

# Enteric Fever in Pakistani Children: Epidemiology, Antimicrobial Resistance, and Public Health Interventions - A Systematic Review

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## ABSTRACT

**Background:** Typhoid and paratyphoid fevers are common in low and middle-income countries, including Pakistan. Typhoid results from *Salmonella Enterica* serotype Typhi and Para typhi, and requires an urgent attention at public health intervention levels.

**Objective:** To synthesize the current findings on enteric fever in children in Pakistan, and integrate data on epidemiology, resistance, and public health interventions for this endemic disease.

**Methods:** This paper uses systematic review as methodology for synthesis of various studies on the effects and ramifications of enteric fever, as well as the effectiveness of diagnostic and therapeutic procedures. The findings will fill the gap in the existing literature that lacks in-depth insight into the integration of a multitude of issues concerning pediatric enteric fever in Pakistan.

**Results:** The findings of systematic review show that enteric fever is widespread and that many strains include MDR, and extremely drug-resistant (XDR) *S. Typhi*. These findings depict the difficulties in the management of patients in the clinical setting due to the increasing resistance to conventional treatments. The study also assesses the efficacy of the Typhoid Conjugate Vaccine (TCV), which proved to be helpful in decreasing the occurrence of the disease. Also, it highlights the importance of multi-sectoral interventions that include vaccination alongside the uptake of clean water, sanitation, and hygiene.

**Conclusion:** Thus, this paper provides an overview on epidemiology, resistance, and public health interventions to minimize the disease burden of enteric fever and curtail its spread among children in Pakistan. The findings also suggest possibilities for future prevention, control measures and policy changes.

**Keywords:** Enteric fever, antimicrobial resistance, XDR *S. Typhi*, typhoid conjugate vaccine, public health strategies.

## INTRODUCTION

Typhoid and paratyphoid fevers are infections that result from *Salmonella Enterica* serotype Typhi and Para typhi. These diseases are common in low and middle-income countries, including Pakistan [1-3]. However, efforts to contain and control the diseases have not been so effective, and Pakistan still records high incidence rates, especially among children and the young [4-6]. Some contributing factors include poor hygiene due to inadequate sanitation, lack of access to clean water, and the emergence of new virus strains that are difficult to combat and control.

This paper seeks to provide an analysis of the epidemiology of the disease, preventive measures, and treatment methods. The high incidence of enteric fever among children in Pakistan (573.2 per 100,000 children yearly [7]) demonstrates that there are ongoing concerns regarding public health, even with the implementation of prevention and treatment guidelines [8]. This bacterial infection is commonly seen in pediatrics and leads to serious consequences and complications. Furthermore, the highly drug-resistant (XDR) Typhi strains pose serious challenges as they don't respond to most of the drugs used to treat the infections, making it difficult to

cure them and resulting in severe complications and even death [9].

For the reasons mentioned above, it is crucial to conduct a detailed assessment of the epidemiological patterns, transmission pathways, and resistance profiles of the disease. This kind of analysis is important to determine the limitations of the current interventions and to come up with better ways of containing this highly contagious disease. There is a growing body of literature addressing these needs, and this review aims to synthesize and critically appraise the available data on the epidemiology of enteric fever in Pakistani children. Therefore, the purpose of this review is to describe the epidemiology, epidemiological determinants, and antibiotic resistance of this population to provide possible practice implications for public health.

Systematic reviews assist in the formulation and synthesis of various studies on the effects and ramifications of enteric fever, as well as the effectiveness of diagnostic and therapeutic procedures. Thus, this systematic review fills the gap in the existing literature that lacks in-depth insight into the integration of a multitude of issues concerning pediatric enteric fever in Pakistan. Furthermore, it will provide insight into disease prevalence and incidence, antimicrobial resistance, diagnostic evaluation, and treatment strategies. Additionally, the review examines fundamental, readily implementable measures that can be promptly adopted to address the shortcomings of

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the current strategy in managing enteric fever, along with recommendations to improve related healthcare processes and interventions. It will also be beneficial for healthcare workers, policymakers, and researchers who are dealing with and combating enteric fever in Pakistan.

