Identification and management of Shigella infection in children with diarrhoea: a systematic review and meta-analysis

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Summary
Background Shigella infections are a leading cause of diarrhoeal death among children in low-income and middle-income countries. WHO guidelines reserve antibiotics for treating children with dysentery. Reliance on dysentery for identification and management of Shigella infection might miss an opportunity to reduce Shigella-associated morbidity and mortality. We aimed to systematically review and evaluate Shigella-associated and dysentery-associated mortality, the diagnostic value of dysentery for the identification of Shigella infection, and the efficacy of antibiotics for children with Shigella or dysentery, or both.

Methods We did three systematic reviews (for mortality, diagnostic value, and antibiotic treatment of Shigella and dysentery), and meta-analyses where appropriate, of studies in resource-limited settings. We searched MEDLINE, Embase, and LILACS database for studies published before Jan 1, 2017, in English, French, and Spanish. We included studies of human beings with diarrhoea and accepted all study-specific definitions of dysentery. For the mortality and diagnostic value searches, we excluded studies that did not include an effect estimate or data necessary to calculate this estimate. The search for treatment included only randomised controlled trials that were done after Jan 1, 1980, and assessed antibiotics in children (aged <18 years) with dysentery or laboratory-confirmed Shigella. We extracted or calculated odds ratios (ORs) and 95% CIs for relative mortality and did random-effects meta-analysis to arrive at pooled ORs. We calculated 95% CIs assuming a binomial distribution and did random-effects meta-regression of log-transformed sensitivity and specificity estimates for diagnostic value. We assessed the heterogeneity of papers included in these meta-analyses using the I² statistic and evaluated publication bias using funnel plots. This review is registered with PROSPERO (CRD42017063896).

Findings 3649 papers were identified and 60 studies were included for analyses: 13 for mortality, 27 for diagnostic value, and 20 for treatment. Shigella infection was associated with mortality (pooled OR 2.8, 95% CI 1.6–4.8; p=0.000) whereas dysentery was not associated with mortality (1.3, 0.7–2.3; p=0.37). Between 1977 and 2016, dysentery identified 1.9–85.9% of confirmed Shigella infections, with sensitivity decreasing over time (p=0.04). Ten (50%) of 20 included antibiotic trials were among children with dysentery, none were placebo-controlled, and two (10%) evaluated antibiotics no longer recommended for acute infectious diarrhoea. Ciprofloxacin showed superior microbiological, but not clinical, effectiveness compared with pivmecillinam, and no superior microbiological and clinical effectiveness compared with gatifloxacin. Substantial heterogeneity was reported for meta-analyses of the Shigella-associated mortality studies (I²=78.3%) and dysentery-associated mortality studies (I²=73.2%). Too few mortality studies were identified to meaningfully test for publication bias. No evidence of publication bias was found in this analysis of studies of diagnostic value.

Interpretation Current WHO guidelines appear to manage dysentery effectively, but might miss opportunities to reduce mortality among children infected with Shigella who present without bloody stool. Further studies should quantify potential decreases in mortality and morbidity associated with antibiotic therapy for children with non-dysenteric Shigella infection.

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Introduction In resource-limited settings, Shigella species (Shigella) are a leading cause of childhood diarrhoea and have case-fatality rates of up to 28% in children with severe disease. The manifestations of Shigella can include watery diarrhoea, dysentery, and complications such as encephalopathy. WHO diarrhoea guidelines focus on rehydration, and the provision of zinc, and they specifically address Shigella infections by recommending ciprofloxacin be given to children with dysentery, defined as observed presence or caregiver report of blood in the patient’s stool. Stool culture is unavailable in many resource-limited settings; therefore, this recommendation is based on evidence showing a strong
association between *Shigella dysenteriae* type 1 and dysentery, and the documented efficacy of antibiotics for treating dysenteric *Shigella*. However, substantial mortality and morbidity are observed in children with non-dysenteric *Shigella* infection and these children might benefit from prompt antibiotic treatment.

