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Antimicrobial Resistance in Paediatrics: An Alarming View

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Abstract

A major global problem is antimicrobial resistance (AMR), particularly in pediatrics because of the immature immune systems. Multidrug-resistant organisms (MDROs) are a result of the overutilization and abuse of antibiotics as well as a dearth of data specifically about children, leading to severe and prolonged illness, longer hospitalization times, and higher mortality rates. The root causes include Improper use of antibiotics, lack of pediatric-specific data, and specific contraindications for certain antibiotics. Genetic and evolutionary factors also contribute to antibiotic resistance, with mutations allowing resistant strains to evolve and survive. Resolving these problems is essential to halting the rise of germs resistant to antibiotics and enhancing public health. Overcoming AMR in pediatrics involves optimizing antibiotic use, promoting antimicrobial stewardship programs, implementing preventive measures like vaccination, and integrating infection prevention and control practices. Governments and international organizations must lead to fight against antibiotic resistance by developing policies that encourage appropriate antibiotic use, support public health initiatives, fund research and development of new antibiotics, and implement stringent regulatory measures.

Keywords: Antimicrobial resistance, Antibiotics, Multidrug-resistant organism. Antimicrobial stewardship programs and preventive measures.

INTRODUCTION

The phenomenon known as antimicrobial resistance (AMR) happens when bacteria, viruses, fungi, and parasites stop reacting to antimicrobial treatments. Drug resistance makes antibiotics and other antimicrobial medicines ineffective, making it harder or impossible to treat infections. This raises the risk of disease transmission, serious illness, and death. AMR is a serious issue on a global scale, particularly in pediatrics.[1]

Children are especially vulnerable to infectious diseases due to their immature immune systems. They have high incidences of AMR and are significant users of antimicrobial drugs. Antibiotic resistance in pediatric illnesses is becoming a greater public health concern due to the overutilization and abuse of antibiotics caused by a lack of pediatric-specific data and a lack of knowledge about the resistance mechanisms of prevalent pediatric diseases. As children are going through a distinctive phase of growth and development, it might be

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challenging to estimate age-dependent doses due to the broad variations in their pharmacokinetic (PK) and pharmacodynamic (PD) properties. Another significant factor contributing to children's illogical antibiotic usage, which results in treatment failure and antibiotic resistance, is the dearth of pediatric-specific data.[2]

ANTIBIOTIC AND MULTIDRUG RESISTANCE

Multidrug-resistant organisms (MDROs) are becoming more common and are linked to an elevated incidence of morbidity and mortality in afflicted patients. MDR bacterial infections are more challenging to cure and are associated with a more severe and protracted illness that results in longer hospital stays, a 20% longer duration of stay, and a worse prognosis, increasing death by as much as 40% in MDR hospital-acquired infections. The main bacterial infections that affect children have developed significant resistance to antibiotics.[3]

Amoxicillin remains a highly effective oral agent against S. pneumoniae and non-β-lactamase-producing H. influenzae strains, while amoxicillin-clavulanate is effective against β-lactamase-producing H. influenzae and M. catarrhalis strains. Parenteral ceftriaxone and fluoroquinolones are also efficient against these species but should be used cautiously due to potential toxicity and resistance development. Urinary tract infections (UTI) are common pediatric infections after Respiratory tract infections (RTI), particularly in developing countries. Antibiotic resistance among pediatric UTI bacteria has increased due to the inappropriate use of antibiotics, with oral medications being the most vulnerable. Escherichia coli is the most common pathogen isolated from cultures, accounting for 48%.[4,5]

CAUSES OF CHILDHOOD ANTIBIOTIC RESISTANCE

Antibiotics Overuse and Misuse

The misuse of antibiotics, which stems from a lack of understanding of pathogens and their pharmacokinetic and pharmacodynamic properties, is mostly to blame for the current spread of antibiotic resistance. This has an impact on treatment length, posology, appropriate dosages, and drug selection. The development of resistant bacteria is facilitated by the over prescription of antibiotics for viral diseases that do not respond, improper selection or dosage, and unfinished antibiotic courses.[6]

LACK OF PAEDIATRIC-SPECIFIC DATA

Absence of pediatric-specific information particular pharmacological treatments are needed for juvenile patients; yet, there is a dearth of high-evidence-level knowledge and pediatric guidelines due to the lack of particular clinical trials and the extrapolation of adult data. Antibiotic-resistant bacteria, overdosing or under dosing, and abuse are all possible outcomes. Techniques are required to maximize dosage, avoid moral dilemmas, and deal with real-world challenges. Different body weights and metabolic rates, together with a lack of knowledge regarding the efficacy and safety of antibiotics in children, further complicate this procedure.[7]

