infection, in both in-patient and out-patient settings [9]. Cotrimoxazole prophylaxis is administered empirically to all HIV-exposed children until they are confirmed to be HIV-negative [13]. There are few studies that directly evaluate the extent and implications of antibiotic use on resistance development in SAM or HIV. Some retrospective clinical sub-studies have shown increasing population-level resistance to antibiotics that are predominantly used in geographical regions with widespread SAM and/or HIV infection [18,19]. The recommended use of therapeutic and prophylactic antibiotics in children diagnosed with SAM and HIV [20], although necessary, may contribute to further selection, transfer and amplification of genetic resistance elements, precipitating increases in mortality caused by antibiotic-resistant infections that become difficult or impossible to treat.

3. Clinical guidelines and impact of antibiotic treatment in severe acute malnutrition

Guidelines: Clinical guidelines vary for treating children with SAM based on the presence or absence of clinical complications. Children diagnosed with SAM who pass an appetite test, and are clinically well, are considered to have uncomplicated SAM and are treated in out-patient settings using community-based management of acute malnutrition guidelines. In contrast, children with SAM who exhibit metabolic disturbances, severe oedema, danger signs or lack of appetite are treated in in-patient settings. The WHO treatment guidelines for children with complicated or uncomplicated SAM recommend antibiotic treatment upon diagnosis.

The antibiotics primarily used in malnutrition treatment and management are β-lactam, sulfonamide and aminoglycoside antibiotics (summarised in Table 1). According to the WHO guidelines, a child diagnosed with SAM who appears to have no complications will receive a paediatric dose of amoxicillin (80 mg/kg/day) administered in two divided doses for 7 days [21]. A child who shows any lethargy or has complications resulting in in-patient care, such as hypoglycaemia, hypothermia or urinary tract infections, will receive parenteral antibiotics on admission to hospital. This is usually an initial dose of ampicillin or penicillin for 2 days, followed by amoxicillin for 5 days in combination with an aminoglycoside, such as gentamicin, for 7 days. A child who fails to improve clinically within 48 hours may receive a broader spectrum antibiotic based on microbiological sensitivity patterns. Some programmes use cephalosporins, such as cefotaxime, ceftriaxone or cefdinir, as second-line treatments [21], whereas others use single or combination regimens, including carbapenems or fluoroquinolones. An anti-staphylococcal drug, such as flucloxacillin, may be used where there is extensive dermatosis. Metronidazole, an antibiotic with anti-anaerobic and anti-protozoal activity, is often used when intestinal complications are suspected. The doses and the combinations used for the above-mentioned antibiotics vary between settings. Suspected opportunistic infections, such as those caused by *Pneumocystis jirovecii*, are treated with other agents, in-

