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Review Article

Re-Emergence of Ampicillin Sensitive *Salmonella* Typhi and the Increase of Ciprofloxacin Resistance in Typhoid Fever Treatment in Asia: A Systematic Review

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ABSTRACT

Typhoid fever is a disease caused by *Salmonella* Typhi infection. In 2000, 2.16 million people were affected worldwide, with more than 90% morbidity and mortality in Asia. Ampicillin is the first-line antibiotic used for typhoid management. However, the rise in resistance to first-line antibiotics has shifted ciprofloxacin as an alternative. This study aimed to describe the trends in ciprofloxacin- and ampicillin-resistant *Salmonella* Typhi in Asia. This study was a systematic review that conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria. Search was indicated toward studies on *Salmonella* Typhi susceptibility toward ciprofloxacin and ampicillin were identified using PubMed, Cochrane Library, and ProQuest. Of the 1542 studies found, only 16 fulfilled the criteria. In 1996, *Salmonella* Typhi was not found to be resistant to ciprofloxacin, whereas 3.5% was resistant to ampicillin. In 2005, ciprofloxacin resistance increased to 19.3%, whereas ampicillin resistance decreased to 13.3%. In 2005-2014, a larger number of *Salmonella* Typhi isolates resistant to ciprofloxacin than to ampicillin. Furthermore, during 2016-2019, resistance to ciprofloxacin increased from 8.1% to 95%, while ampicillin resistance increased from 27.5% to 85.2%. This the high ampicillin resistance in South and East Asia. In Asia, there was an increase in ciprofloxacin-resistant *Salmonella* Typhi from 1996 to 2019, whereas ampicillin-resistant *Salmonella* Typhi decreased from 1996 to 2015. Between 2016 and 2019, contrasting evidence was found in East Asia and South Asia, where resistance toward ampicillin increased.

Keywords: *Salmonella* Typhi, Ciprofloxacin, Ampicillin, Susceptibility, and Resistance.

Highlights: In Asia, there was an increase in ciprofloxacin-resistant *Salmonella* Typhi, while a corresponding decrease was observed in ampicillin-resistant *Salmonella* Typhi.

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INTRODUCTION

Typhoid fever is a serious disease that can threaten life. It is caused by *Salmonella enterica* serovar Typhi (*Salmonella* Typhi).[1–3] There were 2.16 million typhoid cases in the world in 2000, where 90% of its morbidity and mortality occurred in Asia. According to the WHO, five countries in Asia, China, India, Indonesia, Pakistan, and Vietnam, are endemic countries for typhoid fever. However, South Asia incidence is significantly higher than Southeast and Northeast Asia.[4]

First-line antibiotics consist of ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (co-trimoxazole).[5,6] On the other hand, the inappropriate uses of antibiotics caused an increased number of multi drug resistant (MDR) and extensively drug resistant (XDR) *Salmonella* Typhi. MDR is defined as *S.* Typhi that is resistant to first-line antibiotics[7,8] while, XDR is defined as *Salmonella* Typhi that is resistant to fluoroquinolone, third-generation cephalosporin, in addition to first line antibiotics.[9]

Ampicillin is one of the first-line antibiotics against typhoid fever that is often used due to several factors, such as easy access, relatively cheap price, and fewer side effects.[10] Although chloramphenicol reduces fever more quickly, it has notable side effects such as suppression of bone marrow that can lead to bone marrow aplasia and death.[11,12] Therefore, ampicillin is preferred over chloramphenicol.[13]

Chloramphenicol was used as first-line antibiotic against typhoid since 1948; however, increasing resistance and side effects gave rise to increased ampicillin and co-trimoxazole use.[14] Improper use of first-line antibiotics led to the emergence of MDR in the 1960s.[9] Fluoroquinolone was then used as alternative due to the emergence of resistance toward first-line antibiotics.[15] The universal use of fluoroquinolone caused emergence of resistant strains.[16] A study conducted in Cambodia in 2008-2015 reported that, over time, there was a decrease of ciprofloxacin susceptibility from 100% to 93.1% and a decrease in the number of MDR from 62.9% to 17.2%.[17] Another study conducted in India, reported a decrease in ampicillin resistance from 53% to 23% in the course of time after the use of fluoroquinolone, cephalosporin, and azithromycin.[18] This fluctuating trend of *Salmonella* Typhi antibiotic resistance, in addition to the high morbidity and mortality of typhoid fever in Asia, encourages the need to evaluate further the overall trends of ciprofloxacin resistance and sensitivity to ampicillin in Asia. This study aimed to describe the ciprofloxacin and ampicillin resistant *Salmonella* Typhi in Asia.

