The Efficacy of Antibiotics in the Treatment of *Chlamydia Trachomatis* Infections during Pregnancy. A Systematic Review and a Meta-analysis.

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Abstract

Chlamydia trachomatis infections encountered during pregnancy can lead to many complications for both mother and neonate if left untreated. A systematic review and a meta-analysis were conducted to analyse the efficacy of antibiotic treatment infection during pregnancy that established the most effective antibiotic to treat *Chlamydia trachomatis* infections during pregnancy. PubMed and Cochrane Library were searched to the end of 2019. Randomised control trials that aligned with inclusion criteria of relevant antibiotics Azithromycin, Erythromycin, Clindamycin and Amoxicillin during Pregnancy was included. A systematic review and meta-analysis were used to calculate pooled (i) success of treatment for each antibiotic in several trials and (ii) the total adverse side effects for each drug encountered in several trials. Randomised controlled trials (RCTs) selected included 1917 pregnant patients with Chlamydia infections, and 851 have completed follow up assessments. Data from three RCTs observed a higher success of treatment for Azithromycin versus Erythromycin, fixed effect model, odds ratio (OR) = 0.67, 95% confidence interval (CI), 0.32-1.80. Data from three RCTs observed a higher success of treatment for Clindamycin versus Erythromycin OR = 2.43 95%, CI:2.00-2.60. Data from two RCTs showed a higher success of treatment for Amoxicillin versus Erythromycin OR = 3.74, 95%, CI:0.68-13.66. Analysis established that Erythromycin resulted in the most adverse side effects. Azithromycin was determined as the most effective antibiotic to treat C. trachomatis infections during pregnancy due to the high success of treatment. Clindamycin is capable of eradicating C. trachomatis infections in pregnancy and can be considered a secondary antibiotic treatment with fewer incidences of adverse side effects and high levels of successful treatment of the infection, however, due to a lack of studies more analysis will be required to confirm the efficacy of Clindamycin.

Keywords: a meta-analysis, systematic review, Randomized Controlled Trials Chlamydia trachomatis, Sexually Transmitted Diseases (STD), pregnancy infections, the efficacy of antibiotics, Antibiotic dosage, bacteriostatic effect.

1. Introduction

1.1 Chlamydia trachomatis infections
The Gram-negative intracellular bacterium *Chlamydia trachomatis* is the causative agent of one of the most common sexually transmitted disease (STD), Chlamydia (Mohammadzadeh et al., 2019). Studies in the UK showed that on average of 2-26% of pregnant women are found to be positive for Chlamydia during Pregnancy (Cluver et al., 2017). Prevalence of *C. trachomatis*

infections can be attributed to its predominantly calm nature, as infections are largely asymptomatic. The infection, however, in women, can clinically present as mucopurulent cervicitis, urethritis and endometritis. Chlamydia is believed to be the leading cause worldwide of Pelvic Inflammatory Disease (PID) and infertility with links to ectopic pregnancy, miscarriage and premature rupture of membranes (Brocklehurst and Rooney, 1998). *C. trachomatis* infections encountered during pregnancy are usually asymptomatic. However, if left untreated, it can result in spontaneous miscarriage in the first trimester, preterm labour and premature aminorexes, giving rise to premature neonates. Untreated Chlamydia infections leave the neonate exposed to an increased chance of obtaining an infection post-natal, usually presenting itself as ophthalmia neonatorum or pneumonitis (Allaire, Nathan and Martens, 1995). Treatment for Chlamydia is a simple procedure with the prescription of a seven-day course of Doxycycline or a single dose of Azithromycin. Conversely, the exact or primary application of one particular antibiotic to treat *C. trachomatis* infections in pregnancy, safe for both mother and neonate is something still somewhat unclear in medical practice. The World Health Organisation (WHO) guidelines have described therapeutic options for the treatment of Chlamydia during Pregnancy as poor to moderate. WHO recommends that there is an increased need for more Randomised Control trials (RCTs) to compare treatments, dosage, and gestational time frames, on eradicating this such infection (WHO Guidelines for the management of sexually transmitted infections, 2001). Administering antibiotics during pregnancy has to consider both the health of the mother as well as the neonate. The use of antibiotics during pregnancy changes the micro-biotic environment of the birth canal, which is where a neonate obtains its microbiome from during vaginal delivery. This mechanism is vitally important in the developing immune system of a neonate (Kuperman and Koren, 2016).

1.2 Antibiotic treatment for STD during Pregnancy

Antibiotics deemed unsafe to use during pregnancy by the WHO include Doxycycline, Tetracycline and Ofloxacin. Tetracycline and (Doxycycline) are ordinarily used to treat non-pregnant patients with diagnosed Chlamydial infections. Tetracycline antibiotics bind to pathogenic ribosomes preventing the attachment of the aminoacyl tRNA to the RNA-ribosome complex, inhibiting further biosynthesis of proteins, thus eradicating the presence of a bacterial infection (Batagol, 1980).

Tetracyclines, however, have a special affinity for metal cations, especially calcium. This affinity to calcium has led to the consensus of it being unsafe to use Tetracycline antibiotics to treat Chlamydia post the first trimester of pregnancy. These antibiotics are attributed to negative implications on foetal teeth, enamel hypoplasia and bone development of a foetus. The use of Tetracyclines altogether during any stage of pregnancy and the developmental years of a child is no longer medically advisable nor acceptable unless necessary. Another family of drugs ordinarily used to treat *C. trachomatis* infections: Fluoroquinolones such as Ofloxacin which are especially well suited for the treatment of *C. trachomatis* cervical infections in non-pregnant patients but is yet another drug deemed unsafe to use in Pregnancy (Faro et al., 1991). Fluoroquinolones are only to be administered during pregnancy when the benefit for the mother

outweighs the possible risk to the foetus due to its detrimental effects on foetal cartilage formation and bone development.

