

DYSENTERY (SHIGELLOSIS)
CURRENT WHO GUIDELINES AND THE WHO ESSENTIAL MEDICINE LIST FOR CHILDREN

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1. INTRODUCTION

In 2007, the Better Medicines for Children (BMC) initiative of the World Health Organisation (WHO) was developed in response to World Health Assembly (WHA) resolution 60.20, which cited overwhelming evidence that nearly 50% of children under 5 years of age were dying of preventable diseases, for which effective medicines existed. In recognition of the need to improve access to evidence-based paediatric formulations which may be utilised in an optimal manner, an Essential Medicines List for children (EMLc) was created, alongside a children's formulary.¹

This document was prepared in response to a need to update the current recommendations for antibiotic treatment of Dysentery in low- and middle-income settings, where the predominant cause is *Shigella* infection (in contrast to *Salmonella*, the primary cause in developed countries).² The current recommendations are based on evidence up to 2005 (Table 1).³ At that time, due to widespread resistance to ampicillin, co-trimoxazole and nalidixic acid, the recommendation was to treat bloody diarrhoea with ciprofloxacin, irrespective of age. Concerns were noted regarding possible growth inhibition, with previously documented articular cartilage damage in immature animals, but not in human studies. This potential risk of harm was thought to be outweighed by the value of treating dysentery susceptible to this antimicrobial. Ciprofloxacin was chosen due to its high tissue and intracellular penetration, high faecal concentration, ability to be administered orally, and evidence for diminishing symptoms and faecal shedding of pathogens.⁴ Currently, however, several more recent international guidelines suggest the use of azithromycin and other agents to treat shigellosis in children.

2. INFORMATION SUPPORTING PUBLIC HEALTH RELEVANCE

2.1. Microbiology

Shigella is a Gram-negative, non-motile bacillus belonging to the *Enterobacteriaceae* family. There are four species of Shigellae: *S. dysenteriae*, *S. flexneri*, *S. boydii* and *S. sonnei* (designated as serogroups A, B, C and D respectively). The first three species include several 19 serotypes. Acquired immunity to *Shigella* is serotype-specific. While *S. boydii* and *S. sonnei* usually cause a relatively mild illness (watery or bloody diarrhoea only), *S. flexneri* and *S. dysenteriae* are chiefly responsible for endemic and epidemic shigellosis (respectively) in developing countries, with high transmission rates and significant case fatality rates.

2.2. Epidemiology & Pathogenesis

On a global scale, of the estimated 165 million *Shigella* diarrhoeal episodes estimated to occur each year, 99% occur in developing countries, mainly in children.⁵ In 1999, a systematic review reported *Shigella* to be responsible for 1.1 million deaths per year, 61% of which in children less than 5 years of age, based on prevalence in diarrhoea cases and limited data on case-fatality rates amongst hospitalised children.⁵ In 2013, these estimates were revised using a similar modelling strategy, but with updated mortality risk data, suggesting between 28,000 and 48,000 deaths annually amongst children under 5 years due to Shigellosis.^{6,7} In 2016, a quantitative molecular analysis from the Global Enteric Multicentre Study (GEMS) identified an increased burden of Shigellosis and reported it as the leading pathogen among the top six attributable pathogens causing childhood diarrhoea.⁸ The GEMS data and consideration of the indirect risks of malnutrition arising in relation to diarrhoeal episodes may lead to further revisions of *Shigella*-attributable mortality estimates.

Shigellosis occurs predominantly in developing countries due to overcrowding and poor sanitation. Infants, non-breast fed children, children recovering from measles, malnourished children, and adults older than 50 years have a more severe illness and a greater risk of death. Transmission occurs via the faecal-oral route, person-to-person contact, household flies, infected water, and inanimate objects.⁹ *Shigella* species can survive in gastric acid, and infection can occur following exposure to as few as 10-100 organisms.¹⁰ Once infected, all *Shigella* species multiply and cause acute bloody diarrhoea by

invading the colonic epithelium where pro-inflammatory cytokines are released, and the subsequent inflammatory reaction (recruiting a number of polymorphonuclear cells) destroys the epithelial cells lining the gut mucosa, allowing for further direct invasion by *Shigella*. The resultant infectious diarrhoea is associated with loss of water and electrolytes and a clinical picture of abdominal cramping, fever, and bloody/mucoid stools. Stool microscopy – a cheap, rapid and simple diagnostic test – reveals numerous polymorphonuclear cells on methylene blue stain, however microbiological culture is required for differentiating *Shigella* from other causes of colitis.⁹ Multiplex polymerase chain reaction (PCR) platforms for detection of *Shigella* are commercially available, but are limited in their availability in most health care settings.

The species distribution of *Shigellae* varies globally. While *S. sonnei* is the predominant species worldwide, *S. flexneri* is more prominent across developing country settings in Africa and Asia, with the less virulent *S. sonnei* predominating in higher-income settings.^{11,12} *S. dysenteriae* (Type 1; also known as ‘Shiga bacillus’) is capable of causing a more severe and prolonged illness, due to the production of a potent enterotoxin (‘shiga toxin’), which is similar to the verotoxin produced by Enterohaemorrhagic *E. coli* and is associated with life-threatening haemolytic-uraemic syndrome.¹³ Other complications due to Shigellosis include sepsis, rectal prolapse, arthralgia, intestinal perforation, toxic megacolon, electrolyte imbalance, seizures, and leukaemoid reactions.^{14,15}

2.3. Rationale for antibiotic treatment

With effective antibiotic therapy, clinical improvement occurs within 48 hours, resulting in a decreased risk of serious complications and death, shorter duration of symptoms, the elimination of *Shigella* from the stool and subsequently decreased transmission of infection.³ In fact, one of the primary arguments for treatment of *Shigella* infection is due to its public health effect by diminishing transmission through decreasing the duration of faecal carriage (from approximately 4 weeks to 3 days) with effective treatment.^{14,16}

2.4. 2005 guidelines

The 2005 guidelines recommend ciprofloxacin as first-line treatment and noted that pivmecillinam (amdinocillin pivoxil) and ceftriaxone were ‘the only antimicrobials that are usually effective for treatment of multi-resistant strains of *Shigella* in all age groups’, yet their usage is limited by their high cost and formulation (four times daily dosing for pivmecillinam, and parenteral administration for ceftriaxone). Pivmecillinam and ceftriaxone were therefore only listed for usage when local strains of *Shigella* are known to be resistant to ciprofloxacin. Azithromycin was included as a second-line therapy for adult patients; this was (most likely) not recommended for children in these guidelines due to limited evidence at that time in regards to its efficacy.

Antimicrobial	Treatment schedule for children	Limitations
1 st Line: Ciprofloxacin	15mg/kg orally Twice daily For 3 days	-Expensive -Resistance emerging -Drug interactions
2 nd Line: Pivmecillinam	20mg/kg orally Four times daily For 5 days	-Cost -No paediatric formulation -4 times daily dosing -Resistance emerging
OR*: Ceftriaxone	50-100mg/kg Intramuscular injection For 2-5 days	-Requires parenteral administration -Generates antimicrobial resistance
OR: (for Adults) Azithromycin	6-20mg/kg, orally Once daily For 1-5 days	-Cost -Drug interactions -Resistance emerges rapidly, spreads to other bacteria

Table 1: 2005 WHO Guidelines: Antimicrobials for treatment of Shigellosis (adapted)³

*Ceftriaxone is listed as an alternative therapy ‘only for use when local strains of *Shigella* are known to be resistant to ciprofloxacin’

The 2005 guidelines further listed antimicrobials NOT be used in the treatment of Shigellosis (Table 2).

Antimicrobial	Rationale for not prescribing
Ampicillin	Antimicrobial Resistance
Chloramphenicol	Antimicrobial Resistance
Co-trimoxazole	Antimicrobial Resistance
Tetracyclines	Antimicrobial Resistance
Nalidixic Acid	Antimicrobial Resistance; <i>in vitro</i> cross-resistance to Ciprofloxacin observed (MIC increased)
Nitrofurans (nitrofurantoin, furazolidone)	Penetrate the intestinal mucosa poorly
Oral Aminoglycosides (gentamicin, kanamycin)	Penetrate the intestinal mucosa poorly
1 st and 2 nd generation cephalosporins (cefazolin, cephalotin, cefaclor, cefoxitin)	Penetrate the intestinal mucosa poorly
Amoxicillin	Penetrates the intestinal mucosa poorly

Table 2: Antimicrobials highlighted as inappropriate for treatment of Shigellosis in the 2005 WHO Guidelines.³

2.5. 2013 guidelines

The WHO 2013 Pocket book of hospital care for children (second edition) includes a section on the treatment of *Shigella* dysentery.¹⁷ The treatment protocol is concurrent with the 2005 guidelines outlined above, with the exception of a slightly lower dosage range listed for ceftriaxone (50-80mg/kg in the 2013 guidelines, versus 50-100mg/kg in the 2005 guidelines).

