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Burden of *Salmonella Typhi* Isolated from Bloodstream Infection from 2015 to 2020: A Systematic Review and Meta-analysis

Zebunnesa Zeba[1], Shariar Talukder Hasan[2], Ahmed Faisal Sumit[3], Md. Abdullah Yusuf[4]

[1]Assistant Professor, Department of Public Health and Informatics, Jahangirnagar University, Savar, Dhaka, Bangladesh; [2]Post-Graduate [MPH], Department of Public Health and Informatics, Jahangirnagar University, Savar, Dhaka, Bangladesh; [3]Assistant Professor, Department of Genetic Engineering and Biotechnology, University of Dhaka, Dhaka-1000, Bangladesh; [4]Associate Professor, Department of Microbiology, National Institute of Neurosciences & Hospital, Dhaka, Bangladesh

Abstract

Background: Bangladesh is a major contributor to the global problem of typhoid fever, which is predominantly caused by Salmonella typhi. This is due to Bangladesh's subpar healthcare standards, inadequate cleanliness standards, and inappropriate and excessive use of antibiotics. **Objective:** Salmonella typhi antibiotic resistance and the current situation of typhoid fever in Bangladesh were the subjects of this systematic review. **Methodology:** Finding publications about Salmonella typhi in Bangladesh published between 2015 and 2020 required searching Google Scholar, PubMed, and Bangladesh Journals Online with pertinent keywords. A predetermined set of criteria determined who would be included or excluded. **Results:** Initially,50 articles were retrieved. Using PRISMA flow chart 5 were selected for the study. Through forest plot, the overall effect size is found 0.28 which is represented by a diamond with confidence interval of 0.06 – 0.50. Since the confidence interval does not cross the threshold of no impact, the p value is 0.00. We can conclude that the overall effect is statistically significant. Microsoft excel was used to figure out the trend of antibiotic resistance. The effect size of an article was 0.08 (95%CI 0.05 – 0.11) and weighted 20.44%. Another study was reported with the effect size of 0.07 (95%CI 0.00 – 0.14) and weighted 20.07%. **Conclusions:** S. typhi was shown to be quite prevalent, and there were also significant surveillance and data gaps in the research' methodological data. [*Bangladesh Journal of Infectious Diseases, June 2023;10(1):3-10*]

Keywords: *Salmonella Typhi*; Antibiotic resistance; Antimicrobial susceptibility; Meta-analysis; Prevalence; systematic review; Bangladesh

Correspondence: Zebunnesa Zeba, Associate Professor, Department of Public Health and Informatics, Jahangirnagar University, Dhaka, Bangladesh; **Email:** zeba5533@gmail.com; **Cell No.:** +8801711106654; **ORCID:** https://orcid.org/0000-0001-9576-1416

Introduction

Around 21 million incidents of typhoid fever are reported worldwide annually, with 1-4% of those cases ending tragically[1]. Developing and undeveloped nations, particularly those in south and southeast Asia and Africa, where there are inadequate sanitation and water supply conditions, reported the majority of the cases[2]. Typhoid fever is thought to affect 350 individuals per 100,000 in Bangladesh each year, primarily affecting children under the age of five[1]. In most cases, individuals affected with typhoidal infections produce bacteraemic febrile illness with characteristic symptoms of headache, fever, and malaise[3]. If untreated, mental illness, gastrointestinal bleeding, and septic shock will ensue[3].

Salmonella enterica serovar Typhi (*S. typhi*) is the major agent of typhoid fever, which is extremely common in tropical nations like Bangladesh and is mostly spread via the fecal to oral route[4]. Globally, around 17 million people are affected each year by *Salmonella typhi* infections, with fatality rate around 1.0% cases[1,4]. Besides poor sanitation, inappropriate and uncontrolled use of antimicrobial drugs are considered as a reason behind the high prevalence of *Salmonella typhi*[2]. In Bangladesh, *Salmonella typhi* strains were mostly found resistant to first line antibiotics like ampicillin, chloramphenicol, trimethoprim[4,5].