Table 1
Antibiotics used in the management of severe acute malnutrition and HIV

Condition	WHO recommended antibiotics [21,28]	Duration	Antibiotic class [98]	Antibiotic target and mechanism [98]	Resistance genes and associated plasmids [98]
SAM – no complication	Amoxicillin (80 mg/kg/day)	2x daily for 5-7 days	Beta-lactam antibiotic	Inhibition of penicillin binding proteins Disrupts transpeptidation	*TEM-1,TEM-30, OXA-1, OXA-2, blaF, ACI-1, SCO-1*
Complicated SAM – (septic shock, hypoglycaemia, hypothermia, skin/ respiratory/ urinary tract infection and lethargy)	Ampicillin (or Penicillin) (50 mg/kg IM or IV)	4x daily for 2 days	Beta-lactam antibiotic	Inhibition of penicillin binding proteins Disrupts transpeptidation	*TEM-1, SHV-1, OXA-1, NmcA, blaS, CMY-2, CTX-M, PDC-3* (Alternate resistant beta-lactamases) *Mex–, ArcAB* Found on Inc1 plasmid R46 (efflux pump)
	Amoxicillin (15 mg/kg orally) or Ampicillin (25 mg/kg orally)	3x daily for 5 days	Beta-lactam antibiotic	Inhibition of penicillin binding proteins Disrupts transpeptidation	*TEM-1,TEM-30, OXA-1, OXA-2, blaF, ACI-1, SCO-1*
	Gentamicin (7.5 mg/kg IM or IV)	1x daily for 7 days	Aminoglycoside antibiotic	Binds to the 30s subunit Disrupts translation	*AAC(3)-I* (aminoglycoside acyl transferase) Found on plasmid pWP14a, pWP113a, R1033 (acyl transferase)
Complicated SAM - No recovery post 48 hours	Chloramphenicol (25 mg/kg IM or IV)	3x daily for 5 days	Peptidyl transferase inhibitor	Binds to the 50s subunit Disrupts translation	*cml* (exporter protein) *cat* (Chloramphenicol acyltransferase) Found on plasmid R26 (exporter), R387(acyltransferase)
Complicated SAM – Second- line antibiotics	Ceftriaxone (50-75 mg/kg/day)	Daily until resolution effect	Beta-lactam antibiotic	Inhibits peptidoglycan synthesis.	*MexAB-OprM (antibiotic efflux)* *SHV-12, CTX-M, blaS1, CMY-2, PDC-3&5* *(alternative beta lactamases)*
Complicated SAM – Second- line antibiotics	Cefotaxime (100-150 mg/kg/day)	Daily until resolution effect	Beta-lactam antibiotic	Inhibits peptidoglycan synthesis.	*Cme-ABC, abcA, (antibiotic efflux)* *Omp-1(porin),* *CAM-1, ACI-1, CMY-136, sco-1* *(Alternative beta-lactamases)*
Complicated SAM – Second- line antibiotics	Cloxacillin (dosage not specified)	Daily until resolution effect	Beta-lactam antibiotic	Inhibits peptidoglycan synthesis.	*MdtEF-TolC (antibiotic efflux)*
Intestinal repair/ giardiasis	Metronidazole (7.5 mg/kg)	3x daily for 7 days	Nucleic acid synthesis inhibitor	Nitroso radical formation Disrupts DNA under reduced conditions	*msbA, hp1181, hp1184*
Parasitic worms	Mebendazole (100 mg orally)	2x daily for 3 days	Microtubules inhibitor	Inhibits synthesis of microtubules via binding to ß-tubulin	Tubulin gene mutations: Altered tubulin structures
Tuberculosis (~20% of SAM cases)	Isoniazid Rifampicin Pyrazinamide (unknown action) Streptomycin Ethambutol	Depending on availability and extent of use	Monoamine oxidase inhibitor RNA polymerase inhibitor 30s ribosomal binding Arabinosyl transferase inhibitor	Mycobacterial cell wall inhibition	*APH(3')* (aminoglycoside phosphotransferase) Found on plasmid RP4 (aminoglycoside phosphotranferase)
HIV exposed uninfected and infected	Cotrimoxazole (100-200 mg)	HEU: Daily until proven HIV negative HIV+: Daily lifelong	Diaminopyrimidine antibiotic + Sulfonamide antibiotic	Dihydrofolate reductase inhibition + Dihydropteroate synthase inhibition Disrupts folic acid synthesis; integral part of nucleotide and amino acid biosynthesis pathways	*dfra, sul, folP* (Alternate resistant protein) *Lmrs, Mex–, AdeIJK, OqxAB* (Efflux pumps) Found on Inc1 plasmid R46 (efflux pump) & Plasmid pAZ1, pLMO229 (dihydrofolate reductase gene)

cluding cotrimoxazole, and children with lower respiratory tract infections are often investigated for TB, or treated presumptively for TB with combination anti-TB therapy.

Impact: Antibiotic therapy has become an essential part of management of uncomplicated and complicated SAM [22,23]. A randomised clinical trial in Malawi showed significant improvement in recovery, weight and mortality with antibiotic treatment regimens in children with uncomplicated SAM (survival relative risk [RR] = 1.55 for amoxicillin and RR = 1.8 for cefdinir vs. placebo) [23]. Another study that evaluated uncomplicated SAM nutritional recovery in Niger showed a 14% reduction in re-hospitalisation due to antibiotic treatment, with improvement in early weight gains; however, there were no effects on nutritional recovery or mortality in this study [24]. Both studies showed benefits in early weight gain. Although the study from Niger challenged the WHO recommendation on using antibiotics in uncomplicated SAM, a meta-analysis of both these trials showed that, overall, the use of amoxicillin is beneficial in children with uncomplicated SAM [25]. There are no specific trials evaluating the efficacy of the current WHO-recommended antibiotics for children with complicated SAM. Observational studies have provided evidence of benefit when using ampicillin and gentamicin in children with complicated SAM [21]. However, a randomised trial that evaluated the efficacy of cotrimoxazole in reducing post-discharge mortality of children with complicated SAM found that daily cotrimoxazole prophylaxis did not reduce mortality when administered for 6 months post-discharge in an in-patient setting in Kenya [26].