The *Shigella* genus includes four species—*S dysenteriae*, *S sonnei*, *S flexneri*, and *S boydii*—and unique serotypes, such as *S dysenteriae* type 1. These species vary in their tendency to cause dysentery. *S dysenteriae* type 1 and, to a lesser extent, *S flexneri* are most strongly associated with bloody stool. However, recent studies have shown a global decline in the incidence of *S dysenteriae* type 1, which can cause epidemic or pandemic dysentery. In the Global Enteric Multicenter Study of 9439 children with moderate-to-severe diarrhoea in seven countries between 2007 and 2011, no cases of *S dysenteriae* type 1 were identified, and this serotype was not identified in 56,958 diarrhoeal episodes recorded in another multicountry study. Surveillance data from Bangladesh have not documented a case of *S dysenteriae* type 1 infection since 2005, while the prevalence of other *Shigella* serotypes has remained relatively constant. This change in species prevalence might result in fewer children with *Shigella* infection presenting with bloody stool; therefore, fewer children might receive antibiotic treatment with current guidelines.

Because of the ongoing contribution of *Shigella* to childhood diarrhoeal morbidity and mortality, and the changing epidemiology of *Shigella* globally, we aimed to examine evidence supporting dysentery-based *Shigella* management and to systematically review the available literature to assess associations between symptomatic *Shigella* infection, dysentery, and death. We also aimed to examine the diagnostic value of dysentery for identifying individuals infected with *Shigella* and the efficacy of antibiotics for children with *Shigella* or dysentery, or both.

**Methods**

**Search strategy and selection criteria**

We did systematic searches using MEDLINE, Embase, and LILACS database for studies published before Jan 1, 2017. The first search focused on *Shigella*-associated and dysentery-associated mortality (mortality), the second search focused on the use of dysentery as a marker of *Shigella* infection (diagnostic value), and the third search focused on the treatment of *Shigella* infections and dysentery (treatment). The appendix (p 1) shows the full list of search terms used. We considered in all three searches papers published in English, French, and Spanish that reported data from low-income or middle-income countries (as defined by the World Bank, June, 2015), and we only included studies of human beings with diarrhoea. We accepted all study-specific definitions of dysentery, including maternal report of blood with or without mucus in the stool or direct observation at diarrhoea presentation.

For the mortality search, we included studies of any design that reported associations between *Shigella* or dysentery and mortality, or the case fatalities of different *Shigella* species; and we excluded studies that did not include an effect estimate or data necessary to calculate this estimate. In the diagnostic value search, we included studies of any design from which the proportion of participants with laboratory-confirmed *Shigella* infections and dysentery (sensitivity) or the proportion of children not infected by *Shigella* and without dysentery (specificity) could be extracted. We included studies of adults and children in both mortality and diagnostic value searches. Lastly, we limited the treatment search to trials after Jan 1, 1980, and to children younger than 18 years, and we included studies with titles and abstracts that contained the terms *Shigella*, shigellosis, dysentery, or blood in stool. We only included randomised controlled trials of one or more antibiotics among children with dysentery or laboratory-confirmed *Shigella* infections.
Titles and abstracts of eligible studies were independently reviewed by two authors (KDT, PBP, or RLB). If authors disagreed on inclusion, consensus was reached following full-text review. Data were extracted from included studies by a single author (KDT or RLB).

Data analysis
We identified all duplicate data by comparing the study population, sample sizes, and enrolment dates of eligible studies and removed them before analysis. For eligible studies of mortality, we extracted odds ratios (ORs) and 95% CIs for relative mortality. We calculated ORs and 95% CIs using data extracted from the publications or provided by the paper’s corresponding author and did random-effects meta-analysis to arrive at pooled ORs. We assessed the quality of individual studies using modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (appendix p 2). In eligible studies of diagnostic value, we calculated 95% CIs assuming a binomial distribution. We did random-effects meta-regression of log-transformed sensitivity and specificity estimates (proportions) by the middle year of study enrolment to identify a possible time-trend in sensitivity and specificity estimates. We assessed the quality of included studies using the Quality Assessment of Diagnostic Accuracy Studies criteria (appendix p 3). Lastly, for eligible studies of treatment, we summarised clinical, anthropometric, and microbiological outcomes, and assessed the quality of included trials using modified GRADE criteria (appendix p 4). The appendix (p 1) summarises all the variables extracted for each search.