There have been progressively more studies regarding multidrug-resistant strains of *C. trachomatis* bacteria. Antibiotic resistance raises more complications of an infection encountered during pregnancy, with further limitations and restrictions to types of antibiotics that are safe to use. In recent studies, some Chlamydial infections have been noted to show resistance to the antibiotics: Azithromycin. The resistance to Azithromycin has been attributed to mutations in the peptidyl transferase region of 23S rRNA genes of the *Chlamydia trachomatis* bacterium (Figure 1), and these genes prevent the drug from inhibiting the translation of mRNA in the bacteria, enabling the infection to persist (Zhu et al., 2010).
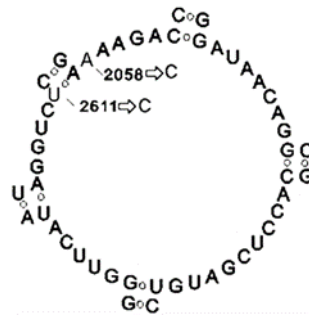

Figure 1. The peptidyl transferase region of 23S rRNA genes of the *C. trachomatis* bacteria attributed to the resistance to Azithromycin.

The side effects can result in the infection persisting due to insufficient exposure of the bacteria to the administered antibiotic. The pregnancy symptoms such as morning sickness (hyperemesis gravidarum), fatigue and headaches have to be taken into consideration when it comes to what is classed as an adverse side effect encountered as a result of a drug, versus a symptom of pregnancy itself. Changes encountered during pregnancy include increased blood volume; therefore an increased glomerular filtration rate altering length of the drug stays in circulation and the efficacy of a drug itself to relay its bacteriostatic or bacteriolytic function (Sarkar, Woodland C, Koren and Einarson, 2006). Considerations need to be made to the changes encountered as a part of normal pregnancy and adjustments in the pharmacokinetics of a drug may need to be calculated to sufficiently inhibit bacterial infections such as Chlamydia in Pregnancy. Similar to issues with the timing of the application of Tetracycline antibiotics (post the first trimester of pregnancy), considerations could be made towards the most inoffensive trimester to administer each different drug. Alongside the side effects encountered during different trimesters of pregnancy could alter the efficacy of each drug.
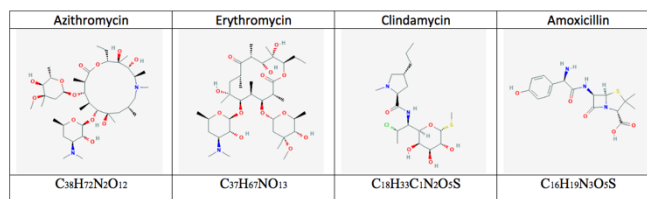
Figure 2. Chemical structures of the selected antibiotics. Relative molecular formula and the structural similarities between of the selected drugs Azithromycin and Erythromycin, and Clindamycin and Amoxicillin during Pregnancy.

All drugs involved in this study are classed as category B pregnancy drugs, and their applications are considered safe to both mother and neonate during pregnancy depicted in Figure 2. Azithromycin and Erythromycin consist of the same elements Carbon, Hydrogen, Nitrogen and Oxygen within different overall structures. Furthermore, despite Clindamycin and Amoxicillin not belonging to the same class of antibiotics (like the macrolides Azithromycin and Erythromycin), they consist of the same elements Carbon, Hydrogen, Nitrogen, Oxygen and Sulphur with different structural compositions.

1.3 Azithromycin

The azalide Azithromycin is a derivative of the more broad-spectrum macrolide Erythromycin. Azithromycin effects by binding and inhibiting peptidyl transferase activity interfering with amino acid translocation during the process of translation bacteria (Engel, 1992). Azithromycin's mechanism of action is not directly toxic to chlamydial elementary bodies but does inhibit the bacterial protein synthesis in chlamydia-infected cells. Its inhibition is characteristically quite rapid and only requires brief exposure to exhibit its effects. Studies suggest that Azithromycin does have a higher failure rate than Doxycycline, which is ordinarily used to treat *C. trachomatis* infections in non-pregnant patients (Sarkar, Woodland C, Koren and Einarson, 2006).

1.4 Erythromycin

Erythromycin is a more broad-spectrum macrolide antibiotic that diffuses through the bacterial cell membrane and reversibly binds to the 50S subunit of the bacterial ribosome, relaying its bacteriostatic effects on the infection. Studies suggest the specific gastrointestinal issues associated with the antibiotic Erythromycin are likely due to an increased risk of pyloric stenosis (narrowing of the opening from the stomach to the small intestines), (Mourad, Sweet, Sugg and Schachter, 1980). Erythromycin's characteristic of undesirable gastrointestinal side effects, it is likely to impede on the efficacy of the drug itself, limiting the drugs exposure to the bacteria.

1.5 Clindamycin

The lincosamide antibiotic Clindamycin acts on Chlamydial trachomatis infections by binding to bacterial 50S ribosomal subunits. It exhibits a bacteriostatic effect, and as it binds to ribosomal sub-units, it has a prolonged post-antibiotic effect (CAMPBELL and DODSON, 1990).

Clindamycin is less notably used to treat Chlamydial infections but is considered a valuable drug for patients that have certain allergies or intolerances to antibiotics (Erythromycin). It is likely to be effective at inhibiting *C. trachomatis* infections, but issues of compliance may affect the total success of treatment (Turrentine, Troyer and Gonik, 1995). A rash is also attributed to intolerance of Clindamycin which could alter patient compliance and success of treatment (Gilbert, 1992).

1.6 Amoxicillin

This penicillin derivative antibiotic inhibits the multiplication of reticulate bodies and the differentiation of reticulate bodies into infectious elementary bodies, without necessarily exerting a lethal effect on the organism (Alary et al., 1994). This allows for the subclinical progression of latent Chlamydial infections to persist. Such infections can be detected by molecular diagnosis methods such as Real-Time Polymerase Chain Reaction to determine the presence of any bacterial genetic remanence active or latent that may retain within a patient. Amoxicillin's mode of action suggests it's likely to be somewhat of a weak agent against *C. trachomatis* bacteria. Amoxicillin is also attributed to an increased need for routine monitoring, exacerbating medical expenses and time (Jacobson et al., 2001). However, notable adverse side effects are not attributed to Amoxicillin application and efficacy of the therapy.