CONTRAINDICATED IN CHILDREN: LACK OF OPTIONS

The variety of antimicrobial alternatives available to treat illnesses is impacted by the specific contraindications of some medications for children. The American Academy of Pediatrics (AAP) emphasizes that fluoroquinolones are typically avoided in children due to concerns about adverse effects, including cartilage damage, musculoskeletal toxicity, and disruption of weight-bearing joints. AAP also recommends the use of drugs only in specific situations where no safe alternatives exist, such as for multi-drug resistant organisms. Another class of antibiotics, including drugs like tetracyclines, is contraindicated for children under eight years of age because of the risk of permanent tooth discoloration and its effects on bone development. Tetracycline ought to be used for pediatric illnesses when the advantages outweigh the possibility of side effects, according to the American Academy of Pediatrics. Exceptions are made in severe cases like tick-borne illnesses, where reduced calcium-binding formulations may be recommended to lower the risk.[8]

RESISTANT BACTERIA TRANSMISSION

The proliferation of resistant microorganisms in communities and healthcare environments leads to transmission between adults and children, especially in homes and daycare centers. International travel and migration can cause antibiotic-resistant germs to spread quickly across borders. When children who have been exposed to resistant diseases return home from the hospital, infected by nosocomial infection may spread the infection through food and drink. Additionally, migrants and refugees from one region introduce antibiotic-resistant illnesses into new nations

when they travel, which could spread among local populations if precautions are not taken.[8]

RESTRICTED PROGRESS IN THE CREATION OF NEW ANTIBIOTICS

Declining investment in antibiotic research and development.This is due to the limited development of new antibiotics, which have evolved strategies to evade their effects. Identifying new targets, such as beta-lactamase production and efflux pumps, is complex due to bacterial adaptation. Developing pediatric antibiotics presents unique challenges, including formulating safe, effective, and palatable drugs. Economic and market factors discourage antibiotic development, leading to a "market failure" in the antibiotic industry.[9]

GENETIC AND EVOLUTIONARY FACTORS IN BACTERIA

Bacteria's biology significantly contributes to antibiotic resistance. Horizontal gene transfer, such as conjugation, transformation, and transduction, allows bacteria to exchange genetic material, including resistance genes, enabling rapid spread within and between populations. Additionally, mutations and prolonged antibiotic exposure, allow the bacteria to evolve and survive, leading to resistant strains outperforming susceptible ones, thereby causing widespread resistance.[10,11]

CONSEQUENCES OF ANTIMICROBIAL RESISTANCE (AMR) IN PEDIATRICS

Development of New and More Resistant Strains

Methicillin-Resistant Staphylococcus Aureus (MRSA) strains were first identified in the 1960s and were prevalent in adults and children until the 1990s. Healthcare-acquired MRSA (HAMRSA) began circulating together with community-acquired MRSA (CA-MRSA). Trimethoprim-sulfamethoxazole and clindamycin are often used in the treatment of CAMRSA: resistance to trimethoprim/sulfamethoxazole is relatively uncommon, though clindamycin resistance has increased in the past decade. Later vancomycin resistance has impacted anti-MRSA antibiotic treatment, particularly for children, with few therapeutic options. Ceftaroline has shown good efficacy against MRSA and has been approved for children over two months old.[7,12]

The spread of multidrug-resistant (MDR) *Escherichia coli* strains, particularly the CTX-M-producing ST131 lineage, has significantly contributed to the rise in extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-Ent) infections in children. Risk factors for ESBL-Ent infections include younger gestational age, low birth weight, antibiotic use, and prolonged mechanical ventilation. Therapeutic options for ESBL-Ent include piperacillin-tazobactam, ceftazidime-avibactam, cefepime, fluoroquinolones, aminoglycosides, tigecycline, and carbapenems. However, these options are limited for children due to safety profiles and unclear dosage guidelines. Resistance to carbapenems in pediatric populations has been increasing, with a 50% mortality rate in hospitalized patients with bloodstream CRE infection. Therapeutic options for Carbapenem-resistant enterobacterales (CRE) are limited, and ESBL-Ent and carbapenemase-producing bacteria often carry other plasmid-transmitted genes that confer resistance to aminoglycosides, sulfonamides and fluoroquinolones.[13,14]

