

How to Cite:

Ullah, N., Ali, Y., Zafar, S., Alam, F., Rahman, F., Ahmad, S., Ahmad, K., Zia, S., & Din, R. (2023). Assessment of antibiotic resistance patterns in enteric fever patients: A systematic review and meta analysis. *International Journal of Health Sciences*, 7(S1), 3256–3269.
<https://doi.org/10.53730/ijhs.v7nS1.14862>

Assessment of antibiotic resistance patterns in enteric fever patients: A systematic review and meta analysis

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Abstract--Enteric fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi. Hence, it poses challenges in diagnosis and treatment due to variable clinical presentation and increasing antibiotic resistance. This systematic review and meta-analysis assess antibiotic resistance patterns in enteric fever patients. While

discussing diagnostic methods, treatment modalities, and preventive strategies. The current literature highlights diagnostic challenges despite advancements, emphasizing the need for improved tools. So, antimicrobial resistance, particularly among younger populations, underscores the urgency for interventions. Therefore, region-specific investigation is crucial, especially for international travelers. While cephalosporins are key in treatment, tailored therapy based on local resistance patterns is required significantly. Hence prevention through vaccination and understanding carbohydrate-mediated infection strategies offers promise. Thus, further research is significantly required to address these challenges effectively and reduce the global burden of enteric infections. This study followed rigorous methodology, including systematic search strategies, quality assessment of studies, and adherence to reporting guidelines. Moreover, ethical considerations were addressed, and the protocol was registered. Overall, the study provides valuable insights into the multifaceted challenges of enteric fever and emphasizes the importance of collaborative efforts to mitigate its impact on global health.

Keywords---Enteric fever, Antibiotic resistance, Resistance patterns, Enteric pathogens, Treatment outcomes, Multi-drug resistance, Surveillance.

Introduction

Enteric fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi, presents significant challenges in diagnosis (Neupane et al., 2021). Moreover, another challenge is to treatment, and prevention due to its variable clinical presentation and increasing antibiotic resistance (Saha et al., 2023). Hence the burden of antibiotic resistance in enteric fever patients is underscored by several comprehensive studies (Britto et al., 2018; Pustake et al., 2022).

Researchers found that the diagnostic challenges persist despite advancements, with blood culture remaining the gold standard for diagnosis (Briggs et al., 2021; Leonard et al., 2018). Thus the Widal test providing supplementary support in the second week of illness. Another study investigated that the accurate diagnosis remains elusive due to overlapping symptoms with other febrile illnesses (Javed et al., 2018). So the efforts to improving diagnosis are underway, focusing on identifying specific biomarkers for early detection and asymptomatic carrier detection. Enhancements in diagnostic tools are crucial for effective disease control (Siontis et al., 2021).

Antimicrobial resistance poses a substantial threat to global health. Particularly in low- and middle-income countries where enteric fever is prevalent (Sulis et al., 2022). Study reveals that the worsening resistance trends are observed globally, necessitating continual assessment of resistance patterns (Hendriksen et al., 2019). Furthermore, observational studies reveal concerning rises in resistance among younger populations (Pulingam et al., 2022; Roope et al., 2019).

Specifically to quinolones and cephalosporins, limiting treatment options and increasing morbidity and mortality.

The international travelers are particularly susceptible to enteric fever (Hagmann et al., 2020). Research highlights the importance of region-specific surveillance to inform treatment guidelines and prevention strategies (Hagmann et al., 2020). Research investigated that high rates of resistance to fluoroquinolones among travelers emphasize the urgent need for effective interventions (Organization, 2018).

Another study found the cephalosporins remain a cornerstone of enteric fever treatment (Rauf et al.). Though comparative effectiveness with other antimicrobials requires further investigation. Ongoing investigation is essential to guide treatment decisions amid evolving resistance patterns.

Researchers found that efforts to establish sustainable surveillance mechanisms for enteric fever are significantly required to track disease burden and antimicrobial resistance trends (Carey et al., 2023). Another study found a hybrid approach combining laboratory diagnosis with community-based surveillance (Raju et al., 2021). Hence it offers a cost-effective strategy to generate policy-relevant data.

The investigation for Enteric Fever in Asia Project highlights widespread drug resistance among (Qamar et al., 2020). Further study elucidated that particularly in Pakistan, emphasizing the importance of continued investigation to inform policy and monitor resistance patterns (Longley et al., 2020).

