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Review Article

# A Review of Azithromycin Resistance: Emerging Trends and Clinical Implications

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## ABSTRACT

Antimicrobial resistance (AMR) represents a critical global health crisis, marked by the evolution of microorganisms that circumvent the effects of antimicrobial agents. Projections suggest AMR could result in 10 million deaths annually by 2050 and incur significant economic losses. This review explores the dynamics of azithromycin resistance—a broad-spectrum macrolide antibiotic—highlighting its rising prevalence and the consequent implications for healthcare. Azithromycin resistance has notably increased, with concerning trends observed in pathogens such as Salmonella species, Escherichia coli, and Neisseria gonorrhoeae. Contributing factors include genetic mutations, horizontal gene transfer, and excessive use of antibiotics in healthcare and agriculture. This review summarizes recent studies on azithromycin resistance, focusing on global patterns, resistance mechanisms, and implications for patient care. It discusses emerging resistance genes, environmental factors, and the increasing incidence of multidrug-resistant strains. The review also addresses the need for enhanced antimicrobial stewardship, novel treatment strategies, and public health interventions to mitigate the impact of azithromycin resistance. Effective measures, including improved surveillance, targeted treatment protocols, and international cooperation, are essential to combat this growing threat and preserve the efficacy of essential antibiotics.

## INTRODUCTION

Antimicrobial resistance (AMR) is a pressing global health crisis characterized by the evolution of microbes that evade the effects of antimicrobial agents. This phenomenon poses significant threats to public health, with projections indicating that AMR could lead to 10 million deaths annually by 2050 and substantial economic losses(1)(2). Genetic Adaptation: Bacteria can acquire resistance through mutations or horizontal gene transfer, leading to multidrug-resistant (MDR) strains(3). Environmental Factors: Misuse of

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antibiotics in healthcare, agriculture, and veterinary practices exacerbates resistance(2).

AMR increases morbidity, mortality, and it presents a serious threat to healthcare systems around the globe.

Azithromycin is a broad-spectrum macrolide antibiotic, derived from erythromycin, known for its long half-life and excellent tissue penetration. It is primarily used to treat various bacterial infections, particularly in pediatric populations, due to its favorable safety profile and efficacy against pathogens like *Haemophilus influenzae* and *Chlamydia pneumoniae* (5). Nonetheless, the rise the proliferation and diffusion of azithromycin-resistant bacteria has increased greatly reduced its effectiveness.

This review article's goal is to give a clear picture of azithromycin resistance, including recent trends and practical implications for healthcare. The purpose of this article is to summarize the most recent studies on azithromycin resistance, emphasizing worldwide patterns and the practical ramifications for patient care. In addition, the review will go over resistance-fighting tactics, diagnostic techniques for identifying azithromycin resistance, and potential future research areas. This review article aims to advance knowledge of azithromycin resistance and offer useful insights to researchers, clinicians, and policymakers by addressing these aspects.

## 2. EMERGING TRENDS IN AZITHROMYCIN RESISTANCE:

Globally, the prevalence of azithromycin resistance is rising, particularly with regard to various pathogens such as Salmonella species, Escherichia coli, and Neisseria gonorrhoeae. Recent research findings have brought attention to concerning trends in resistance rates, emphasizing the need for enhanced stewardship and surveillance. 6% of specimens globally exhibit azithromycin resistance, with 29.3% of countries reporting more than 5% resistance. This indicates a significant increase in macrolide resistance over the preceding three decades (6).

Several resistance genes were discovered during research on azithromycin resistance in Salmonella and E. Coli conducted in Europe. Notably, mef(C)-mph(G) resistance genes are emerging in pig E. Coli, which could be dangerous for food safety and public health (7). In South Asia, a particular mutation in the AcrB efflux pump has been connected to azithromycin resistance in Salmonella Typhi and Paratyphi A. Since 2019, several occurrences of this mutation have been documented in the area, suggesting a potential global expansion (8).Several resistance genes were discovered during research on azithromycin resistance in Salmonella and E. Coli conducted in Europe. Notably, mef(C)-mph(G) resistance genes are emerging in pig E. Coli, which could be dangerous for food safety and public health (7).

Azithromycin resistance in Salmonella Typhi and Paratyphi in South Asia

Certain regions have reported constant resistance rates in spite of these alarming trends, indicating that specific factors can affect resistance dynamics. To counter this growing hazard, targeted measures and ongoing monitoring are crucial.

