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Global emerging resistance in pediatric infections with TB, HIV, and gram-negative pathogens

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Abstract

Infants, children and adolescents are at risk of life-threatening, antimicrobial-resistant infections. Global burdens of drug-resistant TB, HIV and gram-negative pathogens have a particular impact on paediatric age groups, necessitating a paediatric-focused agenda to address emerging resistance. Dedicated approaches are needed to find, successfully treat and prevent resistant infections in paediatric populations worldwide. Challenges include the diagnosis and identification of resistant infections, limited access to novel antimicrobials or to paediatric-friendly formulations, limited access to research and clinical trials and implementation challenges related to prevention and successful completion of treatment. In this review, the particular complexities of emerging resistance in TB, HIV and gram-negative pathogens in children, with attention to both clinical and public health challenges, are highlighted. Key principles of a paediatric-focused agenda to address antimicrobial resistance are outlined. They include quality of care, increasing equitable access to key diagnostics, expanding antimicrobial stewardship and infection prevention across global settings, and health system strengthening. Increased access to research studies, including clinical trials, is needed. Further study and implementation of care models and strategies for child- or adolescent-centred management of infections such as HIV and TB can critically improve outcome and avoid development of resistance. As the current global pandemic of a novel coronavirus, SARS-CoV-2, threatens to disrupt health systems and services for vulnerable populations, this is a critical time to mitigate against a potential surge in the incidence of resistant infections.

Keywords

Drug resistance; antimicrobial resistance; HIV; tuberculosis; gram-negative bacteria; paediatrics; adolescents

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Introduction

Increasing antimicrobial resistance is a very present global threat. The widespread emergence of antimicrobial resistance of bacterial, fungal, viral and parasitic pathogens threatens progress in the treatment and prevention of serious infections. This raises fears of a 'post-antimicrobial' world in which common medical interventions such as surgery or chemotherapy regimens are hampered by a lack of effective antimicrobials for preventing or treating infectious complications. A challenge of antimicrobial resistance is that addressing it requires systematic interventions at various levels of healthcare systems and society [1]. In 2015, WHO published the Global Action Plan on Antimicrobial Resistance which outlined key objectives of addressing the urgent threat posed by antimicrobial-resistant pathogens, and a framework for action [2].

Infants, children and adolescents face particular challenges related to increasing antimicrobial resistance, which require dedicated approaches to find, successfully treat and prevent resistant infections in children worldwide. These include difficulties of diagnosis and identifying resistance, lack of access to novel antimicrobials or child-friendly formulations, limited access to research and clinical trials and implementation related to prevention and successful completion of treatment. TB, HIV and gram-negative infections cause an incredible burden of disease and severe complications in paediatric patients. In this review, the particular complexities of emerging resistance of TB, HIV and gram-negative pathogens in paediatric populations with attention to clinical and public health challenges are highlighted. The key principles of a paediatric-focused agenda to address antimicrobial resistance are outlined.

Emerging TB resistance in paediatrics

Tuberculosis (TB) is still a major global public health challenge and the leading cause of death from a single pathogen [3]. It is estimated that, in 2018, 10.0 million people [95% confidence interval (CI) 9.0–11.1 million] developed TB [3]. Globally, there were 1.2 million deaths (95% CI 1.1–1.3 million) of those without HIV, and an additional 251,000 (95% CI 223,000–281,000) TB deaths in those with HIV [3]. TB is a leading cause of hospitalisation and death of both children and adults with HIV [4].

TB in children is often difficult to diagnose, with poor clinical recognition of clinical manifestations in children, limitations of diagnostics owing to paucibacillary disease and inability of young children to produce sputum, and consequently low rates of case ascertainment and of microbiological confirmation [5,6]. Childhood TB is severely underestimated by passive case finding, and reports of childhood TB by national TB programmes are known to underestimate the actual burden of disease. Case definitions of childhood TB can also be inconsistent between settings. Estimates of childhood TB therefore rely on mathematical modelling [7,8]. It is estimated that, in 2018, 1.12 million children under 15 years of age developed TB and that 205,000 of them died [3].

Drug-resistant TB (DR-TB) is a major global health threat. Classifications of TB drug resistance are based on identified resistance to classes of anti-TB medications (Table 1)

[3,9]. Given their potency, isoniazid and rifampin are the ‘backbone’ of first-line anti-TB regimens. Isoniazid-mono-resistant TB is resistant to isoniazid with susceptibility to rifampin. Rifampin resistance (RR-TB) may coincide with resistance to other anti-TB medications and is treated with second-line regimens [9]. While regimens for multidrug-resistant TB (MDR-TB) are increasingly moving away from the use of injectable medications towards all-oral treatment, historical definitions of extensively drug-resistant TB (XDR-TB) or pre-XDR-TB are based on resistance to these second-line injectable medications.

