Antibiotic Resistance in Paediatric Patients

Mohammad Azeem[1], Namita Arora[2], Pankaj Arora[2], Ume Kulsum[3], Rolla Mohammed Ahmad Alfahhad[1]

Affiliation:
[1]Maternity and Children Hospital, Buraidah, al qaseem, KSA
[2]Lords University Alwar-Bhiwadi-Delhi Highway, Chikani, Alwar, Rajasthan, India
[3]ChhatrapatiShivaji Institute of Pharmacy, Balod Rd, Shivaji Nagar, Durg, Chhattisgarh 491001
E-mail id of author(s):
Mohammad Azeem: drmohdazeemcp@gmail.com
NamitaArora: me_arora2005@rediffmail.com
PankajArora: pankaj_arora1111@yahoo.com
Ume Kulsum: umekulsum123@gmail.com
Rolla Mohammed Ahmad Alfahhad: ro-olla@hotmail.com

Corresponding Author:
Name: Namita Arora
Address:Professor, Faculty of Pharmacy, Lords UniversityAlwar-Bhiwadi-Delhi Highway, Chikani, Alwar, Rajasthan, India - 301028
E-mail address:me_arora2005@rediffmail.com

Abstract

The threat of antibiotic resistance to public health is of the utmost concern, particularly for young children. According to data from the WHO, infections brought on by multidrug resistant bacteria result in 700,000 deaths worldwide each year, including about 200,000 infant deaths. The multifaceted roots of this escalating problem are unique to children's ages.Lack of pediatric-specific data and trials also contributes to the problematic abuse and misapplication of antibiotics including incorrect diagnoses and indications, or at the incorrect dosage. The constantly changing nature of this age group also raises another problem: the partly age-dependent variations of aevolving system of cytochromes regulate a rather assorted population in terms of biochemical traits and pharmacokinetics profiles, making it challenging to easily codify in an age- or weight-dependent dosage.The current clinical and molecular information on paediatric antibiotic-resistant bacterial infections is highlighted in this article, with a focus on communicable resistance and spread via horizontal gene transfer.

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Introduction

One of the biggest coercions to modern public health is antibiotic resistance. Antimicrobial resistance (AMR) is currently one of the biggest global public health coercions, and all healthcare professionals and institutions should consider giving it special emphasis. Though antibiotic-resistant bacteria have been around for millions of years, they have typically only been found in the environment.

The discerning pressure produced by the widespread use of antibiotics in veterinary, human, steers, and agricultural practises is what has induced antibiotic resistance in bacteria to be at the forefront of medicine over the past 70 years. As a result, the number of multi-drug resistant organisms (MDROs) has increased globally in all people, including children. In order to comprehend the importance of the threat posed by AMR, the WHO assessed thatinfections introduced by multidrug resistant (MDR) bacteria result in 700,000 deaths worldwide annually, of which about 200,000 are infant deaths [1]. MDR infections in paediatric patients in Europe may account for up to 30% of all cases [2]. 90% of new-borns with sepsis who were hospitalised in ICU in parts of the Middle East had resistant bacteria [3]; in some parts of South East Asia, 83% of children have E. coli that is resistant to first-line antibiotics [4]; in Sub-Saharan Africa, 66% of neonatal sepsis and meningitis were found to be instigated by antibiotic-resistant bacteria [5]; and in a study conducted in the USA, 20% of paediatric patients who received [6].

Multidrug-resistant organisms (MDROs) are becoming more and more common, and they are linked to significant morbidity and mortality among those who are infected. With a 20% upsurge in span of stay and ainferior outcome, MDR infections are more grim to treat and are closely linked with a added serious and protracted illness that lengthens hospital stays and increases mortality by up to 40% in MDR hospital-acquired infections [7]. Our present condition is problematic, and it threatens our future. It has many different, interrelated causes. A period of antibiotic exploitation in husbandry, steers, veterinary, and human medical practises began after World War II, despite Alexander Fleming's 1945 warning to the scientific and medical communities about antibiotic abuse. The main cause of bacterial resistance evolution was this abuse [9]. Additionally, medical malpractice increased the risk of certain MDR bacterial strains by improperly prescribing antibiotics, which has been seen in 30% to 60% of both inpatient and outpatient antibiotic treatments in some studies [10]. Present study will discuss epidemiology of antibiotic resistance in gram positive and negative bacteria with emerging threat.

