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A systematic review of recent outbreaks and the efficacy and safety of drugs approved for the treatment of *Salmonella* infections

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ABSTRACT

A systematic review was conducted to critically analyze the outbreaks, efficacy, and safety of drugs used to treat various *Salmonella* infections. Four drugs—azithromycin, ceftriaxone, ciprofloxacin, and amoxicillin—are commonly used to treat *Salmonella* infections, and all four drugs were included in this review. This review found that, of these, azithromycin and ceftriaxone were more effective in treating *Salmonella* infections based on the patient's length of stay in the hospital and the rate at which the fever was resolved. Fluoroquinolones are also effective in treating *Salmonella* infection but are not approved for use in children. Azithromycin was found to be the physicians' preferred choice of medication for *Salmonella* infection due to its less resistance development. Almost all these drugs produce varying degrees of adverse events, but they are mild to moderate. However, azithromycin was shown to be comparatively safer than the other three drugs in terms of side effects, adverse events, and relapse associated with *Salmonella* treatment. Developing effective and safe therapies for all strains of *Salmonella* remains a priority, especially given the increasing prevalence of antibiotic-resistant variants.

Introduction

Salmonellosis

Salmonella species are gram-negative, motile, acid-labile, facultative intracellular microorganisms commonly associated with salmonellosis, an infection prevalent in low- and high-resource countries [1–3]. Salmonellosis in humans typically presents as self-limiting food poisoning (gastroenteritis) but can also lead to serious systemic infections, such as enteric fever, which require antibiotic treatment [2].

Types and causative agents of salmonellosis

According to the Centers for Disease Control and Prevention (CDC), there are two species within the genus *Salmonella: Salmonella enterica* and *Salmonella bongori. S. enterica* is further categorized into six subspecies: *enterica* (I), *salamae* (II), *arizona* (IIIa), *diarizonae* (IIIb), *houtenae* (IV), and *indica* (VI). On the other hand, *S. bongori* has no subspecies [3].

Salmonellosis is caused by a subspecies of *S. enterica* and affects a wide range of hosts, including humans, mammals, birds, and fish. *Salmonella* serovars within subspecies *S. enterica* are divided into two groups based on their clinical syndromes, such as typhoidal *Salmonella and* nontyphoidal *Salmonella* (NTS). Typhoidal *Salmonella* is caused by *S. Typhi* and *S. Paratyphi* A, B, and C (Figure 1). Humans serve as hosts to *S. Typhi* and *S. Paratyphi* A, causing enteric fever, whereas *S. Paratyphi* B and C cause a typhoid fever-like illness in other animals, primarily, higher primates. In addition, nontyphoidal *Salmonella* typically leads to gastroenteritis, with host immunity determining the frequency of invasive illness. Individuals with conditions such as HIV infection, falciparum malaria, malnutrition, and other immunocompromised states are more susceptible to invasive NTS [4,5].

Recent outbreaks of Salmonella

According to the Salmonella Surveillance Overview by the CDC, *Salmonella* is known to cause more than 1.35 million illnesses per year, with 26,500 hospitalizations and 420 deaths in the United States [6]. Several outbreaks of *Salmonella* have been reported worldwide, with the most recent one reported in November 2023. The *Salmonella* outbreak was linked to cantaloupes, and, as of December 15, 2023, 302 cases of illness have been reported with 129 cases involving hospitalization, and six reported deaths according to the CDC. Data show that Minnesota reported the highest number of outbreaks (26 cases) of *Salmonella* linked to cantaloupes of 42 states in the United States [7]. In relation to

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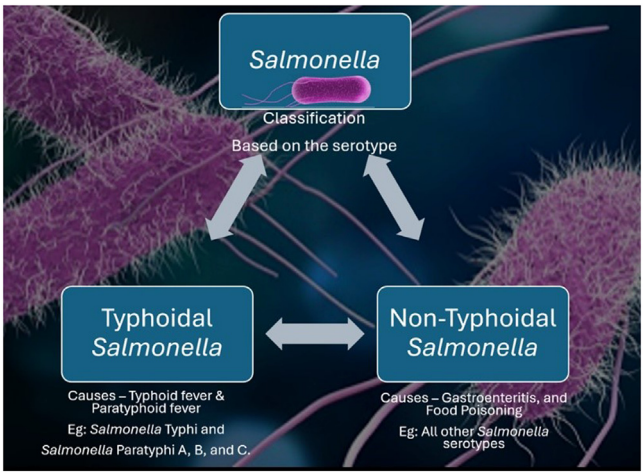

Figure 1. Classification of *Salmonella* infections.

