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Effectiveness of azithromycin and ciprofloxacin in the treatment of typhoid fever: a systematic review

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ABSTRACT

Typhoid fever or commonly referred to as enteric fever is a systemic disease caused by *Salmonella typhi.* It often occurs in developing countries due to poor sanitation. Second-line antibiotics, including ciprofloxacin, have been widely used as the first choice treatment for typhoid fever. However, *S. typhi* has increased resistance to second-line antibiotics, so azithromycin has become an alternative treatment for the typhoid fever. This systematic review assessed the effectiveness of azithromycin and ciprofloxacin against typhoid fever in adults. This research used the PRISMA protocol with predefined Pubmed, Proquest, and EBSCO keywords. After removing duplicates and selecting studies according to inclusion and exclusion criterias, 17 studies about the effectiveness of azithromycin and ciprofloxacin in typhoid fever in adults from 1988-2020 were gathered. Studies were evaluated using JBI Critical Appraisal Tools. The results showed that administration of azithromycin and ciprofloxacin for typhoid fever yields average length of fever (3.5 d and 4.2 d) and average length of stay (9.3 d and 10 d), respectively. The susceptibility of *S. typhi* to azithromycin was 99.9%, whereas a significant decrease in its susceptibility to ciprofloxacin was observed in 2017-2020, from 4% to 2%. Azithromycin showed better effectiveness than ciprofloxacin in treating typhoid fever in adults based on *S. typhi's* susceptibility, average length of fever and average length of stay from 17 studies reviewed.

ABSTRAK

Demam tifoid atau yang biasa disebut demam enterik merupakan penyakit sistemik akibat infeksi *Salmonella typhi.* Demam tifoid masih banyak terjadi di negara-negara berkembang akibat sanitasi yang buruk. Antibiotik lini kedua, termasuk ciprofloxacin, banyak digunakan sebagai pilihan pertama untuk terapi demam tifoid meskipun terjadi peningkatan resistensi terhadap antibiotik lini kedua tersebut, sehingga azithromycin menjadi pengobatan alternatif. Telaah sistematis ini menilai efektivitas azithromycin dan ciprofloxacin untuk demam tifoid pada orang dewasa. Pencarian studi menggunakan protokol PRISMA dengan kata kunci yang telah ditentukan pada PubMed, Proquest, dan EBSCO. Setelah menghilangkan duplikasi pustaka dan memilih penelitian yang sesuai dengan kriteria inklusi dan eksklusi, diperoleh 17 penelitian tentang efektivitas azitromisin dan ciprofloksasin pada demam tifoid pada orang dewasa dari tahun 1988-2020. Penilaian hasil penelitian menggunakan *JBI Critical Appraisal Tools*. Hasil telaah menunjukkan pemberian azitromisin dan ciprofloksasin pada pasien demam tifoid memberikan rata-rata lama demam berturut-turut (3,5 hari dan 4,2 hari), dan rata-rata lama rawat inap (9,3 hari dan 10 hari). Kepekaan *S. typhi* terhadap azitromisin adalah 99,9%, namun terjadi penurunan kepekaan yang signifikan pada ciprofloksasin pada tahun 2017-2020, dari 4% menjadi 2%. Azitromisin menunjukkan efektivitas yang lebih baik daripada ciprofloksasin untuk demam tifoid pada orang dewasa berdasarkan kepekaan *S. typhi* serta lama demam dan lama rawat dari 17 hasil penelitian yang ditelaah.

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INTRODUCTION

Typhoid fever is a systemic disease caused by an infection of *Salmonella* bacteria, especially *Salmonella typhi* (*S. typhi*), that spreads through contaminated food. This disease usually occurs in environments with poor sanitation and inadequate access to clean water.[1] Between 11-20 million cases of typhoid fever which cause 128,000-161,000 deaths were reported annually worldwide.[2]

Early diagnosis and treatment can prevent complications due to typhoid fever. In untreated patients, approximately 10% may experience relapse, and 4% can become chronic carriers. Possible complications include diarrhea due to irritation of the gastrointestinal tract and constipation resulting from Peyer's patch hypertrophy. In severe cases, necrosis of Peyer's patches can occur, leading to ulceration and bleeding. Approximately 5-7% of patients are at risk of developing hepatitis and encephalopathy. Liver and spleen abscesses can also occur due to intra-abdominal infections. The likelihood of complications increases with the duration of the illness before hospitalization, the length of hospitalization, and immunodeficiency conditions caused by chronic diseases such as cancer, tuberculosis, and HIV. Malnutrition can lead to a reduction in normal gut flora, increasing the risk of infection.[3]