We used Stata (version 13.1) for all analyses. We assessed the heterogeneity of papers included in these meta-analyses using the I² statistic and evaluated publication bias using funnel plots (appendix p 6). This review is registered with PROSPERO (CRD42017063896).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
For the mortality search, 1085 titles and abstracts were screened and 13 studies met inclusion criteria (figure 1). The enrolment period of included studies ranged from 1974 to 2013, and 11 (85%) of 13 studies ascertained inpatient deaths only. Eight (62%) were done in Asia, with seven in Bangladesh. Three (23%) were done in sub-Saharan Africa, one (8%) in Turkey, and one (8%) was a multi-site study. Nine (69%) studies included the relative mortality of *Shigella* (n=seven) or dysentery (n=six), all of which used children with other causes or presentations of diarrhoea as a reference group (table 1).

1682 titles and abstracts were reviewed and 27 studies were included from the diagnostic value search (figure 1). 13 (48%) of 27 studies were done in Asia, seven (26%) in Africa, five (19%) in the Middle East, and two (7%) in Latin America. Dysentery was assessed by visual inspection at presentation (14 [52%] of 27 studies), caregiver report (three [11%]), visual confirmation or reported history (six [22%]), or not described (four [15%]). The sensitivity of dysentery for identification of *Shigella* infection was extracted from all 27 studies whereas specificity was available in 20 (74%) studies (table 2).

From the systematic search of treatment, 882 titles and abstracts were reviewed, and 20 trials were included (figure 1). 17 (85%) were in children with dysentery, none were placebo-controlled, and ten (50%) evaluated antibiotics no longer recommended for acute infectious
### Table 1: Odds of death associated with culture-confirmed *Shigella* spp or dysentery at diarrhea presentation as compared with children without *Shigella* infection or dysentery

| Enrolment dates | Population and study characteristics | N | Number of dysentery cases (deaths) | Number of *Shigella* cases (deaths) | Dysentery OR | *Shigella* OR |
|-----------------|--------------------------------------|---|-----------------------------------|-------------------------------------|------------|--------------|
| Dutta et al (1995) | Inpatients aged <5 years with acute watery diarrhoea, persistent diarrhoea, or dysentery; study done in India; dysentery defined as ≥3 loose stools with blood and mucus on caregiver report; *Shigella* spp detected by culture; *Shigella* spp and dysentery compared with other diarrhoeal admission; deaths ascertained during admission to hospital | 380 | 75 (16) | 53 (22) | 1.7 (0.8-3.3) | 5.4 (2.7-10.6)* |
| Kotloff et al (2013) | Children aged 12-23 months with moderate- to severe diarrhoea, study done in multiple countries; dysentery defined as visible bloody stool; *Shigella* spp detected by culture and compared with children with diarrhoea who were negative for *Shigella* spp; deaths ascertained within 90-day follow-up (in and out of hospital) | 3205 | - | 485 (8) | - | 0.9 (0.4-1.8) |
| Islam et al (1986) | Inpatients of all ages with diarrhoea; *Shigella* spp detected by culture and compared with other diarrhoeal admission; deaths ascertained during admission to hospital | 3251 | - | 436 (75) | - | 1.6 (1.2-2.1)* |
| O’Reilly et al (2012) | Inpatients <5 years with watery, mucoid, or bloody diarrhoea; study done in Kenya; dysentery defined as visible bloody stool; *Shigella* spp detected by culture; *Shigella* spp and dysentery compared with other diarrhoeal admission; deaths ascertained during admission to hospital | 1146 | 96 (10) | 42 (12) | 1.1 (0.6-2.3) | 4.2 (1.8-8.5)* |
| Pernica et al (2016) | Children aged <13 years admitted to hospital with diarrhoea in Botswana; dysentery defined as bloody diarrhoea on caregiver report; *Shigella* spp detected by PCR; *Shigella* spp and dysentery compared with other diarrhoeal admission; deaths ascertained during admission to hospital | 671 | 74 (4) | 109 (7) | 1.4 (0.5-4.3) | 1.9 (0.8-4.6) |
| Ronsmans et al (1988) | Community members of all ages with watery, mucoid, or bloody mucoid diarrhoea; study done in Bangladesh; dysentery defined as visible bloody mucoid stool and compared with children with watery or mucoid-bloodless diarrhoea; length of follow-up period not specified, but captured deaths in hospitals and in the community | 46 007 | 17 953 (122) | - | 2.6 (1.9-3.5)* |
| Teka et al (1996) | Inpatients aged <5 years with diarrhoea; study done in Bangladesh; *Shigella* spp detected by culture and compared with other diarrhoeal admission; deaths ascertained during admission to hospital | 184 | - | 24 (14) | - | 5.6 (2.3-13.3)* |
| Uysal et al (2000) | Inpatients aged 1 month to 5 years with diarrhoea, mucoid diarrhoea, or bloody diarrhoea; study done in Turkey; unclear definition of dysentery; *Shigella* spp detected by culture; *Shigella* spp and dysentery compared with other diarrhoeal admission; deaths ascertained during admission to hospital | 400 | NA† | 21 (5) | 0.6 (0.1-3.1) | 5.1 (1.3-16.2)* |
| van den Broek et al (2005) | Severely malnourished inpatients aged <4 years with diarrhoea; study done in Bangladesh; unclear definition of dysentery; *Shigella* spp detected by culture; dysenteric *Shigella* compared with dysentery-negative *Shigella*; deaths ascertained during admission to hospital | 200 | 66 (28) | 200 (100) | 0.6 (0.4-1.2) |