Salmonella infection due to cantaloupes, 97 cases were reported in New South Wales in 2015.

In 2015, there were 44 cases of an outbreak connected to frozen raw breaded chicken products in four provinces of Canada: Ontario, Quebec, Newfoundland, Labrador, and Nova Scotia. In South Australia in 2016, raw mung bean sprouts were identified as the source of infection, resulting in 230 reported cases of *Salmonella*. In addition, 97 cases of an outbreak linked to cantaloupes were reported in New South Wales in the same year [8].

In 2016, a *Salmonella* outbreak affected multiple states in the United States, with 27 patients infected with *Salmonella* Virchow. During the same year, a significant number of individuals, 907 patients, were infected with the *Salmonella* Poona serotype outbreak in the United States, which was traced back to cucumbers imported from Mexico. In 2018, a large number of typhoid fever cases were documented in Syria at the Al-Hol Camp among Iraqi and Syrian refugees. In India in 2018, Woraiyur reported 40 cases of typhoid fever, attributed to contaminated water [8].

Amid these outbreaks, there were instances where the *Salmonella* outbreak was linked to antimicrobial-resistant strains. According to the Morbidity and Mortality Weekly Report, in 2018, an outbreak of *S. enterica* serotype Newport with decreased susceptibility to azithromycin was reported in Mexico. This infection affected 255 individuals in the United States, resulting in the hospitalization of 60 individuals and the death of two [9]. Since 2016, Pakistan has been experiencing an outbreak of extensively drug-resistant typhoid cases, with the situation worsening over the years. From 2016 to 2018, of 8188 cases reported in the Sindh province of Pakistan, 5274 cases were attributed to extensively drug-resistant *S. enterica* serovar typhi, *Salmonella* paratyphi A, and *Salmonella* paratyphi B [10]. The development of resistance against fluoroquinolones and third-generation cephalosporin by the *Salmonella* strains is concerning because these are the main first-line agents used against typhoid fever [11]. Limited information is available regarding the mortality rate of this typhoid fever outbreak, but one study suggests a mortality rate of 1.8%, which may be underestimated because it only includes hospitalized patients and not the general population of Pakistan [12].

Although there are drugs available for the treatment of *Salmonella* infection, to date, these drugs have not been able to control the outbreaks of *Salmonella* infections. This is due to their varying safety and efficacy profiles, which makes it harder for health care providers to choose suitable medication. Therefore, a systematic review was conducted to assess the effectiveness and safety of drugs commonly used in the treatment of various *Salmonella* infections.

Methods

A systematic review provides health care practitioners with the most current and comprehensive information for analyzing and evaluating the reliability and clinical significance of a topic or intervention. It presents crucial information concisely, incorporating thorough data and a methodical literature search while avoiding selection bias that may occur in other types of reviews. This type of review also involves synthesizing previous study results, often accompanied by a meta-analysis to combine and analyze data for an overall outcome. Ultimately, the synthesized information is used to draw conclusions and make recommendations.

Outcome assessment

The focus of this review is to assess the effectiveness and safety of drugs commonly used in the treatment of various *Salmonella* infections. To evaluate the effectiveness of these drugs, a combination of clinical and microbiological responses, fever clearance time, and culture and sensitivity tests (before and after completing antibiotic treatment) were taken into account. Drug safety is determined by a decrease in adverse drug effects or adverse events compared with drugs previously approved by the US Food and Drug Administration (FDA).

Data extraction

The information gathered for this review primarily focuses on the most recent therapies for *Salmonella* infections. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was used to identify publications and reviews that evaluated randomized controlled trials. The main data sources used were PubMed, Nvivo, Mendeley, Evernote, CiteUlike, Biohunter, DelveHealth, Scicurve, MEDLINE, the Cochrane Library, Scopus, Web of Science, and Google Scholar. Articles related to animals were excluded. According to Center Watch, the medications used in our study were approved by the US FDA. Four medications were licensed to treat *Salmonella* infections, resulting in the publication of 546 articles. Finally, 35 articles were selected for review (Figure 2). Each author retrieved relevant material from the publications separately. Any conflicts were resolved through consensus. All identified studies were evaluated for inclusion by two independent investigators (PS and CSI), with any disagreements resolved by a third reviewer (PM). The retrieved data included the study phase, area, subject conditions (mean age, gender, duration of infection, culture and sensitivity test, body temperature, and comorbidities), and outcome measures. This information was gathered and compiled in paragraphs that provided a thorough introduction to each medication. The review protocol is currently registered in PROSPERO under reference number CRD42024580893 and publicly available.