3. METHODS

3.1. Data search and retention of evidence

3.1.1. Search terms

A systematic search for systematic reviews, meta-analyses, multi-centre studies and randomised controlled trials of antibiotic therapy for relevant papers was conducted using the MeSH Search terms ‘*Shigella*’, ‘dysentery’, ‘antibiotics’, ‘antimicrobials’. The databases EMBASE, Cochrane database of systematic review and Pubmed were searched. Trials were limited to those conducted within humans and published since 2005, to ensure accurate and up-to-date information regarding antimicrobial resistance susceptibility patterns were documented.

The search was initially restricted to studies investigating the paediatric population, but due to limited published research conducted in this area, the systematic review was then expanded to include research across all age ranges. International clinical practice guidelines were also reviewed, including the Infectious Diseases Society of America (IDSA), the European Society for Clinical Medicine (ESCMID; which does not have a current *Shigellosis* policy), BMJ Clinical Evidence, the American Academy of Paediatrics, and Therapeutic Guidelines (Australia).

3.1.2. Inclusion and exclusion criteria

Inclusion Criteria:	Exclusion Criteria:
<ul style="list-style-type: none"> • Systematic review, randomised controlled trial or multi-centre study investigating clinical treatment options and outcomes for <i>Shigellae</i> • Paediatric-specific information included • Where resistance patterns were investigated, information on antimicrobial testing methodologies documented 	<ul style="list-style-type: none"> • Published prior to 2005 • Not pertaining to treatment in humans • Data pertaining to carriage rates only

Table 3: Inclusion and exclusion criteria

4. RESULTS

4.1. Search results

The initial search produced 131 results (Figure 1) of which 28 qualified for full text review. Ultimately, 9 studies met the inclusion criteria (Table 3), which were abstracted as detailed in Appendix A. Quality assessment of the studies was performed as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (see Appendix A for description of methodologies).¹⁸

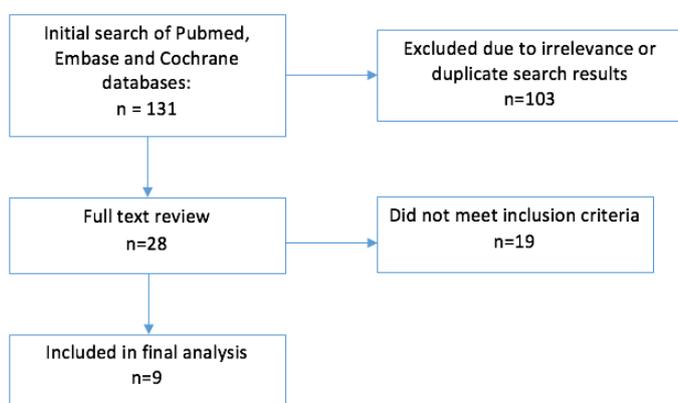


Figure 1: Search Strategy

4.2. Characteristics of Included Studies:

Six studies were systematic reviews and meta-analyses (conducted across an international setting). One paper was a multi-centre study evaluating 600,000 cases of *Shigella* diarrhoea in six Asian countries. Two papers were based on data collated from a multi-centre randomized trial conducted in Vietnam.

Four papers were classified as high-quality evidence, three as moderate-quality evidence and the two papers based on data investigating a multi-centre trial in Vietnam were classified as low-quality evidence.

Two systematic reviews assessed paediatric antimicrobial response exclusively, while the remainder included both adults and children within their population. The papers based on the multi-centre trial in Vietnam investigated clinical outcomes among children <16 years.

4.3. Synopsis of review results:

4.3.1. Evidence for currently recommended ciprofloxacin, pivmecillinam, and ceftriaxone

A systematic review conducted in 2013¹⁹ used CHERG standard rules²⁰ to analyse 48 high-quality randomised controlled trials in children aged <16 years across predominantly developing country settings (of which 7 were ultimately eligible for inclusion). This review found the current WHO Guidelines of treatment with *either ciprofloxacin, pivmecillinam or ceftriaxone* reduced clinical failure rates (which the authors postulated were a proxy for *Shigella* deaths) by 82% (95% CI 67 to 99%). The use of ciprofloxacin, pivmecillinam or ceftriaxone was reported to successfully clear *Shigella* pathogens in 96% (95% CI 88 to 99%) of cases. The authors concluded that there is **strong evidence of current antimicrobial guideline effectiveness against serious mortality and morbidity**. Of note, 98% of the trials reviewed were conducted in developing country settings, increasing generalisability and applicability to the population served by the EMLc. However, all studies were hospital-based, limiting information available on resistance patterns for *Shigella* infections typically treated in the community.

A systematic review in 2010² assessing *ciprofloxacin, pivmecillinam or ceftriaxone* conducted on children in developing countries in 8 studies (again limited to hospital-based settings) also used the CHERG rules and documented clinical failure rates of 0.1% (95% CI -0.2 to 0.5%) (*note: the negative value for the lower 95% CI indicates there is a methodological issue with this analysis*), concluding “**the antibiotics recommended by the WHO are effective** in reducing clinical and bacteriological signs and symptoms of dysentery; and can thus be expected to decrease diarrhoea mortality attributable to dysentery”.

4.3.2. Data on *in vitro* antimicrobial resistance patterns only

A third (high-quality) systematic review¹¹ assessing *in vitro* resistance patterns of all *Shigella* spp. to *ciprofloxacin* alone found **increasing resistance** in the Asia-Africa regions (analysed together), from 0.6% in 1998-2000 (95% CI 0.2 to 1.3%) to 29.1% (95% CI 0.9 to 74.8%) in 2007-2009 – a 49-fold increase over 12 years. This increase in resistance was significantly above the (very minimal) increase documented in the Europe-America region, which only reached 0.6% (95% CI 0.2 to 1.2%) by 2007-2009. Of note, this review also found **higher resistance in children**, with respective rates (globally) of 7.5% (95% CI 4.3 to 11.5%) in paediatric patients versus 3.6% (95% CI 2.2 to 5.3%) in adults.

The same authors conducted a review of *in vitro* resistance of all *Shigella* spp. to third-generation cephalosporins (*ceftriaxone, cefotaxime and ceftazidime*) between 1999-2012,²¹ finding markedly increased resistance in the Asia-Africa region (with ceftriaxone resistance to *Shigella* spp. reaching 14.2% (95% CI 3.9 to 29.4%) by 2012). Both studies, however, exhibited a lack of data pertaining to patient outcomes. The authors concluded that **ceftriaxone and cefotaxime may not be appropriate for treating shigellosis in Asia-Africa**.

Assessing the Asia region independently, a 2006 multi-centre study (of 2,927 *Shigella* isolates in children and adults) across Bangladesh, China, Pakistan, Indonesia, Thailand and Vietnam documented *ciprofloxacin*-resistant *S. flexneri* isolates in China (18/305, 6%), Pakistan (8/242, 3%), and Vietnam (5/282, 2%).¹²

4.3.3. Evidence for Alternative Antibiotic Treatment Options

In light of the above research documenting increasing resistance to ciprofloxacin and ceftriaxone, the literature was reviewed for other alternative therapies that could be used to treat *Shigella* dysentery.

Previously effective agents including *nalidixic acid, amoxicillin and co-trimoxazole* were removed from the 2013 WHO guidelines for treatment of dysentery in light of their extensive resistance, a decision which continues to be supported in light of high levels of resistance documented in the papers included in this review.

Of note, a 2010 Cochrane review¹⁴ investigating antibiotic therapy for *Shigella* dysentery did not find superior efficacy when comparing fluoroquinolones, beta-lactams or macrolides. The authors noted that the current practice of presumptively treating *Shigella* dysentery with antibiotics should continue due to the public health benefits; but that **no specific antibiotic, or antibiotic class, is universally effective for the treatment of *Shigella***. Of note, this study included a number of RCTs of low- to moderate quality; many of which were conducted prior to 1990, likely not reflecting current resistance patterns.