Diagnosis of DR-TB depends on having microbiological confirmation of TB, i.e. by culture and drug-susceptibility testing, by rapid molecular testing and identification of molecular markers of resistance, or by whole genome sequencing [6]. Addressing DR-TB globally has been complicated by limitations in TB case detection, challenges in obtaining specimens for culture (e.g. for extrapulmonary TB or for young children who cannot produce sputum), limited culture sensitivity (particularly in TB-HIV co-infection, or for children with TB), and challenges with availability of diagnostics and treatment for DR-TB in some settings [5]. Unfortunately, most DR-TB cases are not identified [3].

It is estimated that approximately half a million people developed MDR/RR-TB in 2018, with only about a third of these cases identified and enrolled in treatment [3]. WHO has listed 30 countries with the largest burdens of MDR-TB, including 10 countries with the widest gap between estimated MDR-TB cases and the number of cases commenced on MDR-TB treatment [3]. In patients with MDR/RR-TB commenced on treatment, global treatment success is approximately 56%, and more than 70–80% in some countries [3]. Given the lower rates of bacteriological confirmation in children, MDR-TB is more likely to be undiagnosed in children than in adults [6]. In addition, gaps in access to drug-susceptibility testing severely limit current understanding of the epidemiology MDR-TB. A modelling study estimated that 850,000 children developed TB in 2014: 58,000 of them had isoniazid monoresistance, 25,000 had MDR-TB and 1200 had XDR-TB [10]. The vast majority of cases of paediatric DR-TB are not diagnosed [3,10].

Risk factors for DR-TB include previous treatment for TB, travel from a country with a high incidence of DR-TB, or close contact with these risk factors. DR-TB in younger children is typically owing to primary acquisition of resistant TB from a source case with DR-TB—typically a close adult contact—and not from development of resistance during the course of treatment [6]. This relates to the paucibacillary nature of TB in children. In contrast, adult-type forms of TB, i.e. with cavitary lung disease, typically reflect a large burden of TB bacilli and sequestration of these bacilli within cavitations which are difficult to penetrate. In this context, drug resistance typically develops in the setting of intermittent or inadequate anti-TB drug penetration of large populations of *Mycobacterium tuberculosis* organisms within these cavitary lesions [11]. Because of lower rates of bacteriological confirmation in children and the likelihood of acquiring primary TB resistance from a source case, identifying an adolescent or adult close contact with DR-TB is of great importance to obtain the likely sensitivities of the child’s infection. This is generally more feasible in countries with a low burden of TB where the source contact may be more readily identified; in countries with a high TB burden, it may be more difficult to be certain of the source case [6].

Clinical evaluation and management of DR-TB in children cannot be comprehensively reviewed here, but the key clinical pearls are presented (Table 2). Clinical suspicion of TB and vigilant awareness around DR-TB are of critical importance. TB is a clinical diagnosis based on clinical findings; epidemiological context and likelihood of TB exposure; risk factors for progression to TB disease (for example, in infants or young children, those with HIV infection, or those on treatment with TNF- α inhibitors); and results of laboratory or radiographical evaluations [12]. Acid-fast bacilli smears and cultures (on multiple specimens), nucleic acid amplification testing for TB diagnosis and identification of drug resistance, and tuberculin skin testing (TST) and/or interferon-gamma release assays (IGRA) should be performed [12]. Negative results for any of these, however, do not preclude a diagnosis of TB. As discussed, microbiological confirmation can be challenging in young children. Sputum induction is the preferred method of specimen collection but is not feasible in infants and young children. In those too young to produce sputum, multiple early morning gastric aspirates should be obtained for diagnosis. Both induced sputum and gastric aspirates carry a risk of transmission of TB to those performing these procedures, and training is needed to ensure adequate sampling and appropriate infection prevention. Histopathology may aid the diagnosis of extrapulmonary TB. Both TST and IGRA have decreased sensitivity (as low as 60%) in the setting of severe or disseminated forms of TB [13]. Children may present with pulmonary or extrapulmonary disease such as miliary TB, TB meningitis and gastro-intestinal TB; these severe forms can be challenging to diagnose and may carry a poor prognosis if diagnosed late [5]. Given the vulnerability of infants and young children to severe disease, and the potential challenges of initial diagnosis, consultation with a paediatric infectious disease specialist with expertise in paediatric TB should always be sought.

Critically, the finding of TB in a child represents recent TB transmission. Diagnosis or evaluation for childhood TB must prompt thorough evaluation of all household members and close contacts. In order to avoid further onward transmission of DR-TB, this is even more critical in DR-TB.

