

## Review Article

# Irrational use of azithromycin in typhoid endemic areas: A challenge on multidrug-resistant typhoid treatment

Irfan Ullah<sup>1</sup>, Kiran Shafiq Khan<sup>2</sup>, Qasim Mehmood<sup>3\*</sup>, Muhammad Junaid Tahir<sup>4,5</sup>, Muhammad Irfan Malik<sup>4,5,6</sup>, Ali Ahmed<sup>7</sup>, and Muhammad Usman Munir<sup>8</sup>

<sup>1</sup>Kabir Medical College, Gandhara University, Peshawar, Pakistan; <sup>2</sup>Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan; <sup>3</sup>King Edward Medical University, Lahore, Pakistan; <sup>4</sup>Ameer-ud-Din Medical College, Affiliated with University of Health and Sciences, Lahore, Pakistan; <sup>5</sup>Lahore General Hospital, Lahore, Pakistan; <sup>6</sup>European Respiratory Society, Lausanne, Switzerland; <sup>7</sup>School of Pharmacy, Monash University, Bandar Sunway, Malaysia; <sup>8</sup>College of Pharmacy, Jouf University, Sakaka, Aljof, Saudi Arabia.

\*Correspondence:

**Qasim Mehmood**  
King Edward Medical  
University, Lahore,  
Pakistan.

E-mail address:  
qasimehmood1051@  
gmail.com

## Abstract

Typhoid is a food-borne fatal disease caused by *Salmonella typhi*. It causes inflammation of the intestine, resulting in diarrhoea, fever, headache, cough, and muscle pain. Improved hygiene has resulted in a marked decline in typhoid fever cases in many developed countries. However, significant typhoid cases emerge in low and middle-income countries annually, including Pakistan. Typhoid fever accounts for a larger percentage of acute febrile illnesses in Pakistan. Azithromycin is the only effective drug used in multidrug-resistant typhoid. The emergence of drug resistance typhoid has been of more significant concern in recent years due to its irrational use of azithromycin. It is considered the last antibiotic to eradicate multidrug-resistant typhoid fever from Pakistan. In this article, we express our concern of the irrational use of azithromycin in Pakistan and its effect on typhoid in the country.

**Keywords:** *Salmonella typhi*, MDR typhoid, azithromycin, resistant typhoid, Pakistan

## Introduction

Typhoid fever is a global health problem, especially in the tropics and subtropics areas of the world. People are exposed to *Salmonella typhi* (*S. typhi*) through contaminated food or water which results in bacteraemia after an incubation period of two weeks. Clinical signs and symptoms include stepladder pattern fever, headache, cough, muscle pain, spotty red rash on the trunk, and diarrhoea that typically supervenes in the second week (Naveed and Ahmed, 2016).

Typhoid fever is a major public health concern worldwide. A study reported that typhoid affects 11 million people annually with 129,000 deaths per year in low- and middle-income countries (Mogasale et al., 2014). A study conducted in Queensland, Australia, which analysed the data over a 20-year period, found that the incidence rate was 84.2 per 100,000 cases in tropical and 36.1 per 100,000 cases in sub-tropical areas (NIH, 2019). In Pakistan, 12,651 cases have been reported from 2016-2019 (NIH, 2019). In short, typhoid fever is one of the major healthcare burdens for the world and is associated with increased morbidity and mortality (Berger et al., 2019). To date, only a few resistance cases have been observed against azithromycin. However, if its irrational use is not terminated, it would become practically untreatable in many low-and middle-income countries, including Pakistan. This article highlights the need for the careful use of azithromycin in Pakistan and other typhoid fever endemic countries.

## Multidrug resistant (MDR) typhoid in Pakistan

The population-based data obtained from different hospitals in Pakistan showed a high incidence of typhoid fever. Approximately 12,651 typhoid fever cases have been reported from many cities of Sindh from 2016 to 2019 (NIH, 2020). In 2020, the main

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typhoid cases was found in children aged 0-4 years, followed by those of 5-9 years, with an overall attack rate of 16.3/10,000 population (NIH, 2020).

