

EDITORIAL

Are We Returning to the Pre-antibiotic Era?

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Introduction

The early 20th century was a time of groundbreaking scientific progress. One major advance was the development of penicillin and other antibiotics that has prevented thousands, even millions of people from dying of bacterial infections. But the successful use of any therapeutic agent is compromised by the potential development of tolerance or resistance to that compound from the time it is first employed. WHO identifies this as one of the top public health threats around the world. If the world does not move now to preserve the ability to treat infectious diseases that played such a key part in increasing life expectancy and improving human health, the 21st century may see the reversal of that progress.¹

Antimicrobial resistance (AMR) is a worldwide problem and Bangladesh is a major contributor to this owing to its poor healthcare standards, along with the misuse and overuse of antibiotics. Many doctors in Bangladesh are prescribing antibiotics irrationally without taking consideration of the clinical findings and laboratory investigation reports in most cases. According to public health experts, AMR is on the rise in the country as the authority failed to stop the misuse of antibiotics even after the HC passed the directive in 2019 to stop the sale of antibiotics without prescription. Anyone can still buy antibiotics without prescription while many quacks and medicine shop workers suggest antibiotics to patients without diagnosis. The problem is further exacerbated by self-prescribing of antibiotics by individuals without the guidelines of a qualified clinician.

Luyt et al² found that in addition to treatment failure due to AMR, medical malpractice contributed to develop Multidrug-resistant (MDR) strains of bacteria through unnecessary, inappropriate, or suboptimal prescribing, which has been observed in 30% to 60% of the antibiotic therapies given to

outpatients as well as to inpatients. As a result of AMR, infections become difficult or impossible to treat, increasing the risk of disease spread, severe illness and death and reversing gains of medical science. Antimicrobial resistance can increase deaths and disability, causing economic costs to rise sharply. Unskilled personnel are less aware of the deleterious effects of inappropriate antibiotic use. Awareness about harmful effect of unnecessary antibiotic use, adherence to treatment protocol and compliance with treatment course of antimicrobials need to be emphasized at different levels.

In addition to human use, antibiotics are commonly used in animal husbandry, beekeeping, fish farming and other forms of aquaculture, ethanol production, horticulture, antifouling paints, food preservation, and domestically. This provides multiple opportunities for the selection and spread of antibiotic-resistant bacteria. Given the current crisis, it is vital that the nonmedical use of antibiotics is critically examined and that any nonessential use halted.³

Antibiotic Misuse

Antibiotic misuse, sometimes called antibiotic abuse or antibiotic overuse, has potentially serious effects on health. Misuse of antibiotics include: when antibiotics are prescribed unnecessarily; administration is delayed in critically ill patients; broad-spectrum antibiotics are used too generously, or when narrow-spectrum antibiotics are used incorrectly; the dose of antibiotics is lower or higher than appropriate for the specific patient; the duration of antibiotic treatment is too short or too long; saving unused medicine and take it later for another illness and when antibiotic treatment is not streamlined according to microbiological culture data results.

Misuse of antibiotics drives antibiotic resistance. Studies prove that misuse of antibiotics may cause

patients to become colonized or infected with antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and highly resistant *Gram-negative bacilli*.⁴ Excessive antibiotic use has the potential to result in numerous problems. In case antibiotics like penicillin, not used appropriately or used for a very brief period, there is a possibility of bacteria developing resistance to these drugs. Subsequently, resistant strains become capable of neutralizing the impact of penicillin when they come in contact with them again.

Antibiotic resistance

Antibiotic resistance is defined as the ability of a specific bacterium to survive in the presence of an antibiotic that was originally effective to treat infections caused by the bacterium. Though dozens of 'superbugs' resistant to antibiotics have made headlines over the last quarter century, multidrug-resistant gram-negative bacteria pose the greatest risk.⁵

The effects of antimicrobial resistance are more significant in lower and middle-income countries. Patients here may suffer the most from the increasing prevalence of antimicrobial resistance due to challenges in identifying and diagnosing these infections and lack of second and third-line antibiotics to treat resistant bacteria.⁶ It is a contributing factor to the development of antibiotic resistance, including the creation of multidrug-resistant bacteria: relatively harmless bacteria can develop resistance to multiple antibiotics and cause life-threatening infections.⁷ Misuse of antibiotics in hospitals is one of the main factors that drive development of antibiotic resistance. Patients in hospitals have a high probability of receiving an antibiotic and 50% of all antibiotic use in hospitals can be inappropriate.⁸ Studies prove that misuse of antibiotics may cause patients to become colonised or infected with antibiotic-resistant bacteria, such as MRSA, VRE and highly resistant *Gram-negative bacilli*.^{4,9}

Antibiotic resistance in children in Bangladesh

Antibiotic resistance is a public health threat of the utmost importance, especially when it comes to children. According to WHO data, infections caused by multidrug resistant bacteria produce 700,000 deaths across all ages, of which around 200,000 are newborns.¹⁰ Bangladesh is more affected by AMR

because of the widespread misuse of antibiotics, non-human antibiotic use, poor quality of drugs, inadequate surveillance and factors associated with individual and national poverty indicators like poor healthcare standards, malnutrition, chronic and repeated infections, unaffordability of more effective and costly drugs. Ahmed et al¹¹ in a systematic review found a high prevalence of resistance to most antibiotics. Highly pathogenic MDR strains were detected from infected patients in tertiary hospitals of the capital of Bangladesh, which can also contribute to other hospital acquired infections.¹²

