SYSTEMATIC REVIEW

CLINICAL EFFICACY OF ORAL AZITHROMYCIN VERSUS OTHER ANTIMICROBIAL DRUGS IN THE TREATMENT OF TYPHOID PATIENTS ACROSS ALL AGE GROUPS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Muhammad Uzair[1], Saad Wali[1], Anees Ur Rehman[1], Afaq Ahmad[2], Muhammad Hamza Rafique[3], Muhammad Bilal Nadeem[1]

[1]Federal Medical College, Islamabad-Pakistan. [2]Department of General Surgery, [3]Department of ENT Head & Neck Surgery, Pakistan Institute of Medical Sciences (PIMS), Islamabad-Pakistan

Background: Typhoid is a major health concern. Drug-resistant cases of typhoid have given rise to new debates. Azithromycin has shown adequate results. The study is designed to determine the clinical efficacy of oral azithromycin versus other antimicrobial drugs in typhoid patients. **Method:** The studies included in the systematic review are randomized controlled trials, comparing the clinical efficacy of azithromycin to other antimicrobial drugs on typhoid patients. We searched 1180 articles from Google Scholar, PubMed Central, Cochrane Library, PLOS ONE, and JSTOR on 16th October, 2023. The risk of bias was analyzed by visualizing the funnel plot, Begg's and Egger's test, and plotting risk of bias graphs. Forest plots are created to display the findings. **Results:** We identified 14 research articles (1556 participants). Odds ratios of the treatment outcomes were extracted. In a forest plot, the overall effect of the treatment outcome (CI=95%) of azithromycin, in comparison to fluoroquinolones appeared to be favourable (Random Effect Model (REM)=2.15, heterogeneity: I^2=37%, τ^2= 0.1729, p=0.15, the overall pooled effect was towards right side). Compared to chloramphenicol, azithromycin showed a high odds ratio (1.23). However, there was no difference in outcome among ceftriaxone and azithromycin groups (REM=0.67, heterogeneity: I^2=0%, τ^2=0%, p=0.78, the overall pooled effect touched the no-effect line). **Conclusion:** Azithromycin is more clinically efficacious than fluoroquinolones and chloramphenicol. The drug has fewer documented relapses in comparison with other antimicrobial drugs. Fever clearance time of azithromycin is greater than ceftriaxone and chloramphenicol.

Keywords: Clinical efficacy; Azithromycin; Typhoid; Systematic review

Citation: Uzair M, Wali S, Rehman AU, Ahmad A, Rafique MH, Nadeem MB. Clinical Efficacy of Oral Azithromycin Versus Other Antimicrobial Drugs in the Treatment of Typhoid Patients Across All Age Groups: A Systematic Review of Randomized Controlled Trials. J Ayub Med Coll Abbottabad 2024;36(3):642–50.

DOI: 10.55519/JAMC-03-12881

INTRODUCTION

Typhoid is a threat to global health. In many underdeveloped and developing countries, particularly in regions such as South-East Asia, Eastern Mediterranean, Africa, and the Western Pacific, typhoid fever is hyperendemic. The primary reason for this high prevalence is the limited availability of resources. As a result, these regions struggle to provide uncontaminated food and clean water.[1] All these factors lead to the nourishment of none other than *Salmonella typhi and paratyphi*, the basic organisms causing typhoid or enteric fever among children and adults. Globally, 14.3 million people are infected by typhoid and 0.12 million have lost their lives in 2017. Among those who could not survive from typhoid infection were children and geriatrics (GBD Typhoid and Paratyphoid Collaborators).[2] A study conducted in Karachi (Pakistan) reported that typhoid occurred most commonly in males, under 15 years of age, and in the month of April.[3]

The disease worsens when the antibiotics fail to cure it. Recently a lot of cases have been reported that showed multi-drug resistance due to excessive usage of antimicrobial drugs[4]. The challenging situation arises from the fact that the first line of antibiotics is ineffective in treating multi-drug-resistant typhoid. Fluoroquinolone (FQ) resistance has also been reported which was once considered to be a drug of choice.[5]

Numerous randomized controlled trials have highlighted the clinical effectiveness of oral azithromycin (AZM) in treating typhoid fever. For instance, the research conducted by Jin *et al*[6], as well as the study by Siddiqi *et al*[7], have underscored the significance of AZM in managing patients with typhoid. Therefore, it is explicitly important to combine these studies under the umbrella of one systematic review.

This systematic review primarily investigates the clinical efficacy of oral AZM, which refers to its effectiveness in patient recovery, in comparison to other antimicrobials. This research question seeks to evaluate the treatment outcomes and effectiveness of AZM, focusing on patient recovery rates. Alongside this primary inquiry, a secondary question explores various dimensions of AZM treatment, including fever clearance time (FCT), microbiological cure, relapses data, laboratory findings, and adverse effects. In addition, the review takes into account various details from the included studies. These details encompass the timing and location of the trials, the blinding procedure used, the demographic profiles of the participants, the number of participants in both the study and comparator groups, and the dosages of the drug administered.