The appendix (p 2) summarises the associated GRADE quality assessment. GRADE=Grading of Recommendations Assessment, Development and Evaluation. OR=odds ratio. NA=not available. WAZ=weight-for-age Z score. *p<0.05. †Number of children with dysentery not reported. ‡Severe malnutrition was defined using Gomez classification WAZ <60% of National Center for Health Statistics median.

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**Articles**

Odds of death associated with culture-confirmed *Shigella* spp or dysentery at diarrhea presentation as compared with children without *Shigella* infection or dysentery. Additionally, 14 (70%) were done in Asia (eight [40%] in Bangladesh), five (25%) in the Americas, and one (5%) was a multi-centre trial that included African and Asian sites (table 3). 12 (60%) trials were among children with dysentery and confirmed *Shigella* infection, six (30%) among children with dysentery (without *Shigella* confirmatory testing), and two (10%) among children with confirmed *Shigella* infection irrespective of dysentery status (but did not stratify by dysentery). All trials included a clinical outcome, such as clinical improvement or time to resolution of symptoms. 14 (70%) included a bacteriological outcome, such as bacteriological cure or time to negative stool culture. One (5%) study included mortality as an outcome. Of the 20 included trials, three (15%) compared different doses or durations of the same antibiotic, and 17 (85%) compared two different antibiotics, one (5%) of which also included a group treated with no antibiotic.5 One (5%) trial compared an antibiotic to supportive treatment, including the administration of an alternative antibiotic at the clinician’s discretion.6 The quality of evidence for these included studies was very low (five [25%] of 20), low (eight [40%]), or moderate (seven [35%]; appendix p 4).

Five (71%) of seven studies examining *Shigella* mortality relative to other causes of diarrhoea found the odds of death to be significantly higher in children with *Shigella* infection than in those without infection (figure 2, table 1). Substantial heterogeneity ($I^2=78\%$, $p[I^2]<0.001$) was reported, with ORs ranging from 0.9 to 5.6. The random-effects pooled estimate suggested that *Shigella* infection was significantly associated with mortality (pooled OR 2.8, 95% CI 1.6–4.8; $p=0.000$). Six (46%) of 13 studies compared mortality in children with and without dysentery at diarrhea presentation. Dysentery was defined as bloody stool (n=two), blood and mucus in stool
mortality by the presence of dysentery but found no significant difference between inpatients with dysenteric *Shigella* and those with dysentery-negative *Shigella* in the association between *Shigella* infection and death. Four studies reported associations with death for *Shigella* and dysentery within the same population, and three of the four studies showed that *Shigella* infection had a