METHODS

Eligibility Criteria

This study was a systematic review that was made based on PRISMA criteria. This review used data from studies that have been published from 1991-2021 regarding *Salmonella* Typhi susceptibility to ciprofloxacin and ampicillin in Asia. The exclusion criteria were studies designed as case report, review, or systematic review, study with only title or abstract as well as the following: used language other than Indonesian or English, could not be accessed, did not show data of interest, did not specify Salmonella as *Salmonella* Typhi, used methods other than disk diffusion for antibiotic susceptibility test, and did not identify year or location.

Literature Searching

Literature search was done in May 2022 on PubMed, Cochrane, and ProQuest with keywords: "*Salmonella* typhi OR *Salmonella* enterica serovar Typhi OR salmonella typhosa AND ciprofloxacin OR ciprofloxacin hydrochloride OR Ciprofloxacin Hydrochloride Anhydrous

AND ampicillin resistance OR Ampicillin Resistances OR Resistance, Ampicillin OR Resistances, Ampicillin". The search was set to obtain studies from 1991-2021.

Study Selection and Data Extraction

Search results from each database were collected with Zotero to remove duplicates. Next, title and abstract were screened based on inclusion and exclusion criteria defined. The data from studies included that were extracted are : first author, publication year, experiment year, study area, numbers of sample tested, specimen type, numbers of resistant isolates per year, antibacterial resistance testing method, and interpretation criteria.

The main outcomes in this review, which are the number of resistant isolates and total isolates per year tested with the disk diffusion method, were combined, and converted into percentages. These percentages were then made into bar charts grouped for each geographical region (Asia, South Asia, South-East Asia, and East Asia).

Risk of Bias Assessment

All selected studies were assessed for risk of bias using "Critical Appraisal Tools for Use in Joanna Briggs Institute Systematic Reviews for quasi-experimental studies." Study was included if they fulfilled more than 50% of the criteria.

RESULTS AND DISCUSSION

Search Results and Study Characteristics

Out of 1542 studies that were collected from the databases, 72 were excluded for duplicates. A total of 1470 studies were screened by reading the title and abstract. Further screening was carried out resulting in 208 full-text articles. As many as 78 studies could not be assessed, 73 studies did not show data of interest, 23 studies did not specify Salmonella as *Salmonella* Typhi, 12 used methods other than disk diffusion for antibiotic susceptibility test, and six studies which showed unidentified year or location were excluded (Figure 1). All these screenings and selections resulted in 16 studies included and assessed for their quality using JBI. JBI consisted of nine criteria, assessing if the study: 1) showed clearly the cause and effect from the study; 2) similar participants included in any comparisons; 3) participants included in any comparisons received similar treatment or care; 4) studies had a control group; 5) there were multiple measurements of the outcome both pre and post the exposure; 6) the follow up was complete; 7) outcomes of participants included in any comparisons were measured in the same way; 8) outcomes were measured in a reliable way; 9) and appropriate statistical analysis were used. These criteria were answered with yes, no, unclear, or not applicable (Table 1). More than 50% of all questions were answered with "yes" in all the studies, resulted in 16 studies for further analysis.

The studies included were published from 1998-2020 and covered several Asian countries, six from India[19–24], three from Nepal[25–27], two from Bangladesh[28,29] , two from Pakistan[30,31], two from Indonesia[32,33], and one from Iraq[34]. Specimens tested consisted of 7162 blood and 56 feces samples. Susceptibility testing methods used were Kirby Bauer or disk diffusion. All our studies used Clinical & Laboratory Standards Institute (CLSI) or National Committee for Clinical Laboratory Standards (NCCLS) as the interpretation criteria.