INCREASED MORTALITY AND MORBIDITY

AMR in pediatric patients increases mortality and morbidity due to the failure of antibiotics. Bacterial infections like pneumonia, sepsis, and UTIs can become more severe without effective antibiotics, leading to complications, hospitalizations, and long-term health effects. AMR can delay treatment, worsen symptoms, and make treatment more difficult. Lifelong consequences include developmental delays, neurological damage, and hearing loss. In severe cases, AMR can lead to death.[15]

PROLONGED HOSPITALIZATION AND INCREASED HEALTHCARE COSTS

Antibiotic-resistant bacteria (AMR) in children often require longer hospital stays due to the ineffectiveness of standard therapies. This AMR strains leads to extended treatment regimens, including intravenous antibiotics or toxic last-line antibiotics. AMR also drives up healthcare costs by necessitating more complex diagnostic procedures, the use of expensive second- or third-line antibiotics, and the need for specialized care, isolation, and support for complications. These factors contribute to the increased costs of healthcare for children with AMR, highlighting the need for more effective and affordable treatments.[16]

SPREAD OF ANTIMICROBIAL-RESISTANT PATHOGENS

Resistant pathogens can spread easily in settings like hospitals, daycare centers, and schools, Elevating the likelihood of antibiotic-resistant infections. This is particularly problematic

in pediatric wards due to weakened immune systems. Inadequate infection control practices and community spread, such as in daycare or schools, further exacerbate the resistance problem.

IMPACT ON PEDIATRIC SURGERY AND MEDICAL PROCEDURES

AMR increases the risk of postoperative infections in pediatric patients undergoing surgery, leading to complications like wound infections and infections in immunocompromised children. Neonatal infections, such as sepsis and meningitis, are particularly vulnerable due to AMR, Complicating efforts to treat them. Current drugs are ineffective in treating these infections, which often require prompt intervention to avoid long-term complications or death.

OVERCOMING ANTIBIOTIC RESISTANCE IN PEDIATRIC INFECTIONS

Fig. 1 depicts the proportion of resistance to various antibiotics for different pathogens in four distinct populations: Children, Adults, Pediatric, and Blended. Each image represents a different set of pathogen-antibiotic combinations. A distinct collection of pathogen-antibiotic pairings is depicted in each image. Compared to children, adults had a greater overall difference in the proportion of resistant isolates. Adult isolates, for instance, were more likely to have ciprofloxacin-resistant A. baumannii, while pediatric isolates were more likely to contain amikacin-resistant P. aeruginosa. Penicillin-resistant S. pneumoniae was more prevalent in some isolates from kids in mixed institutions. However, when compared to integrated institutions, children treated in pediatric facilities generally had a larger frequency of resistant isolates. For instance, compared to children treated in mixed institutions, isolates from pediatric facilities contained a greater percentage of ceftriaxone-resistant E. aerogenes.[6]