Aminoglycosides: a 2013 systematic review²² assessing patterns of aminoglycoside resistance in *Shigella* worldwide (between 1999-2010) documented increasing levels of *in vitro* gentamicin resistance in the Asia-Africa region, reaching 32.4% (95% CI 17.9 to 48.9%) in 2005-2007. Resistance to gentamicin, kanamycin and amikacin was higher among the paediatric than adult population. The 2010 Cochrane review further supported the clinical ineffectiveness of aminoglycosides, which tend to have poor absorption when administered orally, further limiting their utility.¹⁴

Gatifloxacin, a 4th generation fluoroquinolone, was investigated as an alternative therapy in a multi-centre randomised trial assessing the efficacy of gatifloxacin versus ciprofloxacin in the treatment of Shigellosis in Vietnamese children between 2006-2008.²³ No superiority to gatifloxacin was found in terms of clinical failure rates, which were similar in both groups (gatifloxacin 12% versus 11% for ciprofloxacin, p=0.72) in the treatment of paediatric dysentery. While gatifloxacin may be a more convenient medication due to its longer half-life than ciprofloxacin (allowing administration once daily, rather than twice daily as required by ciprofloxacin), the subgroup of patients with *S. flexneri* treated with gatifloxacin had significantly **worse clinical outcomes** than those treated with ciprofloxacin, regardless of MIC. Overall, no association between MIC and clinical outcome in paediatric shigellosis infections was found.²⁴

Azithromycin, a macrolide antibiotic, is listed as an alternative second-line therapy for adults in the current WHO Guidelines as well as most international guidelines (for both paediatric and adult patients). There have been no published trials comparing the efficacy of azithromycin to ciprofloxacin in children. In the late 1990s, amongst adults in Kenya and Bangladesh, azithromycin was found to be as effective as ciprofloxacin.²⁵

In Tanzanian adults in 2004/2005, 90% of *Shigella* strains isolated were *S. flexneri*, all were reported sensitive *in vitro* to ciprofloxacin, nalidixic acid and cefuroxime, and 98% were sensitive azithromycin. By 2010/2011, in Dhaka, Bangladesh, *in vitro* susceptibility to ciprofloxacin, mecillinam, azithromycin and ceftriaxone were 65%, 50%, 74% and 95% respectively.²⁶ However, more recently, increasing reports of azithromycin-resistant strains of *Shigella* spp. have recently been documented by the Centres for Disease Control and Prevention (CDC).²⁷⁻³¹ Until this year, Clinical & Laboratory Standards Institute (CLSI) guidelines for standardised susceptibility testing of azithromycin against *Shigella* species were not available (with no breakpoints to interpret MIC or disc diffusion test results), impacting the availability of resistance data in the international literature.³² Due to evidence of increasing azithromycin resistance emerging in both high and low-income settings, a lack of data on how this relates to clinical outcomes, and the possibility for interactions with other medications commonly instituted in developing-country settings (such as anti-malarial medication – see ‘adverse effects’ below), **at this stage, there is insufficient evidence to include azithromycin as an alternative first-line therapy for Shigellosis in paediatric patients**. Trials of efficacy are urgently needed because, as above, MICs do not always correlate with patient outcomes .

No other antimicrobial agents were reported in literature meeting the inclusion criteria for this review.

4.1. Alternative Treatment Option

4.1.1. Oral cephalosporins

Cefixime is an oral third-generation cephalosporin which inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs), inhibiting cell wall synthesis. It has a wide distribution throughout the body and reaches therapeutic concentration levels in most tissues and body fluids, with a time to peak serum concentration of 2 to 6 hours and a half-life of 3 to 4 hours.³³ Cefixime has demonstrated efficacy (at 8mg/kg/day in two divided doses) in the treatment of Shigellosis in both adult and paediatric patients,^{26,33,34,35,36} although one study documented inferior efficacy to azithromycin.³⁵ Short (two day) courses have been found to have similar efficacy to five-day courses.³⁷ **Cefixime may be a useful therapy for paediatric patients when cephalosporin therapy is required due to resistance to fluoroquinolones, and can be administered orally** (unlike the parenteral administration required by ceftriaxone). Cefixime is affordable and the suspension can be stored at room temperature. One potential risk of cephalosporin use is driving Extended Spectrum Beta Lactamase resistance in gut bacterial populations in the community (see below). **Clinical trials to investigate cefixime as an alternative treatment option are urgently needed**, as previous randomised controlled trials investigating its efficacy are over a decade old.^{35,37} However, trials will need to address cost and the impact on antimicrobial resistance.

4.2. Synopsis of International Guidelines

Four evidence-based international guidelines were reviewed (listed in order of most recently updated): the Infectious Diseases Society of America (IDSA),³⁸ Therapeutic Guidelines (Australia),³⁹ the American Academy of Paediatrics (AAP),⁹ and BMJ Clinical Evidence.⁴⁰ A summary of their recommendations is listed in Table 4. Aside from the IDSA guidelines which are currently under review (last published in 2001), in line with the 2005 WHO Guidelines, **fluoroquinolones are currently recommended as first-line therapy by most international guidelines**. Of note, comparison of international guidelines reveals differing dosage ranges for ciprofloxacin; from 12.5mg/kg (eTG)³⁹ to 20mg/kg (BNF).⁴¹ The current WHO 2005 guidelines list 15mg/kg as the currently recommended dosage. Ciprofloxacin has high oral bioavailability (approximately 70%), including in malnourished children being given milk feeds, with no substantial loss by first pass metabolism. Maximum serum concentrations are attained one to two hours after oral dosing, with a half-life of approximately 4 hours in patients with normal renal function.⁴² References supporting the efficacy of a higher dose range (20mg/kg) than currently recommended (15mg/kg) were unable to be found in the literature, and due to the associated risk of adverse events when combined with other CYP3A4 inhibitors, there is no evidence-base suggesting a higher dosage of ciprofloxacin than currently recommended would be warranted in treating *Shigellosis*. Furthermore, higher MICs of fluoroquinolones requiring increased ciprofloxacin concentrations have *not* been found to be significantly associated with poorer clinical outcomes.²⁴

Guideline	Last Update	Recommendations
IDSA ³⁸	2001; update in progress	<p>Based on A-1 level of evidence [Where: A = good evidence to support a recommendation for use; and I = Evidence from at least one properly randomized, controlled trial]</p> <p>Selective therapy should be instituted for Shigellosis</p> <ul style="list-style-type: none"> • TMP-SMZ 160 + 800mg respectively (paediatric dose 5 and 25mg/kg respectively) bd for 3/7 if susceptible) <p>or</p> <ul style="list-style-type: none"> • Fluoroquinolone: eg Ciprofloxacin bd for 3/7 (paediatric dosing not listed); 300mg Ofloxacin; 400mg Norfloxacin; or 500mg Nalidixic acid 55mg/kg/day for 5/7 • Ceftriaxone 100mg/kg/day in 1 or 2 divided dose
Therapeutic Guidelines (Australia) ³⁹	2014	<p>Selective therapy for:</p> <ul style="list-style-type: none"> • Children <6 years • Institutionalised populations or food handlers • MSM • Immunosuppressed • Patients with severe disease <p>Empirical Therapy (while awaiting local sensitivities):</p> <ul style="list-style-type: none"> • Ciprofloxacin 500mg (12.5mg/kg up to 500mg) PO bd for 5 days <p>OR</p> <ul style="list-style-type: none"> • Norfloxacin 400mg (10mg/kg up to 400mg) PO bd for 5 days <p>OR</p> <ul style="list-style-type: none"> • TMP-SMZ 160+800mg (4+20mg/kg up to 160+800mg) PO bd for 5 days <p>Second-line therapy:</p> <ul style="list-style-type: none"> • Azithromycin 500mg (10mg/kg up to 500mg) PO on day 1, then 250mg (5mg/kg up to 250mg) PO daily for a further 4 days
American Academy of Pediatrics ⁹	2015	<ul style="list-style-type: none"> • Do not treat mild episodes • Selected therapy: for those with severe disease, or immunosuppressed <p>Empirical Therapy (while awaiting culture/susceptibility results): any of (not hierarchical):</p> <ul style="list-style-type: none"> • Ciprofloxacin 15mg/kg bd for 3 days • Azithromycin 12mg/kg on day 1; then 6mg/kg on day 2-4 (total course: 4 days) • Parenteral ceftriaxone (50-75mg/kg daily) for 2 to 5 days – for seriously ill patients <p>The guidelines also note that oral cephalosporins (cefixime) have been used successfully in treating shigellosis in adults.</p>

Guideline	Last Update	Recommendations
BMJ Clinical Evidence ⁴⁰	2016	<p>Selective Therapy for:</p> <ul style="list-style-type: none"> Malnourished, immunocompromised or elderly patients; food handlers, health care workers Severe disease: defined as bloody diarrhea with cramping while systemically unwell <p>Empirical Therapy (while awaiting local sensitivities):</p> <ul style="list-style-type: none"> Ciprofloxacin: 15 mg/kg (max 500mg) PO bd <p>OR</p> <ul style="list-style-type: none"> Norfloxacin: 10mg/kg (max 400 mg) PO bd <p>Second-line therapy:</p> <ul style="list-style-type: none"> Ceftriaxone: 50-100 mg/kg IM once daily (adults: 1-2 g intramuscularly once daily) <p>OR</p> <ul style="list-style-type: none"> Azithromycin: 6-20 mg/kg PO once daily <p>All therapies state 'consult with a specialist for guidance on duration of treatment'</p>
British National Formulary ⁴¹	2016	Ciprofloxacin 20mg/kg bd (higher dose than 15mg/kg previously recommended)

Table 4: Current international guidelines for the treatment of Shigellosis

5. REVIEW OF HARMS AND TOXICITY – SUMMARY OF EVIDENCE ON SAFETY

5.1. Adverse events

A 2010 systematic review of 1,748 paediatric and adult patients¹⁴ found no statistically significant differences in **adverse events** between patients taking fluoroquinolones, macrolides (including azithromycin), or beta-lactams for the treatment of Shigellosis, concluding that **all classes of currently available antibiotics to treat Shigellosis are safe**. Side effects of the currently recommended therapies for treating Shigellosis, and those which may be of consideration in the future, are highlighted in Table 5.