Treatment of MDR-TB in children must be guided by consultation with experts in paediatric TB and co-ordinated with public health departments. Recent clinical guidelines provide practical, evidence-based guidance for the composition of a regimen for MDR-TB with drugs (at least five) to which the specific TB isolate is likely to be susceptible [6]. This approach is appropriate in settings where individualised treatment is feasible [6]. Whenever possible, all-oral regimens should be used. Currently, bedaquiline can be dosed in children aged ≥ 6 years, and delamanid may be used from ≥ 3 years of age [6,11]. Treatment of DR-TB in children is complicated by limited access to these medications, an absence of child-friendly formulations, potential drug–drug interactions with antiretroviral therapy, and challenges in paediatric dosing with limited pharmacokinetic data [6]. Treatment courses can be as long as 2 years, although the optimal duration of therapy is the subject of ongoing study, with shorter-course all-oral regimens currently being evaluated in adults [11]. Given the prolonged duration of MDR-TB therapy, toxicities of medications for DR-TB, medication burdens, financial costs of treatment and significant stigmatisation and isolation, DR-TB carries significant mental health and psychosocial burdens for patients [15–17]. This is particularly so in the context of co-infection with HIV and DR-TB [15–17].

Children exposed to pulmonary TB should be carefully evaluated for TB disease, and, in the absence of evidence of TB, should be commenced on TB preventive therapy (TPT). In the case of exposure to DR-TB, preventive therapy should be a regimen with activity against the isolate from the source case, for example with levofloxacin [6]. Children started on TPT should be monitored at least monthly during their treatment to evaluate adherence and assess for onset of clinical signs of TB disease.

From a public health standpoint, prevention of MDR-TB requires strong public health infrastructure with reliable active case-finding, contact tracing, access to drug-susceptibility testing, provision of directly observed therapy, and a consistent, funded supply of TB medications. Because TB thrives in poverty and marginalisation, ending the epidemic fundamentally requires ensuring equitable access to healthcare and nutrition, improvements in quality of life, and the realisation of human rights.

Emerging HIV resistance in paediatrics

HIV continues to be a major public health challenge. At present, 37.9 million people are living with the virus, the majority of them in low- and middle-income countries (LMIC), with 68% in sub-Saharan Africa [18]. It is estimated that, globally, 1.7 million children (0–14 years), 1.6 million adolescents (10–19 years) and 3.5 million young people (15–24 years) are living with HIV [18]. In the current era of the Treat All Strategy, all people living with HIV should be commenced on antiretroviral therapy (ART) as soon as possible, regardless of CD₄ count or clinical stage [19]. This strategy is based on years of evidence that early initiation of ART has benefits for the patient and for preventing HIV transmission [20]. With the aim of ending the public health threat posed by the HIV epidemic by 2030, UNAIDS has set key targets that 90% of all people living with HIV are diagnosed, 90% of all those diagnosed will receive sustained ART, and that 90% those receiving ART will achieve viral suppression [21,22]. In this context of widespread scale-up of ART, it is essential also to escalate efforts to identify and combat HIV drug resistance (HIVDR), as well as to study and implement strategies to improve adherence and retention on treatment [23]. This is especially the case for infants, children and adolescents who have lower rates of adherence, retention and viral suppression (VS), placing them at risk of acquired drug resistance (ADR); or those who may experience transmitted drug resistance (TDR), for example, when HIV with resistant mutations is transmitted perinatally [24–27]. Vulnerable groups including infants, children and adolescents must be prioritised to achieve the 90–90–90 goals to improve treatment outcomes and avoid increasing rates of HIVDR which threaten progress to end the global HIV epidemic [24,27].

In the case of ADR, HIVDR may develop during treatment with antiretroviral therapy (ART) or may be detected in ART-naïve persons infected with a virus which already had drug resistance mutations in TDR (Table 3) [28]. Pre-treatment drug resistance (PDR) may be detected when first initiating ART or when reinitiating ART after an interruption of treatment, and may result from ADR or TDR [28]. Recent data have shown alarming trends in global HIVDR [28]. In adults initiating ART between 2014 and 2018, PDR to non-nucleoside reverse-transcriptase inhibitors (NNRTIs) efavirenz and/or nevirapine exceeded 10% in most surveyed countries [28]. In infants and young children (< 18 months) in nine

surveyed countries in sub-Saharan Africa diagnosed with perinatal HIV and newly initiating ART, over half had PDR to efavirenz and/or nevirapine, and in some countries PDR to nucleoside reverse-transcriptase inhibitors (NRTIs) was over 10% [28]. The high prevalence of PDR to nevirapine in infants is largely owing to the use of nevirapine to prevent mother-to-child transmission. Alarming rates of PDR in infants are of particular concern as treatment of paediatric HIV often relies on NNRTI-based or NRTI-based regimens. Recognition of PDR in infants has prompted efforts to adopt non-NNRTI-based paediatric regimens globally [28]. With increasing rates of exposure to antiretrovirals (ARVs) in the global scale-up of universal ART, rates of PDR are projected to increase [28].