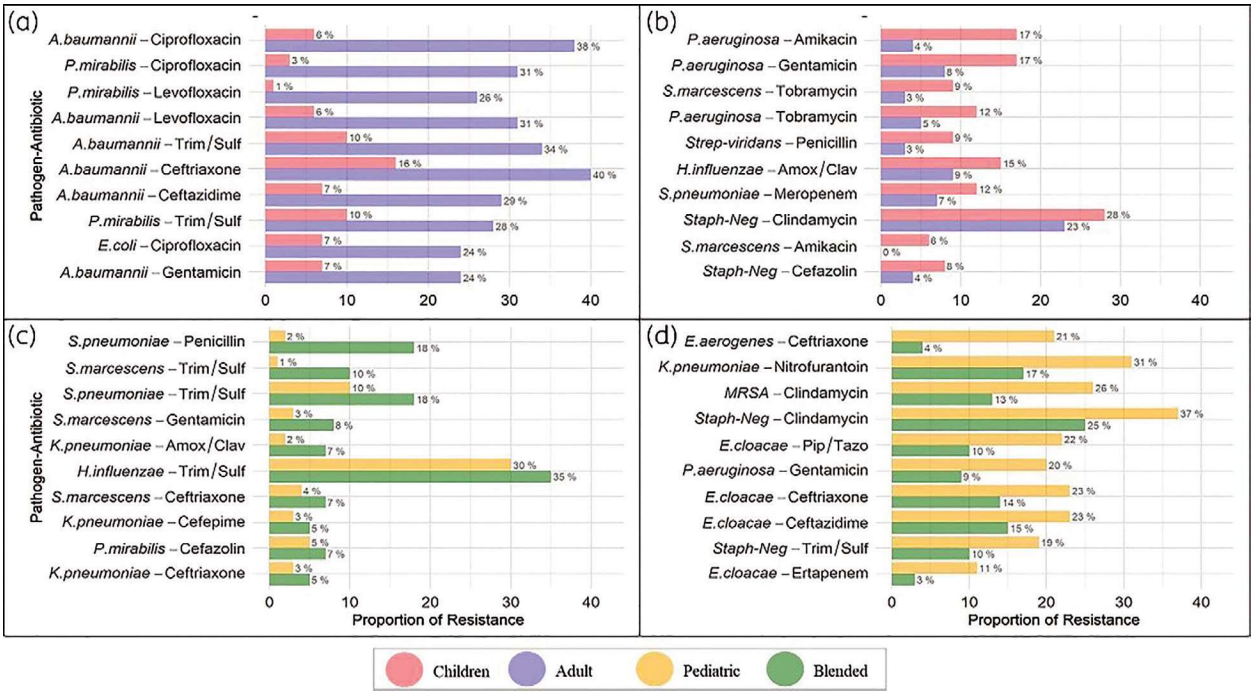

Fig. 1: Difference in level of resistance between subgroups. Higher baseline resistance in isolates from: **(a)** Adults when compared to children. **(b)** Children when compared to adults. **(c)** Children in blended facilities when compared to pediatric facilities **(d)** Children in pediatric facilities when compared to blended facilities.[6]

Optimizing Antibiotic Use

Overuse and misuse of antibiotics in pediatric care are key drivers of resistance. To combat this, pediatricians should follow evidence-based guidelines, prioritize narrow-spectrum antibiotics, and conduct culture and sensitivity testing. De-escalating therapy and shortening treatment courses can help reduce resistance. Pediatricians should examine the data regarding the best times to treat common infections, such as otitis media,

pneumonia, and UTIs, to tailor therapy to the organism and reduce the inappropriate use of broad-spectrum antibiotics.[17]

Health Care Professionals' Interventions - Antibiotic Stewardship

Antimicrobial stewardship is crucial for patient care, with all clinicians playing a role in prescribing antibiotics. Primary care doctors and hospitalists are crucial prescribers who can practice effective stewardship by adhering to the five ""D"s" of antimicrobial stewardship: right Drug, correct Dose, right Drug-route, suitable Duration, and timely De-escalation to pathogen-directed therapy. Pharmacists are integral to the team, helping develop and implement policies to optimize antibiotic use and educate patients about medications. Nurses play a vital role in optimizing diagnostic tests and patient education. Microbiology lab staff guide proper test use and create local anti-microprograms, while infection prevention teams and epidemiologists track antimicrobial resistance and adverse effect trends. Teams working on patient safety and quality improvement promote funding for stewardship initiatives. Incorporating protocols into the stewardship work map requires the assistance of information technology personnel. By using antibiotics sensibly, taking part in the prescription process, and refraining from utilizing them as growth promoters in the community, patients can be good stewards on an individual basis. [17,18]

PREVENTIVE MEASURES

Vaccination is a crucial tool in preventing antibiotic-resistant infections, such as meningitis and pneumonia. Common vaccines include Pneumococcal Conjugate Vaccine (PCV13) and Haemophilus influenzae type b (Hib), which reduce the incidence of these diseases. However, infection prevention and control practices, such as hand hygiene, isolation, and strict adherence to protocols, are essential. Parental education on antibiotic use, its role in viral infections, and the importance of completing the full course, even if the child seems better, is also crucial.[19]

SURVEILLANCE AND MONITORING

Antibiotic resistance surveillance in pediatric populations is crucial for identifying trends and guiding antibiotic therapy. National and international bodies like the (Centers for Disease Control and Prevention) CDC and WHO provide surveillance data, aiding clinicians in making informed decisions. Local resistance patterns should be integrated into clinical practice, allowing pediatricians to tailor therapy based on local challenges. Advances in molecular diagnostics and point-of-care testing, like PCR-based methods, enable rapid identification of pathogens and resistance markers, guiding more accurate antibiotic prescribing.[20]

RESEARCH AND INNOVATION

The creation of novel antibiotics is crucial for treating resistant infections, with a focus on targeting unique bacterial mechanisms or using bacteriophage therapy. Alternative therapies like phage therapy, probiotics, and antimicrobial peptides are also being explored as complementary options to traditional antibiotics. Additionally, research is underway on antibiotic adjuvants, which enhance the effectiveness of antibiotics or inhibit bacterial resistance mechanisms.The demand for novel antibiotics underscores the need for collaboration between pharmaceutical companies, researchers, and governments.[21]