MATERIAL AND METHODS

Eligibility criteria:

The review included those articles that applied randomized controlled trials (RCTs) including open- label controlled trials, and at the same time comparing the clinical efficacy of azithromycin versus other antimicrobial drugs in treating typhoid resistant and non- resistant patients to provide a comprehensive impact of azithromycin in treating typhoid patients. The inclusion criteria did not specify the year of study, study setting, age groups, or gender. The studies included were open-access, easy to interpret implying clarity in data, summarizing results concisely with charts and tables, and written in English.

Information sources:

The databases explored were Google Scholar, PubMed Central, Cochrane Library, PLOS ONE, and JSTOR. No other websites were explored other than these databases. No conference data were collected.

Search strategy:

The research articles were searched by the single-line method. The words used to search were "(*efficacy OR effectiveness of oral azithromycin) AND (ciprofloxacin OR gatifloxacin OR ofloxacin OR ceftriaxone OR cefixime OR fluoroquinolones OR chloramphenicol OR gentamycin OR aztreonam) AND (typhoid patients OR enteric fever OR salmonella typhi) AND (randomized controlled trials OR trials OR experiments)*". there was no limit filter applied on google scholar. For JSTOR, we filtered out only "English" and "research reports".

Selection Process:

The searched articles were reviewed. They were uploaded to EndNote X9 software. The titles of the research were scanned out manually. In case of any doubt, articles were skimmed, and decided whether to include or exclude them.

Data Collection Process:

The studies were inspected especially the abstract and results sections. The whole activity was performed by the authors separately.

Data Items:

The primary outcomes concerned with the clinical efficacy of the drugs upon the patients of study groups and comparator groups were retrieved. The secondary outcomes related to clinical failure, microbiological cure, FCT, and laboratory values of the patients were also reviewed. Fever clearance time is the duration starting from the initiation of antibiotic treatment, or from the onset of a fever of 38.0 °C or higher after antibiotic treatment begins, until the temperature consistently stays below 38.0 °C.[6]

Assessment of Bias:

The bias assessment was performed by visualizing the funnel plot of related studies separately. Heterogenicity (I^2) was observed when the forest plot was made. We performed Egger's test and Begg's test to detect publication bias in the review studies by using MedCalc software. The risk of bias graphs was plotted by using online ROBVIS. A web application created to display the results of risk-of-bias evaluations conducted during a systematic review.

Effect measures:

The odds ratio and confidence interval (upper and lower limits) were calculated from the treatment outcomes of every study.

Synthesis Method:

During the review process, assessment of blinding status in each study was conducted, followed by verification of the number of participants and examination of the basic demographic profile of patients. Additionally, scrutiny of drug dosage for both the study and comparator groups was undertaken. Key parameters encompassed the number of patients treated with the drug, the duration required for fever resolution, rates of microbiological cure, incidence of adverse effects, laboratory test results, and information on any relapses, all supported by their respective p-values. The forest plots (Random effect model, Hedges Olkin test) were generated by using the Rstudio software.

Reporting bias assessment of missing outcomes:

The results of selected studies were analyzed and missing outcomes were scanned from the studies.

Certainty Assessment:

The certainty of any outcome was measured by the *p*-value of the given variable (p=<0.05).

RESULTS

Study Selection:

A total of 1180 articles were identified by the search engines. EndNote X9 software was used to collect all the articles in one place. The duplicated and incorrectly searched articles such as those articles that were concerned with diseases other than typhoid (Scrub typhus etc) were removed at the spot. 1150 articles were screened. Fourteen research articles were selected that matched the inclusion criteria as mentioned in the PRISMA flow diagram (Figure-1)[8]. We did not explore unpublished articles and registers. We did not apply any filter in the search bar. The research articles that were similar to the topic of the systematic review were: Faryad *et al*[9], Antolis *et al*[10], and Faisal *et al*[11]. Faryad *et al* were withdrawn because the study design was not a randomized controlled trial. Antolis *et al* was not considered for the systematic review because the information was not sufficient for the appropriate analysis of the systematic review. The study of Faisal *et al*., 2020 was eliminated because it was a quasi-experimental study and, therefore, out of the study scope.

Study characteristics:

General Findings in the Selected Studies:

The authors recruited 100 patients of typhoid from 1st May 2013 to 31st Oct 2013. The study was a clinical trial conducted in Pakistan by establishing a blinding procedure. This study compared oral AZM (0.01 g/kg, once daily for one week) with IV Ceftriaxone (CRO) (0.075 g/kg, once daily for one week). The age and gender distribution of the AZM group were, as follows: mean age: 6.68±2.27 years, male/female ratio (M/F): 27/23 and of the comparator group, mean age: 7.47±2.93 years, M/F: 27/23.[12]

It was a randomized controlled trial conducted in India. Blinding of all the participants was established. The study included 124 participants of whom 64 patients were selected. It compared oral AZM (20mg/kg/day, maximum 1000mg/kg) to CRO (75mg/kg/day, maximum up to 2.5 g/day). The age and gender of the study group were, as follows: mean age: 11.4±3.6 years, M/F: 14/30 and those of the comparator group, as follows: mean age: 10.4±3.4 years, M/F: 14/34.[13]