Search strategy

The following search strategy was used to collect articles for this review (“salmonella infections”[MeSH Terms] OR (“salmonella”[All Fields] AND “infections”[All Fields]) OR “salmonella infections”[All Fields] OR (“salmonella”[All Fields] AND “infection”[All Fields]) OR “salmonella infection”[All Fields]) AND ((y_5[Filter]) AND (ffrft[Filter]) AND (randomizedcontrolledtrial[Filter]) AND (fft[Filter])).

Inclusion and exclusion criteria

This review included all studies that examined the efficacy and safety profiles of the four drugs approved by the US FDA within the search period: azithromycin, ceftriaxone, ciprofloxacin, and amoxicillin. These four drugs are commonly used for the treatment of *Salmonella* infection

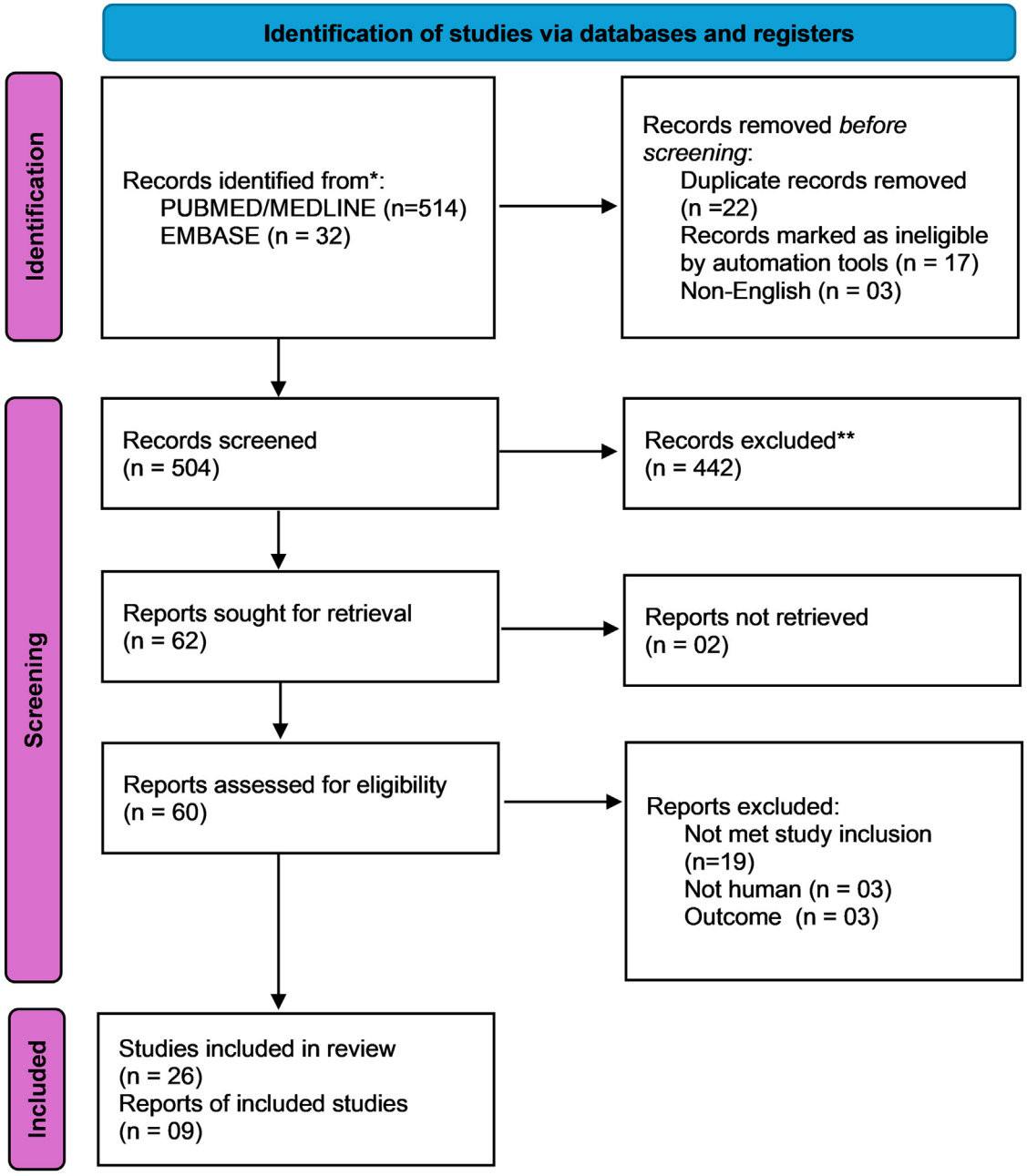

Figure 2. PRISMA flow diagram for the selection of articles for the review.

either alone or in combination. Most people recover from *Salmonella* infection within 4-7 days without antibiotics, with the support of drinking extra fluids as long as the diarrhea lasts. Antibiotic treatment is recommended for people with severe illness, and combination therapy is preferred when the chance of resistance to single-drug therapies is high. Excluded from this review were studies on non-randomized controlled trials, incomplete data, studies with unavailable full texts, frequency of *Salmonella* recurrences, studies of unsatisfactory quality, studies with non-randomized sample selection, research on the frequency of risk factors, and studies not available in English.

Data analysis

The focus of the analysis was on the treatment of *Salmonella* infections, with the culture and sensitivity test being the primary measure of effectiveness for binary outcomes. We examined the rate of initial infections and recurrence, as well as the drug's safety profile in terms of side effects and adverse events, by evaluating the frequency of recorded incidents. Heterogeneity was assessed using the SD of studies. In a sensitivity analysis, we examined the results by subgrouping trials that studied similar treatments, assuming a sufficient number of trials were available.

Management of *Salmonella* infections

This section focuses comprehensively on pharmacotherapy management of *Salmonella* infection. It summarizes the treatment options available for the management of *Salmonella* infections. There are four drugs available for the treatment of these infections: azithromycin, ceftriaxone, fluoroquinolone ciprofloxacin, and amoxicillin. The efficacy and safety of all these drugs are discussed in this section.