Epidemiology of Antibiotic Resistance in Gram Positive Bacteria

Staphylococcus aureus

In the 1960s, methicillin-resistant S. aureus (MRSA) strains were recognized as a clinical peril in populations of adult patients. MRSA infections were relatively rare in children up until the 1990s, when infections (primarily in the skin and soft tissues) were noticed in people of all ages who hadn't previously had any contact with a healthcare provider [11]. These strains were then called community-associated MRSA (CA-MRSA). Healthcare-associated (HA-MRSA) infections continued to plague hospitalised patients as CA-MRSA infections rose, leading to a conflicting epidemiology of MRSA infections in healthcare settings. HA-MRSA and CA-MRSA strains were distinct during the early stages of the community epidemic; nevertheless, recent molecular studies of MRSA infection patients have revealed that CA-MRSA strains are now a communalroot of MRSA infections attained in healthcare settings, blurring the distinction. [12]

The primary change causing resistance in CA-MRSA and HA-MRSA is a single penicillin-binding protein (PBP2a), which is prearranged by the mec gene12. PBPs, which are found on the surface of bacteria, catalyse transglycosylation and transpeptidation, offering defense [13]. The staphylococcal cassette chromosome mec (SCCmec) genetic element, which contains the mec gene, has been the subject of at least 11 reports. Gene cassettes that confer resistance to multiple classes of antibiotics are frequently found in HA-MRSA strains, which restricts treatment options to more expensive or antibiotics with questionable safety profiles. SCCmec types I to III are typically present in HA-MRSA strains in North America, whereas SCCmec type IV is frequently found in CA-MRSA. Studies on CA-MRSA infections in American children typically point out the sharp rise in infections from the mid-1990s to 2005-2006, followed by a decline in infection rates thereafter [14]. Thoughmutually paediatric HA-MRSA and CA-

MRSA infection rates have largely stabilised, there is still a significant geographic variation, and some areas have seen ongoing CA-MRSA infection increases [15,16].

When treating CA-MRSA, the drugs trimethoprim-sulfamethoxazole (TMP/SMX) and clindamycin are frequently used. Over the past ten years, however, resistance to both clindamycin and TMP/SMX has increased in both CA-MRSA and methicillin-sensitive S. aureus (MSSA). According to a current study from the U.S. Military Health System, the percentage of CA-MRSA that was resistant to clindamycin rose from 9.3% in 2005 to 16.7% in 2014 [14].

Application of mupirocin ointment into the anterior nares is one of the infection prevention strategies used to aidexterminate MRSA carriage and rheostat spread, frequently in unification with chlorhexidine baths to further abridge colonisation burden. While decolonization efforts have successfully lowered MRSA infection rates, mupirocin and chlorhexidine resistance have started to appear. The plasmid-based mupA gene, which confers resistance by encoding a novel RNA synthetase, is the main contributor to the rise in mupirocin resistance. The qacA/B chlorhexidine resistance genes, which code for efflux pumps, are also plasmid-mediated. Studies on paediatric MRSA isolates have found that resistance rates array from 2% in St. Louis and the northwest U.S. to 19% in the south [17,18].

Streptococcus pyogenes

Since all clinical isolates of Streptococcus pyogenes are penicillin-susceptible, macrolides are sporadically used to treat infections, predominantly in individuals with unembellished penicillin allergies. Following a sharp rise in the prescription of macrolides for upper respiratory infections in the 1980s, selective pressure led to the emergence of macrolide-resistant strains of S. pyogenes in the clinical setting [19,20]. S. pyogenes uses two main mechanisms to resist macrolides. The first mechanism results in co-resistance to macrolide, lincosamide, and streptogramin (MLS) antibiotics by methylating the 23S ribosomal RNA by erm genes (MLS phenotype). MLS resistance can be inducible (MLSi) or constitutive (MLSc) (MLSi). The second, more prevalent mechanism is a mef gene-related active efflux pump (M phenotype), which is connected to enzymes encoded by mef genes. Double-disk diffusion testing (D-test), which assesses clindamycin (lincosamide) susceptibility in the existence of erythromycin resistance, is frequently used to distinguish between M and MLS phenotypes [19,20].