A major public health concern is the incidence and distribution of azithromycin-resistant bacteria worldwide, which varies significantly among bacterial species and geographical areas. Studies show that resistance in human infections and animals that produce food is especially problematic. In Europe, researchers found that Salmonella and Escherichia coli harbored a variety of azithromycin resistance genes, with resistance rates associated with particular genetic markers such mef(C)-mph(G)(9).Porcine E. Col isolates are the main source of these resistance genes, underscoring the significance of agricultural practices in the evolution of resistance.Neisseria gonorrhoeae resistance to azithromycin is 6%

worldwide, with notable regional variations, according to a systematic analysis; 29.3% of nations reported resistance levels higher than 5%(10)(11).

To address the increased rates of resistance, the study stressed the need for better antimicrobial management. Additionally, studies show that azithromycin resistance genes, such erm(T), can be transferred from Gram-positive to Gram-negative bacteria, which makes treatment choices more difficult for illnesses like Klebsiella pneumoniae(12).

Despite its continued importance as an antibiotic, azithromycin is becoming less effective, which calls for proactive worldwide monitoring and targeted treatments to stop its spread. Comprehensive efforts to counter meropenem resistance are urgently needed, as evidenced by the emergence of resistant strains in community and clinical settings. Strong surveillance, antimicrobial stewardship, infection control strategies, and international cooperation are needed to prevent the spread of bacteria resistant to meropenem and maintain the effectiveness of this essential antibiotic.

**2.2 Factors Influencing the Spread and Sustained Presence of Azithromycin Resistance**

Meropenem resistance spreads and persists due to a number of interrelated causes. A comprehensive strategy that includes the judicious use of antibiotics, strict infection prevention and control measures, improved surveillance and monitoring, and a greater comprehension of the environmental variables causing resistance is needed to address this issue.

Azithromycin resistance spreads due to a number of important variables, including as the function of efflux pumps, selection pressure from antibiotic use, and genetic transmission mechanisms. Comprehending these variables is crucial in tackling the escalating problem of antibiotic resistance.

Gram-positive bacteria have been found to carry the azithromycin-resistant erm(T) gene, which may be plasmid-transferred to Gram-negative bacteria such as Klebsiella pneumoniae(13). Salmonella rapidly spreads azithromycin resistance, which originates in Escherichia coli, thanks to conjugative plasmids carrying the erm(B) gene(14).

Higher azithromycin use induces selection pressure that encourages the establishment of resistant bacteria, especially when treating multidrug-resistant Salmonella Typhi. According to Hooda et al. (2019), the discovery of azithromycin-resistant bacteria during pediatric surveillance emphasizes the critical necessity of keeping an eye on resistance trends. Salmonella azithromycin resistance has been linked to mutations in the AcrB efflux pump, illustrating how genetic modifications might strengthen resistance mechanisms (15). Interspecific MTR allele acquisition raises resistance in Neisseria gonorrhoeae, illustrating the intricate process of resistance building through genetic exchange (16).

Even though these elements play a part in the spread of azithromycin resistance, it's important to remember that not all resistant strains adapt to different settings identically, which could restrict their ability to spread (17).

**2.3 Implications of Azithromycin Resistance for Healthcare Settings and Patient Health Outcomes**

The review article addresses how patient outcomes and healthcare environments are affected by azithromycin resistance. Azithromycin resistance significantly affects the outcomes of patients as well as healthcare environments. Azithromycin resistance has a substantial negative influence on patient outcomes and healthcare environments, increasing morbidity, lengthening hospital stays, and driving up medical expenses. This resistance makes treatment plans more difficult to follow and calls for the use of broader-spectrum antibiotics, which can make resistance problems worse. Patients who get infections resistant to azithromycin, including Shigella, have worse clinical outcomes, such as longer-lasting diarrhea and increased hospitalization rates (18).

Resistant strain infections generate twice as many unfavorable consequences as susceptible strain infections, impacting the clinical and financial aspects of healthcare (19).Increased healthcare expenses as a result of lengthier hospital stays and more intensive treatments are part of the financial burden of antibiotic resistance (20). The use of broader-spectrum antibiotics in treatment guidelines as a result of resistance puts a pressure on healthcare resources (21).

Controlling the spread of antibiotic resistance in hospital settings also requires cohort nursing for patients colonized or infected by resistant strains, surveillance cultures, and contact precautions. Measuring the effect of resistance on patient outcomes requires taking into account the pathogen, the site of infection, and the pharmacokinetic features of the antimicrobial medication.

## 3. CLINICAL CONSEQUENCES OF AZITHROMYCIN RESISTANCE

Reducing the harmful effects of antimicrobial resistance requires optimizing the use of antibiotics, which includes using the right dosage and cutting down on needless antibiotic use. Fighting antibiotic resistance and enhancing patient safety also depend heavily on effective microbiology labs and infection control procedures.

Factors including pathogen resistance, treatment expectations, and compliance have a major impact on the effectiveness of therapies for skin infections, STIs, and respiratory tract infections. It is essential to comprehend these dynamics in order to maximize treatment results.