This study was performed in India. The authors recruited 92 participants out of which 77 patients were finalized. It compared the clinical efficacy of AZM (1/2g x 1 Tablet daily x PO for 1 week) against Chloramphenicol (CHL) (2000-3000 mg x 4 times daily in divided doses for 2 weeks). Blinding of the procedure was assured. The age and gender recorded in the AZM group were, as follows: mean age: 26.2 years, M/F: 34/8 in the CHL group, mean age: 28.5 years, M/F: 25/10.[14]

The study was conducted in Pakistan. Data were collected from 120 typhoid patients. Double blinding was performed in the study. The RCT compared the efficacy of AZM (10mg/kg/dose once daily, PO for one week) with oral ciprofloxacin (15 mg/kg, two times daily, for 1 week). The age and gender distribution in the AZM group were mean age: 7.07±3.25 years, M/F: 28/24, and in the ciprofloxacin group were mean age: 8.27±3.03 years, M/F: 34/31.[15]

The study was carried out at An Giang Provincial Hospital. It was an open-labeled randomized controlled trial study that encompassed 460 participants out of which only 287 patients were selected from April 2004 to August 2005. It compared two drugs: AZM (20 mg/kg) and Gatifloxacin (10 mg/kg). Eleven years was the mean age of the participants and the male-female distribution of the AZM group was 76/66 and, in the comparator, group was 71/74.[16]

The randomized controlled trial was conducted in Pakistan. The authors recruited 92 patients with typhoid from January to July 2016. Blinding of patients was established. The study drug was AZM (20 mg/kg, once daily for 1 week). The comparator group was IV ceftriaxone (100mg/kg, once daily for 1 week). The mean age of the study group participants was 6.97±3.01 years and gender distribution were (AZM group; M/F: 24/21, CRO group; M/F: 23/22).[17]

The study was conducted in Egypt. This clinical trial was performed by masking the patients. A total of 128 participants were recruited for the study, of which 68 participants were selected. Oral AZM (0.02g/kg x daily, up to 1000mg/day for 5 days) and IV CRO (0.075g/day, upto:2.5 g/day for 5 days) were used. The age and gender distribution in the study group were mean age: 11.8±3.6 years, M/F: 19/13 and in the comparator, group were mean age: 10.8 ±3.35 years, M/F: 20/16.[18]

This open randomized controlled trial was conducted in Vietnam. The number of participants in the study was 97 and the selected patients were 88. It compares AZM (1000mg, 1 tablet daily for 5 days) with ofloxacin (0.2 g, 1 tablet daily for 5 days). The mean age in each group was 24.7 years for AZM and 26.6 years for ofloxacin. The gender distribution of each group was, AZM: M/F: 26/18, Ofloxacin: M/F: 20/24.[19]

The study compares AZM (1000mg/day for 6 days) with ciprofloxacin (0.5 g, 2 times daily for 1 week). A total of 108 participants were included in the study and 64 patients were selected for the trial in Egypt. The age and gender distribution of the

AZM group were, mean age: 19.6 years, M/F: 24/12 and in ciprofloxacin group were, mean age: 20.3 years, M/F: 19/9.[20]

It was an open-labelled randomized controlled trial. The study was conducted in the United Kingdom from March 2015 to August 2017. A total of 235 participants enlisted while 81 patients were selected for the trial. The authors compared AZM (0.5g/day) with ciprofloxacin (0.5g, twice daily). The mean age and male-female ratio of the AZM group were 26.2 years and M/F: 34/18 while of comparator group was 27.9 years and M/F: 23/6.[6]

It was an open-labelled clinical trial conducted in Egypt. The study compares AZM (0.01 g/kg, up to 500 mg/day for 1 week) with IM CRO (0.075 g/kg, up to 2.5g/day for 1 week). The number of participants was 108 whereas 64 were selected and the mean age and gender distribution in the AZM group were, mean age: 9.7 years with M/F: 20/14, on the other hand, in the CRO group mean age was 10.1 years with M/F: 17/13.[21]

The RCT study took place in Pakistan at the Paediatric Department of Holy Family Hospital, Rawalpindi. 230 typhoid patients from March to September 2012 were finalized by the authors. The study compares AZM (0.01g/kg, daily for 1 week) with ofloxacin (0.015g/kg/day in two divided doses for 1 week). The mean age of both groups recorded was 7.7±2.45 years and male-female distribution was M/F:125/105.[22]

The clinical trial compared oral AZM (20 mg/kg, daily for 1 week) versus intravenous CRO (100mg/kg/day for 7 days). The study setting was Bangladesh. A total of 98 participants were studied from January to December 2009. The ages of children ranged from 2–12 years.[23]

It was an open-labelled RCT conducted in a provincial hospital in Vietnam. The study compared the treatment outcomes of Ofloxacin and AZM individually and also as a combination. This study also included resistant patients. 241 participants were recruited in entirety while 187 patients were enlisted. It included children (mean age: study group: 10.5 years, Ofloxacin group: 8.8 years). The gender distribution was M/F:22/40 for the AZM group and M/F:33/30 for the ofloxacin group.[24]

Bias risk in included studies:

The bias assessment graph is given in Figure-2.