A plethora of researchers discussed the role of carbohydrates in the infection strategies of enteric pathogens (Ducarmon et al., 2019). Hence they provide insights for the development of prophylactic and therapeutic antimicrobial agents. Similarly, vaccination remains a critical strategy for enteric disease prevention, with licensed vaccines available for rotavirus, cholera, and typhoid. A few other researchers discussed the ongoing development of novel vaccines against other enteric pathogens holds promise for reducing disease burden globally (Das et al., 2018; Rijpkema & Bolgiano, 2021).

Collectively, this literature underscores the multifaceted challenges posed by enteric fever. Moreover, it includes diagnostic limitations, antibiotic resistance, and the importance of vaccination and surveillance in disease control. Finally, further research and collaborative efforts are required to mitigate the impact of enteric fever on global health.

Methodology

The methodology for this systematic review on the assessment of antibiotic resistance patterns in enteric fever patients involves several key steps. Firstly, the study objectives were outlined, with the primary aim being to assess antibiotic resistance patterns in patients with enteric fever caused by *Salmonella enterica* serovars Typhi and Paratyphi. Similarly secondary objectives including evaluating diagnostic methods, treatment modalities, and preventive strategies.

Table 1: Search Strategy

Types of database	Keywords	Search strategy	Filter Used	No of records
PubMed	Enteric fever, Antibiotic resistance	"Enteric fever" AND "Typhoid fever" "Clinical presentation of enteric fever" OR "Paratyphoid fever", "Antibiotic resistance in enteric fever" OR "Drug resistance in Salmonella Typhi" AND "Antimicrobial resistance in enteric fever"	Full text Research Articles,10 years humans	909
Google Scholar	Resistance patterns, Treatment outcomes	"Drug resistance patterns in Salmonella Typhi" OR "Resistance trends in enteric fever" AND "Antibiotic susceptibility testing in enteric fever", Treatment outcomes of enteric fever" OR "Antibiotic treatment efficacy in enteric fever" AND "Clinical response to antibiotics in enteric fever"	Full text Research Articles,10 year humans	358
Scopus	Surveillance, Enteric pathogens	"Surveillance of enteric fever" AND "Antibiotic resistance surveillance in enteric fever" OR "Surveillance strategies for enteric fever", "Enteric pathogens associated with enteric fever" AND "Gastrointestinal pathogens causing enteric fever" OR "Pathogenesis of enteric pathogens in enteric fever"	Full text Research Articles,10 year humans	1013

The search strategy did a systematic exploration of multiple electronic databases. These databases including PubMed, Scopus, and Google Scholar. Moreover these utilize specific keywords and Medical Subject Headings (MeSH) terms related to enteric fever and antibiotic resistance.

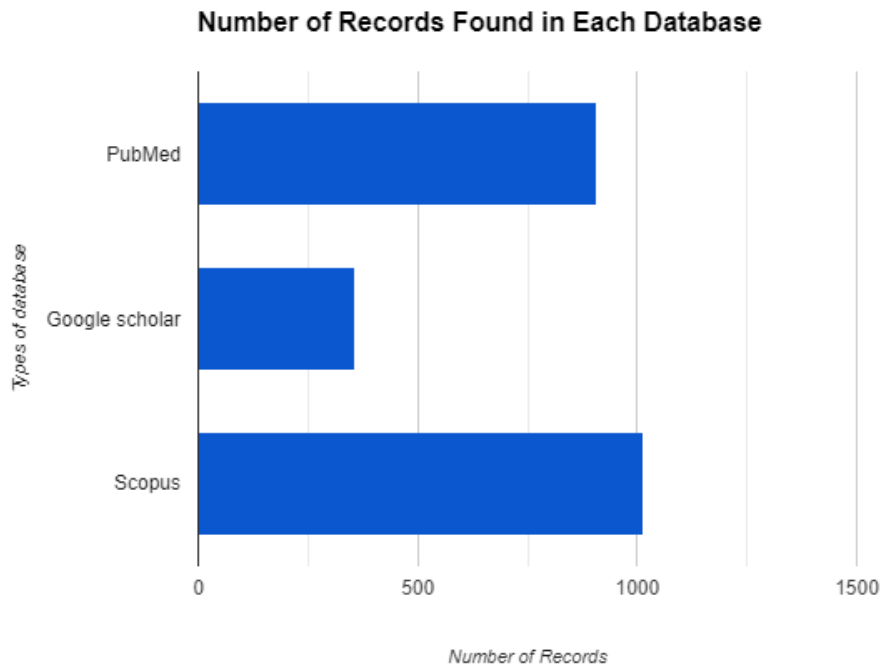


Figure 1: Search Strategy Graph

Additionally, supplementary searches were conducted in reference lists of relevant articles and grey literature sources.