Even ciprofloxacin resistance *S. typhi* strains were found circulating in humans, which complicates the overall treatment policy[6,7]. As an alternative option to ciprofloxacin, third generation cephalosporins like cefixime and ceftriaxone have been proven to be effective and the last choice of option for the treatment of multi-drug resistant *S. typhi* infection. Notably in the quinolone resistance-determining region (QRDR) of the A subunit, mutations in the DNA gyrase (gyr) gene are to blame for *S. typhi* antibiotic resistance[2]. Antibiotic drug induced selective pressure may act as a main factor attributable to mutation in the gyrA gene. Besides, mutation in gyrB and parC in the QRDR region are also associated with quinolone resistance in S. typhi.[7] Furthermore, transferable plasmid mediated antibiotic resistance was also observed[8].

The danger of new strains of resistant organisms arising is further increased by the indiscriminate and improper use of antibiotics. In order to effectively treat *Salmonella typhi* infections, antibiotic dosing should be directed by the results of a blood culture and antibiotic sensitivity test. Most importantly, the recent antibiotic susceptibility and resistance pattern of *Salmonella typhi* strains will assist the physicians and doctors to choose the most effective drugs.

With growing antimicrobial resistance of S. typhi strains, detailed and accurate estimates of prevalence and sensitivity pattern of *Salmonella typhi* strains is required. However, lack of data regarding the prevalence of *Salmonella typhi* strain in Bangladesh and their sensitivity pattern act as a barrier to implement the treatment policy. Moreover, the current understandings of the sensitivity pattern of *Salmonella typhi* strains could not bring any clear conclusion in the present scenario. Therefore, it is an urgent need to determine the pooled prevalence of prevalence of *Salmonella typhi* isolated from blood stream infection and its resistance patterns to commonly used antibiotics in Bangladesh.

This work intends to perform a systematic review and meta-analysis to evaluate the literature on the prevalence and resistance pattern of *Salmonella typhi* in the blood stream infections and determine the combined results of these factors to observe the present scenario of *Salmonella typhi* infections.

Methodology

Study Design: To determine the *Salmonella typhi* prevalence in Bangladesh, this systematic review and meta-analysis was carried out. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Checklist was used to guide this study's methodology.

Literature Search: In addition to personally acquiring hard copies of publications from authors and local libraries nationally, a thorough search of the literature published between January 1, 2015, and December 31, 2020 was conducted in the databases like PubMed, Google Scholar, Science Direct, Google. *Salmonella typhi*, Antibiotics, Resistance, Susceptibility, and Bangladesh served as the search criteria. Boolean operators have been used to search keywords in PubMed, Google Scholar, and Science Direct.

Study Eligibility Criteria: We had gathered all of the studies that were available, and the data from these studies were added based on the eligibility criteria that was predefined, such as studies carried out in Bangladesh, published articles, cross-sectional studies, were published after 2015, had a sample size >10, the total number of samples, the number/percentage of strains was precisely stated and articles reported in English language. Articles that have data redundancy or don't have full text link were excluded from consideration.

Study Selection: Records identified using the search techniques from a variety of sources have been uploaded to Microsoft Excel 2013. Records that were duplicates were found, noted, and eliminated. With the established inclusion criteria, we independently reviewed the titles and abstracts for this. We were also given the autonomous task of gathering whole manuscripts and determining their suitability for inclusion.

Measurement of Outcome Variables: S. typhi prevalence and patterns of antibiotic resistance were the study's findings. By dividing the number of samples that tested positive for S. typhi by the total number of samples examined, the prevalence was determined.

Data Extraction: A standardized data extraction format was used to obtain the relevant information from the included papers. When further information was required or specifics about the approach needed to be clarified, the primary author of the original study was contacted. The primary author, publication year, area, sample size, sample source, research population, diagnostic technique, prevalence, species, and quality score were all included in the data extraction format for S. typhi prevalence.