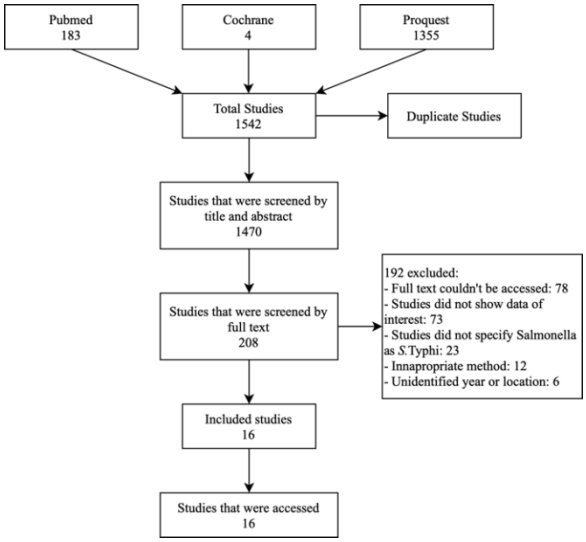

Figure 1. PRISMA Flowchart. PRISMA Diagram That Were Made During Article Searching From May 2022 until July 2022.

Table 1. Quality Assessment for Risk of Bias using JBI Criteria.

No	Study	1	2	3	4	5	6	7	8	9	Conclusion
1	Khadka et al.[25]	✓	✓	✓	✓	✓	✓	✓	✓	✓	Included
2	Ali et al.[28]	✓	✓	✓	✗	✓	✓	✓	✓	?	Included
3	Alam et al.[19]	✓	✓	✓	?	✓	✓	✓	✓	?	Included
4	Shah et al.[30]	✓	✓	✓	?	✓	✓	✓	✓	✓	Included
5	Ahmed et al.[29]	✓	✓	✓	✓	✓	✓	✓	✓	✓	Included
6	Lugito et al.[32]	✓	✓	✓	?	✓	✓	✓	✓	✓	Included
7	Khanal et al.[26]	✓	✓	✓	?	✓	✓	✓	✓	✓	Included
8	Mohanty et al.[20]	✓	✓	✓	✓	✓	✓	✓	✓	?	Included
9	Kumar et al.[21]	✓	✓	✓	✓	✓	✓	✓	✓	✓	Included
10	Saeed at al.[31]	✓	✓	✓	?	✓	✓	✓	✓	?	Included
11	Khanal et al.[27]	✓	✓	✗	?	✓	✓	✓	✓	?	Included
12	Sharvani et al.[22]	✓	✓	✓	✓	✓	✓	✓	✓	?	Included
13	Dutta et al.[23]	✓	✓	✓	✓	✓	✓	✓	✓	?	Included
14	Kumar et al.[24]	✓	✓	✓	?	✓	✓	✓	✓	✓	Included
15	Al-Mayahi et al.[34]	✓	✓	✓	✓	✓	✓	✓	✓	?	Included
16	Amdani et al.[33]	✓	✓	✓	?	✓	✓	✓	✓	?	Included

✓=question answered with "Yes", ✗= question answered with "No", ? = question answered with "Unclear"

Trend of *S.* Typhi Resistance to Ciprofloxacin and Ampicillin

There were 16 studies that reported *Salmonella* Typhi resistance to ciprofloxacin and 13 studies to ampicillin using disk diffusion. Percentage of ciprofloxacin resistance varied from 0%-95%, while ampicillin ranged from 0 to 100%. In this review, there was a study by Ahmed et al.[29] which showed the ciprofloxacin susceptibility data as sensitive, intermediate, and resistant isolates. Intermediate susceptible *Salmonella* Typhi were classified as resistant isolates.

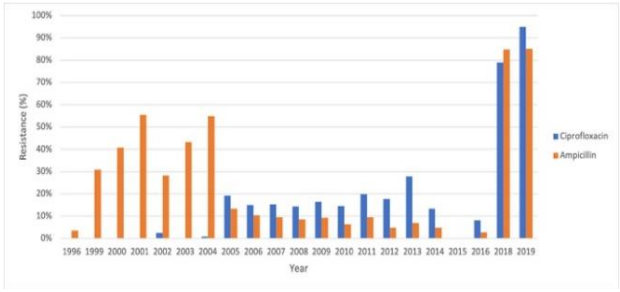

Figure 2. Percentage of *Salmonella* Typhi Isolates Rsistant to Ciprofloxacin and Ampicillin in Asia from 1996 to 2019.