Pharmacological management

This section will focus on the efficacy and safety of the drugs commonly used for the treatment of various *Salmonella* infections and the information is comprehensively presented.

Azithromycin

Azithromycin, an azalide macrolide, has emerged as a promising treatment for typhoid fever. For four decades, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole-resistant *S. typhi* have been the preferred treatments for typhoid fever. However, the rise of multidrug-resistant strains of the virus has made the search for other treatments necessary [12]. Fluoroquinolones, although effective, have not been approved for use in children. Fluoroquinolone-resistant *Salmonella* has also been reported mostly due to topoisomerase genes *gyrA, gyrB, parC*, and *parE*; plasmid-mediated quinolone resistance (PMQR); and chromosomally encoded efflux mechanisms [13]. Therefore, azithromycin has proved to be effective against uncomplicated *Salmonella* infections, specifically, *S. enteritidis* and *S. typhimurium,* in animal studies given the trends of antimicrobial resistance. Azithromycin 500 mg orally (maximum) as a once-daily dose for 5-7 days is administered to the patient [14]. Azithromycin showed a remarkable capacity to accumulate at elevated intracellular concentrations, attaining intracellular values that were 50-100 times higher than the levels found in serum [15].

A previous study reported that azithromycin was the most active macrolide against *S. typhi,* with a minimum inhibitory concentration (MIC) of 8 mg/l [16,17]. In a study involving human volunteers, it was found that the neutrophil concentration of azithromycin exceeds the MIC of *S. typhi* by up to 20 times, which is desirable [18].

Furthermore, azithromycin was effective in treating animal tissue infection caused by *S. enteritidis*. This finding raised questions about the possible future use of azithromycin. Azithromycin has the advantage of once-daily dosing due to its long half-life, which would directly improve patient adherence. In a randomized controlled trial in the United Kingdom in 2019 involving 81 participants, 500 mg of azithromycin was reported to be an effective treatment for fully sensitive strains of *S. typhi*. However, treatment with azithromycin resulted in extended fever clearance and extended bacteremia (median 90.8 hours [95% confidence interval: 65.9-93.8] compared with 20.1 hours [95% confidence interval: 7.8-24.3], P <0.001) compared with ciprofloxacin [18]. Research also reported that azithromycin has no adverse side effects and was found to be safe for children.