Quality Assessment: The author independently evaluated each original study's bias risk. The study's quality was rated out of 10 points (10 stars) using the Newcastle-Ottawa scale as modified for cross-sectional research. The tool is divided into three main sections: methodological quality (rated 5 stars), study comparability (rated 2 stars), and statistical analysis results (rated 3 stars). For systemic review and meta-analysis, papers with scores of five or above were selected.

Data Processing and Analysis: Microsoft Excel 2013 was used to create a format for recording the pertinent extracted data. STATA 16.0 was used to do the data analysis. For outcome measurements and subgroup analyses, the data produced in Microsoft Excel were imported into the STATA programme. Using a limited maximum-like hood random effect model, the variance in genuine effect sizes throughout the population (clinical heterogeneity) was determined. Tables, funnel plots, and forest plots were used to explain the original papers. To calculate the combined prevalence of Salmonella typhi and resistance rate, a random effect model was utilized. It was shown the predicted pooled prevalence by forest plot with a 95% confidence interval and publication bias by funnel plot. Based on the publication year, geographic location, and study population, a sub-group analysis was conducted. The Cochrane Q-test and I^2 statistics were used to calculate the p values and analyze the heterogeneity of reported prevalence. When p 0, the Cochrane Q-test determines if there is heterogeneity. Statistics were judged to be significant at 1, or 1. In contrast to sampling error or random differences, the I^2 statistics gives an estimate of the proportion of the variability in effect estimates that is attributable to heterogeneity. I^2 levels of 25%, 50%, and 75%, respectively, are thought to correspond to low, medium, and high heterogeneity. Several statistical methods are used to examine publication bias in the funnel plot, including the Egger's regression test and the Begg's rank test. A significant correlation suggests publication bias when using the Begg's rank test to analyse the relationship between the effect sizes and their related sample variances. The standardized effect sizes are regressed on their precisions using Egger's test; in the absence of publication bias, the regression intercept is anticipated to be zero. To assess for publication bias, we employed Begg's rank test and Egger's tests at a 5% significant threshold.

Results

A total of 50 articles were initially discovered regarding the prevalence of S. typhi species and antimicrobial susceptibility from various sources in Bangladesh utilizing various data sets. Nine items were eliminated due to redundancy. 21 items that were books, review articles, systematic reviews, book chapters, and encyclopedia entries were eliminated after further screening. According to the qualifying requirements, 7 articles were chosen for their full text versions, while 13 pieces were disqualified. In the end, 2 publications were eliminated from consideration for systemic review and meta-analysis due to inadequate data, leaving 5 studies (Figure I).

All five publications selected had a cross-sectional research design and were published between 2015 and 2020. For these chosen studies, there were 1129 total participants, ranging in age from 30 to 43. These 5 papers detailed the methods for determining antibiotic susceptibility, namely the disk diffusion method and the agar dilution method. Dhaka, Rajshahi, Sylhet, and Chittagong areas were the locations of the four regional states in which these studies were carried out.

The region around Dhaka and Chittagong hosted the majority of the research. Only people were used in the research. One research isolated S. typhi from both people and animals, and they were each subjected to independent analysis.