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### Table 2 Continued on Next Page

| Enrolment dates | Population and study characteristics | Number of children with *Shigella* (Shigella with dysentery) | Number of children with dysentery* | Sensitivity (95% CI) | Specificity (95% CI) |
|-----------------|--------------------------------------|-----------------------------------------------------------|----------------------------------|---------------------|---------------------|
| 2011           | 270 children aged <5 years presenting to hospital with diarrhoea who had a stool culture; study done in Nigeria; unclear definition of dysentery | 9 (5) | 28 | 55.6% (21.2–86.3) | 91.1% (87.1–94.3) |
| 2007-12        | 3399 children aged <5 years presenting to facilities with diarrhoea; study done in Guatemala; unclear definition of dysentery | 261 (5) | - | 1.9% (0.6–4.4) | - |
| 2009           | 172 children aged <4 years referred to hospital for acute diarrhoea or dysentery; study done in Iran; unclear definition of dysentery | 7 (4) | 33 | 57.1% (18.4–90.1) | 82.4% (75.7–87.9) |
| 2009           | 215 inpatients of all ages with watery, bloody, or mucoid diarrhoea; study done in Ethiopia; observation of bloody stool by laboratory technician used to indicate dysentery | 32 (9) | 39 | 28.1% (13.7–46.7) | 83.6% (77.4–88.7) |
| 2007-09        | 35.6 children aged <5 years admitted with acute diarrhoea; study done in Egypt; dysentery defined as visible blood in stool; history of bloody stool by caregiver report used to indicate dysentery | 4 (2) | 69 | 50.0% (6.8–93.2) | 81.0% (76.5–87.9) |
| 2004-05        | 808 inpatients of all ages with acute diarrhoea; study done in Iran; observation of bloody stool by unspecified observer used to indicate dysentery | 155 (39) | 111 | 25.2% (18.5–32.8) | 89.0% (86.3–91.3) |
| 2003-06        | 130 inpatients aged 1-16 years with gastroenteritis whose stool contains blood, mucus, or neither; study done in Turkey; observation of bloody stool (unspecified observer) used to indicate dysentery | 65 (19) | 19 | 29.2% (18.6–41.8) | 100% (94.8–100) |
| 2000-04        | 51 826 Individuals of all ages presenting to community clinics or district hospitals with diarrhoea or dysentery (one loose bowel movement with visible blood); study done in Bangladesh, China, Pakistan, Indonesia, Vietnam, and Thailand; observation of bloody stool by unspecified observer used to indicate dysentery | 2925 (790) | 4751 | 27.0% (24.4–28.6) | 92.7% (92.4–92.9) |
| 1993-99        | 200 severely malnourished infants aged <4 years with diarrhoea and culture-confirmed *Shigella* dysenteriae type 1 or *Shigella* flexneri; study done in Bangladesh; history of visible blood in stool was used to indicate dysentery | 200 (66) | - | 33.0% (26.5–40.0) | - |
| 1995-96        | 106 inpatients aged 1 month to 5 years with acute diarrhoea; study done in Thailand; observation of bloody stool by unspecified observer used to indicate dysentery | 8 (3) | 12 | 37.5% (31.7–44.6) | 90.8% (83.3–95.7) |
| 1994-95        | 265 inpatients aged <5 years with acute diarrhoea; study done in Jordan; observation of bloody stool by clinician used to indicate dysentery | 10 (6) | 28 | 60.0% (36.1–80.9) | 91.4% (87.3–94.5) |
| 1992-93        | 639 inpatients aged <5 years; study done in Zambia; observation of bloody diarrhoea by unspecified observer used to indicate dysentery | 65 (51) | 220 | 78.5% (66.6–87.7) | 70.6% (66.6–74.1) |
| 1989-90        | 916 inpatient and community-based infants and children aged <3 years with acute diarrhoea or dysentery, or both; study done in India; observation of bloody stool by unspecified observer used to indicate dysentery | 152 (94) | 191 | 61.8% (53.6–69.6) | 87.3% (84.7–89.6) |
| 1989-90        | 414 inpatients aged 1-5 years with acute diarrhoea; study done in Brazil; observation of bloody stool by unspecified observer used to indicate dysentery | 66 (35) | 39 | 53.0% (48.0–57.8) | 98.9% (91.7–100) |
| 1987-89        | 792 inpatients aged <15 years with diarrhoea and culture-confirmed *Shigella* spp; study done in Bangladesh; history of bloody stool as indicated in patient record and observation by caregiver used to indicate dysentery | 792 (332) | - | 41.9% (38.6–45.6) | - |
significant association with death whereas dysentery had no association with death. A meta-analysis of these studies (appendix p 5) found Shigella infection to be significantly associated with mortality (OR 3·9, 95% CI 2·5–6·2, p=0·000; I²=18·3%, p(I²)=0·299) whereas dysentery was not (OR 1·3, 95% CI 0·9–2·0, p=0·20; I²=0%, p(I²)=0·636). The quality of evidence for the association between mortality and Shigella or dysentery was low to very low (appendix p 6).