4. Clinical guidelines and impact of antibiotic prophylaxis and treatment in human immunodeficiency virus infection

Guidelines: For infants exposed to HIV in *utero*, the WHO recommends long-term cotrimoxazole prophylaxis starting 4 to 6 weeks after birth until the child is proven HIV-negative by molecular testing at least 6-weeks' after the cessation of breastfeeding. For infants, children and adolescents who are confirmed as living with HIV infection, cotrimoxazole prophylaxis is continued or initiated regardless of clinical status [27,28]. In settings of malaria and high prevalence of severe bacterial infection, cotrimoxazole, in combination with ART, is recommended to be continued into adulthood [28]. Co-occurring acute respiratory infections, pneumonia, TB, malaria and bacterial diarrhoea are managed with a diverse range of antibiotics, often through syndromic management because of a lack of diagnostic facilities.

Impact: The WHO guidelines (2021 update) recommend the discontinuation of cotrimoxazole prophylaxis for HIV-infected children once they reach 5 years of age, provided they have no symptomatic disease and have good ART adherence [28]. However, a randomised clinical trial in children and adolescents from Uganda and Zimbabwe showed a decrease in hospitalisation and incidence of malaria and other infections in those who continued prophylaxis despite good CD4 count recovery after 2 years of ART [14]. Based on these results, lifelong cotrimoxazole prophylaxis is now recommended in children with HIV infection. Cotrimoxazole prophylaxis for HIV-exposed but uninfected children is currently recommended; however, two trials in Botswana and South Africa showed no benefit of cotrimoxazole prophylaxis in this group [29,30], and the benefits of universal cotrimoxazole have been cautiously questioned [31].

5. Rationale of antibiotic usage in human immunodeficiency virus and severe acute malnutrition

Antibiotics play an integral role in decreasing disease burden and enhancing recovery in children with both SAM and HIV. Various studies have reported the clinical advantages of antibiotic use in SAM and HIV, but their effects on growth are mostly postulated. Antibiotics have a definite role in modulating the composition and function of the intestinal microbiome. Molecular genomics and metagenomics have increased our understanding of the major role that the gut microbiome plays in the onset, management and recovery from an undernourished or diseased state [32,33]. Nutritional recovery could be due to the altered or reduced pathogenic bacterial burden of the gut microbiota and resolution of any clinical or subclinical infections present [34]. The gut microbiome also serves as an important reservoir for enteropathogens and associated resistomes that are implicated in adverse clinical outcomes [32]. The incidence of aerotolerant pathogens, such as proteobacteria, and depletion of anaerobes in the gut has been shown to be present in some cases of complicated oedematous SAM [35]. Antibiotics may also aid in recovery by decreasing the burden of enteropathogens and other pathogens causing active infection. There is also a potential for antibiotic-dependent immunomodulation: certain macrolide antibiotics and cotrimoxazole have been shown to exhibit anti-inflammatory effects in the host [36]. This may be driven by direct immunomodulation whereby the antibiotic reduces pro-inflammatory cytokine production, alters neutrophil recruitment and enhances dendritic cell function [36,37]. Tetracycline and fluoroquinolone antibiotics inhibit inflammatory signalling pathways and promote downregulation of inflammatory cytokines, such as IL-1 and TNF-α [38,39]. These immunomodulatory effects and positive clinical outcomes indicate possible alternative mechanisms of action of certain antibiotics in reducing morbidity and mortality in children living with SAM and HIV. However, the effects of broad-spectrum antibiotics in SAM recovery or HIV have not been extensively studied and the use of these drugs could negatively interfere with gut microbial and nutritional recovery.