Figure 2 represents the percentage of *Salmonella* Typhi isolates resistant to ciprofloxacin and ampicillin in each year that were tested with disk diffusion method.

Number of resistant *Salmonella* Typhi isolates reported from 1996-2019 were combined (Figure 2). These data were extracted from India, Nepal, Bangladesh, Pakistan, Iraq, and Indonesia. However, there was no data found that reported results from the year 1997, 1998, and 2017.

In a five year period from 1996 until 2001, there was no ciprofloxacin-resistant *Salmonella* Typhi found. However, there were 3.5%, 30.9%, 40.7%, and 55.5% *Salmonella* Typhi resistant to ampicillin. The number of *Salmonella* Typhi resistant to ciprofloxacin contrasted with ampicillin that increased in those years.

In 2002 to 2003, *Salmonella* Typhi remained relatively sensitive to ciprofloxacin, while highly resistant toward ampicillin. Studies from South Asia in 2004-2005 reported a huge turning point where *Salmonella* Typhi resistant to ciprofloxacin increased from 0.8% to 19.3%, while ampicillin decreased from 54.9% to 13.3%. In the year 2005 until 2014, the number of

Salmonella Typhi resistant to ciprofloxacin always remained higher than the one resistant to ampicillin. Resistance toward ciprofloxacin varied from 13.4% to 27.8% while ampicillin ranged from 4.8% to 13.3%. *Salmonella* Typhi resistant to ampicillin reached 4.8% in 2012, whereas *Salmonella* Typhi resistant to ciprofloxacin increased reaching 27.8% in 2013.

In 2015, a report by Lugito et al.[32] found that no *Salmonella* Typhi was resistant to ciprofloxacin and ampicillin in Indonesia. Furthermore, other studies from 2016 to 2019 reported percentage of *Salmonella* Typhi resistant to ciprofloxacin and ampicillin increased simultaneously; however, it must be noted that, in 2016 and 2019, only one study in each year reported the resistant isolates.

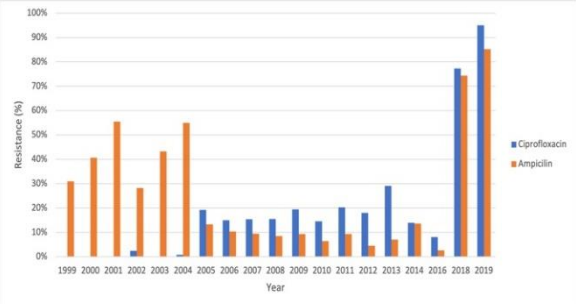

Figure 3. Percentage of *Salmonella* Typhi isolates that are resistant to Ciprofloxacin and Ampicillin in South Asia from 1999 to 2019.

The resistance trend to ciprofloxacin and ampicillin of *Salmonella* Typhi in South Asia countries included from India, Pakistan, Bangladesh, and Nepal is shown in Figure 3. From 1999 until 2004, *Salmonella* Typhi appeared to be relatively susceptible toward ciprofloxacin, while resistance toward ampicillin was quite high ranging from 28.2% to 55.5%. The breaking point was seen in 2005, where the percentage of *Salmonella* Typhi that was resistant to ciprofloxacin increased while ampicillin decreased. The percentage of *Salmonella* Typhi isolates resistant to ciprofloxacin continued to exceed isolates resistant to ampicillin until 2019. From 2005 until 2013, *Salmonella* Typhi resistant to ciprofloxacin remained high, on the other hand, resistance to ampicillin gradually decreased. In 2014, the percentage of *Salmonella* Typhi resistant to ciprofloxacin and ampicillin were relatively similar, with resistance toward ciprofloxacin slightly higher than ampicillin. In 2016, *Salmonella* Typhi resistant to ampicillin fell to 2.7%. From 2018 until 2019, there was a further increase in ampicillin-resistant isolates with both year results reported by Shah et al.[30] and Saeed et al.[31] from Pakistan. This showed that Pakistan had a high percentage of *Salmonella* Typhi resistant to ampicillin in 2018 and 2019.