Given the alarming rates of HIVDR to NNRTIs in those commencing ART, WHO in 2018 released interim recommendations for switching to dolutegravir-based regimens as the preferred first- and second-line treatments for HIV [29]. Dolutegravir, an integrase strand transfer inhibitor (INSTI), has excellent virological efficacy and safety, and an increased barrier for HIVDR [30]. As WHO rolled out its interim recommendations for dolutegravir-based therapy, a prospective surveillance study in Botswana identified a potential increased risk of neural tube defects (NTDs) in infants born to mothers on dolutegravir-based regimens, prompting initial caution regarding the use of dolutegravir for women of childbearing potential [31]. With further surveillance, the observed prevalence of NTDs associated with dolutegravir decreased from 0.94% to 0.30%, though it remained statistically significant [32]. It is noteworthy that Botswana does not have national folate fortification of food which lowers the prevalence of NTDs [33]. With the potential absolute risk of NTDs being low overall, and given crucial advantages of dolutegravir (i.e. improved maternal health, decreased maternal mortality, decreased vertical transmission), WHO updated its guidance, recommending dolutegravir-based regimens as first-line therapy for all populations, including pregnant women and those of childbearing potential [29]. US-based guidelines provide detailed guidance for selecting ARV regimens for women of childbearing potential, noting both the overall low risk of NTDs associated with dolutegravir and the lack of data regarding potential risks associated with other INSTIs [34]. Current guidelines recommend dolutegravir in children ≥ 3 years of age and weighing ≥ 25 kg; studies are ongoing in infants and young children [30,33,35]. In contrast with other INSTIs, raltegravir can be dosed in infants weighing ≥ 2 kg, though data are currently limited in those <2 years of age. In children and adolescents meeting current requirements for age, weight and viral suppression, INSTI-based fixed-dose combination tablets allow for greatly simplified regimens with excellent safety and virological potency [30].

Children and adolescents have specific challenges and risks that can contribute to ADR. These include complex barriers to adherence, limitations in access to ART medication, a lack of paediatric-friendly formulations and barriers to retention in HIV care [25,36,37]. Measurements of adherence in paediatrics are heterogeneous, and, consequently, estimates of adherence may be wide-ranging [36]. Numerous complex barriers to adherence by children and adolescents include family-level factors, socio-economic factors, disclosure issues, stigma, mental health concerns and medication factors [25,36–39]. Adherence can be particularly challenging as children reach adolescence and as they transition into adult HIV care services [26,38,40,41]. While it is widely recognised that adolescents are at risk of decreased adherence to ART, systematic reviews have demonstrated that current evidence

regarding strategies to improve adherence is limited [36,42,43]. However, some interventions have been identified as warranting further exploration and implementation such as youth-friendly services, peer support, counselling and financial incentives [43].

Young children and adolescents are at risk of loss to follow-up for HIV care [25,26,44,45]. Interruption in treatment can result in rapid clinical deterioration, particularly in young children or children and adolescents with advanced immune suppression, and it can contribute to HIVDR and a poor clinical outcome. Predominant challenges to retention of children and adolescents can include stigma and disclosure issues, illness or death of family members and severe poverty [38,46–48]. Improving retention in care of vulnerable children and adolescents may require improved social and family support such as peer- or family-level interventions, although evidence is very limited [43,47,49,50].

It is hoped that further treatment innovations can address the increasing HIVDR. For example, long-acting injectable antiretroviral therapy may allow durable viral suppression without the adherence challenges of daily medication [51]. The implications for care engagement of such regimens remain to be seen, and also how implementation challenges can be addressed [52,53]. Importantly, however, long-acting injectable regimens may be favourable to young people living with HIV, particularly if they struggle with adherence to daily oral medication [52,54]. Ultimately, research continues towards an HIV vaccine or an HIV cure strategy [55,56].

Emerging gram-negative resistance in paediatrics

The continuing development of antimicrobial resistance of enterobacteriaceae and other bacterial pathogens is a global threat. Clinicians constantly face the challenge that empirical antimicrobial regimens used in the past are no longer as effective. Infections caused by *Escherichia coli* are no longer treated effectively by ampicillin or trimethoprim–sulfamethoxazole. Ampicillin resistance in some institutions is so common that broadspectrum cephalosporins such as ceftriaxone or cefepime are now used in newborn infants with suspected serious bacterial infections. Resistance to gentamicin is also on the rise. This upward trend in resistance forces clinicians to use more broadspectrum antimicrobial agents, creating greater potential for resistance. Infants with UTIs caused by extended-spectrum β -lactamases (ESBL) are requiring treatment with carbapenems such as meropenem. Hospitals with high carbapenem use have more infections caused by *Stenotrophomonas maltophilia*, an organism resistant to all β -lactams. A study in 2003 found that 53% of bacteria causing serious bacterial infections in young infants were ampicillin-resistant, while 78% of pathogens causing meningitis were resistant [57].