Hassan et al¹³ in first nationally representative analysis of antibiotic use among under-5 children in Bangladesh, found almost 40% of children received antibiotics for an ARI episode. Resistance to antibiotics is common and often deadly among children with pneumonia in Bangladesh. Chisti et al¹⁴ found that antibiotic resistant Gram-negative bacteremia in young children with pneumonia in Dhaka was associated with a high mortality rate. They found that 40 percent of the gram-negative bacterial infections resisted treatment with first- and second-line antibiotics that are routinely used to treat pneumonia. More alarmingly, children who had antibiotic-resistant bacterial infections were 17 times more likely than others without bacterial infections to die. The pandemic of antibiotic resistance is shortening the lives of young children in Bangladesh, and new approaches to prevent and treat these infections are desperately needed.

Fever in children under five years of age is a common and predominantly self-limiting sign of illness. However, in low- and middle-income countries, antibiotics are frequently used in febrile children, although these children may not benefit from antibiotics. Samir et al¹⁵ performed a multivariable logistical regression to identify the factors associated with antibiotic use in children under five years old with febrile illness in Bangladesh and found 478 (17%) children out of 2784 children aged less than five years with fever received antibiotics. Unqualified sources, including unqualified providers and pharmacies, contributed to 60% of antibiotic prescriptions in children with fever, followed by the private medical sector (29%) and the public sector (23%). The highest use of antibiotics was found in children under six months of age (25%).

Antimicrobial resistance against shigellosis is increasingly alarming. However, evidence-based knowledge gaps regarding the changing trends of shigellosis in Bangladesh exist due to the scarcity of longitudinal data on antimicrobial resistance. Nuzhat et al¹⁶ in their study found that WHO-recommended first-line antibiotic ciprofloxacin resistance gradually reached more than 70% in both the urban and rural site by 2020. In multiple logistic regression after adjusting for age and sex, ciprofloxacin, azithromycin, mecillinam, ceftriaxone, and multidrug resistance (resistance to any two of these four drugs) among under-5 children were found to be increasing significantly ($p < 0.01$) in the last 20 years.

Antibiotics are the most common therapies administered in the intensive care unit setting. The rapid emergence and dissemination of antimicrobial resistant microorganisms in intensive care units (ICUs) worldwide constitutes a serious problem now a days. Mamun et al¹⁷ conducted a study in paediatric cardiac intensive care unit (PCICU) of Bangladesh Shishu Hospital & Institute and they found during the study period total 305 patients were admitted and almost all received broad spectrum antibiotics including third generation cephalosporins, carbapenem even piperacillin and colistin before admission in PCICU. Organisms were isolated in 10.82% cases and majority were gram negative (*Acinetobacter* 42.4%, *Klebsiella* 21.2%, and *Pseudomonas* 24.2%). Multi drug resistant *Acinetobacter* was found in 90.99% cases and 9.09% was pan drug resistant. *Klebsiella*, *Pseudomonas* and *E. Coli* were also found resistant to commonly used antibiotics. Hasan et al¹⁸ conducted another study in cardiac ICU of National Heart Foundation & Research Institute and they found among 680 operated patients during the study period 6% were culture positive. Most common isolated organism was *Pseudomonas* spp 49.2%, followed by *Klebsiella* 13.6%, *Citrobacter* 8.5%, *E coli* 6.8% and *Acinetobacter* 6.8%. *Pseudomonas* was resistant against Penicillin, Ceftriaxone, Macrolid and Colistin in 96.6 - 100% cases. *Klebsiella* was mostly multidrug resistant including Carbapenems (37.5%) and only Colistin was retaining sensitivity against it. Among the other organisms like *E coli*, *Acinetobacter*, *Citrobacter* and *Enterobacter*, Macrolids were mostly resistant and sensitive against 50% cases of *Acinetobacter* and 66% of *Enterobacter*. Ciprofloxacin and Carbapenems were 100% resistant against

Citrobacter but effective against others. *Citrobacter* being most notorious organism mostly multidrug resistant and sensitive to only Colistin in 40% and Tigecycline in 80% case. So there is emergence of multidrug resistant organisms in PCICU with very few options to treat.

There is an urgent need to address factors that are promoting antibiotic resistance in Bangladesh. Antibiotics can be purchased without a prescription in the country and many people use them to self-treat conditions such as dysentery, cold, cough and fever. Misuse of antibiotics promotes the spread of bacteria that resist the medications. Lab testing for diagnosis of bacterial infections is also inadequate in the country. Lack of access to clean water and adequate sanitation helps spread bacteria that are resistant to antibiotics. Improvements in health care infrastructure and policy changes to rein in the misuse of antibiotics are essential and Bangladesh's health care system also needs better access to more advanced antibiotic therapies for resistant infections.

Conclusion

Antibiotics are one of the most important medical innovations. But its inappropriate use leads to potentially untreatable resistant infections. As there is not enough new antibiotics in the pipeline, it is of utmost importance that the existing ones are used cautiously. Immediate action is needed to stop the world from heading towards a pre-antibiotic era in which all achievements made in prevention and control of communicable diseases will be reversed. There is evidence that controlled and lowered use of antibiotics can abate resistance.

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