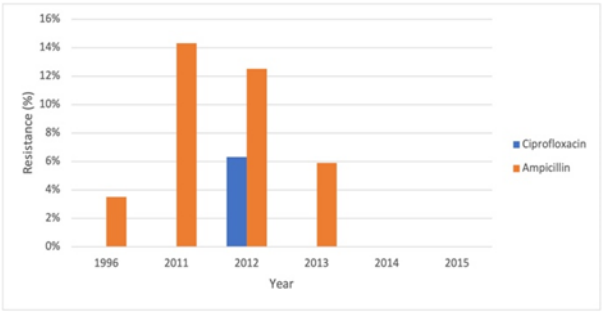

Figure 4. Percentage of *Salmonella* Typhi Isolates that Are Resistant to Ciprofloxacin and Ampicillin in Southeast Asia from 1996-2015.

Salmonella Typhi resistant to ciprofloxacin and ampicillin in South-East Asia is shown in Figure 4. Since 1996, it showed that *Salmonella* Typhi was resistant to ampicillin while there was no isolate that is resistant to ciprofloxacin until 2012. Percentage of *Salmonella* Typhi resistant to ciprofloxacin seemed to be low. This study aligns with studies from Moehario et al.[35] which reported there was no *Salmonella* Typhi isolates that were resistant to ciprofloxacin in 2002-2010, which showed low ciprofloxacin resistance in Indonesia. Percentage of *Salmonella* Typhi that was resistant to ampicillin increased from 1996 to 2011 and decreased each year reaching 0% in

2014 and 2015. A study from Thailand conducted by Techasaensiri et al.[36] reported similar results from 1998 through 2007, *Salmonella* Typhi and *Salmonella* Paratyphi resistant to ampicillin remained below 40% and decreased as of 2007.

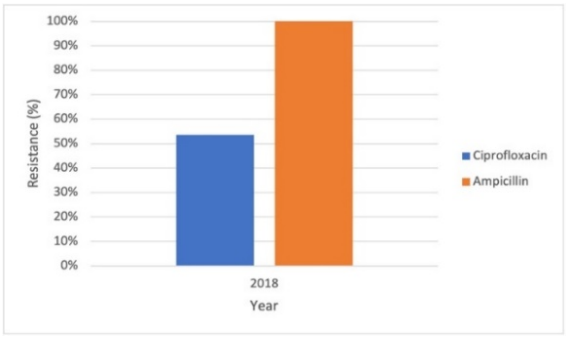

Figure 5. Percentage of *Salmonella* Typhi isolates resistant to Ciprofloxacin and Ampicillin in East Asia.

Figure 5 represents *Salmonella* Typhi isolates resistant to ciprofloxacin and ampicillin that were tested with disk diffusion method and obtained from studies originating from Iraq.

The resistance trend in East Asia only consists of one study from Iraq (Figure 5). This study reported a high level of *Salmonella* Typhi resistance in 2018, which was 53.6% resistant to ciprofloxacin and 100% resistant to ampicillin. This showed similar with results found in Nepal and Pakistan in 2018. Khadka et al.[25] reported 43.5% *Salmonella* Typhi resistant to ciprofloxacin in Nepal. Saeed et al.[31] reported 90.2% reported 90.2% isolates resistant to ciprofloxacin and 74.4% resistant to ciprofloxacin in Pakistan.

Despite all data that have been analyzed, this study still could not represent the whole of Asia, since the studies collected thus far originated from India, Pakistan, Bangladesh, Nepal are South Asia countries, Iraq an East Asia country, and Indonesia a Southeast Asia country, furthermore, limited number of samples were tested in several included studies, and fewer studies found *Salmonella* Typhi resistant to ampicillin more reported amoxicillin instead.

STRENGTH AND LIMITATION

The strength of this study was using PRISMA method as the foundation for doing this study. Critical appraisal was also done for all the studies included. On the other hand, the limitation of this study was we could not include some of the studies which were not in English or Indonesian language.

CONCLUSION

In Asia, there was an increase in ciprofloxacin-resistant *Salmonella* Typhi from 1996 until 2019, while, on the contrary, ampicillin-resistant *Salmonella* Typhi decreased from 1996 until 2015. In 2016 until 2019, contrasting evidence was found in East Asia and South Asia where resistance toward ampicillin rose.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Writer, literature searcher, collecting data from literature: FT. Conceptor and supervision: LHM and IMN. Review and supervision: JN, AMRLT and SS.

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