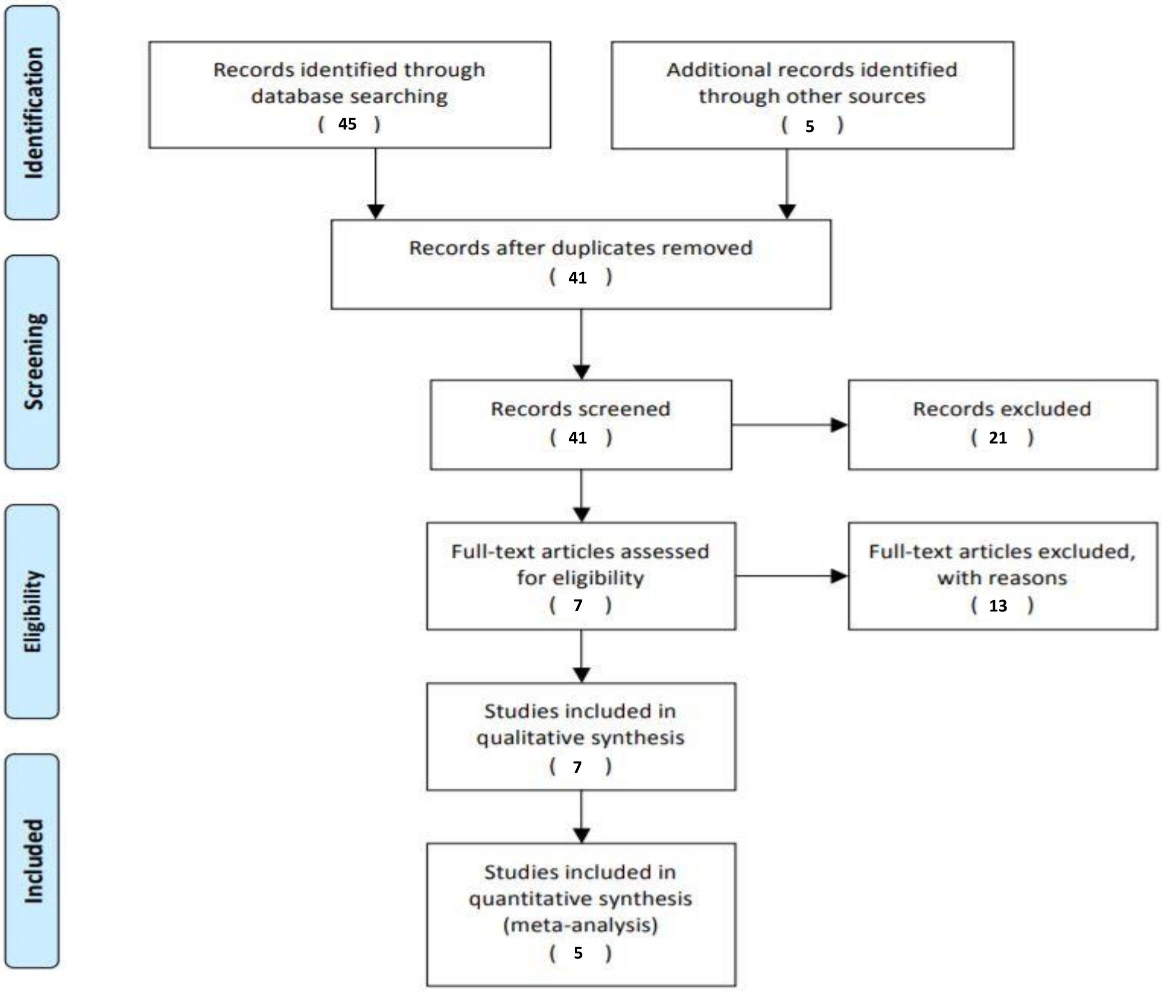

Figure 1: Flow Chart

From the forest plot we found that Tarana et al[6] published an article in 2018 with an effect size 0.08 (CI 0.05 - 0.11) and weighted 20.44%. The study done by Abedin et al[9] with an effect size of 0.07 (CI 0.00 - 0.14) and weighted 20.07%. Rahman et al[2] published a journal in 2020 that has an effect size of 0.17 (CI 0.02 - 0.31) and it is weighted 18.76%. Khatun et al[10] is weighted 22.20 with an effect size 0.61 (CI 0.56 - 0.67). Ahmed et al[11] published an article in 2017 with an effect size 0.46 (CI 0.45 - 0.47) and weight 20.51%[11].