What is driving this resistance? Antibiotic pressure in the ‘community’ is known to select for resistance. Clinicians are prescribing antibiotics as ‘prophylaxis’ for young infants with vesicoureteral reflux, a practice well known to select for resistant organisms [58]. Epidemiological studies have shown that ~50% of outpatient antibiotics are inappropriately prescribed, mostly for the treatment of infections caused by viral pathogens such as bronchitis, most episodes of pharyngitis and other upper respiratory tract infections. On any given day, 60% of inpatients are receiving an antimicrobial agent [59]. While for many the

indications for therapy are appropriate, therapy is frequently too broad in coverage and/or the duration of therapy is too long. In a survey of children's hospitals in the US, 35% of children received one or more antibiotic agents. Of those prescribed an antibiotic for an infection, ~25% were prescribed one or more suboptimal antibiotics. Unnecessary therapy corresponded to 11% of prescriptions, while another ~11% received too broad a regimen. Bug-drug mismatch consisted of ~28% of inappropriate regimens [60].

In the past, clinicians' poor understanding of pharmacodynamics resulted in inadequate dosing leading to subtherapeutic troughs which select for resistance. At some healthcare facilities, the spread of resistant organisms was worsened by a lack of effective infection control measures, especially in countries with limited resources. In some countries, the unregulated use of antibiotics outside formal healthcare systems is frequently associated with an increase in antimicrobial resistance [61]. In most LMIC, antibiotic use is common in children under 5 years of age [62]. Undoubtedly, this has led to greater resistance.

Infections caused by multidrug-resistant (MDR) organisms are commonly associated with morbidity requiring prolonged hospitalisation. Previously, these organisms were exclusively hospital-acquired but many are now acquired in the community [63]. In a large cohort of hospitalised patients with MDR infections, 83% of cases were community-acquired. Methicillin-resistant *Staphylococcus aureus* and ESBL *E. coli* infections were the most common. ESBL-producing organisms are frequently resistant to other antimicrobial agents such as trimethoprim-sulfamethoxazole, tetracycline, chloramphenicol and ciprofloxacin [64].

In many countries, enteric pathogens such as campylobacter spp. and salmonella spp. are resistant to fluoroquinolones. In recent years, MDR gram-negative bacilli have been reported in South Asia. Organisms such as NDM-1 (New Delhi metallo-proteinase) *Klebsiella pneumoniae* or *E. coli* have shown resistance to all antimicrobial agents with the exception of tigecycline and colistin. These organisms have spread beyond Asia as a result of frequent international travel [65]. Infections by extensively drug-resistant (XDR) *Salmonella enterica* serotype typhi, a recognised global threat, have been reported in travellers to Pakistan and Iraq where outbreaks are ongoing. These isolates are resistant to ceftriaxone, ampicillin, chloramphenicol, ciprofloxacin and trimethoprim-sulfamethoxazole [66]. Typhi is transmitted through the faecal-oral route after contact with contaminated food and water. Mortality can be high if left untreated. The emergence of these XDR strains is directly related to the use of antibiotics in the community. Azithromycin or carbapenems may be alternative agents to treat these infections [67]. In the Democratic Republic of Congo, ~87% of non-typhoidal salmonella strains are MDR [68].

There are global variations in the incidence of resistant organisms. Methicillin resistance in *Staphylococcus aureus* is more common in Africa than in Asia. Meanwhile, resistance to fluoroquinolones by gram-negative bacilli is more common in Asia [69].

Carbapenem-resistant enterobacteriaceae (CRE) infections in children are becoming more prevalent in many healthcare settings. Because of the limited number of agents available to treat these infections and the failure to institute effective regimens early while susceptibility