Azithromycin is administered either alone or in combination with other drugs. For instance, a combination of azithromycin and ciprofloxacin is used in some clinical settings to combat *Salmonella* infections. Combination therapy is specifically employed for treating particular forms of *Salmonella* infections, such as those that are life-threatening or resistant to single-drug treatments. It should be noted that the azithromycin and ciprofloxacin combination is not typically the preferred choice for treating *Salmonella* infections. Although both antibiotics are effective against *Salmonella*, they act through different mechanisms and may have varying side effects, which limits their use in combination therapy [16–18].

Ceftriaxone

According to recent guidelines, ceftriaxone is one of the preferred antibiotics for the treatment of typhoid fever and bacterial enteric infections in immunocompromised individuals. This recommendation applies to those who have not developed resistance to ceftriaxone and did not acquire the infection from Pakistan or Iraq, where there is a high prevalence of extensively drug-resistant *S. typhi* [10,19].

Ceftriaxone is a third-generation cephalosporin with a broad spectrum, capable of combating gram-negative and gram-positive bacteria, including the gram-negative *Salmonella* species. It has high plasma protein binding and a half-life of 6-9 hours. Comparable to other β-lactams, ceftriaxone works by inhibiting the cross-linking of peptidoglycan, which is crucial for the structure of the bacterial cell wall [20].

The use of ceftriaxone as a primary antibiotic treatment for typhoid fever dates back to 1986. At that time, chloramphenicol was commonly used for typhoid fever treatment, but its frequent administration and lengthy duration prompted the search for a more effective antibiotic. In a study comparing ceftriaxone to chloramphenicol in 59 patients with typhoid fever, it was found that ceftriaxone achieved satisfactory clinical and antibiotic effects. Although the efficacy of ceftriaxone was initially lower at 79% than chloramphenicol's 90%, blood cultures on day 3 showed that ceftriaxone-treated patients had negative results for *S. typhi*, whereas 65% of chloramphenicol-treated patients were still positive. This indicates that ceftriaxone is superior in terms of treatment duration efficacy and safety because it did not cause significant bone marrow suppression such as chloramphenicol [21].

A previous study investigated the effects of third- and fourth-generation cephalosporins on *Salmonella typhimurium* L forms, a strain known to cause diarrhea in infants and young children. The study revealed that this strain is susceptible to third-generation cephalosporins, such as ceftriaxone [22]. Another study comparing the effectiveness of ceftriaxone with chloramphenicol in treating typhoid fever confirmed that ceftriaxone can reduce fever in patients 1 day faster than chloramphenicol. In Indonesia, Dasopang et al. [23] found that ceftriaxone treatment for typhoid fever is more cost-effective than chloramphenicol, with patients saving Rp. 20,289.

However, recent cases in China have shown ceftriaxone-resistant *Salmonella* in children. The resistance rate was reported to be 5.7%, but another study found a resistance rate of 25.9%. The study identified the gene blaCTA-M-55 as responsible for ceftriaxone resistance, which may be transferred between bacteria in the human intestinal tract [24].

Ceftriaxone injection comes in the form of a powder to be mixed with liquid or as a premixed product to be injected intravenously over a period of 30 or 60 minutes. It can also be administered intramuscularly. Unlike other medications available for the treatment of *Salmonella* infection, ceftriaxone is only available in parenteral formulation, which limits the self-administration of the drug by the patient [20,21].