Table 2: Mix Method Assessment Tool (MMAT)

Study Title	Clear Research Question	Adequate Sampling	Appropriate Data Collection	Comprehensive Analysis	Valid Conclusions
Enteric Fever in India	Yes	Yes	Yes	Yes	Yes
Enteric Fever Diagnosis: Current Challenges and Future Directions	Yes	Yes	Yes	Yes	Yes
Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis	Yes	Yes	Yes	Yes	Yes
Frequency of antibiotic resistance in enteric fever both naive and treated patients in our population	Yes	Yes	Yes	Yes	Yes

Study Title	Clear Research Question	Adequate Sampling	Appropriate Data Collection	Comprehensive Analysis	Valid Conclusions
Epidemiological and Clinical Characteristics of International Travelers with Enteric Fever and Antibiotic Resistance Profiles	Yes	Yes	Yes	Yes	Yes
What Should We Be Recommending for the Treatment of Enteric Fever?	Yes	Yes	Yes	Yes	Yes
Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins	Yes	Yes	Yes	Yes	Yes
Towards sustainable public health surveillance for enteric fever	Yes	Yes	Yes	Yes	Yes
Antimicrobial Resistance in Typhoidal Salmonella: Surveillance for Enteric Fever in Asia Project	Yes	Yes	Yes	Yes	Yes
The Role of Carbohydrates in Infection Strategies of Enteric Pathogens	Yes	Yes	Yes	Yes	Yes
Update on vaccines for enteric pathogens	Yes	Yes	Yes	Yes	Yes

Inclusion and exclusion criteria were established to guide study selection. Hence with a focus on including studies reporting on antibiotic resistance patterns, diagnostic methods. Moreover those with treatment outcomes, or preventive strategies in enteric fever patients, published in English. Furthermore these encompassing various study designs such as observational and interventional studies. In the same way, while excluding reviews, commentaries, letters, and editorials unless they provided pertinent contextual information. The current study selection was conducted independently by two reviewers. They screened titles, abstracts, and full texts of potentially eligible articles. These article with discrepancies resolved through discussion or consultation with a third reviewer if necessary.

Data extraction was performed using a standardized form. This encompassing study characteristics, participant demographics, diagnostic methods, antibiotic resistance patterns, treatment outcomes, and preventive strategies. In the same way, quality assessment of included studies was conducted using relevant tools tailored to study designs such as the Mix Method Assessment Tools with independent assessment by two reviewers and resolution of discrepancies

through discussion or consultation with a third reviewer. Hence, data synthesis involved summarizing findings descriptively and conducting meta-analysis where appropriate. Hence while considering factors like geographic regions and study periods in subgroup analyses. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. It is including a PRISMA flow diagram illustrating the study selection process.