HEALTHCARE SYSTEM-LEVEL APPROACHES

Governments and international organizations must lead the fight against antibiotic resistance by developing policies that encourage appropriate antibiotic use, support public health initiatives, fund research and development of new antibiotics, and implement stringent regulatory measures. Integrated approaches to pediatric care, including clinical decision support systems, team-based care, and ongoing feedback mechanisms, ensure all aspects of care are aligned toward minimizing resistance, including outpatient clinics, emergency departments, and inpatient wards.[22,23]

CONCLUSION

Overcoming antibiotic resistance in pediatric infections requires a comprehensive, multi-disciplinary approach. Key strategies include optimizing antibiotic use, vaccination, prevention, surveillance, and research into new treatments. Pediatricians must remain vigilant in their prescribing practices, prioritize preventive care, and need to inform about emerging resistance trends. Simultaneously, systemic efforts at the institutional, national, and global levels are critical to reducing the spread of antibiotic-resistant pathogens and ensuring that antibiotics remain effective for future generations.

REFERENCES

1. Pana, Z.D., El-Shabrawi, M., Sultan, M.A., Murray, T., (2023). Fighting the hidden pandemic of antimicrobial resistance in paediatrics: recommendations from the International Pediatric Association. *BMJ paediatrics open*, *7*(1), e002084. https://doi.org/10.1136/bmjpo-2023-002084
2. Yu, D., Zheng, Y., Shen, A., Wu, F., Dmitriev, A. V., Kilian, M., & Yang, Y. (2023). Editorial: Antimicrobial resistance in pediatric infectious diseases: antimicrobial resistance, resistance mechanisms and antimicrobial use. Frontiers in Cellular and Infection Microbiology, 13. https://doi.org/10.3389/fcimb.2023.1287051
3. Logan, L.K., Braykov, N.P., Weinstein, R.A., & Laxminarayan, R. (2014). Extended-Spectrum β-Lactamase–Producing and Third-Generation Cephalosporin-Resistant Enterobacteriaceae in Children: Trends in the United States, 1999–2011. Journal of the Pediatric Infectious Diseases Society, 3(4), 320–328. https://doi.org/10.1093/jpids/piu010
4. Gandra, S., Tseng, K.K., Arora, A., Bhowmik, B., Robinson, M.L., Panigrahi, B., Laxminarayan, R., & Klein, E. Y. (2019). The Mortality Burden of Multidrug-resistant Pathogens in India: A Retrospective, Observational Study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 69(4), 563–570. https://doi.org/10.1093/cid/ciy955
5. Gussin GM, McKinnell J.A., Singh R.D., *et al.* Reducing Hospitalizations and Multidrug-Resistant Organisms via Regional Decolonization in Hospitals and Nursing Homes. *JAMA.* 2024; 331(18):1544–1557. doi:10.1001/jama.2024.2759
6. Sivasankar, S., Goldman, J.L., & Hoffman, M.A. (2022). Variation in antibiotic resistance patterns for children and adults treated at 166 non-affiliated US facilities using EHR data. JAC-Antimicrobial Resistance, 5(1). https://doi.org/10.1093/jacamr/dlac128
7. Eva Degraeuwe, Pirkko Lepola, Mark Turner, Kim Jennings, Lieve Nuytinck, Ann Raes, Karel Allegaert, Johan Vande Walle, Fenna Mahler - 31 An update on the challenges of conducting pediatric clinical trials: 15 years of progress since EMA regulation implementation: BMJ Paediatrics Open 2024; 8.
8. Romandini, A., Pani, A., Schenardi, P.A., Pattarino, G.A.C., De Giacomo, C., & Scaglione, F. (2021). Antibiotic Resistance in Pediatric Infections: Global Emerging Threats, Predicting the Near Future. Antibiotics, 10(4), 393. https://doi.org/10.3390/antibiotics10040393
9. Årdal, C., Balasegaram, M., Laxminarayan, R., McAdams, D., Outterson, K., Rex, J.H., & Sumpradit, N. (2019). Antibiotic development — economic, regulatory and societal challenges. Nature Reviews Microbiology, 18(5), 267–274. https://doi.org/10.1038/s41579-019-0293-3
10. Ahmed, S.K., Hussein, S., Qurbani, K., Ibrahim, R.H., Fareeq, A., Mahmood, K.A., & Mohamed, M.G. (2024). Antimicrobial resistance: Impacts, challenges, and future prospects. Journal of Medicine Surgery and Public Health, 2, 100081. https://doi.org/10.1016/j.glmedi.2024.100081
11. Ho, C.S., Wong, C.T.H., Aung, T.T., Lakshminarayanan, R., Mehta, J.S., Rauz, S., McNally, A., Kintses, B., Peacock, S.J., De La Fuente-Nunez, C., Hancock, R.E.W., & Ting, D.S.J. (2024). Antimicrobial resistance: a concise update. The Lancet Microbe, 100947. https://doi.org/10.1016/j.lanmic.2024.07.010
12. Jacobs, M.R., & Dagan, R. (2004). Antimicrobial resistance among pediatric respiratory tract infections: clinical challenges. Seminars in Pediatric Infectious Diseases, 15(1), 5–20. https://doi.org/10.1053/j.spid.2004.01.003
13. Wang, J., He, L., Sha, J., Zhu, H., Huang, L., Zhu, X., Dong, J., Li, G., Ge, Z., Lu, R., Ma, G., Shi, Y., & Guo, Y. (2018). Etiology and antimicrobial resistance patterns in pediatric urinary tract infection. Pediatrics International, 60(5), 418–422. https://doi.org/10.1111/ped.13526
14. Mohamed, A.A., Bastug, Y., Senol, C., Kassim, M.M., Yusuf, A.A., & Mohamed, A.H. (2020). Antimicrobial resistance pattern and uropathogens distribution in children visiting a referral hospital in Mogadishu. Future Science OA, 10(1). https://doi.org/10.2144/fsoa-2023-0298
15. The urgent threat of drug-resistant infections protecting children worldwide a unicef guidance note on antimicrobial resistance - https://www.unicef.org/media/144266/file/The-Urgent-Threat-of-Drug-Resistant-Infections:-A-UNICEF-Guidance-Note-on-Antimicrobial-Resistance-2023.pdf
16. Threats of Antimicrobial Resistance (AMR) in Pediatrics, July 3, 2022, Posted in: AMR Writers Participants' Articles, Articles, Educational Resources, By Jimmy Nkaiwuatei& Janice Odhiambo, https://www.studentsagainstsuperbugs.org/educational-resources/threats-of-antimicrobial-resistance-amr-in-pediatrics/ accessed on 16 November 2024
17. Abo, Y., Freyne, B., Kululanga, D., & Bryant, P. A. (2022). The Impact of Antimicrobial Stewardship in Children in Low- and Middle-income Countries. The Pediatric Infectious Disease Journal, 41(3S), S10–S17. https://doi.org/10.1097/inf.0000000000003317
18. Shrestha, J., Zahra, F., & Cannady, P., Jr. (2023, June 20). Antimicrobial Stewardship. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK572068/
19. Rezk, A.R., Bawady, S.A., & Omar, N.N. (2021). Incidence of emerging multidrug-resistant organisms and its impact on the outcome in the pediatric intensive care. Egyptian Pediatric