Result of synthesis:

Treatment outcome:

Azithromycin (AZM) versus Fluoroquinolones (FQs):

The odds ratios of all the selected studies were calculated as Riaz *et al*[15] (2.24, *p*=0.02, upper value =5.53, lower value=0.91), Dolecek *et al*[16] (0.78, upper value=1.68, lower value=0.36), Manzoor *et al*[22] (2.41, upper value=4.13, lower value=1.40), Chinh *et al*[19] (3.32, *p*=0.27, upper value= 17.43, lower value=0.63), Girgis *et al*[20] (1.00, upper value=50.40, lower value=0.02), Jin *et al*[6] (4.46, *p*=<0.001,upper value=12.40, lower value=1.60) and Parry *et al*[24] (2.67, upper value=6.11, lower value= 1.16). The forest plot (CI=95%) is given in Figure-3. The direction of the diamond is towards the right side indicating a positive effect. The heterogeneity I^2 was 37% with a τ^2 value of 0.1729 and a *p*-value of 0.15. The cause of heterogeneity is variation in patient populations among different studies.

Azithromycin (AZM) versus Ceftriaxone (CRO):

The odds ratios of the selected studies were calculated as described by Frenck, Jr. *et al*[18] (0.43, *p*=0.5, lower value=0.04, upper value= 4.96), Saeed *et al*[12] (0.65, *p*= 0.424, lower value=0.23, upper value=1.87), Nair *et al*[13] (0.42, lower value=0.04, upper value= 4.93), Khokar *et al*[17] (1.75, *p*=0.688, 0.243, lower value=0.39, upper value=7.81), Frenck, Jr. *et al*[21] (0.36, *p*=>0.5, lower value=0.04, upper value= 3.62) and Islam *et al*[23] (0.33, lower value=0.03, upper value=3.32, *p*=0.582). The forest plot (CI=95%) is given in Fig 04. The I^2 and τ^2 values are zero (*p*=0.78) indicating that there is no heterogenicity. The direction of the diamond is left and it touches the line of no-effect.

Azithromycin (AZM) versus Chloramphenicol (CHL):

The odds ratio of Butler *et al*[14] is (1.23, *p*=0.23, upper value=4.66, lower value=0.33, CI=95%). The forest plot is given in Figure-5.

Publication Bias:

It is analyzed by applying Egger's and Begg's tests. For AZM vs FQ: Egger's test: Intercept= 0.8790, 95% CI= -4.6775 to 6.4355, Significance level= 0.6832, Begg's test: Kendall's Tau= 0.2000, Significance level= 0.5730. For AZM vs CRO: Egger's Test: Intercept=-0.9436, 95% CI= -3.2135 to 1.3262, Significance level= 0.3127, Begg's test: Kendall's Tau= -0.2000, Significance level=0.5730). As both tests are showing insignificant results, it rules out publication bias.

Microbiological Cure:

Seven trials have presented the data of microbiological cure in typhoid patients. In the azithromycin (AZM) group, Dolecek *et al*[16] documented three instances of microbiological failure, Girgis *et al*[20] reported one, Chinh *et al*[19] reported one, and Frenck, Jr. *et al*[21] reported one. On the other hand, Butler *et al*[14], Frenck, Jr. *et al*[18], and), Nair *et al*[13] found no cases of microbiological failure in their respective studies. In the fluoroquinolone (FQ) arm, Dolecek *et al*[16] and

Chinh *et al*[19] each recorded two instances of microbiological failure, Girgis *et al*[20] reported no failures in achieving microbiological cure. Within the ceftriaxone (CRO) group, Frenck, Jr. *et al*[18], Nair *et al*[13], and Frenck, Jr. *et al*[21] each documented one case of microbiological failure in their respective trials.

Fever Clearance Time (FCT):

Ten studies have mentioned the fever clearance times. By combining mean FCTs of comparator group, FCT of FQ turned out to be 4.656 days, of CHL 4.3 days and of CRO 4.095 days. The mean FCT for AZM was 4.4965 days as shown in Table-1.

Relapses:

Eight studies reported the relapses data. Dolecek *et al*[16] reported four, Chinh *et al*[19] reported one Girgis *et al*[20] and Parry *et al*[24] documented no relapses in FQ group. In CRO group, Frenck, Jr. *et al*[18] reported eleven, Nair *et al*[13] six, and Frenck, Jr. *et al*[21] documented four relapses. On the other hand, Chinh *et al*[19] reported one and Frenck, Jr. *et al*[18] recorded three relapses in AZM group.

Laboratory Findings:

Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) were raised in AZM groups. Thrombocytosis was recorded according to Frenck, Jr. *et al*[18], Frenck, Jr. *et al*[21], Chinh *et al*[19], Girgis *et al*[20], and Jin *et al*[6]. On the other hand, Parry *et al*[24] study revealed that AST and ALT decreased in each group after treatment. Jin *et al* [6] documented one incidence of raised Alkaline phosphatase (ALP) in one patient of AZM group.