Ciprofloxacin

Fluoroquinolones are broad-spectrum antibiotics with good oral bioavailability, indicated for the treatment of pneumonia, gastroenteritis, urinary tract infections, and gonococcal infections. Ciprofloxacin, a fluoroquinolone, exhibits excellent activity against aerobic gram-negative organisms, making it a mainstay for treating severe *Salmonella* infections and typhoid fever in adults [25]. In addition, ciprofloxacin is known to have potential anti-biofilm effects because biofilms are common factors in developing antimicrobial agent tolerance [26]. However, the efficacy of ciprofloxacin in treating *Salmonella* has declined due to increased levels of resistance to fluoroquinolones and treatment failure from reduced susceptibility to ciprofloxacin. The development of resistance to ciprofloxacin typically involves mutations in gyrA within the quinolone resistance determining region of subunit A of DNA gyrase in quinolone-resistant *S. enterica* [25,26]. Single-point mutations in the quinolone resistance determining region of the gyrA gene, particularly, between amino acids 67 and 106, are associated with decreased susceptibility to ciprofloxacin, whereas double mutations at residues 83 and 87 are observed in highly resistant clinical *S. enterica* serovar typhimurium isolates. Overactivation of multidrug efflux pumps and decreased outer membrane permeability also contribute to *Salmonella* resistance. PMQR occurs when the organism acquires plasmid-encoded proteins protecting fluoroquinolones. Fluoroquinolone-resistant and extended-spectrum β-lactamase-producing *Salmonella* enteric serotype Derby (*S. Derby*) identified three *S. Derby* isolates of 826 non-typhoidal *Salmonella* isolates, with ciprofloxacin MIC of 4 ug/ml. These isolates shared the same genetic structure of quinolone resistance, including silent gyrA mutation and three PMQR genes [26]. As a result, fluoroquinolone is no longer the first-line treatment for *Salmonella* due to reduced effectiveness.

Table 1
The efficacy and safety of the drugs used for the treatment of *Salmonella* infection.

Name of the drugs	Study & author	Study design	Efficacy	Safety
Azithromycin	Giri et al. [29]	This is a double-blind randomized, placebo-controlled trial of azithromycin or trimethoprim. A total of 326 patients older than 2 years old and younger than 65 years old were the participants involved. The patients with temperatures more than or equal to 38.0°C for more than 4 days without any localized signs were presented to two Kathmandu hospitals in Nepal. The primary end point was fever clearance time, whereas secondary end points included treatment failure and adverse reactions.	The median fever clearance time for all patients was 2.7 days (95% CI, 2.6-3.3 days) in the trimethoprim arm and 2.1 days (95% CI, 1.6-3.2 days) in the azithromycin arm. On analysis, it was found that azithromycin resulted in speedier fever clearance time in individuals with sterile blood cultures and fewer relapses of culture-confirmed enteric fever.	Between azithromycin and trimethoprim, the hazard ratio of treatment failures by 28 days was 0.62 (95% CI, 0.37-1.05; $P = 0.073$). There were significantly lower relapses and fewer AEs associated with azithromycin. A total of 11 patients required hospital admission due to grade 3 or 4 AEs, high-grade or persistent fever, or IV rescue therapy administration on one occasion. Two were in the azithromycin arm and nine were in the SXT arm. In all treatment groups, the same number of mild-to-moderate AEs were recorded; these events were all transient and self-limited.
	Girgis et al. [12]	This is a randomized control trial in Egypt on azithromycin vs ciprofloxacin. Female and male patients older than 18 years old, have a fever of ≥38.5°C plus a history of fever for at least 4 days, in addition to two or more of the following: abdominal tenderness, hepatomegaly (>2 cm below the right costal margin), splenomegaly (>2 cm below the left costal margin), and rose spots were admitted to Abbassia Fever Hospital Egypt. This study consisted of 64 subjects with positive blood or stool cultures for *S. typhi* or *S. paratyphi,* 36 individuals received azithromycin and 28 individuals received ciprofloxacin.	All individuals treated with azithromycin or ciprofloxacin were cured and no relapses were found. After the initiation of therapy, the following times (mean ± SD [range]) saw defervescence (highest daily temperatures of ≤38°C) azithromycin for 3.8 ± 1.1 (2-7) days and ciprofloxacin for 3.3 ± 1.0 (1-5) days. The culture of blood and stools of all patients were negative, except the 1 individual who had a positive blood culture on day 4 of treatment with azithromycin.	
Ceftriaxone	Islam et al. [21]	This is a randomized clinical trial that included patients who fit the inclusion criteria: age 6 months to 60 years; fever for >4 days; diarrhea, defined as more than three liquid stools in 24 hours; and a somatic O agglutinin titer of >80 for *S. typhi*, as determined by the Widal test. These patients were requested to stay in the hospital for 14 days and they were randomly assigned using sealed envelopes that contained a numeric treatment code from a table of random numbers, chloramphenicol or ceftriaxone. The samples taken for analysis were venous blood, stool, and urine samples.	Blood cultures obtained on the third day of treatment showed that 20 patients receiving chloramphenicol were still positive, whereas all the patients receiving ceftriaxone turned up negative. This study found that ceftriaxone was more effective based on the patient's length of stay in the hospital and the rate at which the fever was resolved. In both cases, ceftriaxone was quicker than chloramphenicol in achieving the target. Chloramphenicol, on average, took 57% longer than ceftriaxone to achieve discharge, which is about 2.36 days longer. In terms of the resolution of the fever, it was found that ceftriaxone on average, only took 2.3 days to resolve the fever, compared with chloramphenicol, which used an average of 3.5 days.	Patients who received chloramphenicol as their treatment were found to have a significantly lower median hematocrit (30.5%) on the last day than ceftriaxone (34.5%) and the leukocyte count for chloramphenicol was also lower than those treated with ceftriaxone ($P = 0.02$). The ceftriaxone was well-tolerated by the study participants and no side effects or harmful effects were reported.
	Dasopang et al. [23]	This is a cross-sectional study that included 30 patients who were diagnosed with typhoid fever in Indonesia, ranging from age 0 to 25 years, many of whom were 12-16 years old. A total of 13 of these patients were treated with chloramphenicol, whereas the other 17 were treated with ceftriaxone.		
Ciprofloxacin	Khadka et al. [30]	This is a cross-sectional study where blood specimens were taken from clinically suspected enteric fever patients at the outpatient department of Kathmandu Model Hospital in 2018. The signs and symptoms were examined by the physician. 5 mL of blood samples were taken from patients >5 years of age and 3 mL for <5 years of age for culture. A total of 706 blood samples were collected and among them, 46 samples were culture positive for *S. enterica.* Patients who were already receiving antibiotics, pregnant women, and patients who had a fever >14 days were excluded from this study.	Among 46 samples, 95.7% of the isolates were found to be nalidixic acid resistant, and only one of the isolates was found to be susceptible to all three fluoroquinolones (ciprofloxacin, ofloxacin, and levofloxacin). It was found that 54.3% (n = 25) of isolates had intermediate susceptibility to ciprofloxacin, and the remaining 43.5% (n = 20) were resistant to ciprofloxacin.	The ciprofloxacin was well-tolerated by the study participants, with no major side effects or harmful effects reported.
Amoxicillin	Nelson et al. [28]	This is a randomized and double-blind study that involved 44 infants and children who are diagnosed with uncomplicated Salmonella gastroenteritis. The study population was treated with ampicillin (15 patients), amoxicillin (15 patients) or placebo (14 patients).	The findings showed that antibiotic therapy did not show a significant reduction in the length of diarrhea (means 8.8, 7.3, and 7.2 days, respectively). Relapse in bacteria was not seen in individuals who received a placebo, but 8 patients who received ampicillin (53%) and 8 patients who received amoxicillin (53%) experienced bacteriologic relapse ($P = 0.003$). However, the study shows that ampicillin and amoxicillin were still effective *in vitro* against the salmonella isolated in relapse.	Around 53% of patients with amoxicillin had a substantial increase in the risk of bacteriologic and symptomatic relapse ($P = 0.003$).