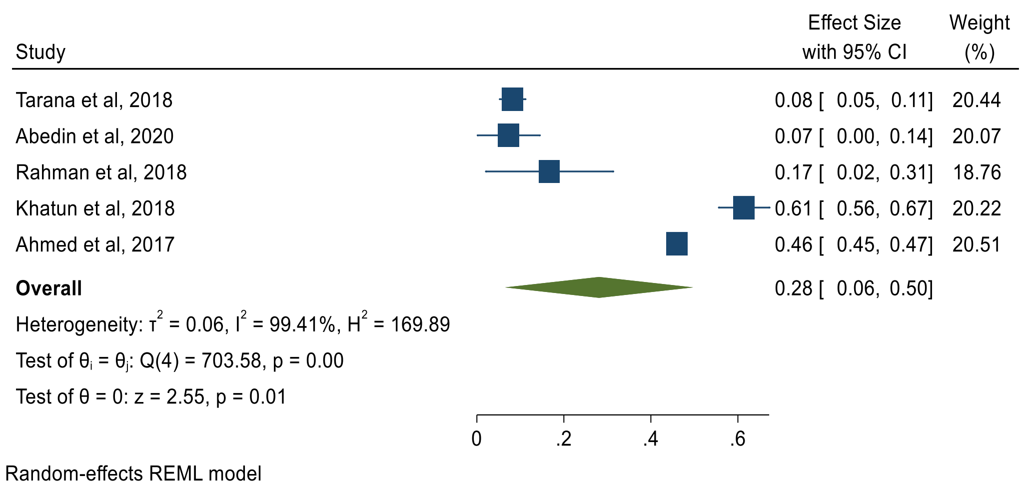

Figure II: **Forest plot.**

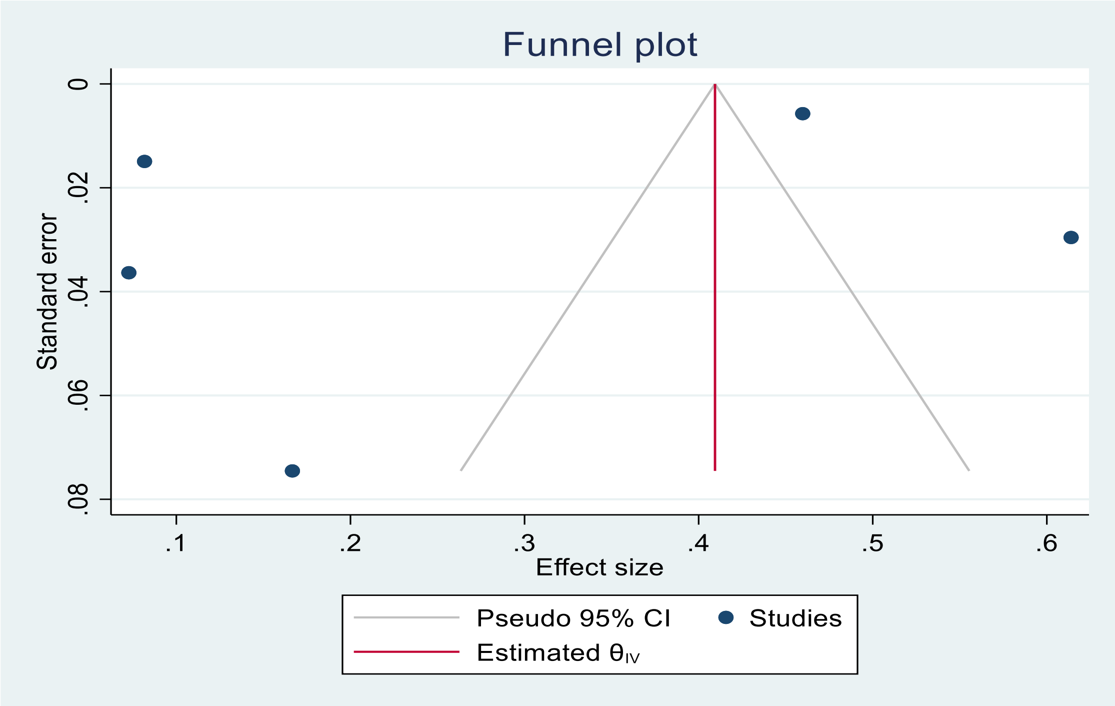

Figure III: **Funnel plot**

The overall effect size 0.28 is represented by a diamond with a confidence interval of 0.06 - 0.50. Since the confidence interval does not cross the line of no effect, and the p value is 0.00, we can say that the overall effect is statistically significant. But as the diamond is much closer to the line of no effect, the overall effect size lower. The heterogeneity (I^2) of this meta-analysis was found 99.41%, indicating that the studies are much disperse to each other and therefore loose the confidence of the preciseness of the study.

Table 1: Antibiotics Resistance Pattern of *Salmonella typhi*

Author	Total Sample	Salmonella prevalence	Antibiotic	n(%)
Tarana et al[6]	367	30	Amikacin	9(30.0%)
			Azithromycin	8(26.7%)
			Ceftazidime	11(36.7%)
			Ceftriaxone	10(33.3%)
			Ciprofloxacin	4(13.3%)
			Chloramphenicol	18(60.0%)
			Cotrimoxazole	16(53.3%)
			Gentamycin	17(56.7%)
			Levofloxacin	16(53.3%)
Ahmed et al[11]	630	72	Ampicillin	21
			Chloramphenicol	15
			Co-trimoxazole	15
			MDR	10
			Nalidixic Acid	70
Khatun et al[10]	702	431	Ampicillin	96 (28.7%)
			Chloramphenicol	115(26.7%)
			Co-trimoxazole	117(27.1%)
			MDR	122(28.3%)
			Nalidixic acid	396(92.3%)
			Azithromycin	7(1.62%)

To see the bias in the studies funnel plot has been used in this study. If any article resides within the triangle that indicates, there has not been bias of that study. As the funnel plot shows that, there's no article within the triangle, we can summarize that, there is a selection of biasness.

The information in table 1 summarizes the findings of investigations on the antibiotic resistance of *Salmonella* spp. Isolated from blood and stool. One sample shown intermediate sensitivity to one or more antimicrobial medications; The vast majority of isolates, however, were found to be multidrug resistant to at least one antimicrobial agent. Ciprofloxacin and azithromycin were generally shown to be efficacious against the Salmonella spp. Isolated from this investigation, but nalidixic acid was found to be less efficient against Salmonella typhi. This was confirmed by antimicrobial resistance testing.