### LITERATURE REVIEW

Typhoid and paratyphoid fever are one of the biggest issues in Pakistan, and children are the main sufferers of these diseases. Hence, the factors linked to the continued prevalence of the disease include a lack of clean water supply, poor hygiene practices, and the relatively new scourge of antimicrobial resistance. The trends of enteric fever in Pakistan demonstrate regional differences in the prevalence of the disease, and, in general, the rates are higher in the urban population, owing to high population density and the poor quality of the facilities [10].

Clinical diagnosis of enteric fever is challenging because enteric fever presents with signs and symptoms that mimic numerous other febrile illnesses in the region, such as fever, headaches, and gastrointestinal disorders. Conventional methods of diagnosis entail culture, and even though they are specific, they lack sensitivity and take a relatively long time to produce a result. Therefore, clinicians use other faster methods like the Widal test and Typhi dot, and these also do not have merits, which lead to either overestimation or underestimation of the disease.

The treatment of enteric fever gets further complicated due to the emergence of MDR and XDR strains of *Salmonella Typhi* [10]. These strains are resistant to first-line antibiotics such as chloramphenicol, ampicillin, trimethoprim, sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins. The appearance of the XDR typhoid is alarming, and it is especially problematic in Pakistan as a big outbreak was noted in Hyderabad, which shows that the traditional antimicrobial treatment does not help. This situation raises the question about other treatment options. In this case, azithromycin or carbapenem may be recommended since they have activity against resistant strains.

Earlier preventive strategies implemented in Pakistan to prevent enteric fever have been mostly WASH-related measures [11]. These strategies are important since the common mode of transmission of *Salmonella Typhi* is through the consumption of food and water contaminated with this bacterium. Even though the government has tried to enhance the public health systems, the issues of water and sanitation hamper the efforts of controlling the diseases. Secondly, the vaccination strategy and, more so, the TCV has been recognized as a strategy for reducing the burden of the disease [11]. Some efforts are currently underway to incorporate TCV into the National Expanded Program on Immunization (NEPI) and other intended groups, particularly children.

While conducting this systematic review of literature, it becomes quite apparent that there is a very complex relationship between social and economic development and the epidemiology of enteric fever in Pakistan. Research also shows that the probability of getting enteric fever is high among people with low socioeconomic status because they lack access to clean water and proper sanitation [11]. In addition, the spatial aggregation of cases in specific urban and peri-urban areas indicates that targeted prevention measures could help decrease disease rates.

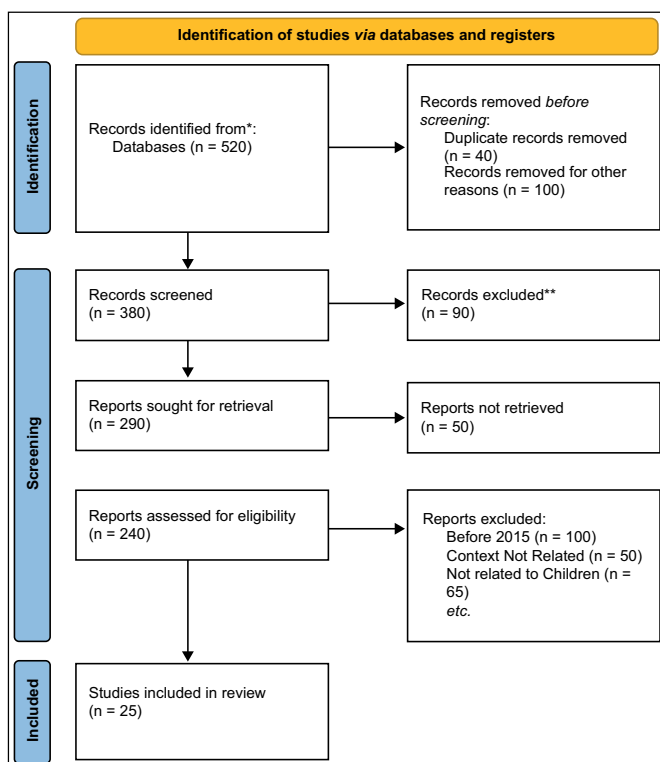
The genetic relatedness of the *Salmonella Typhi* strains in Pakistan reveals information about the development of antimicrobial resistance and the pathways of strain dissemination on the local and international levels [11]. Genomic research has established the genetic variations associated with drug resistance and possible targets for new intervention strategies. Consequently, the emergence of multiple-drug-resistant strains of typhoid fever is a critical global health issue that requires international cooperation in surveillance, drug research, and vaccine deployment.