1.7 Study objectives

This study elucidates to establish the antibiotic with minimal adverse side effects to both mother and neonate but maximum inhibitory effects on the Chlamydial trachomatis infections during pregnancy. Azithromycin, Erythromycin, Clindamycin (macrolide), and Amoxicillin (ß-lactam) antibiotics are considered as they are routinely used in Chlamydial trachomatis infections. The side effects encountered by the mother and neonate for each selected antibiotic was evaluated to help determine the most employable primary drug to administer to a pregnant mother with a *C. trachomatis* infection.

2. Method

2.1 Study design, information sources and search strategy.

This systematic review and meta-analysis follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer, L., et al 2015). The electronic database PubMed was used to extract the studies. As the study method was a systematic review and a Meta-analysis, and not included any patient sensitive/identifiable data, ethical consideration was not considered.

2.2 Inclusion criteria

RCT prioritizing the use of the antibiotics; Azithromycin, Erythromycin, Clindamycin, Amoxicillin or placebo used any time antenatally to treat a Chlamydial infection were included. All articles published from 1980- 2019 were selected. Keywords such as '*C. trachomatis*', 'pregnancy', 'treatment', 'Azithromycin', 'Erythromycin', 'Clindamycin', 'Amoxicillin', 'neonate'. RCTs of pregnant women who tested positive for asymptomatic/symptomatic Chlamydia during

any trimester of pregnancy were considered. Moreover, other comorbidities such as other sexually transmitted infections alongside a Chlamydial infection also included. Only articles reported in the English language were included.

2.3 Exclusion criteria
Studies conducted by case reports, comments, listed opinions, narrative reviews and studies using non-standardised genital testing that did not meet the inclusion criteria were excluded. Also, studies published other than the English language were excluded from this study.

2.4 Quality assessment and data collection.
Eligible studies were selected based on the considering adequate sample size, clarity of research aims, appropriateness of design, recruitment, data collection, analysis and reporting of the study findings. Full text of the eligible studies assessed against the inclusion criteria.

2.5 Outcome of interest
The primary outcome was focused on the comparison of the efficacy of each selected antibiotic on eradicating the Chlamydia infection. In a secondary analysis, focused on comparing the safety of the antibiotic and its side effects upon the mother and the neonate.

2.6 Statistical analysis
The study analysed the pooled prevalence of on Treatment failure of each antibiotic, and comparison of the total amount of side effects encountered by each antibiotic for Chlamydia infection using Review Manager (RevMan) software version 5. A forest plot was analysed using Meta-analysis. The extracted data were analysed, and the results were reported using a random-effects model (Der Simonian R et al., 1986) with 95% confidence interval (CI).

2.7 Study selection
After the evaluation of exclusion/inclusion criteria and the quality of articles, 7 eligible studies, were included in the meta-analysis (Figure 3).
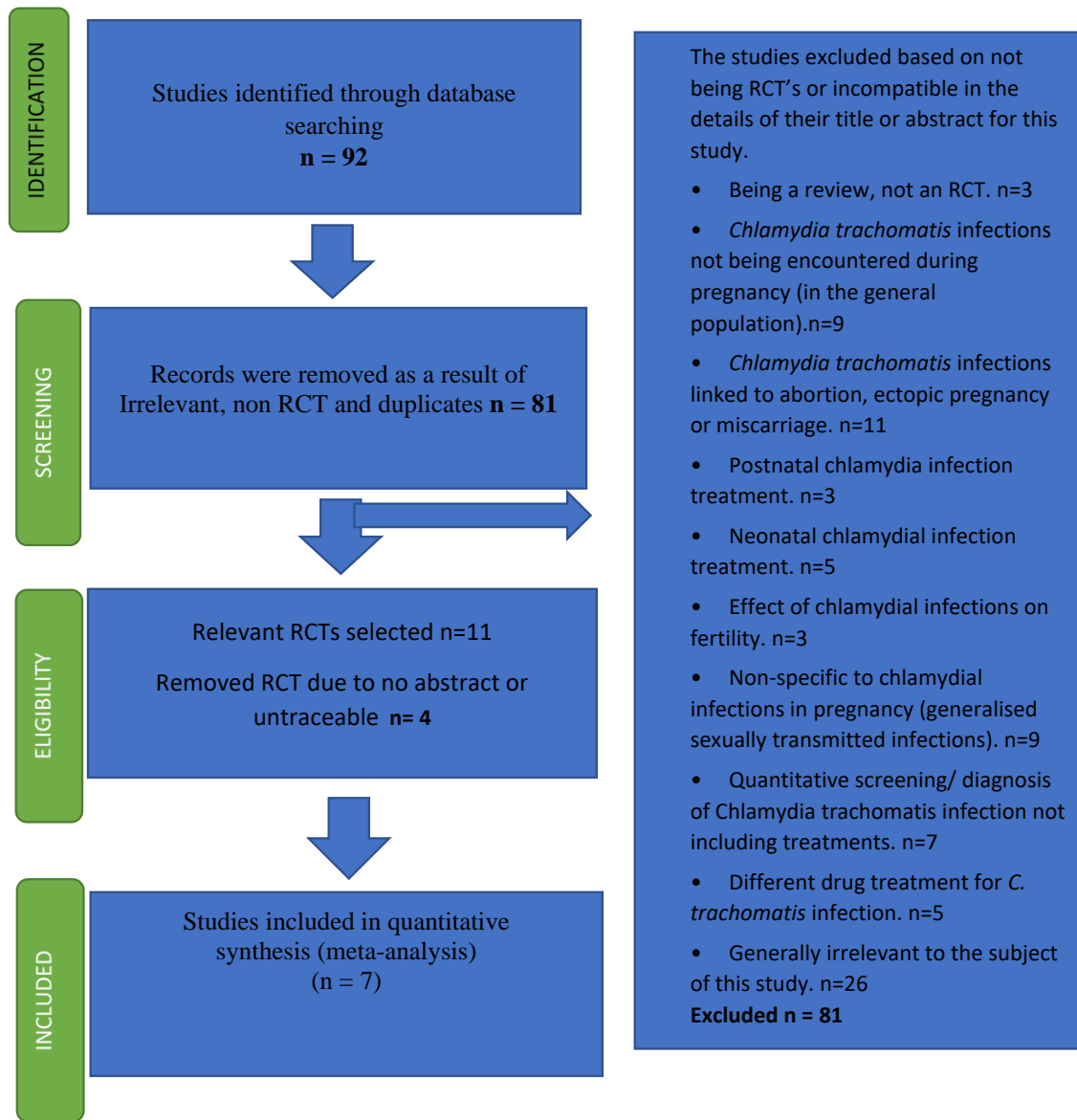
Figure 3. Flow diagram of the reviewed articles establishing the randomised control trials (RCTs) to be used in the meta-analysis.