Initially, first-line antibiotics such as chloramphenicol, cotrimoxazole, and ampicillin were used to treat typhoid fever. Over time, *S. typhi* resistance to these first-line antibiotics, leading to the widespread use of second-line antibiotics from the fluoroquinolone group, such as ciprofloxacin. However, there has been a decrease in susceptibility to second-line antibiotics, including ciprofloxacin, making them less effective. Consequently, alternative antibiotics like azithromycin are now being used in the treatment of typhoid fever.[4-6]

Salmonella typhi exhibits continuously changing resistance to its antibiotics, which can be attributed to the frequency of antibiotic usage in specific regions. In 1998 in Egypt, there was no resistance observed in *S. typhi* against azithromycin or ciprofloxacin. However, between 2009 and 2012, the resistance rates for *S. typhi* to azithromycin and ciprofloxacin reached 71.8% and 38% in Bangladesh, respectively.[7,8] In India, the resistance rates for *S. typhi* to azithromycin and ciprofloxacin were 0.8 and 44.7% (2012-2016).[9] In 2018, resistance to *S. typhi* to azithromycin and ciprofloxacin stood at 4.3% and 43.5% in Nepal.[10] Meanwhile, in Pakistan, resistance rates for *S. typhi* to azithromycin and ciprofloxacin were 5% and 95% (2018).[11]

Ciprofloxacin, a fluoroquinolone-class antibiotic, can be utilized in the treatment of typhoid fever. A study conducted in 1995 reported that the use of ciprofloxacin is effective against multidrug-resistant (MDR) strains of *S. typhi.*[12-14] However, the widespread use of ciprofloxacin led to the development of resistance, reducing its effectiveness. Consequently, with limited treatment options, other antibiotics such as azithromycin, from the macrolide class, are becoming an alternative therapy for typhoid fever resistant to fluoroquinolone class antibiotics. Azithromycin also has a lower resistance rate compared to other antibiotics and demonstrates a high clinical cure rate, ranging from 81-100% after 5-7 d of therapy.[15-17]

A study by Amin *et al.*[18] showed that 90% (18/20) of patients treated with azithromycin recovered, while only 62% (13/21) of patients treated with ciprofloxacin recovered. Azithromycin has a shorter average duration of fever by 2.4 d than ciprofloxacin (8.2 d).[18] Based on other studies, azithromycin has a lower average fever clearance time, clinical failure rate, and relapse rate than other antibiotics.[19,20] Although azithromycin is effective for treating typhoid fever, fluoroquinolone-class antibiotics such as ciprofloxacin are still widely used despite the increasing resistance. This systematic

review evaluated the effectiveness of azithromycin and ciprofloxacin in the treatment of typhoid fever and the trend of its susceptibility to *S. typhi*.

MATERIAL AND METHODS

This systematic review evaluated the effectiveness of azithromycin and ciprofloxacin in the treatment of adult typhoid fever. This study was conducted at the Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia (FKIK UAJ), from January 2023 to June 2023. The study search used keywords: "Azithromycin AND/OR Ciprofloxacin AND Typhoid fever OR Enteric fever" in PubMed, Proquest, and EBSCO. All studies were put into the Zotero reference manager to be screened.

Study selection based on predetermined inclusion and exclusion criteria using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (FIGURE 1) flowchart. The inclusion criteria for this systematic review were experimental and observative studies using azithromycin or ciprofloxacin to treat typhoid fever caused by *S. typhi* and studies with adults population data. Exclusion criterias for this systematic review were case reports, review articles, systematic reviews, meta-analyses, studies with no full text, studies written in other than Indonesian and English languages and research in pediatrics. Several inclusion studies were obtained after selecting and screening.

The studies used in this systematic review were appraised with the Quality Assessment Tool from JBI (Joanna Briggs Institute) Clinical Appraisal Tool.[21] The data that has been obtained were processed using Microsoft Excel. The susceptibility of azithromycin and ciprofloxacin was evaluated from the percentage of sensitive, intermediate, and resistant samples to *S. typhi.* The average length of fever and stay were calculated from the study results.