With mass administration of antibiotics and the emergence of multidrug resistant (MDR) strains, treatment of typhoid fever has become gradually more challenging. Although chloramphenicol, ampicillin, and trimethoprim have been used in the treatment of several diseases, *S. typhi* has shown its resistance to all of these antibiotics (Browne et al., 2020). Abbasi Shaheed Hospital, Karachi, clearly stated that MDR *S. typhi* strains have emerged and spread rapidly in the last two decades due to unnecessary antibiotic prescriptions for common colds (Aziz and Malik, 2018). As a result, azithromycin is considered the last alternative to cope with *S. typhi*-associated infections.

### Mass administration of azithromycin in Pakistan

Azithromycin is recommended for the treatment of a wide range of infections, including upper respiratory tract, middle ear, and sexually transmitted infections (i.e., chlamydia trachomatis, urethritis, cervicitis, and trachoma) (Doan et al., 2018). The addition of azithromycin to standard regimens of prophylaxis antibiotics prior to a non-elective caesarean delivery may also reduce the rate of postoperative infection (Tita et al., 2017). A daily dose of azithromycin has shown prompt results for individuals resistant to doxycycline and other antimalarial agents (Doan et al., 2018).

A previous study reported that about 152 participants purchased antibiotics, including Azithromycin and of them, 116 (76.3%) purchases were without a prescription, while 35 (23%) participants took an incomplete dosage of fewer than 5 days, indicating another factor for the mass antibiotics administration (Mboya et al., 2018). The study also revealed that around 88.8% of antibiotic purchases were irrational (Mboya et al., 2018). In term of azithromycin, it is necessary to reduce the excessive and inappropriate use of azithromycin, especially to treat other diseases that could be cured by other drugs, to prevent the occurrence of typhoid-resistant cases.

### Typhoid vaccination

The typhoid vaccine is considered an efficient tool to prevent typhoid fever. In March 2018, WHO recommended the use of typhoid conjugate vaccines in endemic countries (Andrews et al., 2019). In Pakistan, particularly in Sindh province, a low number (35%) of the population receiving immunization as per Pakistan's Expanded Programme for Immunization (EPI) has been reported (Qamar et al., 2020). After the typhoid outbreak in Hyderabad, a mass immunization campaign with Typbar-TCV™ (a single dose of 0.5 mL intramuscularly) was started in schools and multiple areas in 2019, targeting school and non-school going children aged from 6 months to 15 years old. Almost 324 schools and 39,939 children received typhoid immunization during the school-based vaccination campaign. After this successful campaign, Pakistan became the first country in the world to introduce the WHO-recommended typhoid vaccine to its routine immunization program in 2019 (Organization, 2020). New typhoid conjugate vaccines have exhibited a high and long-lasting immunogenicity. Furthermore, it is safe to be administrated to children 6 months of age with no adverse reaction (Mohan et al., 2015).

Reduction in the typhoid burden depends upon good surveillance systems and an effective vaccine (Mohan et al., 2015). The new generation vaccine, typhoid conjugate vaccines (Typbar-TCV™), exhibited significant impacts on typhoid endemic areas. However, despite the presence of a new vaccine (Typbar-TCV™), we should remain

vigilant and continue to evaluate the most effective antimicrobial treatments (Vashishtha and Kalra, 2020).

## Conclusion

Recently, MDR typhoid has emerged in Pakistan causing significant morbidity and mortality. Compared to drug-susceptible typhoid, the extensive treatment of drug-resistant (XDR) typhoid infection has become burdensome due to irrational use of antibiotics, especially azithromycin. Drug-resistant typhoid is associated with a more severe illness, more significant toxicity, and requires a longer duration of treatment.

Once azithromycin resistant strain develops due to a mass administration of drugs, typhoid fever would become practically untreatable, leading to an irrepressible future outbreak. We therefore recommend that non-rational use of azithromycin must be stopped to prevent a massive outbreak of typhoid, since azithromycin is the only suitable alternative treatment for complicated enteric fever in adults and children in the endemic area of MDR and nalidixic acid-resistant serovar Typhi strains.

## Authors' contributions

IU and KSK conceived the idea, KSK, IU, MJT, QM, MUM and AA retrieved the data and wrote the manuscript. MUM and AA reviewed the manuscript and provided comments. All authors approved the final version of the document.

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## Conflict of interest

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