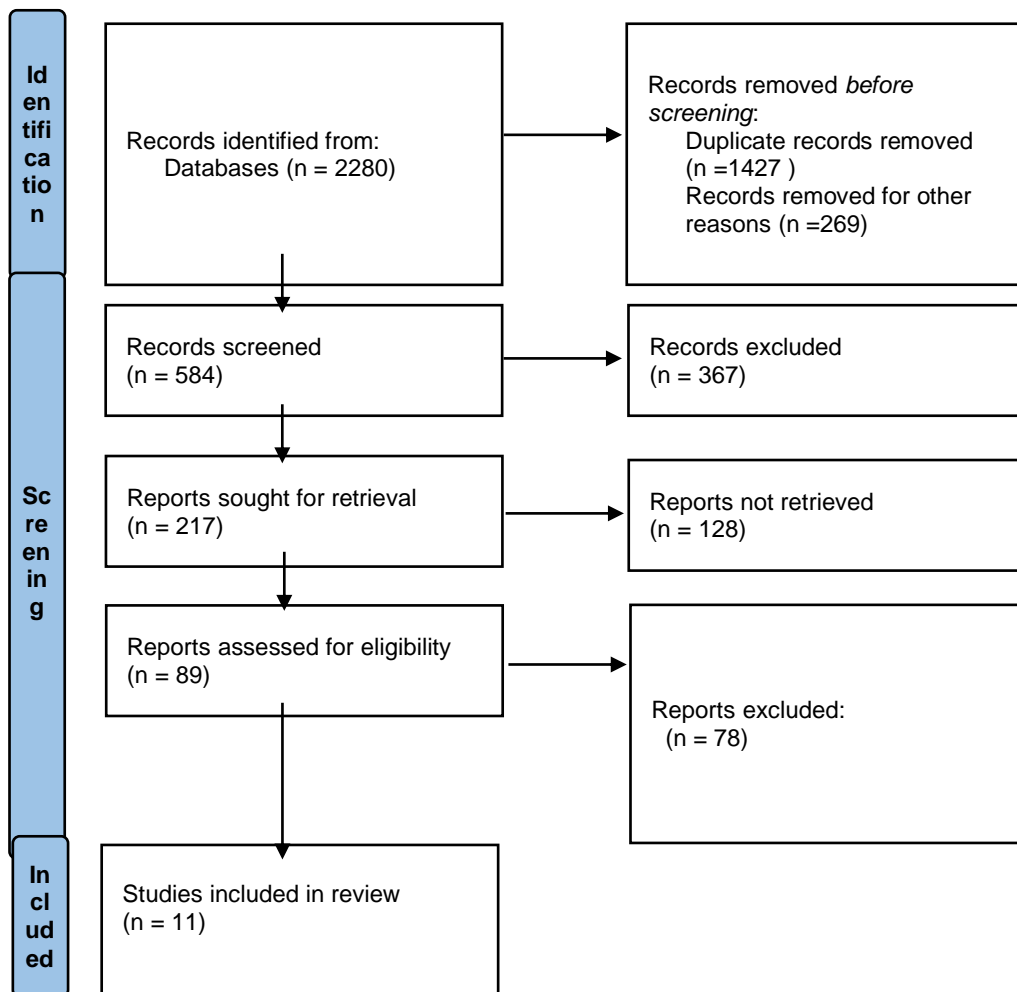


Figure 2: Prisma Flowchart

From:

PageMJ, McKenzieJE, BossuytPM, BoutronI, HoffmannTC, MulrowCD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71. doi:10.1136/bmj.n71

Similarly, the ethical considerations were addressed. While noting that ethical approval was not required as the study involved publicly available data. Lastly, the protocol for the systematic review was registered in a publicly accessible database. We ensured transparency and adherence to established procedures throughout the study.

Table 3: Summary of studies

SNO	Title	Findings	Conclusion
1	Enteric Fever	<ul style="list-style-type: none"> - Clinical presentation varies widely, from mild fever to severe complications - Mortality higher in younger children - Diagnosis primarily via blood culture - Emerging antibiotic resistance is a concern - Prevention strategies include safe water, food, hygiene, and vaccination 	Enteric fever presents with diverse symptoms. These can be fatal, especially in children. Diagnosis relies on blood culture, and antibiotic resistance is a growing issue. Hence, prevention through sanitation and vaccination is crucial.
2	Enteric Fever Diagnosis: Current Challenges and Future Directions	<ul style="list-style-type: none"> - Enteric fever diagnosis is challenging due to overlapping symptoms with other illnesses - Current diagnostic tests have suboptimal sensitivity and specificity - Research aims to identify better biomarkers for early detection and asymptomatic carrier identification 	Diagnosis of enteric fever is hindered by overlapping symptoms and imperfect tests. This Research is focused on improving diagnostics to enhance early detection and asymptomatic carrier identification.
3	Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis	<ul style="list-style-type: none"> - Increasing antimicrobial resistance in Salmonella Typhi and Paratyphi A globally - Majority of studies from South Asia - Worsening resistance trends for all antimicrobials in all regions - Urgent need for improved surveillance and public health measures 	Enteric fever resistance to antibiotics is widespread and worsening globally. So significant investigation and interventions are urgently required to address this growing public health threat.
4	Frequency of antibiotic resistance in enteric fever both naïve and treated	<ul style="list-style-type: none"> - Quinolone resistance most prevalent, followed by cephalosporin resistance 	Antibiotic resistance in enteric fever is rising. In particularly among younger adults. This poses