3. Results

Table 1: Characteristics of the seven RCTs involved in the meta-analysis

Reference and year of publication	Drug	Dosage and treatment period	Gestational age of the patient (mean weeks)	Number of enrolled patients	Number of clinically evaluated patients	Percentage success of treatment	Percentage failure of treatment
Alary et al., 1994	Amoxicillin	500mg x3 a day, 7 days	17.3	105	100	99/100 99.00%	1/100 1%
	Erythromycin	500mg x4 a day, 7 days	16.9	105	99	87/99 87.90%	Dec-99 12.10%
Edwards et al., 1996	Azithromycin	1g single dose	20.4	65	62	58/62 93.50%	Apr-62 6.50%
	Erythromycin	500mg x4 a day, 7 days	28.6	65	64	46/64 71.90%	Aug-64 12.50%
Rosenn, Macones and Silverman, 1995	Azithromycin	1g single dose	19.3+-4.5	24	23	21/23 91.30%	23-Feb 8.70%
	Erythromycin	500mg x4 a day, 7 days	19.5 +-3.5	24	22	17/22 77.30%	22-May 22.70%
Turrentine, Troyer and Gonik, 1995	Amoxicillin	500mg x3 a day, 7 days	24.9+-6.3	57	55	52/55 94.00%	Mar-55 5.50%
	Erythromycin	500mg x4 a day, 7 days	24.3+-6.6	56	53	51/53 96.00%	Feb-53 3.80%
	Clindamycin	600mg x3 a day, 10 days	22.9+-6.2	55	52	51/52 98.00%	Jan-52 1.90%

Reference and year of publication	Drug	Dosage and treatment period	Gestational age of the patient (mean weeks)	Number of enrolled patients	Number of clinically evaluated patients	Percentage success of treatment	Percentage failure of treatment
Jacobson et al., 2001	Azithromycin	1g single dose	20.6+-8.8	63	55	35/55 63.60%	20/55 36.40%
	Amoxicillin	500mg x3 a day, 7 days	21.3+-9.2	66	55	32/55 58.20%	23/55 41.80%
Adair, 1998	Azithromycin	1g dissolved in 60ml of water, single dose	N/A (similar gestational age)	53	42	37/42 88.10%	May-42 11.90%
	Erythromycin	500mg x4 a day, 7 days	N/A (similar gestational age)	53	43	40/43 93.00%	Mar-43 7.00%
Gilbert, 1992	Clindamycin	450mg x4 a day, 14 days	20	42	42	39/42 93.00%	Mar-42 7.10%
	Erythromycin	333mg x4 a day, 14 days	20	42	42	35/42 84.00%	Jul-42 16.70%
	Placebo	N/A	20	42	42	0/42 0.00%	42/42 100%

3.1 Analysis of RCT characteristics.

Table 1 describes the characteristics of seven RCT's included in the meta-analysis of this study. In all seven RCTs, there was very little differentiation in demographic factors such as the number of sexual partners, gestational age (excluding Edwards et al., 1996). In two RCT's the treatment of both pregnant mother and their consistent sexual partner was mentioned with the contraceptive protective methods also being advised. However, in one study it was insinuated that the sexual partners of two of the patients were not treated for the Chlamydia and did not follow the advice of having protected sex for the duration of the study. As a result, the two patients in the study showed a positive reading for the *C. trachomatis* infection after completion of the course of antibiotic treatment during the trial likely due to reinfection.

In three RCTs, Azithromycin was administered as a single 1g powdered tablet dose, in one RCT (Adair, 1998) it was given as a single 1g dose dissolved in 60ml of water to the patients. Five RCTs applied the same dose and treatment period for Erythromycin of 500mg, four times a day, for seven days, with one RCT (Gilbert, 1992) administering 333mg, four times a day, for fourteen days. Clindamycin was administered at different doses for different lengths of time, in one RCT (Turrentine, Troyer and Gonik 1995) the dose and treatment period was 600mg, three times a day, for ten days; in another RCT (Gilbert 1992) Clindamycin was administered at 450mg, four times a day for fourteen days. Amoxicillin was consistently administered at 500mg four times a day, for seven days in all three RCTs.

3.2 Azithromycin versus Erythromycin treatment failure

Study or Subgroup	Azithromycin Events	Total	Erythromycin Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI	Odds Ratio M–H, Fixed, 95% CI
Adair, 1998	5	42	3	43	17.8%	1.80 [0.40, 8.07]	
Edwards et al., 1996	4	62	8	64	50.3%	0.48 [0.14, 1.69]	
Rosenn, Macones and Silverman, 1995	2	23	5	22	31.9%	0.32 [0.06, 1.88]	
Total (95% CI)		127		129	100.0%	0.67 [0.30, 1.49]	
Total events	11		16				

Heterogeneity: Chi² = 2.59, df = 2 (P = 0.27); I² = 23%
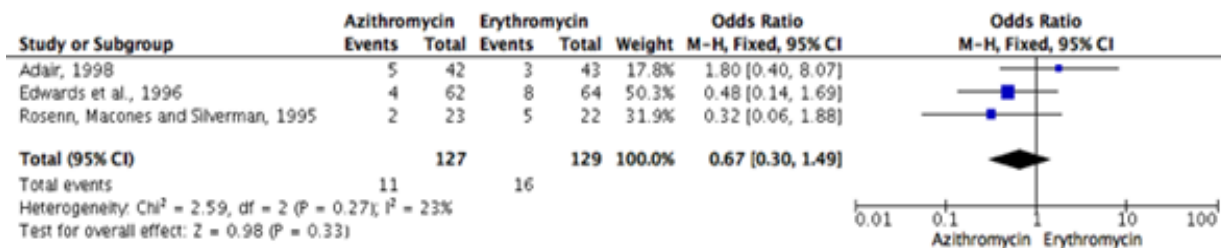Test for overall effect: Z = 0.98 (P = 0.33)

Figure 4. Forest Plot showing treatment failure of Azithromycin compared to Erythromycin in clinically evaluated patients.