AEs, adverse events; CI, confidence interval.

Furthermore, the safety of fluoroquinolones can be evaluated based on their adverse effects. Adverse effects of ciprofloxacin at therapeutic doses are usually mild, causing gastrointestinal disturbances, such as nausea and diarrhea. Serious side effects may include prolonged QT interval, photosensitivity, and hyper-/hypoglycemia. FDA warnings also include tendinitis and tendon rupture due to the two- to four-fold increased risk of tendinopathy associated with fluoroquinolones [25]. Tendinopathy onset is highest within the first month after drug exposure and commonly affects the Achilles tendon, causing severe pain. The incidence of tendinopathy can be up to 2% in patients aged 65 years and older. The use of steroids and advanced age can increase the risk of tendinitis due to collagen degradation caused by upregulation of matrix metalloproteinases. In addition, fluoroquinolone use is associated with aortic aneurysm and aortic dissection, with increased risk during prolonged therapy and in older patients. Ciprofloxacin should be immediately discontinued if aortic dissection is suspected [26].

Amoxicillin

According to recent guidelines for the treatment of *Salmonella* infection, amoxicillin is considered one of the possible alternative agents, although it is not the first line of defense. Amoxicillin is a commonly used β-lactam antimicrobial drug approved by the FDA for primary care settings in the treatment of various infectious diseases. It offers additional coverage against certain gram-negative pathogens while remaining effective against a wide range of gram-positive bacteria. Amoxicillin has demonstrated effectiveness against *Salmonella* species, *Actinomyces* species, *Shigella* species, and some strains of *Escherichia coli*. It is often the preferred or alternative antibiotic within its class due to its high rate of absorption through oral administration [27].