According to projections, there is presently 5% more macrolide resistance in the U.S. than there was in the 1990s. Since there have been instances of children who were given macrolides for S. pyogenes pharyngitis who later developed acute rheumatic fever, it is clear how clinically significant this resistance is. Overall, there are significant regional variations in the prevalence of macrolide resistance in paediatric S. pyogenes isolates, with reported rates ranging from 2.6% in Germany to as high as 95% in studies of Chinese children [19,20].

Streptococcus pneumoniae

S. pneumoniae passes on penicillin resistance via PBPs, much like S. aureus does. However, circulating penicillin-resistant S. pneumoniae are significantlyassorted than MRSA, where resistance is primarily brought about by the spread of clonal strains24. S. pneumoniae, like S. pyogenes, can prompt the M and MLS phenotypes, which confer confrontation to macrolides and clindamycin [21,22].

The beginning of the twenty-first century witnesses an increase in penicillin and macrolide resistance across the globe. However, after the starter of pneumococcal vaccines, infection rates overall and with penicillin-resistant serotypes substantiallyreduced. Laterwith the starter of the 7-valent vaccine (PCV7), early studies conducted in the United States noted a temporary decline in pneumococcal activity, with residually high resistance by serotypes not protected by PCV7 [23]. One of the most dangerous (and resistant) circulating serotypes decreased as a result of serotype 19A being roofed by the 13-valent vaccine (PCV13), and since 2010, there has been a general decline in non-susceptible invasive

pneumococcal infections. There are still regional variations in the amount of antibiotic-resistant S. pneumoniae in circulation, but this resistance doesn't seem to be linked to a dominant non-vaccine serotype [24].

Notable Antibiotic Resistance

Mycoplasma pneumoniae

The number of reports of infections with macrolide-resistant Mycoplasma pneumoniae has increased since the turn of the century. A point mutation in the 23S ribosome, which results in ineffective antibiotic binding, is the cause of resistance to macrolides. Globally, there are diverse patterns of M. pneumoniae isolate resistance. Macrolide resistance in Mycoplasma may reach 90% in Asian nations where macrolides are frequently prescribed [25]. Although resistance may be increasing, macrolide resistance in M. pneumoniae has remained relatively low in the United States. Approximately 13% of M. pneumoniae isolates from 6 paediatric centres in the United States were found to be resistant to macrolides in a recent study. Tetracyclines or quinolones are frequently used to treat macrolide-resistant Mycoplasma infections, but their indications in young patients are constrained due to their side effect profiles. As a result, monitoring M. pneumoniae that is resistant to macrolides could become more crucial [26].

Epidemiology of Antibiotic Resistance in Gram Negative Bacteria

Fluoroquinolone Resistance

Fluoroquinolone antibiotic resistance (FQR) is frequently caused by changes in porins, efflux pumps, and genes encoding the gyrase or topoisomerase enzymes (gyrA/parC). For non-lactose fermenting gram-negative bacilli (GNB), like Pseudomonas and Acinetobacter species, this is primarily chromosomally based resistance. FQR genes are widespread among Enterobacteriaceae and can be carried on plasmids (PMFQR). Acetyltransferases, efflux pumps, and pentapeptide proteins are some of the mechanisms by which PMFQR is connected to antibiotic use in agriculture and veterinary medicine. In isolates with both PMFQR and chromosomal mechanisms present, FQR levels may be high [27].

There is a lack of information on FQR GNB infections in the paediatric population, and even though quinolones are rarely prescribed to younger children, they are still a problem since they are given to adolescents for the treatment of certain conditions and for MDR GNB infections. A major U.S. medical center's FQR in GNB is believed to range between 5 and 14 percent, according to data available [28]. Additionally, this upward trend may be a result of rising PMFQR in MDR Enterobacteriaceae found in children both locally and internationally [29,30]. Studies from Asia have found significant PMFQR in enterobacteriaceae infections in children, with prevalence rising over time and ranging from 10% in Korea to 23% in China [31,32].

Beta-Lactam Resistance

The discovery of ampicillin-resistant Haemophilus influenzae meningitis in 1974 was one of the first notable paediatric clinical effects of beta-lactam resistance caused by lactamases in GNB [33].

Since then, GNB has continued to adapt in response to the rise in -lactam usage and the development of broad-spectrum -lactams; as a result, the numeral of -lactamase genes in GNB has now exceeded 2,100 [34]. These -lactamase genes were originally chromosomally-based and narrow-spectrum, but the existing pandemic of Enterobacteriaceae (ENT) that produce -lactamases is caused by the sharp rise in transmissible ESBL and carbapenemase genes.