Adverse effects:

Nine studies documented the adverse events. The prominent adverse effects recorded in the AZM group were vomiting and diarrhoea according to Nair *et al*[13] and Frenck, Jr. *et al*[18]. Dolecek *et al*[16], Chinh *et al*[19], reported maculopapular rash at the injection site and Frenck, Jr. *et al*[21] reported pain at the injection site for 24 hours in AZM group. While the rest of the studies indicated mild gastrointestinal effects in AZM arms.

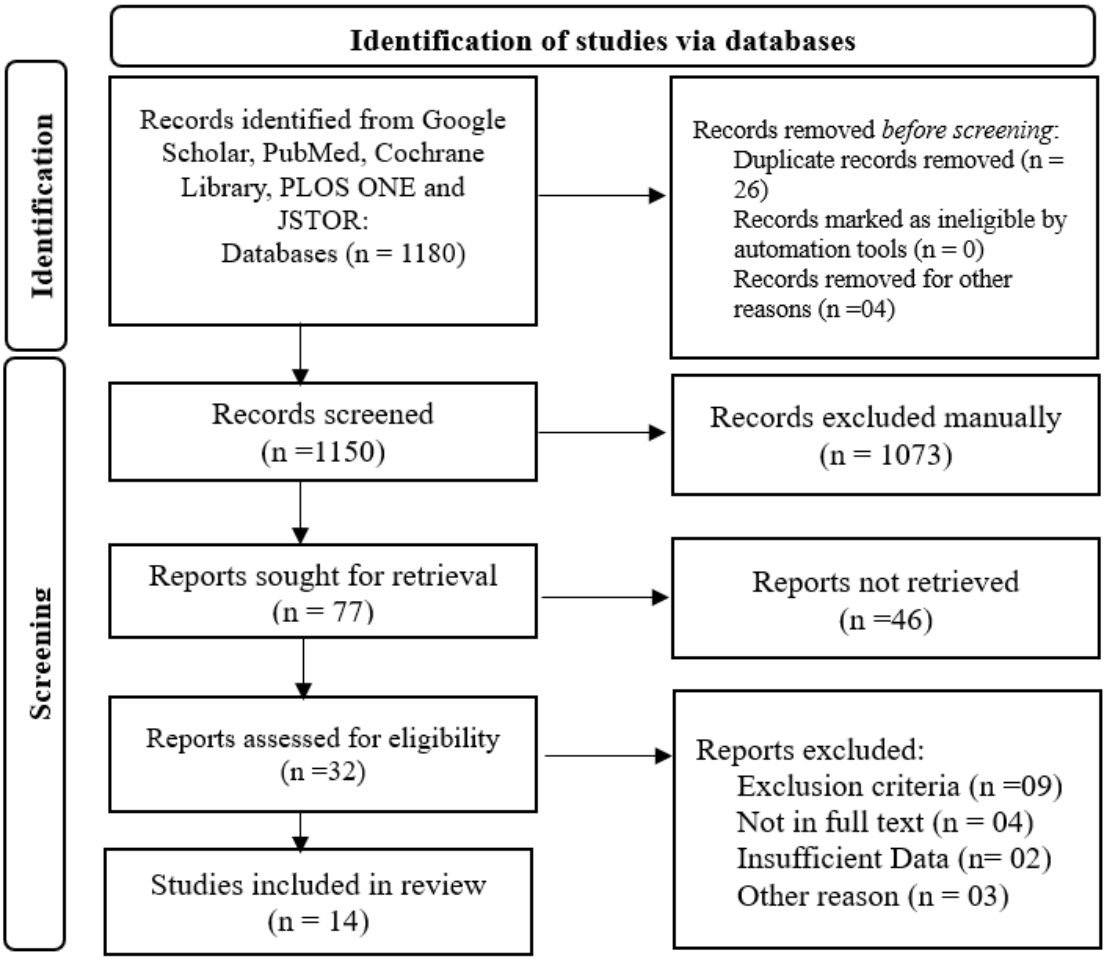

Figure-1: PRISMA flow diagram

Figure-2: Bias Assessment Graph

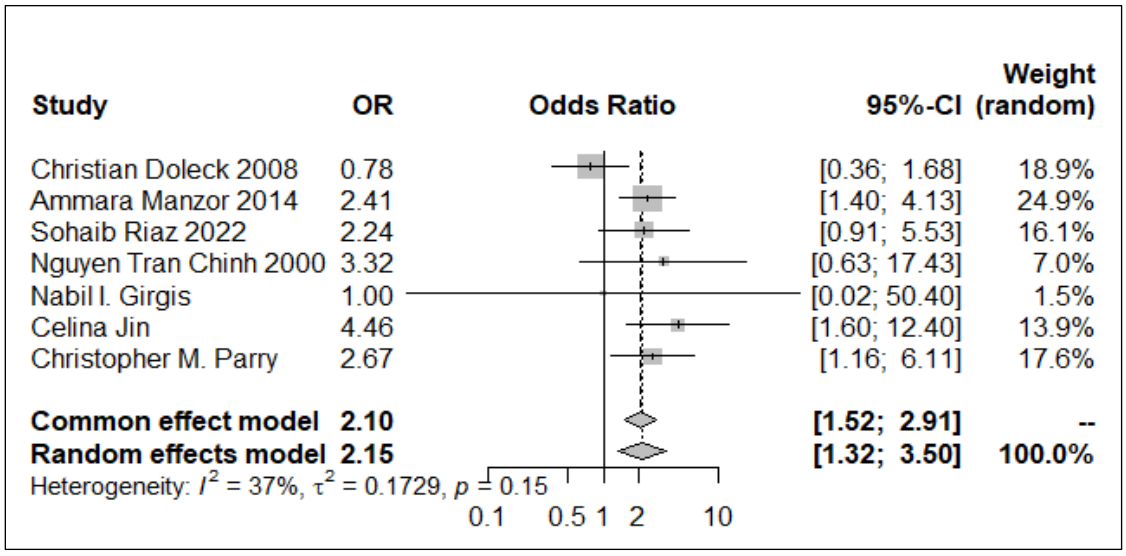

Figure-3: Forest plot of Azithromycin versus Fluoroquinolone

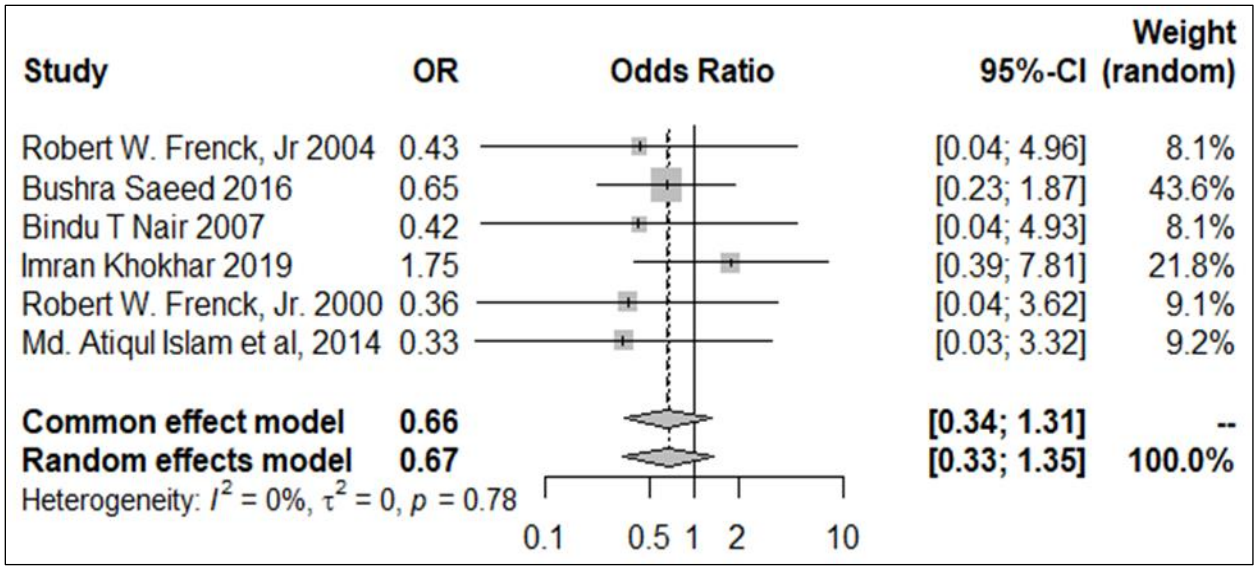

Figure-4: Forest plot of Azithromycin versus Ceftriaxone

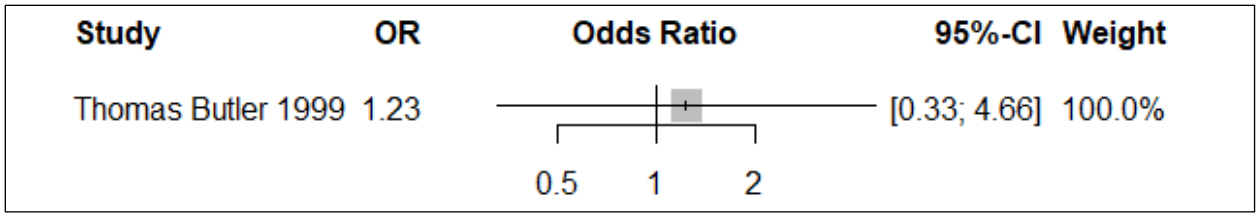

Figure-5: Forest plot of Azithromycin versus Chloramphenicol

Table-1: Fever Clearance Time (FCT) of Azithromycin versus Other Drugs

Article/Author	Fever Clearance Time (Days)		
	Azithromycin	Other drugs	Mean FCT of drugs
Christiane Dolecek 2008	4.4	4.4 **(Gatifloxacin)**	
NABIL I. GIRGIS,1999	3.8 ± 1.1	3.3 ± 1.0**(Ciprofloxacin)**	
NGUYEN TRAN CHINH, 2000	5.625	5.58 **(Ofloxacin)**	**4.656** (Fluroquinolones)
Celina Jin,2019	2.7	1.8**(ciprofloxacin)**	
Christopher M. Parry,2006	5.8	8.2 **(Ofloxacin)**	
Thomas Butler 1999	4.1±2.4	4.3±3.1**(Chloramphenicol)**	**4.3** (Chloramphenicol)
Frenck R 2004	4.5 ±1.9	3.6±1.6 **(Ceftriaxone)**	
Bindu T Nair 2007	5.5±1.9	4.5±1.6 **(Ceftriaxone)**	**4.095** (Ceftriaxone)
Robert W. Frenck,Jr.2000	4.1 ± 1.1	3.9 ± 1.0 **(Ceftriaxone)**	
Md. Atiqul Islam, 2014	4.44 ± 1.25	4.38 ± 1.21 **(Ceftriaxone)**	
Mean FCT of Azithromycin	**4.4965**		

DISCUSSION

In the context of the selected studies, AZM turns out to be clinically efficacious in comparison with FQs. The overall effect of both drugs can be established by observing the forest plot (Random Effect Model (REM): 2.15). By analyzing studies that showed significant results like Jin *et al*[6] (p<0.001) and Riaz *et*