Undernutrition causes immune dysregulation [40]; furthermore, there may be a two-way interplay between immune dysfunction and the onset of undernutrition. The co-occurrence of HIV infection and SAM worsens outcomes for children through immunomodulation, enteropathy, diarrhoea, malabsorption and increased metabolic demand [41]. Whether antibiotic exposure, the dynamics of ARG carriage, or their influence on microbiome composition have any direct modulatory effects on the immune system and downstream effects on child health outcomes is not well understood [40]. Defining the functional use of antibiotics, whether for use as antibiotics, immunomodulators or microbiome-modulators, would be helpful for prioritising and dosing these drugs. Regardless of the potential for non-antibacterial functions of antibiotics, increasing resistance to conventional antibiotics is quickly rendering the antimicrobial function obsolete, thus forcing the use of last-resort antibiotics.

6. The impact of antibiotic resistance in severe acute malnutrition and human immunodeficiency virus

6.1. Mechanisms of resistance

Antibiotic usage in patients with SAM and HIV increases the risk of antibiotic resistance, thereby threatening the successful treatment of subsequent infections. Resistance to commonly used antibiotics is through substrate modification, active site modification, competitive inhibition, and efflux of antibiotic compounds. These modifications are stabilised genetically in resistance-encoding genes and are sometimes shared in an intracellular (between plasmid and chromosome or transconjugation), intra- and cross-species manner via transposons, integrons and plasmids [42,43], which are collectively termed mobile genetic elements (MGEs). MGEs are an important marker in the spread of resistance, as they are assembled with multiple resistance genes and co-selected under antibiotic pressure, leading to

broad community-level acquisition of multidrug resistance. A study in Central Africa showed that up to 57% of healthy children are carriers of extended-spectrum beta-lactamase-producing Enterobacteriaceae with isolated MGEs showing transconjugation capability [44]. Large plasmids carrying multidrug resistance genes and transfer machinery were also isolated from children in sub-Saharan Africa and South Asia [45,46]. A multicentre study in Asia and Africa showed that MGEs recovered from these countries do not appear to have species or strain specificity; rather, they are stably carried by organisms within a geographical region through selection corresponding to the levels of antibiotic usage in the area [46]. This is evidence for the possible horizontal transfer of MGEs driven by the current prescription practices and antibiotic prophylaxis interventions in regions with a high burden of HIV-infection and complicated SAM.

ARG carriage is ubiquitous among populations living in HIV and SAM endemic regions [22]. However, most resistance data are derived from samples taken during a hospital visit or from clinically relevant bacterial species implicated in infection-related deaths [17]. Children with HIV and SAM are major beneficiaries of antibiotic interventions and carry the highest risk of resistant infections. Understanding population-level resistance gene carriage may help predict the effectiveness of different antibiotics in a region. Commensal organisms can harbour a myriad of resistance genes, which may help them survive antibiotic exposure, but resistant commensals may also serve as a reservoir of ARGs for pathogenic organisms [47]. Understanding the role of resistance genes in a healthy microbiome is key to understanding the impact of ARGs during infection and in poor outcomes in child health.

6.2. Antimicrobial resistance in severe acute malnutrition

The acquisition dynamics of antibiotic resistance in both complicated and uncomplicated SAM are integral to understanding the role of resistant infections in health outcomes for children. A study at a therapeutic feeding centre in Niger showed that there is high transmissibility of plasmid-based, extended-spectrum beta-lactamase genes in children with SAM [48], with many of these plasmids conferring resistance to one or more antibiotics in their antibiotic class. The study also showed that most of the enterobacteria recovered were resistant to amoxicillin and cotrimoxazole, 50% were resistant to cefalotine and 20% were resistant to gentamicin, with species-specific resistance observed across multiple subjects in the study [49]. Nine percent of the children died, mostly due to sepsis, but the contribution of antibiotic resistance in this study is unknown due to the limited availability of microbiological data [49]. The observed resistance phenotypes and genotypes are to antibiotics commonly used as early therapeutic interventions in SAM. Targeted clinical investigations coupled with microbiological evaluations delving into the pathobiology of infections are needed to discern the impact of antibiotic resistance in infection-related mortality.