RESULTS

There were 3,829 studies obtained from the search results, and 1231 duplicate studies were eliminated. Study selection was carried out based on exclusion and inclusion. All of the titles and abstracts were screened, and 17 inclusion studies were obtained (FIGURE 1). These inclusion studies were assessed with Quality Assessment Tool from JBI (Joanna Briggs Institute) Clinical Appraisal Tool, and all studies were included in this systematic review (TABLE 1).

Demographic data

Out of the 17 inclusion studies, demographic data were collected from 10 studies, which included a total of 451 adult typhoid fever patients. Among the available demographic data, it was found that a higher percentage of males (72%) were affected by typhoid fever compared to females (28%). Out of the 451 patients, 26% received treatment with azithromycin, while 42% received treatment with ciprofloxacin (TABLE 2).

Trends of susceptibility of azithromycin and ciprofloxacin against *S. typhi*

Out of the 17 inclusion studies, there were 9 studies on the susceptibility of *S. typhi* to azithromycin, and 13 studies on the susceptibility of *S. typhi* to ciprofloxacin from several countries. The samples were taken between 1989-2020. *Salmonella typhi* was highly susceptible to azithromycin in 1998 (100%) but decreased from 2009 to 2012 (28.2%). However, between 2011 and 2013, there was an increase in susceptibility (78.5%), which then grew steadily (99.9%) until 2020. On the other hand, the susceptibility of *S. typhi* to ciprofloxacin in 1988-2002 was very high (100%) in 6 studies. However, it decreased to 62% between 2009-2012 decreased and continued to decline (2%) until 2020 (TABLE 3).

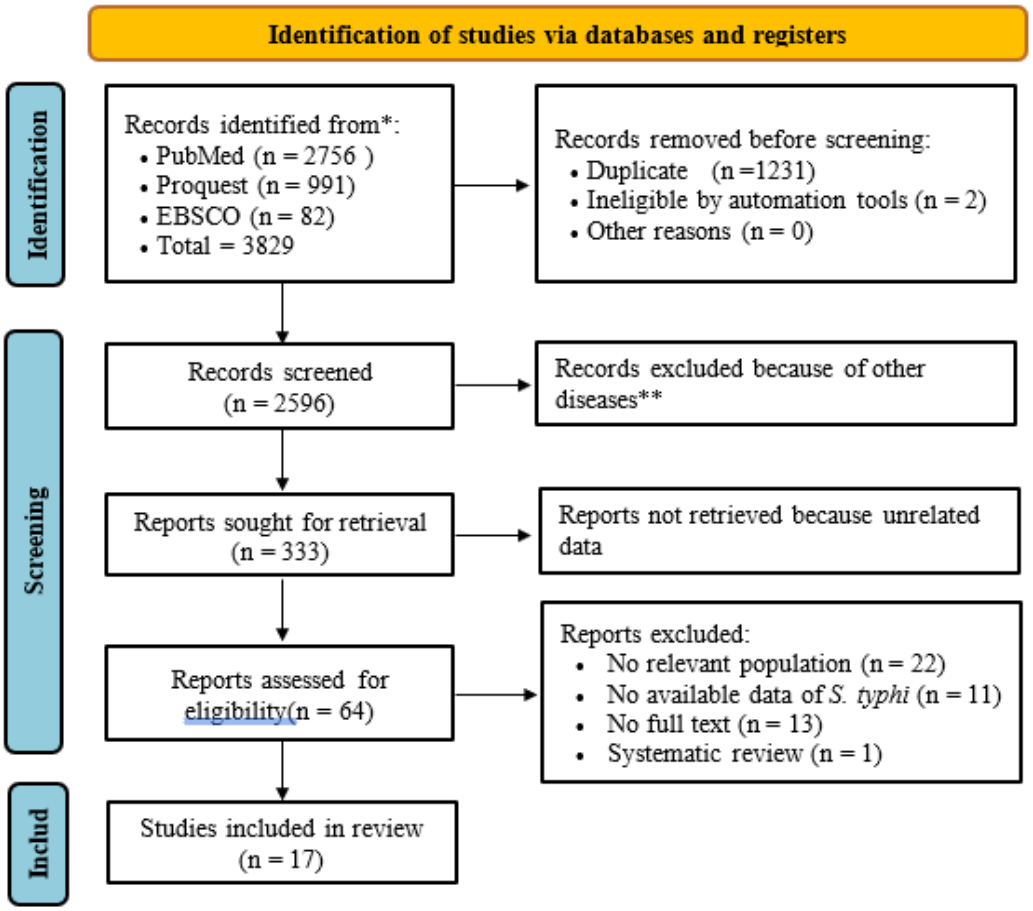

FIGURE 1. PRISMA chart[22]