The Bush-Jacoby-Medeiros classification system classifies -lactamase genes according to their substrate and inhibitor roles, while the Ambler classification classifies them according to their amino acid motifs. In 1983, a single nucleotide polymorphism in Germany led to the emergence of a transferable SHV gene, which led to the discovery of the first organisms carrying ESBL genes [35]. Up till the appearance of CTX-M-type ESBLs in the mid-1990s, SHV- and TEM-type ESBLs harboring GNB were the primary basis of transmissible -lactam resistance. A clonal lineage of E. coli is primarily linked to the CTX-M pandemic (known as ST131). These clonal strains are

MDR and contain additional plasmids that produce resistance to aminoglycosides, TMP/SMX, and fluoroquinolones. Clade C, ST131-H30 E. coli strains are one such strain that falls under this category.Ambler classes A, B, or D are used to categorise carbapenemases based on their molecular structures. While Class B, the metallo—lactamases (MBLs), need zinc for -lactam hydrolysis, Class A and D carbapenemases need serine at their active sites. Metal-chelating substances like ethylenediaminetetraacetic acid inhibit MBL activity (EDTA).

The Klebsiellapneumoniaecarbapenemases (KPC), which are the most notable Class A carbapenemases, frequently acquire resistance to various (>3) antibiotic classes, making them MDROs [36]. K. pneumoniae strains belonging to clonal complex 258 and, moreexplicitly, ST258 strains carrying a KPC-2 or KPC-3 gene institute on a Tn3-based transposon, Tn4401, are the main causes of the comprehensiveblowout of KPC-Ent. The spread of KPC genes is much more complicated, and the two main strains of ST258 K. pneumoniae (I and II) belong to separate genetic clades [37]. In addition, strains with various categorization have been linked to KPC deportment and a variety of plasmids [36,38].

The Class B metallo-lactamases are a distinct group, and some prominentcontagious MBL genes are IMP (active on imipenem), NDM (New-Delhi MBL), and VIM (Verona integron-encoded MBL) [36]. Class 1 integrons often include VIM-type and IMP-type MBLs that are accompanying to plasmids or transposons that promote spread [39]. The NDM-type MBL are a serious global threat because they have spread extensively among Enterobacteriaceae in less than ten years. The NDM-1 gene, which is the most prevalent NDM MBL gene in circulation, is thought to have descended from Acinetobacterbaumannii [40]. Numerous epidemic clones have been found to contain NDM-type MBL genes, and it is believed that the bacterial promiscuity of the genetic components facilitates the quick and theatricalblowout of NDM MBLs.

Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae

As a result of the current ESBL-Ent pandemic introduced by the blowout of MDR ST131 CTX-Mproducing E. coli strains, the prevalence of ESBL-producing Enterobacteriaceae (ESBL-Ent) infections in the paediatric populace has sharply augmented in the U.S. over the past ten years [40].

By region, age, healthcare exposure, organism, and ESBL genotype, the acquisition of ESBL-Ent significantly varies. Younger gestational age, protracted mechanical ventilation, low birth weight, and antibiotic use are menaceaspects for infection in this populace. International studies report an upsurge in ESBL-Ent colonisation and infection in the neonatal population in healthcare settings. However, data from the United States indicate that children aged 1 to 5 are at the greatest risk [41]. The menaceaspects for ESBL-Ent infections outside of the neonatal period are more similar to those of the adult population and compriserevelation to antibiotics, chronic illnesses, healthcare exposure, and recurrent infections. Children may be particularly at risk for neurologic conditions [42,43]. However, the majority of available data have not distinguished genotype-specific risk factors for ESBL-Ent infection [44].

AmpCCephalosporinase Producing Enterobacteriaceae

In a study of four paediatric medical centres in three distinct U.S. regions, extended-spectrum cephalosporin-resistant (ESC-R) E. coli and Klebsiella sp. isolates had AmpC genes in 29% of them, and the CMY-2 gene was responsible for 87% of the AmpC phenotype. The majority of CMY-2constructing isolates were found in the West. The prevalence of AmpC genes in ESC-R isolates from children was 14.2% in the six-center Chicago area study, and the ACT/MIR-type AmpC genes dominated (78%) [45].