One cannot underestimate the contribution of healthcare practices in the spread of the resistant Typhoid strains. Antibiotic misuse, including the choice of an antibiotic and its administration time, is also one of the major causes of the emergence of resistance [12-14]. It is crucial to spread awareness among healthcare professionals and the general population about the proper use of antibiotics [9, 15-17] to prevent the development of new antibiotic-resistant strains. Also, increasing laboratory capabilities for the correct diagnosis and drug resistance profiling is crucial for the proper management of the cases [18-20].

In conclusion, there are various aspects of enteric fever management in Pakistan, including clinical, epidemiological, and molecular approaches. Other recommendations for future research include the consideration of integrated clinical surveillance data to monitor and predict disease occurrences to facilitate appropriate public health interventions. However, the future of enteric fever control requires further research and development of new and better vaccines and anti-causal agents due to the increase in resistance to the currently available antibiotics.

### METHODOLOGY

The structure of this systematic review was strategized to gather the most recent research on enteric fever in children in Pakistan, its epidemiology, clinical diagnosis, prevention, and management. This study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure the systematic review of the literature and the synthesis of the data based on the best practices as depicted in Fig. (1).



**Fig. (1):** Screening Process using PRISMA Flow-diagram [21].

**Search Strategy:** I researched major databases like PubMed, Scopus, and Web of Science to gather articles published in the last five years. The search was designed using specific keywords and Boolean operators: [enteric fever OR typhoid OR *Salmonella Typhi*] AND children OR pediatric AND Pakistan]. With this approach, the research aimed to capture all the published articles that present data on the prevalence, resistance, diagnostic approach, and treatment outcome for enteric fever in children in Pakistan.

**Inclusion and Exclusion Criteria:** Literature reviews were included if they were published in a refereed journal including and after 2015, included subjects up to 18 years of age from Pakistan, and addressed one or more of the following aspects: epidemiology, diagnosis, management, or prevention of enteric fever. The following types of studies were excluded from the analysis: those published in a language other than English, those conducted with adults, as well as case reports, editorials, or commentaries. This approach was chosen to limit the retrieval of the systematic review topics to those studies that have large and methodologically proper data sets.

**Data Analysis:** Given the aim of identifying the detailed patterns and meanings of the collected data regarding epidemiological patterns, diagnostic challenges, therapeutic efficacy, and preventive measures of enteric fever in children in Pakistan, Thematic Analysis was suitable. One of the main benefits of thematic analysis is that it is relatively flexible and can provide a detailed account of the data while still being relatively

straightforward. Using the PRISMA guidelines (**Fig. 1**) ensured that a clear protocol was followed and that potential sources of bias were minimized in the process.

For the requirement of analyzing the epidemiology, clinical patterns, diagnostic tools, disease burden, and treatment measures, thematic analysis is suitable. This analytical framework identifies different themes and codes mapped to these themes. This analytical method is flexible and provides an account of data associated with themes.

The outcome of the Review Process: Using the PRISMA flow diagram (**Fig. 1**), the screening process from database searching to the final selection of articles yielded a total of 25 articles. The detailed process is depicted in the form of a PRISMA flow diagram as follows in **Fig. (1)**:

## RESULTS

### Epidemiology and Burden of Disease

Surveillance for Enteric Fever in Asia Project revealed that 22% of patients tested in Karachi had culture-confirmed enteric fever, which is indicative of its high epidemiological burden in this urban center [22]. More studies confirm this finding; for instance, a cross-sectional survey conducted in Islamabad found that 88% of *Salmonella* isolates from children were resistant to one or more antibiotics, which is a risk to public health [23]. This widespread resistance not only complicates the treatment of the infections but also increases the chances of severe disease complications.