TABLE 1. Results of inclusion study assessment with the JBI clinical appraisal tool

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Results
Chinh *et al.*[20]	√	√	√	x	√	√	√	√	√	Suitable
Amin *et al.*[18]	√	√	√	x	√	√	√	√	√	Suitable
Gasem *et al.*[30]	√	√	√	x	√	√	√	√	√	Suitable
Zmora *et al.*[31]	√	√	√	x	√	√	√	√	√	Suitable
Limson *et al.*[23]	√	√	√	x	√	√	√	√	√	Suitable
Tribble *et al.*[27]	√	√	x	x	√	√	√	√	x	Suitable
Liberti *et al.*[29]	√	√	√	x	√	√	√	√	x	Suitable
Butler *et al.*[28]	√	√	√	x	√	√	√	√	√	Suitable
Wallace *et al.*[26]	√	√	√	x	√	√	√	√	√	Suitable
Chew *et al.*[24]	√	√	x	x	√	√	√	√	√	Suitable
Girgis *et al.*[7]	√	√	x	x	√	√	√	√	√	Suitable
Joshi *et al.*[9]	√	√	√	√	√	√	√	√	√	Suitable
Shah *et al.*[11]	√	√	√	√	√	√	√	√	√	Suitable
Veeraraghavan *et al.*[34]	√	√	√	√	√	√	√	√	√	Suitable
Bhetwal *et al.*[33]	√	√	√	√	√	√	√	√	√	Suitable
Harichandran *et al.*[32]	√	√	√	√	√	√	√	√	x	Suitable
Khadka *et al.*[10]	√	√	√	√	√	√	√	√	√	Suitable
Afroze *et al.*[8]	√	√	√	√	√	√	√	√	x	Suitable

TABLE 2. Demographic data of adult typhoid fever patients

Authors	Subjects (n)	Age (yr)	Gender [n (%)]		Antibiotics [n (%)]		
			Male	Female	Azithromycin	Ciprofloxacin	Other
Limson *et al.*[23]	28	18-77	NA (NA)	NA (NA)	0 (0.00)	15 (53.57)	13 (46.40)
Chew *et al.*[24]	22	20-46	NA (NA)	NA (NA)	0 (0.00)	22 (100)	0 (0.00)
Uwaydah *et al.*[25]	62	13-46	56 (90.32)	6 (9.68)	0 (0.00)	62 (100)	0 (0.00)
Wallace *et al.*[26]	42	26-28	NA (NA)	NA (NA)	0 (0.00)	20 (47.6)	22 (52.40)
Tribble *et al.*[27]	14	21-47	10 (71.00)	4 (29.00)	14 (100)	0 (0.00)	0 (0.00)
Butler *et al.*[28]	77	17-60	59 (76.62)	18 (23.38)	42 (54.50)	0 (0.00)	35 (45.50)
Girgis *et al.*[7]	60	18-32	NA (NA)	NA (NA)	34 (56.70)	26 (43.30)	0 (0.00)
Liberti *et al.*[29]	48	19-54	20 (42.00)	28 (58.00)	0 (0.00)	20 (41.70)	28 (58.30)
Gasem *et al.*[30]	50	15-35	NA (NA)	NA (NA)	0 (0.00)	25 (50.00)	25 (50.00)
Zmora *et al.*[31]	48	>18	NA (NA)	NA (NA)	27 (56.25)	0 (0.00)	21 (43.75)
Mean			(72)*	(28)*	(26)*	(42)*	(32)*

Note :n = number of adult typhoid fever patients; NA = not available; *The calculation results are only from studies with complete sex data