al[15] (*p*=0.021), it becomes evident that AZM manifests better treatment outcomes as compared to FQs. AZM is more effective in resistant typhoid than ofloxacin as reported by Christopher M. Parry *et al*., 2006.

Regarding CHL, only one study, conducted by Butler *et al*[14], is included in the systematic review. It demonstrates a favourable outcome and a high odds ratio (1.23) for AZM compared to CHL. However, the findings of this study were statistically insignificant (*p*=0.12).

The treatment outcome of AZM in comparison with CRO is not conclusive. As far as the findings of the forest plot are concerned (REM=0.67), both treatments show no discernible differences. However, studies like Saeed *et al*[12], Nair *et al*[13], Frenck, Jr. *et al*[18] and Frenck, Jr. *et al*[21] indicate that CRO is more efficacious than azithromycin during 7 days treatment. Nonetheless, Khokar *et al*[17] found different efficacies of AZM and CRO in various age groups. Between 2-6 years of age group children, CRO was more efficacious than AZM while in children of 7–12 years, AZM was more effective.

The FCT of AZM is greater than that of CRO and CHL while mildly less than FQs. On the other hand, relapse of typhoid is less documented in patients who were on AZM than in those on other antimicrobial drugs. Vomiting and maculopapular rash were reported as adverse effects of AZM. Raised ALT and AST were also appreciated in patients taking AZM. Thrombocytosis is also documented.

Suggestions for future research:

It is crucial to conduct more research into the growing problem of patients resistant to drugs, a challenge that hits developing countries especially hard. A thorough investigation is needed to fully understand this complex issue and to create effective solutions to lessen its effects. Additionally, the effectiveness of the antibiotic ceftriaxone in treating these patients warrants further study based on the findings of the chosen studies.