data are pending, poor outcomes are common. *K. pneumoniae*, *E. coli* and enterobacter species are among the most common CRE in children. Travel to countries with high numbers of CRE infections is partially responsible for the spread of these organisms throughout the world [65]. CRE and multi-drug resistant *Pseudomonas aeruginosa* can be serious hospital-acquired infections in neonatal intensive care units and paediatric burns units. The production of carbapenemases encoded in highly transmissible mobile elements or by production of extended-spectrum β -lactamases (ESBLs, AmpC β -lactamases) in combination with porin-mediated mutations resulting in poor membrane permeability are responsible for broad resistance to antimicrobial agents [70]. The most commonly reported carbapenemase in children is *Klebsiella pneumoniae* carbapenemase (KPC), an Ambler class A carbapenemase. NDM (New Delhi metallo- β -lactamases or Ambler Class B) carbapenemases, usually endemic in South Asia and the Balkan states, have now spread throughout the world. Unfortunately for clinicians and patients, these carbapenemase-producing pathogens express mutations which cause resistance to other classes of drugs, increasing the difficulty of treating infections. Class D oxacillinase carbapenemases are distributed mostly in the Middle East and the Mediterranean basin. Depending on the minimal inhibitory concentration (MIC) of the organism, extended-infusions of meropenem in combination with an aminoglycoside may be required, or alternative agents such as polymyxin, tigecycline, fluoroquinolone or ceftazidime-avibactam plus aztreonam [70,71]. Newer combination agents such as meropenem–vaborbactam and imipenem–relebactam have been approved for the treatment of these highly resistant pathogens.

In a study at a children's hospital in China, ~72% of gram-negative bacilli were found to be MDR, with ESBLs being most prevalent [72]. Other studies have demonstrated similar findings [73]. In Ethiopia, all isolates of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were resistant to three-to-six antibiotics from different classes. MDR isolates were resistant to at least six different classes [74]. In Nepal, ~62% of isolates of *E. coli*, *K. pneumoniae* and *Klebsiella oxytoca* exhibited multidrug resistance with close to one-third being ESBL-producers [75]. In a study of Finnish travellers, 21% acquired an ESBL-producing enterobacteriaceae organism while abroad [76]. Traveller's diarrhoea (TD) and UTIs were the most common. Receiving an antimicrobial agent, especially for TD, was associated with colonisation with these resistant organisms [77].

With increased migration throughout the world, especially in Europe and within the African continent, antibiotic resistance is common in migrants and refugees in crowded camps. As they seek refuge in countries throughout the world, antibiotic resistance follows [78]. Attention to diagnostic microbiological testing along with enhanced surveillance, hygiene and improved living conditions will help diminish this threat. In refugee camps in Ethiopia, strains of salmonella and shigella demonstrate high rates of resistance to ampicillin and amoxicillin, chloramphenicol and trimethoprim–sulfamethoxazole, all frequently used to treat these infections [79].

Misuse of antibiotics in humans and animals and their presence in the environment are responsible for the emergence of resistance [80]. Food contamination with resistant organisms with poor food preparation, along with widespread environmental pollution, especially in LMIC, contribute to their sustainment and eventual spread. Disposal of

inadequately treated water and contact with animal waste and inappropriately disposed of medical waste worsen the problem. An increase in small-scale farming in countries with limited resources has resulted in an increase in resistant organisms as antibiotic agents are frequently used and families live closer to their herds and flocks. A good example of this is the observation that backyard chickens in Ecuador were found to be a source of resistant organisms [81].

The introduction of rapid diagnostic tests which provide susceptibility determinants combined with antimicrobial stewardship programmes which emphasise the correct selection and use of antibacterial therapy in inpatient and outpatient settings is certain to decrease the emergence of resistant pathogens. While initial investment in these diagnostic strategies may seem expensive, the resulting reduction in hospitalisations, during of hospital stays, complications, need for prolonged courses of broad antibiotic regimens and mortality will soon decrease healthcare expenditure. The application of correct infection control measures such as hand hygiene will have further benefits [82].

Recent antibiotic consumption is associated with the carriage of resistant respiratory pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae* [83]. Widespread vaccination against these will reduce the infection burden caused by resistant organisms. This is most critical in LMIC where antibiotic use and resistance is highest. Use of pneumococcal conjugate and live attenuated rotavirus vaccines had a ~ 20% protective effect against antibiotic-treated episodes, preventing millions of antibiotic-treated illnesses in children under 5 years of age [84]. The routine use of a typhoid conjugate vaccine effective in young children would also be of significant benefit. The vaccination of over 10,000 children in Nepal showed a vaccine efficacy of ~81% in preventing blood culture-confirmed typhoid fever [85]. The immunogenicity of the vaccine was excellent with a safety profile similar to that of the placebo group. Similar results were observed in an earlier study in Vietnam [86]. Only the introduction of engineering controls such as more space between patients, more wash-hand basins or hand sanitizer for proper hand hygiene and greater availability of single-use sterile items such as endotracheal, nasogastric and suction tubes will help reduce the spread of resistant germs in healthcare settings. Achieving good source control will lead almost always to shorter durations of therapy.