Regarding the resistance, the main issue concerns the MDR and XDR strains of *Salmonella Typhi*. A study done in Islamabad indicated that 59% of *Salmonella Typhi* isolates were MDR, meaning that there is an added difficulty in managing this disease using conventional drugs [23]. Such high levels of resistance lead to increased morbidity and mortality rates, overwhelming the healthcare system and highlighting the need for new treatment regimens. However, in Hyderabad, the cases of XDR strains have been relatively high. As found in other studies, many isolates are resistant to multiple first-line antibiotics, hence limiting the drugs that can be used in treating them [24, 25].

The effects of such high levels of resistance are not only felt within the clinical domain but also in the sphere of public health. Although the prevalence rates are high, so is drug resistance, and thus, there is a need for a combination of efforts to tackle this. Therefore, the situation entails the uptake of improved standards in health, such as the administration of vaccines against enteric fever, improved supply of water, and better sanitation standards to check the spread of the disease. Consequently, focus should be placed on research and development of new antibiotics and treatment plans to combat those cases, especially the resistant ones.

In conclusion, to prevent and control enteric fever in Pakistan, there is a need to know its epidemiology and resistance patterns. For example, the Surveillance for Enteric Fever in Asia Project is a systematic study that generates useful information that can be applied in decision-making in the field of public health. Therefore, by aligning these strategies with the current context of enteric fever, health officials can play a vital role in combating this endemic disease and work towards reducing the impact on the most vulnerable population in the country, *i.e.* children [22].

### Clinical Presentation and Diagnosis

Enteric fever in children is characterized by a diverse range of symptoms, making the diagnosis of the disease difficult. The symptoms of the disease have been reported to include high fever, abdominal pain, vomiting, nausea, and hepatosplenomegaly; however, severe cases may lead to severe complications such as intestinal perforation and hemorrhage [23, 26, 27]. Such severe manifestations, however, require proper and efficient management tactics [28, 29]; however, due to the nature of early symptoms that are variable and not well defined, diagnosis and treatment are often delayed. The use of diagnostic tools such as blood cultures and the Widal test further worsens this delay. Even though such tests are still in use, they are known to have varying sensitivity and specificity, especially in the face of drug resistance by the pathogen [30].

The diagnosis of enteric fever becomes more challenging due to the emergence of extensively drug-resistant typhoid fever, as seen in Hyderabad, Pakistan [31]. These strains have been reported to exhibit high levels of resistance to almost all the known antimicrobial agents, including fluoroquinolones and third-generation cephalosporins. There are such strains that necessitate enhanced diagnostic measures in a bid to get better and faster outcomes so that the appropriate medication can be administered. Moreover, the high incidence rates in areas with poor hygiene standards show that only large-scale interventions can help in the prevention of the disease spread [31].

Considering the mentioned challenges, it is important to enhance the current diagnostic approaches for enteric fever in Pakistan. Improvement of diagnostic work may entail the use of better molecular tools that can easily detect even low levels of *Salmonella Typhi* and *Salmonella paratyphi* in blood tests. In addition, enhancing the lab equipment for these tests would aid in the early detection of the disease and the right management to prevent the development of severe and lethal consequences [23, 30]. Such advancements would not only improve patient care but also the overall public health approach toward the prevention and management of enteric fever especially in vulnerable children.

### Antimicrobial Resistance and Treatment Challenges

The problem of AMR is discussed in several studies on enteric fever, especially the growing rates of XDR typhoid fever. Former first-line antibiotics such as fluoroquinolones and cephalosporins, which were previously used in treating typhoid fever, are now ineffective in treating XDR strains due to their high drug resistance [31, 32]. This resistance makes the treatment more complicated because the cheaper and more common antibiotics are not as effective [14]. The presence of such strains should be a cause for concern for the need to establish drug resistance patterns and adapt treatment measures for managing the disease among the affected population, including high-risk groups such as Pakistan [31, 32].