Limitations:

The systematic review encompasses open-access research articles. It does not include conference papers, thesis, or dissertations.

CONCLUSION

The clinical efficacy of azithromycin against fluoroquinolones and chloramphenicol is well established. The fever clearance time of AZM is longer than ceftriaxone and chloramphenicol. Nevertheless, the benefits of AZM are superior, as there is less evidence of relapses and has fewer side effects in patients taking it.

Implications:

It is evident from the studies that AZM is clinically more efficacious than fluoroquinolones and chloramphenicol. Therefore, AZM should be part of the regimen for typhoid patients. However, it must be kept in mind that the FCT of AZM is greater than that of CRX and CRO which makes it practically unacceptable in patients but the benefits are greater, as there is less evidence of relapses in patients taking AZM.

Declarations:

Acknowledgement: There are no individual, organization, or funding sources to acknowledge.

Funding Statement: Not applicable

AUTHORS' CONTRIBUTION

MU: Conceptualization, data curation, formal data analysis, methodology, project administration, software, manuscript writing, manuscript review and editing, resources, investigation. SW: Data curation, manuscript writing, manuscript review and editing, visualization. AUR: Visualization, data curation. AA: Supervision, data curation, validation, resources. MHR: Validation, visualization, resources. MBN: Visualization, data curation, conceptualization.

Registration of Review:

The systemic review is registered on PROSPERO (ID: CRD42023473856). The amendments are made to ensure a better analysis technique of the systemic review with more authors on board.