Antimicrobial stewardship (AMS) programmes have been shown to be effective in reducing the unnecessary use of agents such as carbapenems, fluoroquinolones and vancomycin. AMS programmes have taught clinicians how to appropriately dose agents using sound pharmacodynamic parameters, including the use of order sets. Educational and enhanced prescriptive programmes to control access to certain agents with greater potential for pressuring resistance have been implemented. Even when dosing is appropriate, resistance can develop, frequently emerging as a result of prolonged antibiotics, or secondary to poor source control. An undrained abscess is a major source of resistance [87]. Shorter courses of antibiotic therapy have been shown to be as effective as longer courses, and they have less tendency to select resistance. Hospital-acquired pneumonia can be treated with only 7 days of therapy rather than longer courses. Longer courses are reserved for specific organisms such as *Pseudomonas aeruginosa*.

While the unnecessary use of antibiotic agents in the community is a major risk factor for the development of resistance, well targeted mass-distributed antimicrobial agents may have a beneficial effect in LMIC, resulting in a reduction of infections and mortality. The mass distribution of azithromycin over 3 years in over 300 communities in Niger resulted in a third fewer deaths from meningitis and dysentery in children aged 1–59 months, and a fifth fewer deaths secondary to malaria and pneumonia [88]. The Mortality Reduction after Oral Azithromycin (MORDOR) study published in 2018, a randomised trial assessing the effect of broad-spectrum antibiotic therapy on childhood mortality in sub-Saharan Africa, demonstrated that azithromycin resulted in a 13.5% lower mortality rate compared with placebo in Niger, Malawi and Tanzania. The greatest effect was in children aged 1–5 months. A follow-up study showed that the effect was sustained 3 years later [89]. However, the administration of amoxicillin to children in Niger failed to demonstrate benefits in respect of nutritional recovery in children with severe acute malnutrition [90].

Addressing globally emerging antimicrobial resistance in paediatrics

Global burdens of drug-resistant TB, HIV and gram-negative pathogens have a particular impact on infants, children and adolescents, necessitating a paediatric-focused agenda for emerging resistance (Table 4). As illustrated by the challenges highlighted above, there are several key targets for such an agenda from a global health perspective. Most central is to ensure quality of care for children and adolescents with infectious diseases across several fronts. Significantly increasing equitable access to key diagnostics will improve ascertainment of infections and identification of resistance, and allow de-escalation of antibiotics when appropriate. Furthermore, there is a critical need to expand AMS and infection prevention programmes, including in LMIC where relatively few are in place. Overall, health system strengthening is needed to support each of these key elements to address and prevent emerging resistance in paediatric infections.

Including the needs of children, adolescents and pregnant women in research agendas is critical to preventing and treating resistant infections. Finding ways to increase access to research studies, including clinical trials, will generate evidence for use of novel treatments or strategies in these groups. Further study and implementation of care models and strategies for child- or adolescent-centred management of infections such as HIV and TB can critically improve paediatric outcome and avoid development of resistance.

To address the particular burden that resistant infections place on children and adolescents, advancement of global public health agendas and priorities concerning emerging resistance of paediatric infections is needed. This has become even more essential in the current global pandemic of a novel coronavirus, SARS-CoV-2, which threatens to disrupt health systems and services for vulnerable populations, including children and adolescents with infectious diseases. This is a critical time to fight a potential surge in the incidence of dangerous, resistant infections, and the case for strengthening health systems, global public health and disease surveillance and a global infectious disease research agenda could not be stronger.

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Abbreviations

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| ADR | acquired drug resistance |
| AMS | antimicrobial stewardship |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| CRE | carbapenem-resistant enterobacteriaceae |
| DR-TB | drug-resistant TB |
| ESBL | extended-spectrum beta-lactamase |
| HIV | human immunodeficiency virus |
| HIVDR | HIV drug resistance |
| IGRA | interferon-gamma release assay |
| INSTI | integrase strand transfer inhibitor |
| KPC | <i>Klebsiella pneumoniae</i> carbapenemase |
| LMIC | low- and middle-income countries |
| MIC | minimal inhibitory concentration |
| MDR | multidrug-resistant |
| MDR-TB | multidrug-resistant TB |
| NDM | New Delhi metallo- β -lactamase |
| NDM-1 | New Delhi metallo-proteinase-1 |
| NRTI | nucleoside reverse-transcriptase inhibitors |
| NNRTI | non-nucleoside reverse-transcriptase inhibitor |
| NTD | neural tube defect |
| PDR | pre-treatment drug resistance |
| RR-TB | rifampin resistance |
| TB | tuberculosis |
| TD | traveller's diarrhoea |

| | |
|-------------------|-----------------------------------|
| TDR | transmitted drug resistance |
| TPT | TB preventive therapy |
| TST | tuberculin skin testing |
| UTI | urinary tract infection |
| VS | viral suppression |
| XDR | extensively drug-resistant |
| XDR-TB | extensively drug-resistant TB |
| pre-XDR-TB | pre-extensively drug-resistant TB |

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Table 1.