As represented in Figure 5, Azithromycin compared with Erythromycin in two RCTs (Edwards et al, 1996 and Rosenn, Macones and Silverman, 1995) showed fewer incidences of treatment failure for Azithromycin. 256 clinically evaluated (CE) patients, fixed effect model, odds ratio (OR) = 0.67, 95% confidence interval (CI), 0.32-1.80, data from three RCTs). However, one RCT (Adair, 1998) showed to support Erythromycin over Azithromycin with a higher rate of treatment failure regarding Azithromycin in that one RCT.
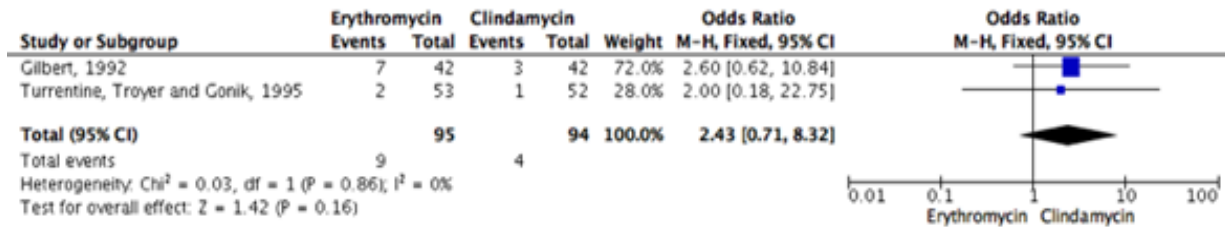
3.3 Clindamycin versus Erythromycin treatment failure

Study or Subgroup	Erythromycin Events	Total	Clindamycin Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gilbert, 1992	7	42	3	42	72.0%	2.60 [0.62, 10.84]
Turrentine, Troyer and Gonik, 1995	2	53	1	52	28.0%	2.00 [0.18, 22.75]
Total (95% CI)		95		94	100.0%	2.43 [0.71, 8.32]
Total events	9		4			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

Figure 5. Forest Plot showing treatment failure of Erythromycin compared to Clindamycin in clinically evaluated patients.

The treatment failure of Erythromycin was considerably higher than what was encountered in the trials of Clindamycin in clinically evaluated patients of both RCTs (Gilbert, 1992 and Turrentine, Troyer and Gonik, 1995), with 189 clinically evaluated patients, fixed effect model, odds ratio (OR) = 2.43 95% confidence interval (CI), 2.00-2.60, data from two RCTs.

3.4 Amoxicillin versus Erythromycin treatment failure

Study or Subgroup	Erythromycin Events	Total	Amoxicilin Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Alary et al., 1994	12	99	1	100	23.6%	13.66 [1.74, 107.16]
Turrentine, Troyer and Gonik, 1995	2	53	3	55	76.4%	0.68 [0.11, 4.24]
Total (95% CI)		152		155	100.0%	3.74 [1.21, 11.52]
Total events	14		4			

Heterogeneity: Chi² = 4.85, df = 1 (P = 0.03); I² = 79%
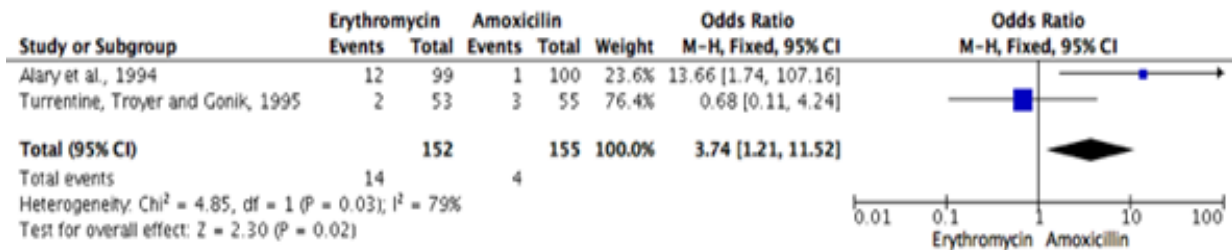Test for overall effect: Z = 2.30 (P = 0.02)

Figure 6. Forest plot showing treatment failure of Erythromycin compared to Amoxicillin in clinically evaluated patients.

The two RCTs compared in the forest plot diagram do not corroborate that same account. One RCT (Alary et al,1994) appears to show a higher affiliation to Amoxicillin describing a higher rate of failure concerning Erythromycin in this trial. However, in the other RCT (Turrentine, Troyer and Gonik, 1995) it describes a higher rate of failure of treatment concerning Amoxicillin with the forest plot appearing to have a higher affiliation towards and a closers position to Erythromycin. 307 clinically evaluated patients, fixed effect model, odds ratio (OR) = 3.74, 95% confidence interval (CI), 0.68-13.66, data from two RCTs).

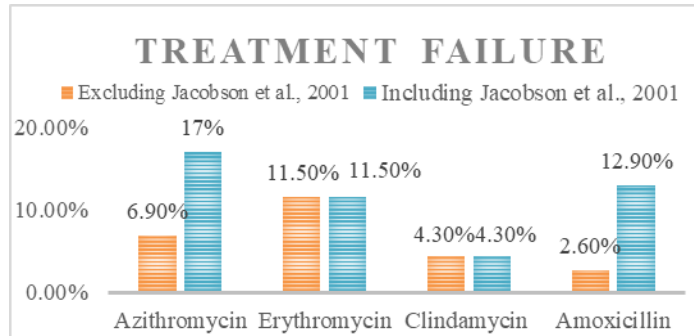*3.5 Treatment failure of each drug from the RCTs*

Figure 7. The overall treatment failure encountered for each antibiotic. In blue, all seven RCTs were included regarding the total percentages of treatment failure. In orange, the RCT of Jacobson et al., 2001 was excluded from the overall percentage treatment failure.