Bacteraemia on average affects 1 in 6 children with SAM, with a mortality rate of approximately 30%, and the co-occurrence of HIV further increases mortality [50]. A study in Nigeria reported that almost half of children with SAM were bacteraemic [51]. Most of the bacteria isolated from children with SAM and bacteraemia are resistant to first- and second-line antibiotics, as defined by the WHO [52,53]. A study to evaluate routine amoxicillin for uncomplicated SAM in Niger found that a significant proportion of enterobacteria recovered from gastroenteritis (35%), sepsis (66%) and bacteriuria (81%) were resistant to amoxicillin [24]. Another cohort study tracking the mortality of children with SAM in Uganda found organisms isolated from blood cultures resistant to ampicillin, gentamicin and ceftriaxone [54]. Bacteraemia with a resistant organism worsens the outcome for children with SAM. A cross-sectional study of bacteraemia in children with SAM from Tanzania showed that high levels of resistance to ampicillin, amoxicillin, gentamicin, cephalosporins and ciprofloxacin were implicated in higher mortality [55]. Another study in Nigeria in children with SAM revealed resistance to amoxicillin, cotrimoxazole, gentamicin and ceftriaxone in children with bacteraemia [51]. Pre-existing resistance during bacteraemia is also a precursor for acquisition of novel resistance and recurring bacteraemia, due to the antibiotics used to treat primary infections and as prophylaxis [54]. Although there are few studies that focus on evaluating the impact of resistance in these populations, retrospective studies show that rising resistance to antibiotics is a concern [53].

6.3. Antimicrobial resistance in human immunodeficiency virus

Cotrimoxazole is the primary antibiotic used in HIV management. Despite high rates of resistance, cotrimoxazole prophylaxis decreases hospitalisation and mortality rates in HIV and, therefore, has become the gold standard for antibiotic prophylaxis [14,56,57]. Cotrimoxazole has been shown to reduce neonatal mortality when administered antenatally to HIV-infected mothers by reducing the rates of pre-term birth and chorioamnionitis [58,59]. However, baseline resistance to cotrimoxazole is a growing concern. *Escherichia coli* and *Klebsiella pneumoniae* are common carriers of cotrimoxazole resistance, with 50-60% of recovered isolates exhibiting cotrimoxazole non-susceptibility [60,61]. After initiation of cotrimoxazole prophylaxis, 80-100% of recovered isolates of *E. coli* and *K. pneumoniae* are resistant to cotrimoxazole [60,61]. A culture-based survey of a cohort of HIV-infected children in Ghana showed that up to 60% of certain strains are resistant to cotrimoxazole and a variety of beta-lactamases [62]. Another study showed an increase in cotrimoxazole resistance gene prevalence/carriage after initiation of prophylaxis in HIV-exposed uninfected children [63]. Despite this extensive resistance to cotrimoxazole, there does not seem to be a corresponding increase in resistance-dependent morbidity and mortality in children with HIV [14,56,57]. More targeted investigations are necessary to stratify the effect of resistance on mortality and morbidity in these populations. The actual antibiotic or antibacterial function of cotrimoxazole may be less important in HIV prophylaxis, as highlighted by the non-specific and immunomodulatory effects of cotrimoxazole observed in the Anti-Retroviral Research for Watoto (ARROW) trial [36]. Cessation of cotrimoxazole prophylaxis in HIV-infected children in the ARROW trial also did not reduce cotrimoxazole resistance or alter the overall resistance gene diversity in the microbiota of ARROW participants [64]. This result is reassuring and supports the continued use of cotrimoxazole in HIV-infected children. However, cotrimoxazole plays a major role as an antibiotic against malaria, *Pneumocystis jirovecii* and *Toxoplasma gondii* in HIV-infected children and pregnant women, reducing disease incidence and hospitalisation [65–68]. The spread of resistance to these organisms may be detrimental in the post-infection recovery of an immunocompromised child. A study to evaluate the nasopharyngeal carriage of respiratory infection-causing resistant *Streptococcus pneumoniae* and *Hemophilus influenzae* in HIV-infected children in Zambia showed significant increases in phenotypic cotrimoxazole resistance in these two organisms compared with the control group, rendering the antibacterial ineffective [69]. Although the direct immunomodulatory effects of cotrimoxazole might be effective in the presence of resistance, the growing resistance against this antibiotic will become a health concern in situations requiring an antibacterial. A non-inferiority trial in South Africa to evaluate cotrimoxazole prophylaxis in HIV-exposed, uninfected children showed no difference in relative risk of mortality between continuing and stopping prophylaxis [29]. As HIV-exposed, uninfected infants comprise a significant proportion of the population receiving cotrimox-

azole prophylaxis, the efficacy and need for prophylaxis should be re-evaluated to better inform health policy.