The literature suggests that clinicians use aggressive antibiotics and medicines such as Ciprofloxacin, carbapenems, and azithromycin more frequently due to antibiotic resistance [33]. These drugs are active against the multi-drug resistant strains of *Salmonella Typhi* and *Paratyphi* and are useful in the treatment of severe cases of XDRTF. Nevertheless, such drugs are often expensive and not easily accessible, especially in the resource-poor regions of the world, which raises concerns about the fairness in accessing treatment. This situation not only impacts the quality of patient care but also further strains the already over-stretched healthcare systems that are already struggling with managing the burden of infectious diseases [23, 34].

It is important to discover new vaccines and agents to curb infections in patients. Policymakers and government agencies should strengthen the basic healthcare systems to ensure diagnosis and treatment facilities in rural and urban areas. These intervention measures at the mass level will reduce mortality rates due to enteric fever in low-socioeconomic populations [10, 30].

### Prevention and Public Health Strategies

According to different studies, vaccines like the Typhoid Conjugate Vaccine [TCV] proved to be very effective in preventing the onset of Typhoid [35]. Other field trials confirm the efficacy of the vaccine apart from some specific resistant strands identified in children [34, 36]. This situation reinforces the use of the vaccine as a preventive tool and as an adjunct in the control of the disease, particularly in typhoid-endemic areas. Moreover, the TCV deployment, especially in the high transmission region, will greatly reduce the incidences of the disease and, subsequently the pressure on health facilities.

Regarding typhoid fever, it is important to support vaccination with the improvement of water, sanitation, and hygiene. Typhoid is a water-borne disease that is contracted through the intake of contaminated water and food due to poor hygiene. The same studies have also shown that increasing water quality, access to safe water, and sufficient sanitation facilities are effective in

the prevention of typhoid fever [30]. Consequently, it is possible to cut the transmission risk by integrating WASH with vaccination and ensuring that the community appreciates the need to tackle both the cause and symptoms of the diseases.

Also, there is a need to educate the public on the causes of typhoid fever and other diseases that are related to it. Expanding the awareness of people in the communities concerning hygiene, food handling, and the impact of vaccines could help improve the outcomes of the WASH and TCv interventions [34, 37].

### **Socioeconomic Factors and Public Health Implications**

The literature confirmed socioeconomic status as one of the strong determinants or risk factors for infectious diseases, including enteric fever [34, 37]. The poor population in rural areas doesn't have access to proper sanitation facilities and tends to adopt unhygienic practices for food management. Studies in Pakistan have also revealed that the incidence rate of Typhoid is high in areas that lack proper infrastructure and access to health facilities [30]. These findings point out that there are many barriers that public health interventions must consider for the prevention of typhoid fever, not only through medical approaches in disadvantaged areas.

Hence, it is crucial to understand that public health efforts should not only focus on the medical aspects of the disease but also on the social determinants that lead to the development of typhoid fever in these most vulnerable populations. Water quality improvement, sanitation, and hygiene promotion should also include other aspects of people's lives, such as education and income [30]. Also, targeted vaccination can help reduce the number of people who fall sick, especially children who are at high risk of being affected by the disease. Such problems are challenging for government departments, public health organizations, and society to implement the changes that may help in the prevention of Typhoid fever [31, 37].

### **Health System Challenges**

The health system's efficiency in managing enteric fever and the resources, healthcare, and treatment available for it differ in the urban and rural areas. In several developing countries, including some regions of Pakistan, variations in healthcare services may have the potential to affect the outcomes of enteric fever treatment and the effectiveness of disease prevention and control measures [34]. The healthcare facility may be better in urban areas and the medicines and diagnostic equipment may be more easily available as compared to the rural areas. However, in rural areas, there is a limited number of health facilities. In the case of typhoid fever, patients do not get proper diagnosis and treatment at the right time, which leads to increased morbidity and mortality rates [6, 37].

These differences emphasize the need to improve the overall performance of health systems and promote equal distribution of resources and equal opportunities for care. In addition to the medical aspect, a robust health system should be put in place to support prevention through vaccination and the promotion of health [31]. Hence, it is important to improve and expand such infrastructure, even in rural and remote areas. Moreover, it is important to increase the physical infrastructure of the healthcare delivery system and to deploy the healthcare workforce across the regions to allow persons to access the services they need [7, 32, 38].