Treatment success was described as a negative test for Chlamydia at the end of the trial in all seven RCTs included in the meta-analysis. Treatment failure was determined by all studies as a positive test result for *C. trachomatis* at the end of the trial or failure to complete the trial itself and the subsequent absence of follow up information. The RCT Jacobson et al., 2001 treatment failure was treated as an anomaly within this study, due to the abnormally large treatment failure encountered that was inconsistent to the results of the relative drugs (Azithromycin and Amoxicillin) involved in other RCTs.

Table 2: Adverse side effects encountered by each antibiotic, including the total number of side effects encountered across all RCTs.

Antibiotic used to treat *C. trachomatis* infection in RCT.	Reference and year of publication	Percentage of reported gastrointestinal issues (nausea, diarrhoea, abdominal pain) or rash during the trial.	Total number and relative overall percentage of the side effects encountered for each drug from the respective RCTs.
Azithromycin	Edwards et al., 1996	12/62 (17.7%)	28/181 (15.5%)
	Rosenn, Macones and Silverman, 1995	4/22 (18.2%)	
	Jacobson et al., 2001	6/55 (10.9%)	
	Adair, 1998	6/53 (11.3%)	
Erythromycin	Alary et al., 1994	32/99 (31.3%)	139/333 (41.7%)

	Edwards et al., 1996	42/64 (65.6%)	
	Rosenn, Macones and Silverman, 1995	10/22 (45.5%)	
	Turrentine, Troyer and Gonik, 1995	14/53 (24.5%)	
	Adair, 1998	31/53 -58.50%	
	Gilberts, 1992	10/42 (23.8%)	
Clindamycin	Turrentine, Troyer and Gonik, 1995	7/52 (9.6%)	11/94 (11.7%)
	Gilbert, 1992	4/42 (9.5%)	
Amoxicillin	Alary et al., 1994	6/100 (6.0%)	12/210 (5.7%)
	Turrentine, Troyer and Gonik, 1995	3/55 (5.5%)	
	Jacobson et al., 2001	3/55 (5.5%)	

According to Table 2, four RCTs concerning Azithromycin a total of 28 out of 181 (15.5%) of the patients displayed intolerance to the drugs including gastrointestinal issues (including nausea, diarrhoea, abdominal pain) and one patient exhibited signs of a rash. In the four RCTs concerning Erythromycin 139 out of 333(41.2%) of patients displayed gastrointestinal issues or a rash. In the two RCTs regarding Clindamycin 11 out of 94 (11.7%) patients involved encountered intolerance to the drug. In the three RCTs concerning Amoxicillin a total of 12 out of 210 patients (5.7%), displayed gastrointestinal issues. However, there were no reports of a rash encountered by any of the patients in the RCTs concerning Amoxicillin.

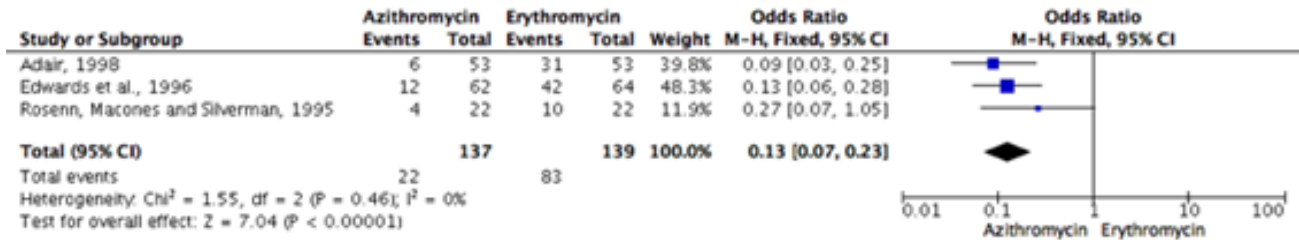*3.6 Azithromycin versus Erythromycin adverse side effects*

Figure 8. Forest plot comparing the total adverse side effects encountered by patients administered with Azithromycin and Erythromycin.

According to Figure 8, there is a much higher occurrence of adverse side effects in patients administered Erythromycin comparative to Azithromycin. In two of the RCTs (Edwards et al., 1996 and Rosenn, Marcones and Silverman, 1995) adverse side effects referred to patients that had been clinically evaluated whilst one RCT (Adair, 1998) adverse side effects referred to the total number of patients the trial had initially intended to treat. (172 CE patients, 106 patients that were deemed intended to treat, fixed effect model, odds ratio (OR) =0.13, 95% confidence interval (CI), 0.09-0.27, data from three RCTs).

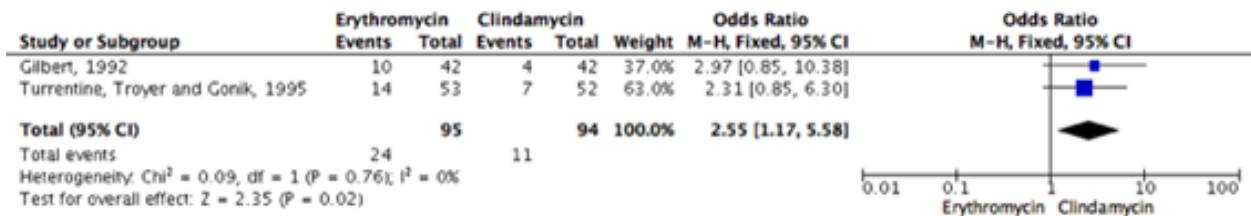*3.7 Clindamycin versus Erythromycin adverse side effects*

Figure 9. Forest plot comparing the total adverse side effects encountered by patients administered Erythromycin and Clindamycin.

According to Figure 9, the total number of adverse side effects encountered in Patients prescribed Erythromycin (24) is more than double comparatively when compared to Clindamycin (11). The forest plot displays a higher affiliation positioned towards Clindamycin where fewer side effects were encountered. Both RCTs totals referred to patients that had been clinically evaluated, (189 CE patients, fixed effect model, odds ratio (OR) = 2.55, 95% confidence interval (CI), 2.31-2.97, data from two RCTs).