Studies focused on estimating the clinical impact of antibiotic-related resistance are needed to better direct healthcare policies around antibiotic usage. Indeed, further research on the interaction between resistance and other antibiotics used as prophylaxis and treatment of HIV and SAM is warranted in the wake of growing antibiotic resistance in LMICs. Antibiotics are currently necessary to prevent morbidity and mortality in these high-risk groups. However, current understanding of the impact of resistance on clinical outcomes in these populations is poor. New trials that evaluate and link antibiotic use and microbiome ARG carriage to resistant infections and clinical outcomes in children with SAM and HIV in LMICs are essential. The studies that report bacterial resistance in children with SAM and/or HIV infection or exposure are summarised in Table 2. Thirty-six percent of the studies reported that antibiotic resistance plays a role in mortality and all included studies reported non-susceptibility of disease-causing organisms to one or more of beta-lactams, macrolides, cephalosporins and cotrimoxazole (Table 2).

7. Discussion and Future directions

SAM and HIV in children in LMICs are an immense healthcare concern. A meta-analysis showed that during an infection, children with SAM have double the likelihood of death, whereas SAM in the presence of HIV infection triples the risk of death [15,16,70]. The presence of an antibiotic-resistant bacteraemia increases the mortality rate by five-fold [71]. Children with SAM-HIV and bacteraemia caused by a multidrug-resistant organism have up to a thirty-fold higher likelihood of mortality. This stresses the immediate need to understand the ecological dynamics of antibiotic resistance in response to antibiotic usage, particularly in non-critical usage settings. As LMICs have one of the highest concentrations of antibiotic resistance in the world, the evaluation of ARGs dynamics and the impact of current antibiotic usage practices at the population level are needed. Although prophylactic, broad-spectrum antibiotics may reduce infections and improve growth in the near term, continued widespread and long-term antibiotic use may impact future population health and more granular evidence is urgently needed to inform health policy.

In addition to the emergence of AROs and ARGs in direct response to antibiotic usage in healthcare, particularly unnecessary antibiotic prescriptions for viral illnesses, AROs and ARGs can also be disseminated through food and the environment. For example, high levels of sulfonamides, tetracyclines, extended-spectrum beta-lactamases and plasmid-encoded quinolone and methicillin resistance have been detected in food animals [72] and in soil microbes in agricultural areas of Asia and Africa [73–76]. Domestic livestock play an important economic role in the livelihoods of people in rural areas of LMICs, and children in these areas have intensive exposure to farm animals [72]. All livestock are administered antibiotics for health maintenance and sometimes as growth enhancements, with poultry receiving the highest amount of antibiotic per kg biomass [77]. The continued use of antibiotics as growth enhancers in farm animals and agriculture is a major contributor to ARGs and AROs exposure in children.

So far, attention has naturally focused on decreasing the infection-related morbidity and mortality in patients with SAM and HIV using prophylactic and therapeutic antibiotics. However, more granular recommendations for antibiotic management practices can be made in groups such as children with uncomplicated SAM and in those who are uninfected despite HIV exposure. The evidence for the use of antibiotics in children with uncomplicated SAM is unclear as these children do not appear ill, but may carry the risk of less clinically overt infections. The effect of antibiotics on recovery from uncomplicated SAM in the studies in Malawi [23] and Niger [24] were contradictory. The use of antibiotics in conjunction with ready-to-use therapeutic food significantly reduced mortality in children with SAM in Malawi [23], but not in Niger [24]. Regular, low-dose, broad-spectrum antibiotics also enhance growth in children living in SAM endemic regions [25,32,78,79], thus possibly having non-specific desirable outcomes. Current WHO recommendations state that any child diagnosed with SAM should be started on antibiotic treatment for up to 10 days [80,81]. Specific recommendations for antibiotic use in uncomplicated SAM require more evidence. In HIV-exposed uninfected infants receiving cotrimoxazole prophylaxis, there was no survival benefit in studies from South Africa [29] and Botswana [30]. The need for antibiotic use in these populations could be re-evaluated.