Hence, the strategies for capacity strengthening for health systems in the management of enteric fever entail the provision of adequate training to the health care providers on the best practices in the management of enteric fever and ensuring that the required medical commodities are available, including the effective antibiotics against the drug-resistant typhoid strains. It is also important to invest in having proper health information systems that will assist in the tracking of diseases and the management of epidemics. These measures have to be supported by effective financial planning and by delivering a robust health system that aims to address not only the manifestations of the typhoid fever epidemic but also its causes [10, 34]. These are crucial measures to enhance the health systems to combat diseases that are prevalent in societies.

### **Role of Public Awareness and Education**

The literature has highlighted the need for public health education to prevent enteric fever, with an emphasis on hygiene and vaccination [10, 34]. Well-coordinated educational interventions can lead to a change in people's behavior, which means that the cases of typhoid fever will be less frequent, particularly in the high-risk zones. Research done by Tahir *et al.* [34] showed that by educating the public on the ways through which Typhoid can spread and precautions that can be taken to avoid it, there could be a great reduction in cases that are newly reported. Many of these programs focus on the importance of hand washing, proper food handling, and the safe use of water to encourage behavior change that is sustainable in the long term.

However, it is important to increase the awareness of the public on the effectiveness of the Typhoid Conjugate Vaccine [TCV], especially in the regions that are most affected. When people comprehend how vaccination helps to avoid disease, they are more willing to join immunization programs, as highlighted by Thobani *et al.* [36], Qamar *et al.* [37], and Siddiqui *et al.* [30].

The health authorities back such campaigns and can greatly increase the coverage of vaccinations, which will, in turn, reduce the cases of Typhoid and thus emphasize the importance of education in health campaigns.

## Economic Impact of Enteric Fever

It is not only human suffering in terms of illness and death, which is caused by enteric fever, but also the financial burden in terms of cost of treatment, loss of time due to hospitalization, and wages lost due to illness. Families suffer tremendous costs in treating enteric fever since they have to use their money to pay for medical bills, loss of income, and adverse health effects related to the disease [39]. These costs are particularly damaging in poverty-stricken regions where they can lead to excessive expenditures on the part of the patients and their families and may even lead to a perpetuation of poverty; this underlines the importance of accessible health care and family support for those in need.

The other implication of the economic impacts of the outbreaks is on the health sector because resources are diverted to the containment of the outbreaks. Preventive measures like early typhoid vaccination and better sanitation can reduce the incidence of Typhoid and hence the cost of healthcare facilities [30]. With early prevention and treatment measures adopted by governments and other health organizations, it is possible to improve the health of the populace besides cutting down on the costs of management for the disease, which is enteric fever, hence the need for early intervention.

The Summary of the systematic review findings is presented in Table 1 as follows:

**Table 1:** Main results of the systematic review of studies.

Authors	Study Setting	Study Design	Main Results
Rasheed MK, Hasan SS, Babar Z-U-D, Ahmed SI [26]	Hyderabad, Pakistan	Observational	Highlighted the public health challenges of XDR typhoid fever, stressing urgent interventions like sanitation improvement and vaccination.
Rahman SK, Halim A, Hayat M, <i>et al.</i> [23]	Shifa International Hospital, Islamabad, Pakistan	Retrospective	Demonstrated significant resistance to conventional antibiotics, suggesting a need for revised treatment strategies.
Ahmad S, Zahid SB, Salahuddin A, <i>et al.</i> [40]	Tertiary care hospital, Peshawar, Pakistan	Retrospective	Revealed high resistance rates to traditional antibiotics and suggested the effectiveness of carbapenems for resistant strains.
Jamro B, Shaikh NA, Sohu KM, <i>et al.</i> [41]	Ghulam Muhammad Mahar Medical College Hospital, Sukkur	Retrospective descriptive	Indicated significant morbidity from delayed diagnosis and drug-resistant strains, emphasizing the need for improved diagnostics and rational antibiotic use.
Nasir S, Rafique M, Jamal A, <i>et al.</i> [27]	Dr. RKMP Civil Hospital, Karachi, Pakistan	Observational	Identified hematological markers crucial for early diagnosis, recommending further research for clinical management improvements.
Ullah H, Razzaq A, Ahmad AM, <i>et al.</i> [28]	Combined Military Hospital, Peshawar, Pakistan	Cross-sectional	Found a significant portion of MDR <i>Salmonella Typhi</i> , advocating for monitoring inflammatory markers to detect MDR cases early.
Naveed A, Ahmed Z [33]	Holy Family Hospital, Rawalpindi, Pakistan	Randomized controlled trial	Demonstrated superior efficacy of Ceftriaxone over Ciprofloxacin in pediatric typhoid treatment, suggesting a shift in treatment guidelines.
Sohail M, Anjum ZM, Masood J, <i>et al.</i> [10]	Children Hospital and Institute of Child Health, Faisalabad	Observational	Reported high prevalence of XDR strains, recommending continuous surveillance and public health measures to control the spread of Typhoid.
Yousafzai MT, Irfan S, Thobani RS, <i>et al.</i> [22]	Multiple hospitals in Karachi, Pakistan	Observational	Part of SEAP showed a high burden of XDR strains, advocating for improved surveillance and vaccination strategies.
Shaikh <i>et al.</i> [42]	Pakistan	Observational	Discussed the role of illicit antibiotic sales in resistance, calling for stringent regulations and community awareness programs.
Longley <i>et al.</i> [35]	Bangladesh, Nepal, Pakistan	Review	High rates of hospitalizations and sustained Typhoid symptoms require strong intervention measures like TCv in Asian regions.

## DISCUSSION

The findings of this systematic review are relevant to the epidemiology, clinical management, and prevention of enteric fever in children in Pakistan as summarized in Table 1. The systematic review of papers mentioned in Table 1 points to the continued need to fight the disease burden of enteric fever in children in Pakistan. The implications of the findings of this study are very broad and practical and can be seen in the real world. First, the high prevalence and incidence of drug-resistant strains, including XDR typhoid, calls for enhancement and further enforcement of antimicrobial stewardship programs. It should also address the issue of how to treat diseases that cannot be treated without the use of antibiotics in a way that will not add to the problem.

Thus, the evidence presented in this review regarding the efficacy of the Typhoid Conjugate Vaccine (TCV) could be used to advocate its use in Pakistan and other areas where typhoid fever is prevalent. With vaccination, there is a decreased prevalence of diseases like typhoid fever in individuals who have taken the vaccine. However, vaccination should not be the only strategy for controlling the disease; there is a need to enhance WASH practices. Therefore, public health campaigns should focus on both vaccination as well as WASH in the urban and rural populace.