TABLE 3. Susceptibility of *S. typhi* to azithromycin

Antibiotics/Authors	Sample origin	Sample intake	Resistant [n* (%)]	Intermediate [n* (%)]	Sensitive [n* (%)]
Azithromycin					
• Butler *et al.*[28]	India	1998	9/82 (11)	0 (0.0)	73/82 (89.0)
• Girgis *et al.*[7]	Egypt	1998	0 (0.00)	0 (0.0)	60/60 (100)
• Afroze *et al.*[8]	Bangladesh	2009-2012	51/71 (71.8)	NA (NA)	20/71 (28.2)
• Harichandran *et al.*[32]	India	2011-2013	NA (NA)	NA (NA)	62/79 (78.5)
• Joshi *et al.*[9]	India	2012-2016	1/159 (0.8)	0/159 (0.0)	132/159 (99.2)
• Bhetwal *et al.*[33]	Nepal	2015-2017	6/162 (3.7)	0/162 (0.0)	156/162 (96.3)
• Veeraraghavan *et al.*[34]	India	2017-2020	NA (NA)	NA (NA)	2030/2032 (99.9)
• Khadka *et al.*[10]	Nepal	2018	2/46 (4.3)	NA (NA)	44/46 (95.7)
• Shah *et al.*[11]r	Pakistan	2019	4/81 (5.0)	0 (0.0)	77/81 (95.0)
Ciprofloxacin					
• Limson *et al.*[23]	Phillipine	1988	0 (0.0)	0 (0.0)	28/28 (100.0)
• Uwaydah *et al.*[25]t	Qatar	1991	0 (0.0)	0 (0.0)	62/62 (100.0)
• Wallace *et al.*[26]	England	1993	0 (0.0)	0 (0.0)	42/42 (100.0)
• Liberti *et al.*[29]	Italia	1997-1999	0 (0.0)	0 (0.0)	48/48 (100.0)
• Girgis *et al.*[7]	Egypt	1998	0 (0.0)	0 (0.0)	60/60 (100.0)
• Gasem *et al.*[30]	Indonesia	2002	0 (0.0)	0 (0.0)	50/50 (100.0)
• Afroze *et al.*[8]	Bangladesh	2009-2012	27/71 (38.0)	NA (NA)	44/71 (62.0)
• Harichandran *et al.*[32]	India	2011-2013	NA (NA)	NA (NA)	26/79 (33.0)
• Joshi *et al.*[9]	India	2012-2016	71/159 (44.7)	78/159 (49.0)	10/159 (6.3)
• Bhetwal *et al.*[33]	Nepal	2015-2017	4/162 (2.4)	95/162 (58.6)	63/162 (39.0)
• Veeraraghavan *et al.*[34]	India	2017-2020	NA (NA)	NA (NA)	43/2032 (2.1)
• Khadka *et al.*[10]	Nepal	2018	20/46 (43.5)	25/46 (54.3)	1/46 (2.2)
• Shah *et al.*[11]r	Pakistan	2019	77/81 (95.0)	1/81 (1.2)	3/81 (3.7)

Note: *n/N: n (number of resistant, intermediate, and sensitive *S. typhi* samples)/N (total of all assessed *S. typhi* samples; NA = not available

Length of fever

Fever was the primary symptom of typhoid fever with varied duration of fever. There were 10 of 17 studies with data on the average length of fever in adult typhoid fever patients. The mean duration of fever in patients treated with azithromycin ranged from 1.6 to 4.3 d, and the average duration in patients treated with ciprofloxacin ranged from 1.5 to 5.7 d. The total average from the collected data was 3.46 d in patients treated with azithromycin and 4.22 d in patients treated with ciprofloxacin (TABLE 4).

Length of stay

Length of stay was defined as the length of stay after the therapy started. There were 4 of 17 inclusion studies with data on the length of stay in adult typhoid fever patients treated with azithromycin or ciprofloxacin. Typhoid fever patients treated with azithromycin had an average duration ranging from 8.7 to 10 d. The average duration of fever in patients treated with ciprofloxacin ranged from 8 to 5.7 ± 2.3 d. The overall average duration of fever in typhoid fever treatment with azithromycin was shorter (9.31 d) than with ciprofloxacin (9.97 d) (TABLE 4).