Amoxicillin is commonly used in combination with clavulanic acid, a β-lactamase inhibitor, to prevent degradation by β-lactamase-producing bacteria, which are resistant to a broad range of β-lactam antibiotics, including penicillin [27]. Combining amoxicillin with clavulanic acid increases its effectiveness by reducing susceptibility to β-lactamase resistance.

Research published in 1980 found that using ampicillin or amoxicillin to treat uncomplicated *Salmonella* gastroenteritis was ineffective and significantly increased the risk of bacteriologic and clinical relapse [28]. However, according to recent guidelines, amoxicillin can be used as an alternative agent to treat *Salmonella* infection in children, although its usefulness is limited due to high rates of multidrug resistance. Fluoroquinolones are effective in treating *Salmonella* infection but are not approved for use in children. For children with *Salmonella* infection, a dose of 100 mg/kg of amoxicillin in thrice daily doses orally can be given, with a maximum daily dose of 3 g. For adults, a dose of 1 g of amoxicillin can be given thrice daily orally, and the treatment duration for adults and children is 10-14 days [28].

Prenatal exposure to antibiotics, specifically, amoxicillin, may have adverse effects on children if mothers take it during pregnancy, potentially by altering the gut microbiome. These findings raise questions about the relationship between changes in the mother's microbiome during pregnancy and significant malformations. However, earlier studies concluded that exposure to amoxicillin and clavulanic acid, either as a group or individual medications, during the first trimester of pregnancy was not linked to major malformations in general or by organ systems [27–29]. The efficacy and safety of the drugs used for the treatment of *Salmonella* infection are summarized in Table 1.

In addition to the pharmacotherapy for treating *Salmonella* infection, water, sanitation, and hygiene (WASH) infrastructure, encompassing water, sanitation, and hygiene facilities, is a cornerstone of public health and sustainable development. Access to clean water and proper sanitation reduces the spread of waterborne diseases, improves hygiene practices, and enhances overall well-being. Adequate WASH infrastructure empowers communities, particularly, women and children, by reducing the time spent on water collection and improving sanitation conditions. It also contributes to economic growth by promoting healthier populations and reducing health care costs. Investing in WASH infrastructure is not only a matter of human rights but also a strategic investment in the future of our communities.

Conclusion

Salmonella has proved to be a pathogen of concern for human health when not treated properly or when antimicrobial stewardship is not practiced. It can cause symptoms ranging from mild gastroenteritis to severe systemic diseases, such as enteric fever. Recent outbreaks may be caused by contaminated food, especially in regions with poor sanitation. In addition, there has been an emergence of antibiotic resistance within certain communities, which complicates treatment. To address this, an understanding of the mechanisms of *Salmonella* infection and the development of its antimicrobial properties are necessary to develop effective prevention and treatment strategies. Vigilant surveillance of antimicrobial stewardship is crucial in combating antibiotic resistance.

The treatment of *Salmonella* infections typically involves non-pharmacologic methods, such as rehydration therapy, antidiarrheal therapy, and zinc supplementation. Pharmacologic treatment, including antibiotics, is preferred in cases of typhoid fever. Azithromycin, among other antibiotics, has emerged as a preferred option for typhoid fever due to its ability to accumulate intracellularly and its broad-spectrum activity. However, the use of ceftriaxone should be approached with caution due to the occurrence of resistance. Similarly, fluoroquinolones have decreased efficacy in treating *Salmonella* infections due to widespread resistance, whereas amoxicillin can be used as an alternative agent, particularly, in children.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethics statement

Not applicable.

Author contributions

P.S. was the lead author responsible for conceptualization of the work and incorporation of all intellectual content including feedback from the other authors. L.S.Y. and C.S.Y. led the acquisition of the data, reviewed data quality, verified with different data sources, performed the statistical analyses, and developed the data visualizations. I.K. and F.H.S.E wrote the manuscript. P.S., L.S.Y., C.S.Y., I.K., F.H.S.E., and P.M. contributed to the conceptualization and provided intellectual input into shaping the manuscript. All authors provided valuable input to the interpretation of the data and critically reviewed the paper for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author, Palanisamy Sivanandy, upon reasonable request.

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