Antibiotic	Life threatening	Mild adverse effects, which may result in discontinuation of treatment	Other	Relevant Interactions
Fluoroquinolones: Ciprofloxacin Norfloxacin Ofloxacin	Hypersensitivity Reactions; Prolonged QT syndrome	Dyspepsia, headache, diarrhoea, vomiting, hypotension	<p>Tendinitis and tendon rupture; polyneuropathy (see text).</p> <p><i>In 2011, a systematic review of ciprofloxacin safety in paediatric patients concluded that although musculoskeletal adverse events may occur due to ciprofloxacin use (predominantly arthralgia), these events are reversible.</i>⁴³</p>	<p>-All fluoroquinolones should be used with caution in patients receiving drugs known to prolong the QT interval</p> <p>-The toxicity of fluoroquinolones is increased by the concurrent use of systemic steroidal medications</p> <p>-Fluoroquinolones' effects are reduced by the co-administration of iron- and zinc- containing products, of importance when zinc-containing products are</p>

Antibiotic	Life threatening	Mild adverse effects, which may result in discontinuation of treatment	Other	Relevant Interactions
				<i>used to treat diarrhoea in children</i> -Fluoroquinolones cause additive toxicity with non-steroidal anti-inflammatory drugs (Ibuprofen, Meloxicam, Naproxen)
Azithromycin	Hypersensitivity Reactions; Prolonged QT Syndrome	Dyspepsia, flatulence, headache, disturbance in taste, anorexia	Malaise, paraesthesia	-Macrolides are advised to be avoided with other drugs which prolong the QT interval, (including anti-malarial medications such as artemether-lumefantrine) due to the risk of ventricular arrhythmias. <u>However, azithromycin has been identified as a safer macrolide</u> (in terms of its ability to prolong the QT interval) within this class of antibiotics. -Plasma concentrations of azithromycin are increased by ritonavir -Azithromycin in combination with rifabutin results in increased side-effects of rifabutin, including neutropenia
Ceftriaxone	Hypersensitivity reactions	Diarrhoea, headache, abdominal discomfort	Transient cholestatic jaundice due to biliary sludge formation	Relevant interactions for all cephalosporins: -Increased risk of nephrotoxicity when co-administered with aminoglycosides -Enhance anticoagulant effect of coumarins
Cefixime	Hypersensitivity reactions; immune-mediated haemolytic anaemia	Flatulence, headache, abdominal pain, defecation urgency, nausea, constipation, vomiting	Transient cholestatic jaundice due to biliary sludge formation	As per ceftriaxone
Pivmecillinam	As per all penicillins: hypersensitivity reactions, serum-sickness-like reactions, anaphylaxis	Diarrhoea, joint pain, rashes, urticaria	Avoid usage in acute porphyrias	-Contraindicated for concurrent use with Sodium Valproate

Table 5: Common adverse reactions to antibiotics currently indicated to treat Shigellosis in children.^{14,41}

5.1.1. Mechanisms of cardiac risks

Previous case reports of prolongation of the QT interval have been associated with fluoroquinolones and macrolides.^{44,45} Independently, mild delays in ventricular repolarisation are clinically unnoticeable, though these antimicrobials may serve to amplify the risk for torsades de pointes (TdP), a potentially fatal polymorphic ventricular tachyarrhythmia which may present as sudden death (due to ventricular tachycardia), syncope, palpitations, seizures or asymptotically if the duration is short and terminates spontaneously.⁴⁶ Of note, the current literature identifies this risk as requiring the presence of other risk factors, as highlighted in Table 6. The predominantly reported risk factor is **co-administration of other medications which are substrates and/or inhibitors of cytochrome P450 (CYP) enzymes**, and the associated with 'metabolic liability' resultant from co-administration of medications synergistically interacting with this enzyme. This risk is enhanced by individual allelic variations in CYP3A4, the most important enzyme in human drug metabolism. CYP3A4 is responsible for the biotransformation of approximately 60% of all oxidised drugs⁴⁷ and allelic variations can result in patients being **poor metabolisers of CYP3A4 inducing medications**,⁴⁶ resulting in reduced clearance of drug substrates and increasing exposure to toxicity effects. **In conclusion, existing evidence suggests that the individual risk of cardiac arrhythmias secondary to these antimicrobials is minimal**; yet when combined with genetic propensity to poor metabolism of CYP3A4 inducing medications and co-administration with other CYP potentiators, the risk may be magnified, but it is unclear how this may affect clinical outcomes.

Another important risk factor to consider is the risk of acute renal failure in the setting of severe dehydration secondary to Shigellosis, which could result in decreased clearance and enhanced toxic effects, increasing the prolongation of the QT interval in a clinical setting.

Risk Factor	Examples
Genetic Risk Factors	Channelopathies CYP3A4 poor metaboliser
Underlying cardiac disease	Bradycardia Congestive Cardiac Failure Myocardial ischaemia Atrial fibrillation
Electrolyte derangements	Hypokalaemia Hypomagnesaemia Hypocalcaemia
Organ impairment, altering medication toxicity	Renal insufficiency Severe hepatic disease
Use of medication to increase QT liability	Concurrent CYP medications administered

Table 6: Risk factors for the development of torsades de pointes⁴⁶

5.1.2. Prolonged QT Syndrome and Azithromycin:

The predominantly reported risk for macrolide-associated TdP is the co-administration of other CYP3A4 inhibitors, resulting in increased drug toxicity. However, *azithromycin has been identified as distinguishable from other macrolides as a group in terms of its cardiac toxicity*, as it minimally inhibits CYP3A4, resulting in a lack of appreciable interaction with other CYP3A4 substrates, and is classified as **one of the safer macrolide antibiotics from a cardiac perspective**.^{46,48} In recent years, however, increasing attention has been paid to azithromycin's risks following a report of increased risk of cardiac death in a cohort of 347,795 patients aged 30-74 years of age taking azithromycin. This study found that patients taking 5 days of azithromycin, in comparison to taking no antibiotics, had an increased risk of cardiac death (hazard ratio 2.88, 95% CI 1.25-2.75, p<0.0001) as well as death from any cause (HR 1.85; 95% CI 1.25-2.75, p=0.002). However, this risk was found to be most pronounced in patients with a high baseline risk of cardiovascular disease, and there was evidence of confounding by factors associated with both azithromycin use and risk of cardiovascular disease – namely a history of smoking, high body mass index, poor diet, and low physical activity.⁴⁹ At present, published case reports of increased risk of sudden cardiac deaths in patients taking azithromycin are limited to the adult population.⁵⁰

5.1.3. Prolonged QT Syndrome and Fluoroquinolones

As with macrolides, there is interclass variability in the QT prolongation effect of fluoroquinolones. Ciprofloxacin's inhibition of CYP1A2 has been described as 'relatively inconsequential',⁴⁶ and the US Food and Drug Administration (FDA)'s Adverse Event Reporting System (AERS) supports the notion of multifactorial causes of fluoroquinolone-associated TdP, usually occurring in the context of co-administration with another QT-prolonging drug, underlying cardiac disease, renal impairment, and electrolyte anomaly.

5.1.4. Fluoroquinolone use and Polyneuropathy:

In 2013, the FDA issued a communique to specifically address the risk of peripheral neuropathy (PN) for all oral fluoroquinolones,⁵¹ predominantly in response to case reports of this adverse event,^{52,53} in the absence of large epidemiological studies.⁵⁴ The neurotoxic mechanism is thought to be through the inhibition of GABA-receptors, which occurs within days of use, and may be permanent. Between 1997 to 2012, the FDA's AERS recorded 539 reports (1% of all submitted events for fluoroquinolones) pertaining to peripheral neuropathy. A review of these reports found the majority of affected patients were females, with a median age of 48 years (range 9-100 years).⁵⁵ This evidence was further investigated by a 2014 pharmaco-epidemiological study which quantified this risk, revealing a relative risk of developing peripheral neuropathy with fluoroquinolone use of 2.07 (95% CI 1.56 to 2.74).⁵⁴ In regards to ciprofloxacin specifically, the increased risk was quantified as RR=1.93 (95% CI 1.32 to 2.82).⁵⁴ However, this research was based on a cohort of men with a mean age of 68 years, and it is impossible to extrapolate this data to the paediatric population.