Definitions of DR-TB according to the World Health Organization [9].

| Category | Definition |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| Drug-resistant TB (DR-TB) | Resistance to any anti-TB medications |
| Isoniazid-monoresistant TB | Resistance to isoniazid Susceptibility to rifampin (rifampicin) |
| Rifampin-resistant TB (RR-TB) | Resistance to rifampin ^a |
| Multidrug-resistant TB (MDR-TB) | Resistance to at least isoniazid and rifampin |
| Pre-extensively drug-resistant TB (Pre-XDR-TB) | MDR-TB <i>and</i> Resistance to a fluoroquinolone <i>or</i> to a 2nd-line injectable agent (amikacin, capreomycin, or kanamycin) |
| Extensively drug-resistant TB (XDR-TB) | MDR-TB <i>and</i> Resistance to a fluoroquinolone <i>and</i> Resistance to a 2nd-line injectable agent (amikacin, capreomycin, or kanamycin) |

^aRequires treatment with second-line agents.

Table 2.

Key clinical pearls in the diagnosis and management of DR-TB in children.

Key clinical pearls

Consult with experts in paediatric TB on diagnosis and management, particularly for cases of DR-TB.

Clinical guidelines have been published regarding TB diagnosis and treatment [6,12,14].

Diagnosis and evaluation

TB is a clinical diagnosis based on clinical findings, epidemiological context and likelihood of exposure, risk factors for progression to TB disease and laboratory/radiographical evaluations. Negative TB testing does not preclude a TB diagnosis.

A high index of suspicion is critical to diagnosis of paediatric TB and identification of DR-TB.

Children may present with pulmonary or extrapulmonary disease. TB in children can be challenging to diagnose and may carry a poor diagnosis if diagnosed late.

Infants must have CSF studies performed to evaluate for TB meningitis as part of their diagnostic evaluation. A low threshold to obtain CSF studies in young children is recommended.

Seek culture data from a likely source case whenever possible.

HIV testing should be done when evaluating for TB in any age group.

TB in children represents recent TB transmission. A careful history may reveal TB exposure, including to contact with chronic cough not yet diagnosed with TB. All family members and close contacts should be evaluated.

Management

Clinical guidelines review the current evidence base and guide the composition of a regimen for MDR-TB with drugs to which the specific TB isolate is probably susceptible [6].

Treatment courses for MDR-TB are prolonged and can be as long as 2 years. Optimal treatment duration and all-oral treatment regimens are currently being studied.

Preventing TB

Children exposed to pulmonary TB should be carefully evaluated for TB disease and, in the absence of evidence of TB, should be commenced on TB preventive therapy (TPT).

Children exposed to pulmonary DR-TB found not to have TB disease should be commenced on TPT with activity against DR-TB.* They should be monitored at least monthly during treatment to assess adherence and for clinical signs of TB.

* For example, with levofloxacin. Refer to clinical guidelines [6] and current evidence in choosing a TPT regimen. Note: These are not comprehensive, and consultation should always be sought from an expert in paediatric TB and with reference to current clinical guidelines.

Table 3.

Definitions of HIVDR according to the World Health Organization [28].

| Category | Definition |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acquired HIV drug resistance (ADR) | Resistance that develops because of viral replication in the presence of antiretroviral (ARV) drugs. |
| Transmitted HIV drug resistance (TDR) | Resistance detected among ARV drug-naive people with no history of ARV drug exposure owing to infection with virus with drug resistance mutations. |
| Pretreatment HIV drug resistance (PDR) | Resistance detected in those initiating or reinitiating 1st-line ART with some previous ARV drug exposure. Can be TDR, ADR or both. (Previous ARV exposure may include previous ARVs for preventing mother-to-child transmission, pre- or post-exposure prophylaxis or previous 1st-line ART with interruption of treatment.) |

Adapted from WHO [28].

Table 4.

Key priorities of a paediatric-focused agenda to address emerging resistance of TB, HIV and gram-negative pathogens.

| Priorities |
|------------------------------------------------------------------------------------------------------------------------------------------------|
| Ensure equitable access to and development of infectious diagnostics. |
| Develop and expand antimicrobial stewardship in inpatient and community settings in low-, middle- and high-income countries. |
| Support and expand infection prevention and control strategies for clinic and hospital sites. |
| Improve recognition and management of resistant infections. |
| Study and implement child- and adolescent-centred care models for managing infections such as HIV and TB. |
| Increase access to research, including clinical trials of new treatment regimens and strategies, for children, adolescents and pregnant women. |
| Ensure an antimicrobial pipeline for novel treatment of resistant infections. |
| Support global public health agendas to tackle resistant infections in children and adolescents. |