Baseline resistance to many commonly used antibiotics is already high in LMICs. Although the WHO has prioritised antibiotic resistance as a global health threat, only 25% of African countries have any national action plan in place for resistance management [82]. Despite recent antibiotic stewardship efforts, antibiotic use is rising in healthcare and agriculture [72,83–86], leading to widespread amplification of ARG carriage. Most antibiotics imported into sub-Saharan Africa are for food animals, with an average of 36.28 ± 10.11 tonnes per year, comprising antibiotics implicated in resistant infections in humans, such as beta-lactams, macrolides, sulfonamides, quinolones and tetracyclines [77,87]. Higher rates of resistance in organisms that cause the most common infections globally, such as pneumonia and urinary tract infections, are rendering conventionally used antibiotic regimens less effective, with the class and generation of antibiotics prescribed shifting in response to the growing rates of resistance. The impact of antibiotic usage in healthcare on the development, selection and amplification of antibiotic resistance needs more attention. The possibility of alternative antibiotics as first-line regimens and local baseline-resistance-dependent prescription practises could be evaluated. Novel antibiotic discovery has slowed, with few new and effective antimicrobial agents on the horizon. This is projected to result in global annual antibiotic resistance-related healthcare costs of $\sim$100 trillion USD per year by 2050, with the majority of direct human costs borne by people living in LMICs [88]. The opportunity cost of not understanding the role of antibiotic resistance in children with SAM and HIV is high, particularly when antibiotics are essential in this high-risk population. However, until alternative antimicrobial therapies are available to prevent illness and death in children with SAM or those exposed to HIV, there are few alternatives to widespread antimicrobial treatment and prophylaxis.

The increasing rates of SAM in children under the age of 6 months and the increasing population of HIV-exposed, uninfected children [89] will contribute to an increased need for antibiotics. The continued use of antibiotics for SAM and HIV may influence resistance rates, compromise future antibiotic effectiveness in these populations, and lead to a myriad of long-term health implications into adulthood via microbiome dysbiosis-induced pathologies, such as allergies and autoimmune diseases [90]. However, the direct link between antibiotic use in SAM and HIV and the growing selection of disease-causing ARGs and AROs requires careful study in these vulnerable patient populations. The effect on resistance is already being observed in general nosocomial infections in sub-Saharan Africa and South Asia, where third-generation cephalosporins are ineffective, and there are increasing rates of bacteraemia due to organisms resistant to first- and second-line antibiotics [46]. In addition, the accessibility of antibiotics as over-the-counter drugs, where up to 70% of antibiotic dispensing occurs without a prescription [91], infectious comorbidities, and strained antimicrobial resistance surveillance systems contribute to the unregulated antibiotic use and extensive communal spread and per-

Table 2
Studies reporting antibiotic resistance in SAM and/or HIV with respect to antibiotic prophylaxis in children.