### 3.1 Public Health Implications: Treatment Failures and Increased Morbidity:

Treatment failures have serious consequences for public health since they raise morbidity and mortality rates for a variety of illnesses. This problem is most evident in the treatment of HIV, TB, and pneumonia, where poor treatment outcomes are made worse. According to a research conducted in Ethiopia, 18.9% of patients receiving first-line antiretroviral therapy failed to respond to treatment, mostly as a result of poor adherence and younger age (22–23). This underscores the need for focused treatments.

Studies reveal that children who are not HIV-positive but have been exposed to the virus have a 47% treatment failure rate for pneumonia, and their mortality rate is four times higher than that of their HIV-negative peers (23). Effective tracking and support mechanisms are crucial, as demonstrated by the much higher mortality rates (54.1%) of tuberculosis patients in Nigeria who interrupted their treatment compared to those who finished it (24). These results show that treatment failures increase morbidity and put a burden on healthcare resources; therefore, comprehensive initiatives to enhance treatment efficacy and adherence across groups are required.

### 3.2 Rising Multidrug-Resistant Pathogens Featuring Azithromycin Resistance:

A rising public health concern is the rise of multidrug-resistant organisms that show azithromycin resistance, especially Neisseria gonorrhoeae and Salmonella. The epidemiological patterns and genetic factors behind this resistance are highlighted by recent investigations. Salmonella has been shown to be resistant to the antibiotic azithromycin in food animals and retail meats, and there is also notable co-resistance to other antibiotics such as ciprofloxacin and ceftriaxone (25).

Mobile genetic elements often carry resistance determinants like mph(A), erm(42), and erm(B), which aid in the dissemination of these determinants among different serovars (27).A significant 3.1% of nontyphoidal Salmonella isolates in Taiwan were azithromycin-resistant, making up over half of the isolates resistant to multiple drugs (2). Azithromycin-resistant Neisseria gonorrhoeae isolates in Russia rose dramatically from 0% in 2018–2019 to 16.8% in 2020–2021, and these isolates were associated with particular genetic alterations. Mutations in the 23S rRNA gene and the mtrCDE efflux system were linked to resistance, suggesting a complicated genetic foundation for resistance (28).

The advent of azithromycin resistance presents important concerns, but it also emphasizes the necessity for further study and surveillance to comprehend the mechanisms underlying the propagation of resistance and create workable countermeasures.

**3.3 Need for alternative treatments and combination therapies:**

Due to the shortcomings of conventional therapies, the necessity for alternative treatments and combination therapies is becoming more widely acknowledged in a variety of medical sectors. This change is a result of the ongoing search for safer, more potent alternatives that can treat complex illnesses more thoroughly.

The investigation of plant-derived phytochemicals as potential substitutes for conventional chemotherapeutics has been prompted by the latter's frequent toxicity and lack of selectivity. These natural compounds have lesser toxicity and numerous methods of action. A planned strategy to treatment is suggested by the potential for improving anticancer efficacy through the combination of phytochemicals with already available chemotherapeutics (29). Combining TRAIL with other medications to treat cancer can overcome resistance and improve treatment results (30).

Combination therapy are necessary for diabetic peripheral neuropathy (DPN) since the condition is complex, much as managing hypertension (31). Multi-target medication methods may be beneficial for neurodegenerative illnesses such as synucleinopathies, as they combine medicines that target distinct disease processes (32–33). Although combination and alternative medicines appear promising, further study is necessary to evaluate these techniques in clinical settings due to the complexity of diseases.

**4. Strategies to Combat Azithromycin Resistance:**

A variety of tactics, such as antibiotic stewardship, surveillance, infection control, combination therapy, the discovery of novel antibiotics, alternate treatment choices, and transmission prevention, are used to address meropenem resistance.

**4.1 Appropriate use of azithromycin antibotic (antibiotic stewardship programs):**

To maximize treatment outcomes and fight antibiotic resistance, azithromycin must be used appropriately within antibiotic stewardship programs (ASPs). With the prevalence of antibiotic resistance on the rise, ASPs work to guarantee the appropriate choice, dosage, and length of antibiotic treatment.

Antibiotic-associated side effects are intended to be reduced and clinical outcomes are intended to be improved by ASPs (38). They aid in avoiding side effects including Clostridium difficile infections, which are connected to improper antibiotic use (39). Strong leadership, sufficient funding, and a multidisciplinary strategy including pharmacists, infectious disease experts, and healthcare professionals are necessary for ASPs to be successful(40)(41).

Important tactics that improve efficacy and compliance are pre-approval for antibiotic prescriptions, early monitoring, and feedback systems (42).

Although ASPs are essential for optimizing azithromycin use, implementation might be challenging due to issues like finance and provider misperception. To effectively improve antibiotic stewardship, ASPs must overcome these challenges.