REFERENCES

1. Brockett S, Wolfe MK, Hamot A, Appiah GD, Mintz ED, Lantagne D. Associations among Water, Sanitation, and Hygiene, and Food Exposures and Typhoid Fever in Case-Control Studies: A Systematic Review and Meta-Analysis. Am J Trop Med Hyg 2020;103(3):1020–31.
2. GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019;19(4):369–81.
3. Essa F, Hussain SZ, Batool D, Usman A, Khalid U, Yaqoob U, *et al*. Study of socio-demographic factors affecting the prevalence of typhoid. Morb Mortal 2019;1(2):9.
4. Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, *et al*. Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. Biomed Res Int 2020;2020:6432580.
5. Walker J, Chaguza C, Grubaugh ND, Carey M, Baker S, Khan K, *et al*. Assessing the global risk of typhoid outbreaks caused by extensively drug resistant Salmonella Typhi. Nat Commun 2023;14(1):6502.
6. Jin C, Gibani MM, Pennington SH, Liu X, Ardrey A, Aljayyoussi G, *et al*. Treatment responses to azithromycin and ciprofloxacin in uncomplicated Salmonella Typhi infection: a comparison of clinical and microbiological data from a controlled human infection model. PLoS Negl Trop Dis 2019;13(12):e0007955.
7. Siddiqi FG, Rais H, Zafar F, Bina TA, Ally Z, Kumar A, *et al*. Treatment of 21st-Century typhoid fever in children with mono vs combination drug therapy: An open-label randomized comparative trial. Int J Endorsing Health Sci Res 2021;9(3):384–94.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: an

updated guideline for reporting systematic reviews. Int J Surg 2021;88:105906.
9. Faryad N, Riaz L, Hanif HH, Tariq A, Asghar M, Raza SMA. Efficacy of Oral Azithromycin in Treatment of Uncomplicated Enteric Fever in Children. Pak J Med Health Sci 2022;16(7):301–2.
10. Antolis Y, Rampengan T, Wilar R, Rampengan NH. Azithromycin vs. chloramphenicol for uncomplicated typhoid fever in children. Paediatr Indones 2013;53(3):155–9.
11. Hussain I, Faisal MS, Khan A, Jamal A, Hayat W. Clinical effectiveness of azithromycin versus ciprofloxacin in the treatment of uncomplicated enteric fever in children. J Med Sci 2020;28(4):372–6.
12. Saeed B, Riaz T. Comparison of efficacy of oral azithromycin with intravenous ceftriaxone for the treatment of uncomplicated enteric fever. Isra Med J 2016;8(4):228–32.
13. Nair B, Simalti A, Sharma S. Study comparing ceftriaxone with azithromycin for the treatment of uncomplicated typhoid fever in children of India. Ann Trop Med Public Health 2017;10(1):205.
14. Butler T, Sridhar CB, Daga MK, Pathak K, Pandit RB, Khakhria R, *et al*. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999;44(2):243–50.
15. Riaz S, Hussain G, Javed Z, Yaqoob N, Rasheed S, Safir N. Clinical Efficacy of Azithromycin Versus Ciprofloxacin in Treatment of Typhoid Fever in Children. Pak J Med Health Sci 2022;16(7):678–80.
16. Dolecek C, Phi La TT, Rang NN, Phuong LT, Vinh H, Tuan PQ, *et al*. A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. PLoS One 2008;3(5):e2188.
17. Khokar I, Afzal S, Khokar SN, Afzal S, Naeemullah S. Comparison of Oral Azithromycin and Intra Venous Ceftriaxone for Treatment of Uncomplicated Enteric Fever in Children. J Rawal Med Coll 2019;23(2):1097.
18. Frenck Jr RW, Mansour A, Nakhla I, Sultan Y, Putnam S, Wierzba T, *et al*. Short-Course Azithromycin for the Treatment of Uncomplicated Typhoid Fever in Children and Adolescents. Clin Infect Dis 2004;38(7):951–7.
19. Chinh NT, Parry CM, Ly NT, Ha HD, Thong MX, Diep TS, *et al*. A Randomized Controlled Comparison of Azithromycin and Ofloxacin for Treatment of Multidrug-Resistant or Nalidixic Acid-Resistant Enteric Fever. Antimicrob Agents Chemother 2000;44(7):1855–9.
20. Girgis NI, Butler T, Frenck RW, Sultan Y, Brown FM, Tribble D, *et al*. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. Antimicrob Agents Chemother 1999;43(6):1441–4.
21. Frenck Jr RW, Nakhla I, Sultan Y, Bassily SB, Girgis YF, David J, *et al*. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. Clin Infect Dis 2000;31(5):1134–8.
22. Manzoor A, Mahmood T, Zulfiqar R. Azithromycin Versus Ofloxacin in Treatment of Enteric Fever in Children. J Rawal Med Coll 2014;18(2):335618660.
23. Islam MA, Mobarak MR, Hasan AR, Hanif M. Clinical Efficacy of Azithromycin in Typhoid and Paratyphoid Fever in Children. J Enam Med Coll 2015;5(1):34–8.
24. Parry CM, Ho VA, Phuong LT, Bay PV, Lanh MN, Tung LT, *et al*. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. Antimicrob Agents Chemother 2007;51(3):819–25.

Submitted: January 23, 2024	*Revised: April 7, 2024*	*Accepted: April 25, 2024*

Address for Correspondence:

Muhammad Uzair, F-6/3, House 28, Street 10, 44220, Islamabad-Pakistan
Cell: +92 337 753 3353
Email: drmuhammaduzairofficial@gmail.com