Authors	Study Setting	Study Design	Main Results
Wani JN, Bhat AS, Yusuf S, <i>et al.</i> [29]	Government Medical College Srinagar, India	Observational	Outlined the clinical spectrum in children, stressing the efficacy of ceftriaxone as a monotherapy and the importance of accurate diagnostics.
Thobani RS, Yousafzai MT, Sultana S, <i>et al.</i> [36]	Sindh, Pakistan	Observational	Evaluated the effectiveness of TCV in a field campaign, demonstrating high vaccine efficacy and stressing the need for integrated health interventions.
Kumar N, Dayo A, Ghoto MA, <i>et al.</i> [43]	Tertiary Care Hospital, Hyderabad, Pakistan	Retrospective cross-sectional	Assessed resistance and prescribing trends, urging the need for updated treatment protocols based on local resistance patterns.
Ahmad M, Shah N, Siddiqui MA [30]	Services Hospital, Lahore, Pakistan	Observational	Reported high prevalence of MDR and XDR strains, advocating for continuous monitoring and updated antibiotic prescribing practices.
Batool <i>et al.</i> [44]	Lyari Town, Karachi	Cross-sectional	The immunization coverage rate for the effectiveness of TCV for Typhoid was satisfactory for the population.
Mohsin <i>et al.</i> [45]	Gadap Town, Karachi, Pakistan	Cross-sectional	Investigated drug-resistant <i>Salmonella Typhi</i> and Paratyphi A in children. Found high resistance to several antibiotics, emphasizing the public health threat in Karachi.
Iftikhar A, Bari A, Jabeen U, <i>et al.</i> [46]	The Children's Hospital and Institute of Child Health, Lahore	Prospective cross-sectional	Identified the frequency and spectrum of complications, stressing the need for vaccination and vigilant monitoring to reduce severe outcomes.
Yousafzai <i>et al.</i> [25]	Hyderabad	Cohort Study	TCV was effective against different strands of Typhoid.
Memon <i>et al.</i> [47]	Karachi	Descriptive Observational	Use of different risk factors like fever before hospitalization and use of unclean water is strongly linked to XDR <i>Salmonella</i> infection.
Rashid, Muhammad, Bano, Iqbal, & Hanif, Asif [48]	Children's Hospital Lahore, Pakistan	Cross-sectional	Explored the prevalence of infectious diseases, highlighting the burden of enteric fever and calling for enhanced public awareness and preventive measures.
Iftikhar, A., Hamid, M. H., & Masood, Q. [49]	Tertiary care hospital in Lahore, Pakistan	Case-control	Identified risk factors for complications, emphasizing early recognition and intervention to prevent severe outcomes in enteric fever.
Shahid, S., <i>et al.</i> [50]	Karachi, Pakistan	Observational	Discussed the epidemiology and burden of enteric fever, highlighting the resistance challenges and the need for targeted public health interventions.
Batool <i>et al.</i> [51]	Karachi	Case-control	TCV showed varying effectiveness for typhoid patients.
Tharwani, Z.H., Kumar, P., Salman, Y., <i>et al.</i> [11]	Pakistan	Review	Explored challenges and efforts in typhoid management, advocating for improved water and sanitation infrastructure and comprehensive vaccination campaigns.

However, the systematic review in this study is not without certain limitations. A possible concern is that some of the included studies in the review may have been of a higher or lower quality than others, which may have an impact on the transferability of the findings. However, the majority of these studies are carried out in the urban setting. In contrast, the epidemiology of the disease in rural areas might be different and may have different risk factors than the urban ones. Further study should be planned to include patients from other regions of Pakistan to get a more comprehensive view of enteric fever in the different areas of the country.

In conclusion, this review contributed to the identification of the current epidemiological situation of enteric fever in Pakistan, emphasizing the necessity of further research and monitoring. For this reason, surveillance must be carried out to determine whether the public health policies for AMR are still relevant and productive. It should be noted that the described measures require the support of various government agencies, healthcare facilities, and other interested parties. Thus, it is important to strengthen the effectiveness of the interventions that are being implemented to prevent enteric fever, which remains a major health issue in Pakistan.

## CONCLUSION

In conclusion, this systematic review of enteric fever among children in Pakistan provided important findings. It is a valuable contribution to the understanding of the epidemiology, management, and control of the disease in the country. High incidence rates of enteric fever and increasing resistance to commonly used drugs through MDR and XDR *S. Typhi* strains indicate that there is an immediate need for better diagnostic, treatment, and preventive measures. The ongoing emergence and dissemination of antibiotic resistance pose a prolonged challenge to treatment guidelines and are associated with worse outcomes in the management of patients, and thus highlight the importance of enhancing existing antimicrobial stewardship programs and the use of new antibiotics and treatment regimens that target resistant strains.

Furthermore, the review establishes the efficacy of TCV in decreasing the incidence of typhoid fever, thus advocating for increased use of the vaccine as part of national immunization programs in endemic regions. However, there is a need to address the problem of enteric fever in Pakistan through an integrated approach that entails addressing key determinants of water quality,

sanitation, and hygiene practices, as well as raising awareness among the public. These measures are very important in preventing the spread of enteric fever and its effects on the population, especially children. Therefore, this review is timely as Pakistan struggles with this health issue, and it is a wake-up call to the policymakers, healthcare professionals, and academics to step up the fight against enteric fever.

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## CONFLICT OF INTEREST

The author declares no conflict of interest.

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