Association Gazette, 69(1). https://doi.org/10.1186/s43054-021-00071-1

20. Banerjee, R., & Patel, R. (2022). Molecular diagnostics for genotypic detection of antibiotic resistance: current landscape and future directions. JAC-Antimicrobial Resistance, 5(1). https://doi.org/10.1093/jacamr/dlad018
21. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations,The Review on Antimicrobial Resistance Chaired by Jim O'Neill December 2014.
22. Storr, J., Twyman, A., Zingg, W., Damani, N., Kilpatrick, C., Reilly, J., Price, L., Egger, M., Grayson, M.L., Kelley, E., & Allegranzi, B. (2017). Core components for effective infection prevention and control programmes: new WHO evidence-based recommendations. Antimicrobial Resistance and Infection Control, 6(1). https://doi.org/10.1186/s13756-016-0149-9
23. Union for International Cancer Control (UICC) , Antimicrobial resistance and its impact on cancer care, 21 November 2023 https://www.uicc.org/what-we-do/thematic-areas/antimicrobial-resistance-amr?gad_source=1&gclid=Cj0KCQiAire5BhCNARIsAM53K1hp2w4pUIN1knwa7fcrbePd0zVOci-ebDjCZZ1hiIm891yHSL7Cno0aAtRnEALw_wcB accessed on 16 November 2024