Emerging Threat

A list of bacteria for which new antimicrobials are instantlydesired was recently published by the WHO. This is a result of the observation that the pipeline for new antibiotics in research and development is steadily drying

up, which contrasts sharply with the alarming increase in infections with resistant organisms. Oral formulations for community-acquired infections with increasedindisposition, such as drug-resistant ESBL-producing Enterobacteriaeceae, Neisseria gonorrhoeae, and Salmonella typhi, are the utmostimperativerequests in terms of antibiotics R&D for the paediatric populace [46].

Colistin Resistance

A multi-centered, paediatric case-series found that 4% of children experienced neurotoxicity and 22% of children experienced nephrotoxicity as a result of the use of polymixins (polymixin B and colistin). Polymixins are therefore only used in MDR GNB infections and when less toxic alternatives have been exhausted [47]. The majority of polymixin resistance is chromosomally based, and it is linked to changes in the mgrB gene, PmrAB or PhoPQ two-component systems, or both. However, the mcr-1 gene was linked to numerous plasmid backbones in 2016, the year of the first reports of plasmid-mediated colistin resistance in Enterobacteriaceae. Colistin therapy has long been used in veterinary and agricultural settings, and resistance to it has been connected to animal sources [48,49].

Three mobile colistin resistance genes (mcr-1 to mcr-3) have so far been identified, mostly in E. coli. Only one report of a child in China having plasmid-mediated colistin-resistant E. coli in their stool supports the notion that plasmid-mediated colistin resistance is uncommon in the paediatric population [50].

Conclusion

Bacterial antibiotic resistance is still evolving and poses an increasing risk to all populations, including children. A timely approach to prevention and treatment may be possible if this comprehensive public health peril is identified through molecular and clinical epidemiologic studies, as well as focused surveillance. Multiple strategies should concentrate on education and training, bundled infection deterrence measures, antibiotic stewardship programmes, and addressing modifiable risk factors for infection to reduce the spread of these dangerous organisms. To stop the blowout of these dangerous pathogens in our most vulnerable populace, national and international programmes, particularly those devoted to children's health, must raise awareness and allocate targeted resources.

References

1. *4th Global Conference of Women Deliver.* WHO Regional Office for Europe; Copenhagen, Denmark: 2016. [(accessed on 18 Feb. 23)]. Fight Antimicrobial Resistance: Protect Mothers and Newborns. Available online: http://who.int/drugresistance/activities/Women-Deliver-AMR-side-event-Handout-May2016.pdf?ua=1
2. Cassini A., Högberg L.D., Plachouras D., et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: A population-level modelling analysis. *Lancet Infect. Dis.* 2019;19:56–66. doi: 10.1016/S1473-3099(18)30605-4.
3. Al Jarousha A.M., El Jadba A.H., Al Afifi A.S., El Qouqa I.A. Nosocomial multidrug-resistant Acinetobacterbaumannii in the neonatal intensive care unit in Gaza City, Palestine. *Int. J. Infect. Dis.* 2009;13:623–628. doi: 10.1016/j.ijid.2008.08.029.
4. Le Doare K., Barker C.I., Irwin A., Sharland M. Improving antibiotic prescribing for children in the resource-poor setting. *Br. J. Clin. Pharmacol.* 2015;79:446–455. doi: 10.1111/bcp.12320.
5. Okomo U., Akpalu E.N.K., Le Doare K., et al. Aetiology of invasive bacterial infection and antimicrobial resistance in neonates in sub-Saharan Africa: A systematic review and meta-analysis in line with the STROBE-NI reporting guidelines. *Lancet Infect. Dis.* 2019;19:1219–1234. doi: 10.1016/S1473-3099(19)30414-1.
6. Tamma P.D., Newland J.G., Pannaraj P.S. et al. The use of intravenous colistin among children in the United States: Results from a multicenter, case series. *Pediatr Infect. Dis. J.* 2013;32:17–22. doi: 10.1097/INF.0b013e3182703790.