An updated boxed warning was released in July 2016⁵⁵, restricting the use of fluoroquinolone antibiotics in adults with acute sinusitis, bronchitis and complicated UTI to situations in which no other alternative treatment is available. This was in response to a review of the FDA adverse event reporting system (FAERS) from 1997 to 2015, which identified 178 cases (predominantly aged 30-59 years) of apparently healthy patients who were prescribed an oral fluoroquinolone to treat acute bacterial sinusitis, bacterial exacerbation of chronic bronchitis, or uncomplicated urinary tract infections and developed 'disabling and potentially irreversible adverse reactions that appeared as a constellation of symptoms, primarily affecting the musculoskeletal system, peripheral nervous system, and central nervous system.⁵³ Long-term pain was the most commonly reported symptom. However, the FDA notes 'the benefits of fluoroquinolones outweigh these risks for treatment of serious infections caused by fluoroquinolone-susceptible bacteria'. and in the setting of global *Shigella* non-susceptibility, **the public health benefits of treatment are thought to outweigh the small (yet statistically significant) risk of this adverse event occurring.** A recent review reiterates this point and highlights the methodological weakness of previous research investing these adverse events.⁵⁶

5.1.5. Co-administration of azithromycin with artemisinin-based antimalarial drugs.

Co-administration of macrolides or quinolones with other QT prolonging agents could present a clinical risk. Again, nearly all data are from adults, often with pre-existing cardiac risks; and genetic differences between populations may limit interpretation. A 2007 review concluded that most antimalarial medications do not have significant effects on ventricular repolarisation (manifest as a prolonged QT interval), with the exception of quinidine and halofantrine;⁵⁷ rather, it is the process of recovery from malaria which is associated with significant lengthening of the QT interval which has mistakenly been ascribed to antimalarial treatment.⁵⁷ Azithromycin is a weak antimalarial that has been used in combination with several other antimalarials, or co-administered to treat non-malarial infections.

Azithromycin and chloroquine:

- In an RCT in children in 6 countries, AZCQ (30 mg/kg AZ + 10 mg/kg CQ base) or AL was administered to n=261 children. Amongst adverse events, vomiting, malaria and pruritus were more common in the AZCQ group⁵⁸

- In an RCT investigating azithromycin-chloroquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of *Plasmodium falciparum* malaria infection in pregnant women, no differences in SAEs in mothers or neonates were found.⁵⁹
- One study examined azithromycin/chloroquine in guinea pigs; there was no increase cardiac instability.⁶⁰

Azithromycin and artesunate/artemether:

- A systematic review was published in 2013 which identified one RCT involving 261 patients (as above) compared the safety of azithromycin with artemether-lumefantrine (AL) in paediatric patients.⁶¹ This study showed that children taking azithromycin have a significantly higher risk of vomiting than those on AL ($p = 0.02$). The risk of other AEs such as dizziness, convulsion, respiratory and dermatological events were not significantly different in both treatment groups. No QT effects were investigated or reported.
- In 2009, an RCT compared azithromycin plus artesunate versus artemether-lumefantrine for treatment of uncomplicated malaria in Tanzanian children ($n=129$) revealed no severe adverse events or deaths were recorded. 39 children in the AZ+AS arm and 33 in the AL arm had clinical adverse events; with the exception of gastrointestinal complaints, none were considered likely to have been due directly to the drugs, and most were probably due to intercurrent infections.⁶²

Azithromycin and piperazine:

There are no reports of QT changes for this combination. Several authors report on QT prolongation for dihydroartemisinin-piperazine without azithromycin.

- In Burkina Faso, 10,925 uncomplicated malaria patients were treated with dihydroartemisinin-piperazine.⁶³ Most patients (95%, 10,359/10,925), did not report any adverse event following at least one dose of therapy. A total of 797 adverse events were reported. The most frequently reported, by system organ classification, were infections and infestations (3.24%) and gastrointestinal disorders (1.37%). In the nested cohort, no patient had QTcF > 500ms prior to day 3. Three patients had QTcF > 500ms (509 ms, 501 ms, 538 ms) 3-4 hours after intake of the last dose. All the QTcF values in the 3 patients had returned to <500 ms at the next scheduled ECG on day 7 (470 ms, 442 ms, 411 ms). On day 3 pre- and post-dose 3, 70 and 89 patients, respectively, had a QTcF increase of ≥ 60 ms compared to their baseline, but returned to nearly baseline values on day 7.
- Piperazine-associated QT changes may be more likely to be dose related than for other antimalarials. Using high dose in adults, a trial of an accelerated two-day regimen of dihydroartemisinin/piperazine for malaria prevention halted for concern over prolonged corrected QT interval.⁶⁴

6. SUMMARY OF COMPARATIVE COST AND COST-EFFECTIVENESS

Antibiotic	Per Unit Cost	Cost per treatment course, for ~20kg child	Notes
Ciprofloxacin 15mg/kg orally Twice daily For 3 days	\$14.10 per 100ml bottle = 0.1410/mL	\$1.02	250mg/5mL suspension (250mg tablets, whilst more cheaply available, are unsuitable for young children)
Norfloxacin 10mg/kg Twice daily for 5 days	\$0.0246 per tablet (per 100 tablet packet)	Not yet available as suspension	Not available as suspension Price as per 400mg tablet
Oxfloxacin	\$0.058/tablet (per 100 tablet packet)	Not yet available as suspension	Not available as suspension Price as per 200mg tablet
Azithromycin 12mg/kg on day 1; then 6mg/kg on day 2-4	Median Price: \$0.058/mL	\$0.87	200mg/5mL Suspension
Cefixime 8mg/kg/day for 5 days	\$1.40 per 30ml bottle = \$0.0467/mL	\$1.87	100mg/5mL Suspension
Ceftriaxone 50-100mg/kg/day for 5 days	Median price: 1 vial of 1g Ceftriaxone = \$0.4192/vial	\$2.10-\$4.19	Parenteral administration

Table 7: Comparative costs of medications used to treat Shigellosis (prices in USD)⁶⁵

The Management Sciences for Health (MSH) International Drug Price Indicator Guide indicates that the current first-line therapy, ciprofloxacin, remains a slightly more expensive treatment option for Shigellosis than azithromycin. While other fluoroquinolones may be treatment options, until paediatric suspension formulations are available, they are not viable alternatives. Ceftriaxone is more expensive and costs are underestimated due to the additional equipment (syringes, vials and qualified personnel) required for its administration. Cefixime, a possible alternative as an oral third-generation cephalosporin in the future once clinical trials are completed, is an option.

A comprehensive review of the cost-effectiveness of preventative interventions against diarrhoeal diseases in children (comparing breastfeeding promotion, water and sanitation, and rotavirus/cholera/measles immunisation) has previously been published.⁶⁶

7. THE SPREAD OF MULTI-DRUG RESISTANCE AND NEED FOR IMPROVED SURVEILLANCE

The literature suggests that **antibiotic resistance is an increasing challenge for the therapeutic management of Shigellosis**, as was recognised by the WHO prioritising ciprofloxacin-resistant *Shigella* as a matter of current international focus on AMR.⁶⁷ There are multiple mechanisms by which this may occur. In *Shigellae* species, antimicrobial resistance is often due to class 1 and class 2 integrons that contain resistance gene cassettes, which are mobile and transferrable from one bacterium to another, providing a flexible approach for bacteria to adapt to the environmental pressure caused by antibiotics. This mechanism of action may account for the dissemination of resistant genes and the emergence of MDR strains, and explain why *Shigellae* resistance patterns vary worldwide – as the distribution of integrons varies according to the species and resistance phenotype (with *S. sonnei* and *S. boydii* strains

containing a single class 2 integron, while *S. flexneri* and *S. dysenteriae* carry a class 1 integron, often in combination with a class 2 integron which increases the propensity of dissemination of MDR strains of *Shigella*).⁸ **This underpins the importance of antimicrobial resistance surveillance programmes, including documenting changes in regionally prevalent species and linking susceptibility patterns to patient characteristics and outcomes.**

7.1. Resistance to fluoroquinolones:

The primary target of fluoroquinolones is the DNA gyrase, a type II topoisomerase essential for DNA replication and transcription, and mutations in the *gyrA* gene increase the MICs of fluoroquinolones for *Shigellae* and other Enterobacteriaceae (while plasmid-mediated quinolone resistance genes can also be acquired.²⁴ Of concern, **complete ciprofloxacin resistance (MIC \geq 4 mg/L) has recently been reported** in both domestic and imported *S. sonnei* isolates in the USA, Vietnam and elsewhere.⁶⁸⁻⁷⁰ Furthermore, patients infected with fluoroquinolone-resistant *Shigella* infections have been shown to have a longer duration of diarrhoea compared with those infected with fluoroquinolone-susceptible strains.^{71,72} Ciprofloxacin resistance should continue to be closely monitored and non-susceptibility should be reported where data is available.

7.2. Resistance to cephalosporins:

Cephalosporin resistance is also of concern, arising from the production of plasmid-mediated β -lactamase.⁸ Resistance to third-generation cephalosporins due to the production of extended-spectrum β -lactamases (ESBLs), which confer resistance to all β -lactamases (except cephamycins and carbapenems) is an increasingly prevalent issue with documented resistance occurring in recent laboratory analyses in Asia.^{21,73-75} ESBL resistance in *Shigella* spp. needs to be closely monitored in light of the necessity of treatment with expensive carbapenems, one of our last options for treating multi-resistant gram-negative organisms. There has been a considerable increase in the prevalence of extended spectrum beta lactamase (ESSBL) resistance, including in *Shigellae*. Thus, prior reports of efficacy of ceftriaxone and cefixime may not reflect today's situation. Furthermore, use of these agents rapidly induces ESBL and resistance to other antibiotic classes.