TABLE 4. Duration of fever and length of stay in adult typhoid fever patients treated with azithromycin and ciprofloxacin

Antibiotics/Authors	Number of pasients (n)	Length of fever (d)	Average length of fever (d)	Length of stay (d)	Average length of stay (d)	
Azithromycin						
• Gasem *et al.*[30]	NA	NA		NA	NA	
• Zmora *et al.*[31]	27	1.6		NA	NA	
• Limson *et al.*[23]	NA	NA		NA	NA	
• Tribble *et al.*[27]	14	4.31		NA	NA	
• Liberti *et al.*[29]	NA	NA	3.46	NA	NA	9.31
• Butler *et al.*[28]	41	4.1		41	8.7	
• Wallace *et al.*[26]b	NA	NA		NA	NA	
• Chew *et al.*[24]	NA	NA		NA	NA	
• Girgis *et al.*[7]	36	3.8		36	10	
• Uwaydah *et al.*[25]	NA	NA		NA	NA	
• Uwaydah *et al.*[25]	NA	NA		NA	NA	
Ciprofloxacin						
• Gasem *et al.*[30]	28	5.1		28	11.7 ± 2	
• Zmora *et al.*[31]	NA	NA		NA	NA	
• Limson *et al.*[23]	20	5		NA	NA	
• Tribble *et al.*[27]	NA	NA		NA	NA	
• Liberti *et al.*[29]	20	1.5		NA	NA	
• Butler *et al.*[28]	NA	NA	4.22	NA	NA	9.97
• Wallace *et al.*[26]	20	4		NA	NA	
• Chew *et al.*[24]	25	4		25	8	
• Girgis *et al.*[7]	28	3.3		28	10	
• Uwaydah *et al.*[25]	28	5.7 ± 2.3		NA	NA	
• Uwaydah *et al.*[25]	34	4.5 ± 1.3		NA	NA	

Note: NA = not available

DISCUSSION

Azithromycin and ciprofloxacin act in different ways. Azithromycin functions by binding to the 23S component of the bacterial 50S ribosome subunit, thereby inhibiting bacterial protein synthesis through the prevention of aminoacyl-tRNA transit and the growth of proteins via the ribosome. It exhibits bacteriostatic properties.[35] On the other hand, ciprofloxacin operates by inhibiting DNA replication, binding to DNA gyrase and topoisomerase IV, and demonstrating bactericidal properties.[36]

Orally administration, azithromycin has a bioavailability of approximately 37% and reaches peak concentrations within 2 h.[37] Oral ciprofloxacin has a bioavailability of 70-80% and reaches peak concentrations between 1 to 1.5 h.[36] Azithromycin has a lower percentage of bioavailability and takes longer to reach peak concentrations compared to ciprofloxacin. Azithromycin is metabolized in the liver and excreted through bile and urine, while ciprofloxacin is also metabolized in the liver and excreted through feces and urine.[35,36]

The present systematic review showed that the susceptibility of *S. typhi* to azithromycin exhibited a decreased from 100% (1988) to 28.2% (2009-2012), but there was an increase in susceptibility to 78.5% (2011-2013) and continued to rise to 99.9% (2017-2020). Comparing these findings to the systematic review conducted by Marchello *et al.*[38] most results were similar. However, there was a lower resistance rate (4.1%) reported in 2010-2014 compared to the inclusion study (71.8%) from 2009-2012. The susceptibility of *S. typhi* to ciprofloxacin decreased from 100% (1988) to 62% (2009-2012) and continued to decrease to 2.1% (2017-2020). Results that were found are similar to the systematic review conducted by Marchello *et al.*[38] which reported that there is an increase in S. *typhi* resistance to ciprofloxacin from 0% (1985-1989) to 37.8% (2010- 2014). The differences could be attributed to variations in sampling locations and years, leading to differences in the prevalence of resistant strains.

Azithromycin treatment for typhoid fever resulted in an average duration of fever of 3.46 d and an average length of stay of 9.31 d. On the other hand, ciprofloxacin had an average duration of fever of 4.22 d with an average length of stay of 9.97 d. In a study by Amin *et al.*[18] there were the following results: average length of fever (5.8 d and 8.2 d), average length of stay (12.6 d and 13. 7 d) from azithromycin and ciprofloxacin treatment for typhoid fever patients.

There are several limitations of this study. There are not many studies regarding the susceptibility of *S. typhi* to azithromycin and ciprofloxacin and the use of azithromycin and ciprofloxacin as a treatment for typhoid fever in the adult population. Some data need to be completed on some studies, and the included studies were dominated by studies conducted in Nepal and India, thus not reflecting the broader situation.

CONCLUSION

There has been an increase in *S. typhi*'s susceptibility to azithromycin from 1998-2020 and a decrease in *S. typhi*'s susceptibility to ciprofloxacin from 1988-2020. Typhoid fever treatment with azithromycin is more effective than those treated with ciprofloxacin based on the duration of fever and length of stay from the inclusion studies.

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