Literature/ studies	Study type	Country	n	SAM (percentage)	HIV positive (percentage)	Mortality (percentage)	Primary co-morbidity	Antibiotics used	Resistance observed to	Resistance in mortality
Rabasa, 2002 [99]	Prospective	Nigeria	194	100	NR	NR	UTI***	Excluded**	Cotrimoxazole, Nitrofuratonin	NR
Noorani, 2005 [100]	Cross-sectional survey	Kenya	91	100	43	NR	Bacteraemia	NR*	Ampicillin, Chloramphenicol, Ciprofloxacin, Cotrimoxazole, Erythromycin, Oxacillin	NR
Babirekere-Iriso, 2006 [101]	Cross-sectional	Uganda	134	100	44	20.1	Bacteraemia	Chloramphenicol, Cotrimoxazole, Amoxicillin	Ampicillin, Chloramphenicol, Ciprofloxacin, Cotrimoxazole, Gentamicin	yes
Bachou, 2006 [50]	Prospective	Uganda	450	100	36.7	23.7	Bacteraemia	NR	Ampicillin, Chloramphenicol, Ceftaxidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Cotrimoxazole, Gentamicin	yes
Abrha, 2011 [102]	Cross-sectional study	Ethiopia	170	100	NR	7.1	Bacteraemia	Excluded**	Amoxicillin, Ceftriaxone, Chloramphenicol, Ciprofloxacin, Cotrimoxazole, Gentamicin	yes
Okomo, 2011 [103]	Prospective	Gambia	140	100	28.7	5.7	Bacteraemia, UTI***, Respiratory infections	NR	Ampicillin, Ceftriaxone, Chloramphenicol, Cotrimoxazole	NR
Chisti, 2015 [104]	Prospective	Bangladesh	407	100	NR	8.5	Pneumonia, Bacteraemia	Ampicillin, Gentamicin	Ceftriaxone, Ciprofloxacin	NR
Ahmed, 2017 [55]	Prospective	Tanzania	402	44.3	NR	17.4	Bacteraemia	Cotrimoxazole, Cephalosporins	Amoxicillin, Ampicillin, Ceftazidime, Ceftriaxone, Ciprofloxacin, Gentamicin, Meropenem, Oxacillin	yes
Idris, 2018 [51]	Cross-sectional	Nigeria	90	100	Excluded**	NR	Bacteraemia	Excluded**	Amoxicillin, Ceftriaxone, Ciprofloxacin, Cotrimoxazole, Gentamicin	NR
Yona, 2020 [52]	Cross-sectional	Tanzania	232	100	34.9	NR	Bacteraemia	NR	Amoxicillin, Ceftriaxone, Chloramphenicol, Ciprofloxacin, Gentamicin, Penicillin	NR
Nalwanga, 2020 [54]	Cohort study	Uganda	260	100	12.2	25.2	Bacteraemia	NR	Ampicillin, Ceftriaxone, Gentamicin	NR

*NR – Not reported.
**Excluded – Children with recent or current antibiotic use were excluded from the study/Children with HIV were excluded from the study
*** UTI – Urinary Tract Infection

sistence of ARGs. Measurement of antibiotic resistance dynamics in response to therapeutic and prophylactic antibiotic use is critical in the management of antibiotic regimens for SAM, HIV and other comorbidities. The Mortality Reduction after Oral Azithromycin (MORDOR) trial evaluated mass administration of azithromycin to pre-school children and included gut microbiome measurements and antibiotic resistance surveillance assessments [92,93]. This level of surveillance coupled with research will inform targeted health policy and stewardship to preserve antibiotic effectiveness in regions with high levels of resistance. In addition, alternative, non-antibiotic, therapies that retain desirable antibiotic functions, such as improved child growth and immunomodulation, should be evaluated. For example, the use of pre-, syn-, and probiotics have been shown to decrease diarrhoeal episodes in undernourished and SAM children [94–96]. Another example is the use of mesalazine to treat enteric dysfunction in children with SAM, which showed immunomodulatory effects, including the downregulation of inflammatory markers and increases in growth hormones [97].

8. Conclusion

The role of antibiotic resistance in adverse clinical outcomes is well understood. However, the important role of antibiotics in the reduction of HIV and SAM-related morbidity and mortality in early life is undeniable. Antibiotic prophylaxis has become the recommended approach to combat morbidity and mortality in patients with SAM and HIV due to its ready availability, affordability and demonstrated improvements in health outcomes. However, growing antibiotic resistance in response to the expanding use of antibiotics in agriculture and healthcare is an immediate concern that cannot be ignored. It is particularly important in the case of SAM and HIV, as they underlie a wide variety of infectious diseases that are concentrated in LMICs, and further increase the need for broad-spectrum antibiotic use. This review highlights the current need for antibiotics, shows where antibiotic therapies succeed in SAM and HIV, and points to areas of inconsistency. Although antibiotic prophylaxis is currently saving the lives of children with SAM and HIV, it is necessary to understand the long-term impact of these antibiotics and the effects of the current management methods and policies on antibiotic resistance and future child health.

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FF ideated and wrote the manuscript. RR contributed to ideation, writing and discussion. MD provided expertise with most recent guidelines for management of SAM and HIV. AP and AM guided the authors with the review topic organisation, research question and writing of the manuscript. All authors contributed to the editing of the manuscript.

Declarations of Competing Interests

No competing interests to declare.

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