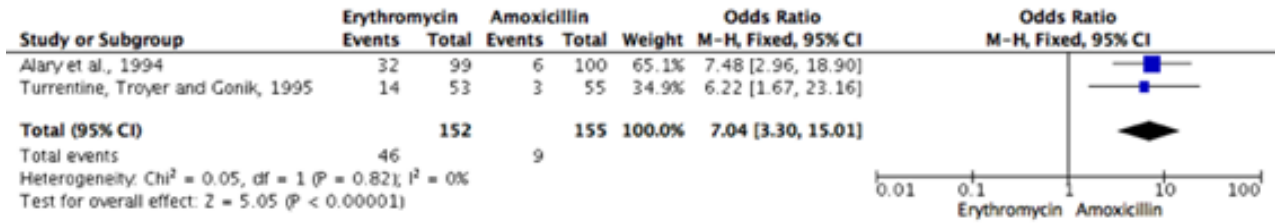*3.8 Amoxicillin versus Erythromycin adverse side effects*

Study or Subgroup	Erythromycin Events	Total	Amoxicillin Events	Total	Weight	Odds Ratio M–H, Fixed, 95% CI
Alary et al., 1994	32	99	6	100	65.1%	7.48 [2.96, 18.90]
Turrentine, Troyer and Gonik, 1995	14	53	3	55	34.9%	6.22 [1.67, 23.16]
Total (95% CI)		152		155	100.0%	7.04 [3.30, 15.01]
Total events	46		9			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 5.05 (P < 0.00001)

Figure 10. Forest plot comparing the total adverse side effects encountered by patients administered Erythromycin and Amoxicillin.

As depicted in Figure 10, there is a higher affiliation towards Amoxicillin compared to that of Erythromycin. Erythromycin had 46 accounts of adverse side effects encountered in two RCTs compared to 9 accounts of side effects from patients administered Amoxicillin. Both RCTs referred to patients that had been clinically evaluated, (307 CE patients, fixed effect model, odds ratio (OR) = 7.04, 95% confidence interval (CI), 6.22-7.48, data from two RCTs).

3.9 Comparison of the total amount of side effects encountered by each drug in RCTs
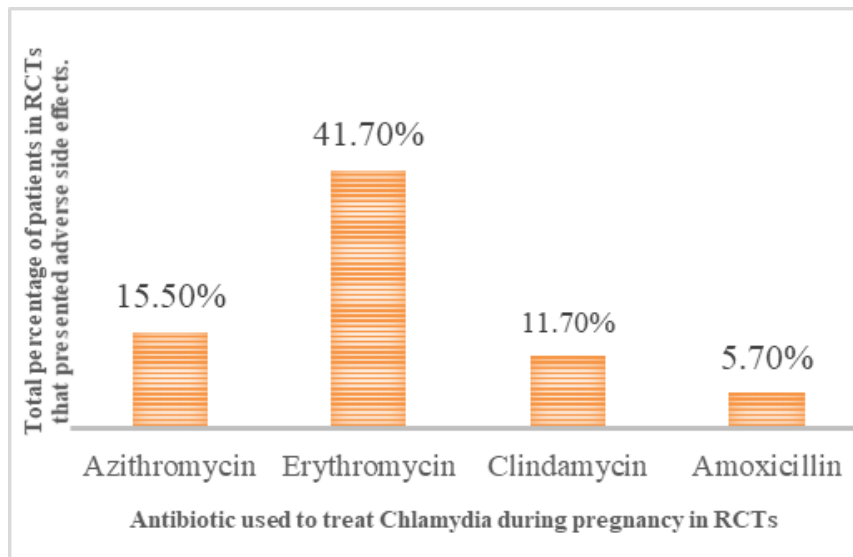

Figure 11. Total percentage of side effects encountered for each antibiotic treatment used to treat *C. trachomatis* infections during pregnancy from the seven RCTs used in this study.

Figure 11 shows the total percentage of adverse side effects encountered by patients for each drug. The most side effects encountered was regarding Erythromycin (41.7%), followed by Azithromycin (15.5%), Clindamycin (11.7%), and Amoxicillin with the lowest amount of side effects encountered (5.7%).

3.10 Azithromycin versus Clindamycin

Despite RCTs being non-comparable for a meta-analysis, from Figure 11 there was a higher total percentage incidence of adverse side effects encountered in the four RCTs (15.5%) concerning Azithromycin compared to the two RCTs of Clindamycin (11.7%).

3.11 Azithromycin versus Amoxicillin

Figure 11 shows that Beta-lactam antibiotic Amoxicillin had the lowest percentage total incidences of adverse side effects of all antibiotics evaluated in this study (5.7%). Compared to that of Azithromycin (15.5%) from its four RCTs, Amoxicillin had less than half the total percentage incidences of recorded side effects.

3.12 Clindamycin versus Amoxicillin

Both Clindamycin and Amoxicillin had the lowest total percentage of adverse side effects recorded during their respective RCTs. However, in Figure 11 its shows that Clindamycin had more than double the percentage of adverse side effects encountered in the two RCTs concerning the drug (11.7%), compared to Amoxicillin (5.7%) from its three RCTs.

4. Discussion

The results from the meta-analysis and total condensed data of all RCTs (Figure 7) evaluating treatment success of eradicating *C. trachomatis* infections in pregnancy, suggested that the therapy of Erythromycin was the least efficacious antibiotic treatment evaluated in this study. Erythromycin's predicted characteristic undesirable gastrointestinal side effects led to understandable high levels of non-compliant patients in RCTs which significantly related to treatment failure. Gastrointestinal side effects encountered as a result of Erythromycin are thought to be caused by interactions of the drug with motilin receptors, inducing strong gastric and pyloric contractions and subsequent side effects characteristic to the macrolide.