7. Naylor N.R., Atun R., Zhu N.,et al. Estimating the burden of antimicrobial resistance: A systematic literature review. *Antimicrob. Resist. Infect. Control.* 2018;7:58. doi: 10.1186/s13756-018-0336-y.
8. Travers K., Barza M. Morbidity of infections caused by antimicrobial-resistant bacteria. *Clin. Infect. Dis.* 2002;34:S131–S134. doi: 10.1086/340251.
9. Ventola C.L. The antibiotic resistance crisis: Part 1: Causes and threats. *Pharm. Ther.* 2015;40:277–283.
10. Davies J., Davies D. Origins and evolution of antibiotic resistance. *Microbiol. Mol. Biol. Rev.* 2010;74:417–433. doi: 10.1128/MMBR.00016-10.
11. Luyt C.E., Bréchot N., Trouillet J.L., Chastre J. Antibiotic stewardship in the intensive care unit. *Crit. Care.* 2014;18:480. doi: 10.1186/s13054-014-0480-6.
12. CDC Report: Antibiotic Resistance Threats in the United States. [(accessed on 18 February 2023)];2013 Available online: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
13. Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA. 1998; 279:593–8
14. Popovich KJ, Weinstein RA, Hota B. Are community-associated methicillin-resistant Staphylococcus aureus (MRSA) strains replacing traditional nosocomial MRSA strains? Clin Infect Dis. 2008; 46:787–94.
15. Sauvage E, Kerff F, Terrak M, et al. The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis. FEMS Microbiol Rev. 2008; 32:234–58.
16. Sutter DE, Milburn E, Chukwuma U, et al. Changing susceptibility of Staphylococcus aureus in a US pediatric population. Pediatrics. 2016; 137:e20153099.
17. David MZ, Daum RS, Bayer AS, et al. Staphylococcus aureusbacteremia at 5 US academic medical centers, 2008–2011: significant geographic variation in community-onset infections. Clin Infect Dis. 2014; 59:798–807
18. Iwamoto M, Mu Y, Lynfield R, et al. Trends in invasive methicillin-resistant Staphylococcus aureus infections. Pediatrics. 2013; 132:e817–e824.
19. Fritz SA, Hogan PG, et al. Mupirocin and chlorhexidine resistance in Staphylococcus aureus in patients with community-onset skin and soft tissues infections. Antimicrob Agents Chemother. 2013; 57:559–68.
20. McNeil JC, Hulten KG, Kaplan SL, et al. Mupirocin resistance in Staphylococcus aureus causing recurrent skin and soft tissue infections in children. Antimicrob Agents Chemother. 2011; 55:2431–3
21. Green MD, Deall B, Marcon MJ, et al. Multicentre surveillance of the prevalence and molecular epidemiology of macrolide resistance among pharyngeal isolates of group A Streptococci in the USA. J AntimicrobChemother. 2006; 57:1240–3.
22. Logan L, McAuley J, Shulman S. Macrolide treatment failure in Streptococcal pharyngitis resulting in acute rheumatic fever. Pediatrics. 2012; 129:e798–802
23. Hakenbeck R, Briese T, Chalkley L, et al. Antigenic variation of penicillin-binding proteins from penicillin-resistant clinical strains of Streptococcus pneumoniae. J Infect Dis. 1991; 164:313–9.
24. Stephens DS, Zughaier SM, Whitney CG, et al. Incidence of macrolide resistance in Streptococcus pneumoniae after introduction of the pneumococcal conjugate vaccine: population-based assessment. Lancet. 2005; 365:855–63.
25. Tanz RR, Shulman ST, Shortridge VD. Community-based surveillance in the United States of macrolide-resistant pediatric pharyngeal group A Streptococci during 3 respiratory disease seasons. Clin Infect Dis. 2004; 39(12):1794–801.
26. Tomczyk S, Lynfield R, Schaffner W, et al. Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. Clin Infect Dis. 2016; 62:1119–25
27. Meyer Sauteur PM, van Rossum AM, Vink C. Mycoplasma pneumoniae in children:

carriage, pathogenesis, and antibiotic resistance. CurrOpin Infect Dis. 2014; 27:220–7.
28. Zheng X, Lee S, Selvarangan R, et al. Macrolide-resistant Mycoplasma pneumoniae, United States. Emerg Infect Dis. 2015; 21:1470–2.
29. Hawkey PM. Mechanisms of quinolone action and microbial response. J AntimicrobChemother. 2003; 51(Suppl 1):29–35.
30. Jackson MA, Schutze GE. Committee on infectious diseases. The use of systemic and topical fluoroquinolones. Pediatrics. 2016; 138:e20162706.
31. Logan, LK., Hujer, AM., Marshall, SM., et al. ASM Microbe 2016. Boston, MA: Fluoroquinolone Resistance (FQR) Mechanisms in Extended-Spectrum Beta-Lactamase producing Enterobacteriaceae (Ent) Isolates from Children.
32. Medernach, RL., Rispens, JR., Marshall, SH., et al. ASM Microbe. New Orleans, LA: 2017. Resistance Mechanisms and Factors associated with Plasmid-Mediated Fluoroquinolone Resistant (PMFQR) Enterobacteriaceae (Ent) Infections in Children.
33. Xue G, Li J, Feng Y, et al. High prevalence of plasmid-mediated quinolone resistance determinants in Escherichia coli and Klebsiella pneumoniae isolates from pediatric patients in China. Microb Drug Resist. 2017; 23:107–114.
34. Kim NH, Choi EH, Sung JY, et al. Prevalence of plasmid-mediated quinolone resistance genes and ciprofloxacin resistance in pediatric bloodstream isolates of Enterobacteriaceae over a 9-year period. Jpn J Infect Dis. 2013; 66:151–4.
35. Tomeh MO, Starr SE, McGowan JE Jr, et al. Ampicillin-resistant Haemophilus influenzae type B infection. JAMA. 1974; 229:295–7.
36. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother. 2010; 54:969–76.
37. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. ClinMicrobiol Rev. 2005; 18:657–86.
38. Nordmann P, Cuzon G, Naas T. The real threat of Klebsiellapneumoniaecarbapenemaseproducing bacteria. Lancet Infect Dis. 2009; 9:228–36
39. Chen L, Mathema B, Pitout JD, et al. Epidemic Klebsiella pneumoniae ST258 is a hybrid strain. mBio. 2014; 5:e01355–14.
40. Dortet L, Poirel L, Nordmann P. Worldwide dissemination of the NDM-type carbapenemases in Gram-negative bacteria. Biomed Res Int. 2014; 2014:249856.
41. Logan LK, Braykov NP, Weinstein RA, Laxminarayan R. CDC Epicenters Prevention Program. Extended-spectrum β-lactamase-producing and third-generation cephalosporin-resistant Enterobacteriaceae in children: trends in the United States, 1999–2011. J Pediatric Infect Dis Soc. 2014; 3:320–8.
42. Zerr DM, Miles-Jay A, Kronman MP, et al. Previous antibiotic exposure increases risk of infection with extended-spectrum-β-lactamase- and AmpC-producing Escherichia coli and Klebsiellapneumoniae in pediatric patients. Antimicrob Agents Chemother. 2016; 60:4237–4243.
43. Zerr DM, Weissman SJ, Zhou C, et al. The molecular and clinical epidemiology of extendedspectrum cephalosporin- and carbapenem-resistant Enterobacteriaceae at 4 US pediatric hospitals. J Pediatric Infect Dis Soc. 2017 Epub ahead of print.
44. Rispens, JR., Medernach, RL., Hujer, AM., et al. IDWeek. San Diego, CA: 2017. A Multicenter Study of the Clinical and Molecular Epidemiology of TEM- and SHV-type Extended-Spectrum Beta-Lactamase producing (ESBL) Enterobacteriaceae (Ent) Infections in Children.
45. Logan LK, Hujer AM, Marshall SH, et al. Analysis of Beta-Lactamase Resistance Determinants in Enterobacteriaceae from Chicago Children: a Multicenter Survey. Antimicrob Agents Chemother. 2016 May 23; 60(6):3462–9.
46. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery,

and Development of New Antibiotics. [(accessed on 18 February 2023)]; Available online: https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

47. Tamma PD, Newland JG, Pannaraj PS, et al. The use of intravenous colistin among children in the U.S: results from a multicenter, case series. Pediatr Infect Dis J. 2013; 32:17–22.
48. Olaitan AO, Morand S, Rolain JM. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. Front Microbiol. 2014; 5:643.
49. Liu YY, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infect Dis. 2016; 16:161–8.
50. Gu DX, Huang YL, Ma JG, et al. Detection of colistin resistance gene mcr-1 in hypervirulent Klebsiella pneumoniae and Escherichia coli isolates from an infant with diarrhea in China. Antimicrob Agents Chemother. 2016; 60:5099–5100.