**4.2 Development of novel antibiotics and alternatives to azithromycin:**

The creation of new antibiotics and azithromycin substitutes is essential to combating the rising problem of antibiotic resistance. Recent studies have identified a number of novel tactics and substances that have promise for treating bacterial infections.

**4.2.1 Novel Antibiotic Classes**

Novel classes of chiral non-racemic macrocycles have been synthesized, and they show promise in opposing the cell walls of bacteria, suggesting that they may one day become strong antibiotics (43). A innovative approach to antibiotic creation is the use of computational methods to produce inhibitors that target the bacterial dihydrofolate reductase (DHFR) found in plasmids (44).

**4.2.2 Alternatives to Traditional Antibiotics**

Quorum Sensing Inhibitors: Particularly in pathogens like Pseudomonas aeruginosa, focusing on bacterial communication systems like quorum sensing has demonstrated potential in lowering virulence and increasing drug susceptibility (45). Metal nanoparticles and phytochemicals: These substances can strengthen the effectiveness of conventional antibiotics against resistant germs by acting as a supplement (46). Although these developments are encouraging, more research is still needed to completely comprehend and successfully apply these alternatives due to the intricacy of bacterial resistance processes.

**Public health interventions and scientific policy implications**

Public health initiatives that target azithromycin resistance must emphasize policy reform, education, and safe antibiotic use. The abuse of azithromycin, especially during the COVID-19 pandemic, has contributed to the emergence of resistant strains by causing its indiscriminate usage to proliferate (47). Strict prescription guidelines can help cut down on unnecessary antibiotic use. It is essential to monitor and control azithromycin use in both human and veterinary medicine. Campaigns for public awareness can educate communities about the risks associated with self-medication and the value of following doctor's orders. Careful prescription practices can be encouraged by educational initiatives aimed at medical professionals (48).

Making effective policies requires a One Health approach that integrates the health of people, animals, and the environment. To solve the resistance challenge, more funding must be allocated to the development of novel antibiotics and complementary and alternative medicine (49). Even while these actions are essential, there are still problems, like the necessity for international cooperation and the financial incentives that prevent pharmaceutical companies from creating new antibiotics.

## SUMMARY

The ability of bacteria to become resistant to antimicrobial agents is the primary cause of antimicrobial resistance (AMR), a serious global health concern that endangers people's health everywhere. This issue is made worse by the overuse of antibiotics in veterinary, agricultural, and medical settings. AMR has been associated with higher rates of sickness and mortality; by 2050, estimates indicate that it may be responsible for 10 million deaths yearly. Mutations and horizontal gene transfer are two genetic adaptations that lead to bacterial resistance and the development of multidrug-resistant (MDR) strains.

The long-half-life macrolide antibiotic azithromycin is widely used to treat STIs and respiratory infections, particularly in pediatric patients. However, its efficiency has been greatly diminished because to the rising incidence of bacteria resistant to azithromycin.

Azithromycin resistance is particularly concerning in infections such as *Escherichia coli*, *Neisseria gonorrhoeae*, and *Salmonella* species; studies indicate a 6% global rate of resistance. Newly discovered resistance genes, such mef(C)-mph(G) in pig *E. coli*, emphasize how agriculture contributes to the evolution of resistance. The review looks at the clinical ramifications of azithromycin resistance, such as more treatment failures, prolonged hospital stays, and more medical expenses. Hospitalization rates rise along with the prevalence of azithromycin-resistant infections including *Shigella* and *Salmonella*. These infections have a negative impact on patient outcomes. Treatment becomes more difficult due to resistance, which forces medical systems to employ broader-spectrum antibiotics, which in turn might exacerbate resistance.

Public health initiatives, the creation of novel antibiotics and substitutes, and antibiotic stewardship programs are some of the tactics used to prevent azithromycin resistance. While public health interventions promote international collaboration, education, and policy reform, antibiotic stewardship stresses the responsible use of antibiotics. Further investigation into innovative treatments, such as quorum sensing inhibitors and substitute substances like phytochemicals, is encouraging for the development of new therapeutic approaches. Global mobilization against azithromycin resistance will necessitate coordinated action from a variety of sectors.

## CONCLUSION

A major threat to world health is antimicrobial resistance (AMR), especially azithromycin resistance. Increasing resistance rates in many infections, like *Escherichia coli* and *Neisseria gonorrhoeae*, greatly complicate treatment regimens, which lower patient outcomes and increase healthcare expenses. Misuse of antibiotics, bacterial genetic adaptation, and environmental variables are contributing factors. A multimodal strategy including improved surveillance, conscientious use of antibiotics, and the creation of new medicines is necessary to counter this escalating threat. In order to lessen the impact and spread of resistant strains, international cooperation and public health initiatives are essential.

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