8. ONGOING TRIALS

Review of international trial registries <http://www.who.int/ictrp/en/>; <https://clinicaltrials.gov/>; <http://www.isrctn.com/>; <http://www.anzctr.org.au/>; <https://www.clinicaltrialsregister.eu/>) has confirmed that there are no current trials investigating the clinical therapeutic treatment of Shigellosis in adult or paediatric patients.

9. DISCUSSION & FURTHER RESEARCH:

Shigella is a gram-negative Enterobacteriaceae responsible for 165 million diarrhoeal episodes each year, of which 99% occur in developing countries, and 69% among the paediatric population. 1.1 million deaths are caused by Shigellosis each year, 61% of which occur in children less than 5 years of age. With effective antibiotic therapy, clinical improvement occurs within 48 hours, diminishing the risk of mortality and decreasing transmission by eliminating *Shigella* from the stool. The WHO's 2005 'Guidelines for the control of shigellosis, including epidemics due to *Shigella dysenteriae* type 1' listed the fluoroquinolone ciprofloxacin (15mg/kg orally twice daily for 3 days) as first-line treatment for shigellosis in children, with (more expensive and less available) pivmecillinam (amdinocillin pivoxil) and (parenteral) ceftriaxone listed as second-line therapy when local strains were known to be resistant to ciprofloxacin. The macrolide azithromycin was listed as a possible therapy for adults.

This systematic review (of the international literature and current international guidelines) has revealed low-quality evidence supporting the current antimicrobial guideline's effectiveness against serious mortality and morbidity; although resistance is gradually increasing among both fluoroquinolones and cephalosporins. A large proportion of this evidence is based on *in vitro* studies which do not necessarily correspond with clinical outcomes; while a systematic review which evaluated ciprofloxacin, pivmecillinam and ceftriaxone efficacy together found clinical efficacy but did not evaluate individual drugs.¹⁴

Azithromycin is currently listed as a first⁹ and second-line therapy^{39,40} in a number of international guidelines for treating Shigellosis in children. While there have been no published trials comparing the efficacy of azithromycin to ciprofloxacin to treat *Shigellosis* in children, previous trials in adults have revealed similar efficacy to ciprofloxacin and higher *in vitro* susceptibility. However, there are increasing reports of azithromycin-resistant strains documented by the CDC.⁷⁶ In areas where ciprofloxacin resistance is evident, azithromycin may be an appropriate second-line alternative therapy due to its oral administration and affordability. Safety concerns – predominantly based on adult data which is not necessarily able to be extrapolated to the paediatric population – have been documented in regards to both ciprofloxacin use (risk of polyneuropathy) and azithromycin (risk of prolonged QT syndrome; although this risk is lower in azithromycin than that among other macrolide antibiotics).

Of note, there is a lack of current research assessing the clinical treatment of Shigellosis in paediatric or adult patients, despite rising antimicrobial resistance rates worldwide. Prior research has investigated the current WHO guidelines together, rather than assessing individual therapies. Research investigating non-susceptibility of Shigellosis – particularly community-acquired strains – is urgently required; and *in vitro* non-susceptibility studies need to be correlated with clinical outcomes. Further randomised controlled trials (RCTs) adhering to CONSORT guidelines are required to guide future treatment options in Shigellosis, especially in populations at high case-fatality risk (such as malnourished or HIV positive children). The efficacy of affordable oral cephalosporins (cefixime) to treat Shigellosis should be a priority research area; specifically, a large RCT in children in the Asia-Africa region should compare the efficacy of ciprofloxacin, azithromycin and cefixime as the first-line treatment of Shigellosis in children, assessing MICs in relation to treatment outcomes.

10. CONCLUSIONS

- The current WHO guidelines supporting the use of fluoroquinolones (first line), beta-lactams (second-line) and cephalosporins (second-line) accord with the currently available evidence and other international guidelines – **there is no strong reason to change this guidance.**
- Azithromycin is currently listed in WHO guidelines as a second-line therapy for adults with Shigellosis and as first-line for children in other guidelines. Due to evidence of increasing resistance worldwide and the uncertain potential to cause cardiac conduction problems when co-administered with other CYP3A4 inducing drugs, we do not recommend upgrading this medication to a first-line therapy without further trial evidence of clinical efficacy and safety for children. **Listing azithromycin as a second-line therapy may be appropriate for regions with known high-rates of ciprofloxacin non-susceptibility.**
- While there is very limited evidence to suggest azithromycin is associated with an increased risk of cardiac arrhythmias in paediatric patients, this has been documented in adult populations with underlying cardiovascular risk factors in high-income settings. However, research suggests azithromycin is safer than other macrolide antibiotics from a cardiac point of view.
- Peripheral (poly)neuropathy is a rare but recognised adverse effect of fluoroquinolone use, including ciprofloxacin
- Most available data reports **resistance patterns which are up to a decade old**, and are therefore likely underestimates, and **do not necessarily correlate with clinical outcomes.**
- There is limited research examining the efficacy of individual antibiotics in developing country settings, and a vast amount of published research analyses ciprofloxacin, pivmecillinam and ceftriaxone together, rather than providing individual susceptibility data.
- There is a lack of evidence assessing non-susceptibility of community-acquired strains. Almost all published research pertains to microbiological data from hospital-based settings. Research investigating non-susceptibility of community-acquired Shigellosis is urgently required.
- There is increasing evidence of resistance emerging to third-generation cephalosporins in the Asia-Africa region. There is also increasing evidence of ciprofloxacin resistance emerging in the Asia-Africa region, although wide confidence intervals reported in these reviews indicate imprecision of these estimates, and further information is necessary.
- **Research assessing antimicrobial non-susceptibility to individual antibiotics that includes patient characteristics and outcomes is urgently required.**
- Where possible, microscopy and susceptibility testing should continue to be of paramount importance prior to commencing therapy; or on a local ‘sampling’ basis, to guide individual therapy and provide information on species prevalence and resistance data
- Further randomised controlled trials which adhere to the CONSORT guidelines are required to address current non-susceptibility patterns, and the class (or classes) of antibiotics most appropriate to treat Shigellosis in populations at risk of high case-fatality (such as malnourished or HIV-infected children, and patients presenting with serious complications due to Shigellosis), in whom such trials are lacking.
- The efficacy of alternative fluoroquinolones (norfloxacin) to treat Shigellosis should be priority research areas; however, their utility is currently limited by the lack of availability of suspension formulations.
- The efficacy of oral cephalosporins (cefixime) to treat Shigellosis should be a priority research area. This is an affordable medication which provides ease of administration compared to the currently

recommended parenteral ceftriaxone. Trials need to be conducted in relation to antimicrobial susceptibility patterns for Shigella, but also address risks of exacerbating resistance in other intestinal bacteria, especially Extended Spectrum Beta Lactamase.

- Specifically, **a large trial in children in the Asia-Africa region should compare the efficacy of ciprofloxacin, azithromycin and an oral cephalosporin as first line treatment**, as well as assessing MICs in relation to treatment outcomes. In a large trial, careful safety reporting of adverse events should be undertaken. However, simply identifying that some children develop a mildly prolonged QT interval will not advance policy decisions.

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	Author	Year	Title	Setting	Population	Method	Findings	Level of Evidence
1	Das, J. Ali, A. Salam, R. Bhutta, Z. ¹	2013	Antibiotics for the treatment of Cholera, Shigella and Cryptosporidium in children	Systematic Review and Meta-Analysis (international)	Children <16 years 48 papers relevant to Shigella were included; of which 47 were from developing country settings All studies were hospital-based	The CHERG standard rules were applied to determine the final effect of treatment with antibiotics on diarrhoea morbidity and mortality Studies were included if they reported the effect of antibiotics on morbidity and mortality associated with diarrhoea due to Cholera, Shigella and cryptosporidiosis in children, as observed by clinical and bacteriological failure and mortality. There were no studies that compared antibiotics to placebo or a control group, so studies with an antibiotic comparison group were also included. Only studies with a confirmed diagnosis of the respective infection and on immunocompetent patients were included.	-Using clinical failure rates as a proxy for <i>Shigella</i> deaths (as there was no data on mortality), the authors propose that treatment for <i>Shigella</i> dysentery with antibiotics results in an 82% (67-99%) <u>reduction in diarrhoea mortality</u> due to <i>Shigella</i> . - <u>Bacteriological Failure</u> : Antibiotics (including Ciprofloxacin, Pivmecillinam and Ceftriaxone) successfully clear <i>Shigella</i> pathogens in 96% (88-99%) of cases -The overall conclusion is that there is strong evidence of effectiveness against serious mortality and morbidity -All antimicrobials were analysed together	A
2	Gu et al. ²	2012	Comparison of the prevalence and changing resistance to nalidixic acid and ciprofloxacin of Shigella between Europe-America and Asia-Africa from 1998 to 2009.	Systematic review comparing Africa-Asia region with Europe-America	N=26,877 specimens from adults and children in LMIC and HIC	-SR for articles published between 1998 - 2011 using search strategy 'Bacterial surveillance' OR 'antimicrobial resistance' OR 'bacterial resistance' AND 'shigella' -102 studies met inclusion criteria, LMIC and HIC all included -In all the studies collected, a total of 26,877 isolates were positive for <i>Shigella</i> , amongst which 15,731 isolates had information about prevalence of subtypes.	- The predominant species isolated was S.sonnei , representing 8,900 (56.6%) of total isolates, followed by <i>S.flexneri</i> (5,749 isolates, 36.5%); <i>S.boydii</i> (601 isolates, 3.8%) and <i>S.dysenteriae</i> (481 isolates, 3.1%) - Quinolone resistance in Asia-Africa: • NALIDIXIC ACID: Resistance to nalidixic acid increased gradually from 12.1% (95% CI 4.3-23.2%) from 1998-2000, to 64.5% (13.8-99.3%) in 2007-2009; a 5.3-fold increase in resistance rates • CIPROFLOXACIN: Resistance to Ciprofloxacin increased from 0.6% (0.2-1.3%) in 1998-2000 to 29.1% (0.9-74.8%) in 2007-2009; a 49-fold	A