The azalide derivative of Erythromycin; Azithromycin proved somewhat more successful at eliminating the Chlamydial infection. Only 3 RCTs that fitted the inclusion criteria were comparable through a meta-analysis where two RCTs confirmed Azithromycin to have a higher success rate compared to Erythromycin (Edwards et al., 1996 and Rosenn, Macones and Silverman, 1995). One RCT however (Adair 1998) had a different method of application of Azithromycin compared to all other RCTs, where a single dose 1g of Azithromycin administered was dissolved in 60ml of water, this method seemingly decreased the efficacy of the drug. Azithromycin overall had a higher success rate of eradicating a *C. trachomatis* infection in pregnancy (from 88.1%-93.5%) compared to that of Erythromycin (71.9%-93.0%). Despite the azalide Azithromycin being a derivative of Erythromycin and having similarities chemically and somewhat structurally (Figure 2), there were noted differences in the two drugs evaluated in the results. Gastrointestinal side effects and resultant noncompliance were significantly related to treatment failure with Erythromycin (Edwards et al., 1996). Lack of compliance of patients in the RCTs of each drug can be considered a contributing factor to the decreased success rates in the trials involved in the comparison of these two macrolides. Erythromycin's links to pyloric

stenosis and subsequent gastrointestinal issues understandably led to a reduction in the patients involved in RCTs. (Sarkar, Woodland C, Koren and Einarson, 2006).

Despite the low compliance rate of Erythromycin, the success of treatment and cure rates were relatively high. Which may suggest a shorter exposure to the drug may exert the desired effects on the infection but limit the adverse gastrointestinal side effects encountered. (Jelić and Antolović, 2016) The differences chemically between the two macrolides is Azithromycin consists of a lactone ring which gives it its unique pharmacokinetic profile, and this difference structurally can be considered to contribute to fewer incidences of gastrointestinal issues. (Allaire, Nathan and Martens, 1995).

Clindamycin had a slightly higher success rate at eradicating *C. trachomatis* infections in pregnancy (93-98%) compared to Erythromycin (84%-96%). Again, this was likely linked to the reduced compliance encountered in RCTs by patients administered Erythromycin and experiencing adverse gastrointestinal side effects. In the meta-analysis of these two drugs, it was limited to the evaluation of only two RCTs, due to the lack of trials completed regarding Clindamycin and Chlamydial infections during pregnancy. Clindamycin's mode of action enabled a post-antibiotic effect due to its method of binding to bacterial ribosomal subunits and is, therefore, more likely to prevent persistent infections. Alongside this, there were few adverse side effects attributed to this antibiotic. However, more RCT's would be required to help strengthen the reliability of these findings.

Amoxicillin appears to have the highest percentage treatment success and the lowest incidences of adverse side effects encountered during the RCTs. The meta-analysis for the success of treatment resulted in conflicting results which is similar to the opinions of varying articles regarding the use of Amoxicillin to treat *C. trachomatis* infections (especially in vitro). Amoxicillin had the lowest incidences of adverse side effects compared to Erythromycin in the meta-analysis attributed to its mode of action. Secondary to this, the mode of action of Amoxicillin resulted in an increased likelihood of reinfection with the presence of latent *C. trachomatis* genetic material likely to remain within the patient (detectable by RT-PCR). In pregnancy, the risk of reinfection by using this antibiotic would be too high with consequences not just for the mother but for the developing foetus and eventual neonate too.

The detrimental capabilities of *C. trachomatis* infections to both pregnant mothers, foetus and subsequent neonate make eradicating such infections a priority in pregnancy. Due to a lack of RCT's performed on pregnant women with such infections, there is not a defined consensus of the exact application of one specific antibiotic (Rahangdale et al., 2006). Difficulties arose when comparing the efficacy of each antibiotic against each other due to a shortage of RCT's to facilitate the research.

5. Limitations of the study

There were very few studies regarding the use of Amoxicillin to treat such infections during pregnancy and even fewer for the lincosamide Clindamycin. Weaknesses encountered during the research included the lack of comparative RCTs for each drug compared in this study, with comparative RCTs largely focused on the comparison of Azithromycin and Erythromycin there were noticeable limitations surrounding the drugs Clindamycin and Amoxicillin to align with all

of the inclusion criteria of this study. To improve upon this, alike what the WHO suggested, further research and RCTs of antibiotics applied in pregnancy need to be made. For the obvious ethical reason there lie some restrictions attaining willing participants to partake in such trials during pregnancy with risks not only to themselves but to the foetus too.

The treatment failure encountered during the RCTs evaluated in this study could also be attributed to incorrect drug uptake by patients, reinfection of *C. trachomatis* by an untreated partner, organism resistance to the drugs (Azithromycin resistance *C. trachomatis* bacteria), or incomplete penetration of the drug at the site of infection (Adair 1998).

6. Conclusion

To conclude, Azithromycin can be considered as the most effective antibiotic to treat *C. trachomatis* infections in pregnancy. Azithromycin had a high success rate of eradicating the active infection, minimal gastrointestinal side effects encountered, and high levels of compliance from patients due to its unique pharmacokinetic profile. This antibiotic facilitates the fast and complete elimination of *C. trachomatis* infections in pregnancy with low recorded levels of recurrent infections attributed to its mode of action. More data regarding Azithromycin was accessible to this study compared to that of Clindamycin. Clindamycin, although very capable of eliminating *C. trachomatis* infections in pregnancy, there was a severe lack of data supporting these capabilities. Future research on more RCTs needs to be completed to determine the efficacy of Clindamycin. Moreover, Clindamycin could be considered as a second antibiotic to Azithromycin, in allergic circumstances of when antibiotic resistance of *C. trachomatis* to the azalide prevails.

Table 03: Abbreviating each of the acronyms used in the text.

sexually transmitted disease	STD
Pelvic Inflammatory Disease	PID
World Health Organisation	WHO
Randomised Control Trials	RCTs
Real-Time Polymerase Chain Reaction	RT-PCR
transfer Ribo Nucleic Acid	tRNA
Ribosomal Ribo Nucleic Acid	rRNA
Messenger Ribo Nucleic Acid	mRNA
odds ratio	OR
confidence interval	CI

Author Contribution

SS has conceived and designed and wrote the manuscript. KD and SB performed data analysis helped manuscript preparation.

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