Discussion

There haven't been many studies on the prevalence of Salmonella typhi in Bangladesh, and those that have been done don't include all of the demographic groups and areas of the nation. The majority of research were conducted in Dhaka, and risk variables, such as the variety of serovars, that may have an impact on the disease's incidence, were not properly addressed to give a complete picture of the disease's epidemiology. Typhoid fever prevalence estimates were hampered by the small number of studies, aggregate reporting, and a dearth of information specific to sample type and age group.

This study shows the prevalence and antibiotic resistance pattern of Salmonella typhi from 2015 to 2020 by reviewing 5 articles published within these years. The overall effect size 0.28 and the diamond does not cross the no effect line making the study statistically significant, which is relevant to other studies. It is challenging to compare results across different nations and laboratories, and occasionally even within the same nation, because to the lack of uniformity in measurement as well as reporting of susceptibility data.

Cruz Espinoza et al[12] found that 27% occurrence of Salmonella typhi with CI 95% (21%-32%), where heterogeneity (I^2) is 90.9% which goes with this study. Browne et al[13] had also a high level of heterogeneity (I^2) that is 80%. In 2014, a study conducted in Ethiopia by Tadesse[14] also faced high heterogeneity of 87.3%. Khademi et al[15] also faced high level of heterogeneity (95% CI; I2=84.4%). Due to inconsistency in data obtained, high rate of heterogeneity has become common for most of the studies. Common first-line antibiotics have disappointing results when used to treat Salmonella typhi. Africa has had a similar circumstance. The majority of studies demonstrating significant first-line antibiotic resistance to *Salmonella typhi* were reported. Due to the similar tendency of improper antibiotic usage in emerging nations, the situation in India and Africa is comparable.