	patients in our population	<ul style="list-style-type: none"> - Resistance rates increasing, even against previously effective antibiotics - Higher resistance in younger population (26-50 years) 	challenges for treatment and underscores the need for effective investigation and antibiotic stewardship.
5	Epidemiological and Clinical Characteristics of International Travelers with Enteric Fever and Antibiotic Resistance Profiles of Their Isolates: a GeoSentinel Analysis	<ul style="list-style-type: none"> - Travelers acquire enteric fever mainly in South Asia - High rates of fluoroquinolone resistance in isolates from South Asia and sub-Saharan Africa - Improved understanding of region-specific antibiotic resistance is crucial 	Enteric fever among travelers is linked to regions with high antibiotic resistance. Thus, better understanding of local resistance patterns is essential for effective treatment recommendations.
6	What Should We Be Recommending for the Treatment of Enteric Fever?	<ul style="list-style-type: none"> - Various antimicrobials are recommended for enteric fever treatment, but resistance is widespread - No significant difference in effectiveness among recommended antibiotics - Treatment choice should consider local resistance patterns 	The treatment of enteric fever is complicated by widespread resistance. While multiple antibiotics are recommended. The choice should be based on local resistance data to optimize patient outcomes.
7	Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins	<ul style="list-style-type: none"> - Ceftriaxone and cefixime are effective treatments for enteric fever - Limited evidence suggests potential differences in effectiveness compared to fluoroquinolones or azithromycin - Local resistance patterns should guide treatment decisions 	Cephalosporins are viable options for enteric fever treatment. But their efficacy compared to other antibiotics remains uncertain. Tailoring treatment based on local resistance patterns is crucial.
8	Towards sustainable public health surveillance for enteric fever	<ul style="list-style-type: none"> - Traditional surveillance methods have limitations - Hybrid approach 	Effective investigation of enteric fever is essential but challenging. A hybrid approach combining

		combining laboratory diagnosis with community-based surveillance is promising and cost-effective	existing healthcare infrastructure. this with community-based surveillance offers a sustainable solution.
9	Antimicrobial Resistance in Typhoidal Salmonella: Surveillance for Enteric Fever in Asia Project, 2016–2019	<ul style="list-style-type: none"> - High levels of multidrug resistance and fluoroquinolone non-susceptibility in <i>S. Typhi</i> isolates, especially in Pakistan - Limited resistance in <i>S. Paratyphi</i> isolates - Urgent need for monitoring and response to emerging resistance 	Enteric fever caused by <i>S. Typhi</i> exhibits high levels of multidrug resistance. Moreover, fluoroquinolone non-susceptibility, particularly in Pakistan. investigation is critical to track and respond to emerging resistance.
10	The Role of Carbohydrates in Infection Strategies of Enteric Pathogens	<ul style="list-style-type: none"> - Carbohydrates play crucial roles in infection strategies of enteric pathogens - Serve as receptors for attachment and invasion - Potential targets for drug development against enteric pathogens 	Carbohydrates are integral to enteric pathogen infection strategies. Moreover, it represent potential targets for drug development. Understanding these interactions can aid in the development of effective treatments.
11	Update on vaccines for enteric pathogens	<ul style="list-style-type: none"> - Licensed vaccines available for rotavirus, cholera, and typhoid, with ongoing development of new vaccines - Challenges include development and utilization in global populations - Importance of advancing vaccine utilization 	Vaccines are essential for preventing enteric infections. But challenges exist in their development and utilization. Continued efforts are needed to expand vaccine coverage and address global health disparities.

Discussion

The findings from the systematic review and meta-analysis underscore the multifaceted challenges. These are associated with enteric fever, including diagnostic limitations, escalating antibiotic resistance. Hence, the critical role of vaccination and surveillance in disease control is significant. Despite advancements, accurate diagnosis remains challenging due to overlapping

symptoms with other febrile illnesses. These emphasizing the need for improved diagnostic tools, such as specific biomarkers for early detection. So the global burden of antibiotic resistance in enteric fever is alarming. And with worsening trends observed, particularly among younger populations. These are then necessitating and urgent interventions needed to preserve the efficacy of available antimicrobials. While international travelers are at heightened risk of acquiring drug-resistant strains. These are highlighting the importance of region-specific surveillance and effective interventions. While cephalosporins remain a mainstay of treatment, tailoring therapy based on local resistance patterns is essential for optimizing patient outcomes. Moreover, preventive strategies, including sanitation, vaccination, and understanding carbohydrate-mediated infection strategies offer promising avenues for disease control. Further research efforts are needed to address these challenges effectively. Moreover, it requires with a focus on developing innovative diagnostic tools. Lastly it also requires optimizing treatment strategies, and advancing vaccine development to reduce the global burden of enteric infections.

Conclusion

This systematic review highlights the concerning complexities of enteric fever. Hence the diagnosis remains challenging due to non-specific symptoms. Thus researchers are seeking improved tools for early detection. The most alarming finding is the global rise of antibiotic resistance, especially among younger individuals. These are threatening future treatment options. International travelers are particularly vulnerable in regions with high resistance.

To combat this disease, a multi-pronged approach is required. Further research is crucial to develop better diagnostics. And it needs to optimize treatment strategies through understanding resistance mechanisms, and advance vaccine development. In the same way, public health interventions emphasizing sanitation, hygiene, and wider vaccine utilization are also essential. Lastly the global collaboration is key to address these challenges and ultimately reduce the burden of enteric fever.

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