						<p>increase in resistance over 12 years</p> <ul style="list-style-type: none"> • Overall rates are much higher than those documented in: <p>Quinolone resistance in Europe-America:</p> <ul style="list-style-type: none"> • NALIDIXIC ACID: 1.3% (0.6-2.1) 1998-2000 to 2.1% (1.3-3.0) in 2007-2009 • CIPROFLOXACIN: 0.0% (1998-2000) to 0.6% (0.2-1.2%) in 2007-2009 • le SIGNIFICANTLY lower than resistance rate increases in Africa-Asia • S. Flexneri showed higher resistance rates than S. Sonnei to Ciprofloxacin, with a general upward trend in resistance over time internationally • In Asia-Africa, the resistance patterns differed – S.Sonnei appeared to be more resistant than S.Flexneri to nalidixic acid • Resistance rates to quinolones were much greater in children than adults, with the respective rates being 33.05% (23.9-42.8) vs 14.3% (8.30-21.7) for nalidixic acid, and 7.5% (4.3-11.5) vs 3.6% (2.2-5.3) for ciprofloxacin <p>-“Owing to widespread use of nalidixic acid as the first-line agent for empirical treatment of infectious diarrhoea, resistance to nalidixic acid in Asian–African countries increased to 64.5% (95% CI 13.8–99.3%) in 2007–2009. Thus, this drug should no longer be considered appropriate empirical therapy”</p> <p>-“Progressively increasing resistance to ciprofloxacin is still a serious cause of concern and several studies have emphasised that most nalidixic acid-resistant strains exhibit some degree of cross-resistance to ciprofloxacin”</p>	
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3	Gu et al ³	2013	Prevalence and trends of aminoglycoside resistance in <i>Shigella</i> worldwide, 1999-2010.	Systematic review and meta-analysis evaluating aminoglycoside resistance in <i>Shigella</i> , Asia-Africa v's Europe-America	Adults and Children	3,176 publications were retrieved from MEDLINE and EMBASE reported from 1999 to 2012, of which 68 met the inclusion criteria	<ul style="list-style-type: none"> • The summarized prevalence of gentamicin, kanamycin and amikacin resistance was found to be 3.95% (95%CI: 3.59%-4.22%) (n/N=937/14,059), 6.88% (6.36%-7.43%) (n/N=1,106/8,647) and 1.29% (0.97%-1.68%) (n/N=432/8,614), respectively. Importantly, evident heterogeneity was observed ($P < 0.001$). • The most common drug resistance was observed for kanamycin. Among kanamycin resistance, the highest drug resistance rate by geographic areas was found in Asia with a prevalence of 16.78% (7.58%-28.71%). • Similarly, the most common resistance was observed for 2005-2007 and <i>S. flexneri</i> with a summarized combined prevalence of 12.05% (11.18%-14.21%) and 9.25% (7.69%-10.96%), respectively. • A lower prevalence of gentamicin resistance was found in European-American countries at 0.68% (0.39%-1.05%). • "After analyzing the study data on years, we observed a minimal change in the resistance prevalence of gentamicin, from 0.25% (0.04%-0.64%) to 0.84% (0.08%-2.40%) in European-American countries, in contrast to data in Asian-African countries, which fluctuated from 6.05% (1.18%-14.28%) to 20.83% (12.67%-30.40%). " • "It is worth noting that the resistance prevalence of gentamicin increased annually in Asian-African countries, while the resistance prevalence decreased year by year in European-American countries": The prevalence of gentamicin resistance in Asian-African countries increased 	A
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4	Gu et al. ⁴	2015	Comparison of resistance to third-generation	Europe-America and Asia-Africa	Adults and children	-A systematic review was conducted to compare resistance to 3 rd generation	<ul style="list-style-type: none"> • In Asia-Africa, the prevalence of resistance of total and different subtypes to ceftriaxone, cefotaxime 	A

		<p>cephalosporins in <i>Shigella</i> between Europe-America and Asia-Africa from 1999-2012</p>			<p>cephalosporins in <i>Shigella</i> strains between Europe-America and Asia-Africa from 1998-2012</p> <p>-Only high quality studies were included for analysis (defined as prospective cohort or retrospective consecutive cohort studies; where susceptibility tests were conducted according to CLSI guidelines with external quality control). 104 articles met these inclusion criteria.</p>	<p>and ceftazidime increased markedly over the study period, with a total prevalence of resistance up to 14.2% [95% confidence interval (CI) 3.9–29.4], 22.6% (95% CI 4.8–48.6) and 6.2% (95% CI 3.8–9.1) during 2010–2012, respectively.</p> <ul style="list-style-type: none"> • By contrast, resistance rates to these TGCs in Europe-America remained relatively low – less than 1.0% during the 15 years • A noticeable finding was that certain countries both in Europe-America and Asia-Africa, had a rapid rising trend in the prevalence of resistance of <i>S. sonnei</i>, which even outnumbered <i>S. flexneri</i> in some periods • Comparison between countries showed that currently the most serious problem concerning resistance to these TGCs appeared in Vietnam, especially for ceftriaxone, China, especially for cefotaxime and Iran, especially for ceftazidime. • Shifts in the prevalent serogroups and changing resistance patterns in antimicrobial susceptibilities in <i>Shigella</i> are posing major difficulties in determination of an appropriate drug for the treatment of shigellosis • “Based on our meta-analyses, two main recommendations can be given for empirical antibiotic therapy. First, the current situation in Europe-America supports the use of ceftriaxone and cefotaxime for treating shigellosis according to the relatively lower prevalence of resistance to the study drugs (although a mild upward trend should be noticed). To some extent, data suggest that ceftriaxone and cefotaxime may not be appropriate for treating shigellosis in Asia- 	
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5	Traa, B. et al ⁵	2010	Antibiotics for the treatment of dysentery in children.	<p>-Systematic Review</p> <p>-Developing Countries</p> <p>-All studies were conducted in clinical or hospital settings</p>	Children aged <16years	<p>-Systematic Review investigating the effect of Ciprofloxacin, Ceftriaxone and Pivmecillinam for the treatment of dysentery in children in developing countries; CHERG Standard Rules were applied</p> <p>-8 papers were selected for abstraction; 4 reported on bacteriological failure and 5 reported on bacteriological relapse</p> <p>-All studies were RCTs which were judged to be of good quality</p>	<p>Africa.</p> <ul style="list-style-type: none"> • Treatment with ciprofloxacin, ceftriaxone or pivmecillinam resulted in a clinical failure rate of 0.1% (95% CI -0.2 to 0.5% - not significant) • Treatment with ciprofloxacin, ceftriaxone or pivmecillinam resulted in a cure rate of >99% while assessing clinical failure, bacteriological failure and bacteriological relapse • “Therefore, the antibiotics recommended by the WHO are effective in reducing the clinical and bacteriological signs and symptoms of dysentery and thus can be expected to decrease diarrhea mortality attributable to dysentery” • NB: The methods of susceptibility testing was not discussed and treatment benefit was summarized for all therapies together 	B
6	Von Seidlein ⁶	2006	A Multicentre Study of Shigella Diarrhoea in Six Asian Countries: Disease Burden, Clinical Manifestations, and Microbiology	Surveillance of 600,000 persons of all ages	Bangladesh, China, Pakistan, Indonesia, Vietnam and Thailand	<p>Shigella was isolated from 2,927 (5%) of 56,958 diarrhoea episodes detected between 2000 and 2004.</p> <p>Swabs were inoculated in MacConkey agar and <i>Salmonella-Shigella</i> agar and incubated overnight then checked for non-lactose fermenting enteropathogens.</p> <p>Antimicrobial sensitivity testing against ampicillin, cotrimoxazole, nalidixic acid and ciprofloxacin was performed by disk diffusion following CLS methods, and subject to external laboratory validation</p>	<ul style="list-style-type: none"> • The overall incidence of treated shigellosis was 2.1 episodes per 1,000 residents per year in all ages and 13.2/1,000/y in children under 60 months old. • S. flexneri was the most frequently isolated Shigella species (1,976/2,927 [68%]) in all sites except in Thailand, where <i>S. sonnei</i> was most frequently detected (124/146 [85%]). • The majority of <i>S. flexneri</i> isolates in each site were resistant to amoxicillin and cotrimoxazole. Ciprofloxacin-resistant <i>S. flexneri</i> isolates were identified in China (18/305 [6%]), Pakistan (8/242 [3%]), and Vietnam (5/282 [2%]) 	B