The studies indicate ciprofloxacin as most effective against salmonella, whereas some studies from India suggests that ciprofloxacin is less effective in terms of fighting against *Salmonella typhi*. So, more data is needed to summarize the pattern. The availability and heterogeneity of the resistance data for the other diseases showed substantial variations in resistance rates. In low- and middle-income nations, typhoid fever is pervasive, and the situation is becoming worse. Implementing clinical and public health interventions, such as enhancing water quality and sanitation, distributing the Salmonella typhi vaccine, and making an educated treatment decision are crucial. For *Salmonella paratyphi* A, there isn't a licensed vaccine, though. Salmonella spp. Is extremely common and highly resistant to antibiotics in Bangladesh; thus, both the general public and the medical community must pay special attention to this problem. The community must be made aware of the need of dose completion and careful usage. Self-medication must be outlawed in the neighborhood. Guidelines for the use of antibiotics in agriculture and human health should be applicable[16].

Limitations: Because these isolates did not fully reflect the antibiogram of Bangladesh isolates, this study had several limitations. Even while it is conceivable that the antibiogram of isolates in community and hospital settings wouldn't differ much in terms of enteric fever, the majority of the isolates in this investigation were collected from tertiary care settings, with essentially no representation from community settings. The majority of the papers that made up this review were concentrated in Dhaka, therefore there is a chance of selection bias and this study may not accurately reflect the entire nation. In addition, because there is a dearth of data, the degree of heterogeneity is comparable to that of previous research.

Conclusion

The review's three main conclusions are as follows. First, Bangladesh has a relatively high frequency of salmonella typhi. Second, there are large gaps in monitoring; across the majority of the nation, there were no prevalence statistics available, and there wasn't enough research on the disease to determine its patterns of prevalence. Finally, several studies had methodological data gaps that raised concerns about their validity and complicated inter-study comparisons. Therefore, standardized methods for surveillance and constant countrywide observation are required, coupled with appropriate steps to reduce the current rate. There should be more research done as well as more systematic reviews. Based on the results, we suggest suitable actions to monitor and manage S. typhi prevalence, as well as national surveillance using standardized procedures.

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None

Conflict of Interest
The authors affirm that they have no known financial or interpersonal conflicts that would have seemed to have an impact on the research presented in this study.

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Contribution to authors
Co-ordination of the review: Zeba Z. Search and collection of studies for inclusion in the review: Zeba Z, Hasan ST, Sumit AF. Data extraction: Hasan ST, Sumit AF. Assessment of risk of bias in the included studies: Yusuf MA. Data analysis: Yusuf MA. Assessment of the certainty of the evidence Zeba Z, Hasan ST, Sumit AF. Data interpretation: Zeba Z, Hasan ST, Sumit AF, Yusuf MA. Writing of the review: Zeba Z, Hasan ST, Sumit AF. Review of manuscript: Zeba Z, Hasan ST, Sumit AF. All authors read and approved the final manuscript.

Data Availability
The corresponding author should be contacted with any inquiries on the accessibility of the study's supporting data; upon reasonable request, they will be happy to answer. The only data gathered or analyzed for this review were from research that were publicly available.

Ethics Approval and Consent to Participate
Not Applicable

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ORCID
Zebunnesa Zeba: https://orcid.org/0000-0001-9576-1416
Shariar Talukder Hasan: https://orcid.org/0009-0003-5117-1686
Ahmed Faisal Sumit: https://orcid.org/0000-0002-8856-9079
Md. Abdullah Yusuf: https://orcid.org/0000-0002-8551-7185

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