7	Vinh et al ⁷	2011	<p>A multi-centre randomized trial to assess the efficacy of Gatifloxacin vs Ciprofloxacin for the treatment of Shigellosis in Vietnamese children</p>	Vietnam	<p>n=494 children <15years admitted to a paediatric Ward with a history of passing bloody or mucoid stools, with or without abdominal pain, tenesmus or fever for <seventy-two hours prior to admission</p> <p>-EXCLUSION CRITERIA = any prior treatment with a fluoroquinolone during the current bout of disease, or children with a trophozoite or <i>Entamoeba histolytica</i> present in their stool on microscopic examination</p>	<p>Randomised, open-label, controlled trial with two parallel arms at two hospitals in southern Vietnam.</p> <p>-The study was designed as a superiority trial and children with dysentery meeting the inclusion criteria were invited to participate.</p> <p>-Participants received either gatifloxacin (10 mg/kg/day) in a single daily dose for 3 days or ciprofloxacin (30 mg/kg/day) in two divided doses for 3 days.</p> <p>-The primary outcome measure was treatment failure; secondary outcome measures were time to the cessation of individual symptoms.</p> <p>-494 patients were randomized to receive either gatifloxacin (n = 249) or ciprofloxacin (n = 245), of which 107 had a positive <i>Shigella</i> stool culture</p>	<ul style="list-style-type: none"> • "We could not demonstrate superiority of gatifloxacin and observed similar clinical failure rate in both groups (gatifloxacin; 12.0% and ciprofloxacin; 11.0%, p = 0.72)." • The median (inter-quartile range) time from illness onset to cessation of all symptoms was 95 (66–126) hours for gatifloxacin recipients and 93 (68–120) hours for the ciprofloxacin recipients (HR [95%CI] = 0.98 [0.82–1.17], p = 0.83). • Gatifloxacin showed a similar efficacy of both drugs in the treatment of childhood dysentery, including those with a stool culture confirmed <i>Shigella</i> infection. • However, gatifloxacin has a longer half-life than ciprofloxacin and the once-a-day administration may be considered more convenient than twice-a-day regime of ciprofloxacin. • Data show similar overall risks of treatment failure in the 2 treatment groups (11% in the ciprofloxacin group versus 12%) • The most commonly isolated <i>Shigella</i> species here was S. sonnei • <i>S. dysenteriae</i> causes a considerably more severe syndrome than <i>S. sonnei</i>, which is largely associated with the secretion of shiga toxin • These data suggest that whilst there has been a notable increase in MIC to nalidixic acid in <i>Shigella</i> in Vietnam over the last 10 years, it may not yet be substantial enough to hinder the bactericidal effect of ciprofloxacin in vivo. • A similar effect of both antimicrobial agents, despite gatifloxacin having greater in vivo activity, supports the theory of a less severe infection, which may not, in all cases, require an antimicrobial for the cessation of 	B
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							<p>symptoms. Alternatively, <i>Shigella</i> may respond in an atypical manner to gatifloxacin, with respect to other Gram- negative organisms, and mutations in the <i>gyrA</i> and <i>parC</i> gene may have a greater effect on reducing the potency of the antimicrobial agent.</p> <ul style="list-style-type: none"> "We conclude that in Vietnam, where nalidixic acid resistant <i>Shigellae</i> are highly prevalent, ciprofloxacin and gatifloxacin are similarly effective for the treatment of acute shigellosis" 	
8	Thompson et al ⁸	2016	Clinical implications of reduced susceptibility to fluoroquinolones in paediatric <i>Shigella sonnei</i> and <i>Shigella flexneri</i> infections	Vietnam	<p>N=490 paediatric patients <15 years admitted to tertiary units in Vietnam</p> <p>-Clinical information and bacterial isolates were derived from a randomized controlled trial comparing gatifloxacin with ciprofloxacin (above, Vinh et al.) for the treatment of paediatric shigellosis.</p> <p>-Time-kill experiments were performed to evaluate the impact of MIC on the in-vitro growth of <i>Shigella</i> and Cox regression modelling was used to compare clinical outcome between treatments and <i>Shigella</i> species.</p> <p>-Patients were excluded if they had received any fluoroquinolones within the time of this bacterial illness.</p> <p>-Stool samples were collected on admission and standard microbiological techniques were employed to identify <i>Shigella</i> and <i>Salmonella</i> isolates</p> <p>-Antimicrobial susceptibility testing was performed by disc diffusion following methods prescribed by the CLSI</p> <p>-MICs were calculated by Etest as per the manufacturer's</p>	<p>-Clinical information and bacterial isolates were derived from a randomized controlled trial comparing gatifloxacin with ciprofloxacin (above, Vinh et al.) for the treatment of paediatric shigellosis.</p> <p>-Time-kill experiments were performed to evaluate the impact of MIC on the in-vitro growth of <i>Shigella</i> and Cox regression modelling was used to compare clinical outcome between treatments and <i>Shigella</i> species.</p> <p>-Patients were excluded if they had received any fluoroquinolones within the time of this bacterial illness.</p> <p>-Stool samples were collected on admission and standard microbiological techniques were employed to identify <i>Shigella</i> and <i>Salmonella</i> isolates</p> <p>-Antimicrobial susceptibility testing was performed by disc diffusion following methods prescribed by the CLSI</p> <p>-MICs were calculated by Etest as per the manufacturer's</p>	<ul style="list-style-type: none"> <i>Shigella flexneri</i> patients treated with gatifloxacin had significantly worse outcomes than those treated with ciprofloxacin. However, the MICs of fluoroquinolones were not significantly associated with poorer outcome. The presence of S83L and A87T mutations in the <i>gyrA</i> gene significantly increased MICs of fluoroquinolones. Elevated MICs and the presence of the <i>qnrS</i> gene allowed <i>Shigella</i> to replicate efficiently in vitro in high concentrations of ciprofloxacin. Conclusions: We found that below the CLSI breakpoint, there was no association between MIC and clinical outcome in paediatric shigellosis infections. However, <i>S. flexneri</i> patients had worse clinical outcomes when treated with gatifloxacin in this study regardless of MIC. <i>Shigella</i> harbouring the <i>qnrS</i> gene are able to replicate efficiently in high concentrations of ciprofloxacin and we hypothesize that such strains possess a competitive advantage against fluoroquinolone-susceptible 	C

						<p>instructions (AB Biodisk, Sweden).</p> <p>-Strains that were identified as resistant to ceftriaxone were subjected to further phenotypic tests to confirm ESBL production using discs containing only cefotaxime (30 mg) and both cefotaxime and ceftazidime combined with clavulanic acid (10 mg), according to current CLSI guidelines</p>	<p>strains due to enhanced shedding and transmission.</p> <ul style="list-style-type: none"> NOTE that data was collected between 2006-2009 	
9	Christopher, P. David, K. John, S. Sankarapandian, V. ⁹	2010	Antibiotic therapy for Shigella dysentery	Systematic review (international)	<p>-16 RCTs met the inclusion criteria, which totalled N=1748 (children and adult) participants based on clinical symptoms of dysentery, prior to bacteriological confirmation</p>	<p>-Of the 16 RCTs included, this was composed of 2 RCTs comparing antibiotics and placebo v's no drug; and 14 RCTs comparing effectiveness of different antibiotic regimens for treatment of <i>Shigella</i></p> <p>-All RCTs were low- to moderate-quality evidence: Of the 16 trials, 7 were at risk of bias due to inadequate allocation concealment; and 12 due to incomplete reporting of outcome data</p> <p>-Limited data from one 3-armed trial of people with moderately severe illness suggest that antibiotics reduce the episodes of diarrhea at follow-up</p> <p>-Many RCTs included in the review were conducted prior to 1990 and included Abx no longer used currently due to high resistance (cotrimoxazole, ampicillin, nalidixic acid)</p> <p>-Reviewed both developed and developing countries, limiting generalisability of findings to developing country settings</p>	<p>-There was insufficient evidence to consider any class of antibiotic superior in efficacy in treating Shigella dysentery, but heterogeneity for some comparison limits confidence in the results</p> <p>-There were no statistically significant differences in adverse events between participants taking macrolides, beta-lactams or fluoroquinolones, leading the authors to conclude that all antibiotics were safe</p> <p>-There was inadequate evidence regarding the role of antibiotics in prevention of complications]</p> <p>-CONCLUSION: Low- to moderate-quality evidence that antibiotic therapy significantly reduces the number of children with dysentery on follow-up compared to no antibiotic</p>	C

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