Six studies reported inpatient case-fatality rates that were species specific, but none found S dysenteriae type I to be associated with a significantly higher inpatient case fatality than other species (table 4). No species-specific case-fatality rates for children who were not admitted to hospital were available. The quality of evidence for these rates was very low (appendix p 2) because of sparse and observational data. Too few mortality studies were identified to meaningfully test for publication bias.

The sensitivity of dysentery for laboratory-confirmed Shigella infection ranged from 1·9% to 85·9% (table 2). Random-effects meta-regression showed that a significant amount of heterogeneity (p=0·04) was explained by a decreasing proportion of Shigella infections presenting with dysentery (sensitivity) over time (figure 4). Specificity had a narrower range of 64·4–100%, but there was no evidence of an association (p=0·60) between the absence of dysentery as a marker of Shigella’s absence (specificity) and time. 16 of the included studies were found to be of high quality (appendix p 3). 13 studies were downgraded for not offering clear definitions of dysentery. Four were downgraded because the indication for Shigella testing might have been influenced by the presence of dysentery. No evidence of publication bias was found in this analysis.

In the single trial that compared non-antibiotic supportive therapy with co-trimoxazole or furazolidone, antibiotic treatment had clinical and bacteriological benefit compared with no antibiotic treatment.17 In this study, the effect of antibiotics on clinical cure was strongest in children with Shigella, Salmonella, diarrhoeagalenic Escherichia coli, or Campylobacter isolated at baseline (stratification by each bacteria was not reported). Three trials18,19,20 specifically evaluated ciprofloxacin, the recommended treatment for dysentery by WHO. These trials reported equivalent clinical efficacy of ciprofloxacin compared with gatifloxacin23 or pimavcilamin,24 and a slightly higher bacteriological efficacy with ciprofloxacin than with pimavcilamin (table 2).25 One study24 found that treatment duration

### Table 2: Sensitivity and specificity of dysentery at diarrhea presentation for the identification of Shigella infection in children

| Enrolment dates | Population and study characteristics | Number of children with Shigella (Shigella with dysentery) | Number of children with dysentery* | Sensitivity (95% CI) | Specificity (95% CI) |
|-----------------|--------------------------------------|-----------------------------------------------------------|-----------------------------------|---------------------|---------------------|
| Ahmed et al (1997)26 | 1987–89 1756 community-based children aged <5 years with diarrhea or dysentery (diarrhea described as bloody); study done in Bangladesh; history of bloody diarrhoeal episodes by caregiver report at enrolment or any time during 31 days of follow-up used to indicate dysentery | 219 (86) 313 | 39·3% (32·8–46·1) | 85·2% (83·4–87·0) |
| Kaga1awa et al (1992)27 | 1985–90 229 inpatients aged <13 years with diarrhoea, haematochezia, or abdominal pain and culture-confirmed Shigella spp; study done in Saudi Arabia; observation of bloody stool by unspecified observer used to indicate dysentery | 229 (86) | 37·6% (31·7–44·6) | |
| Dutta et al (1992)28 | 1985–88 950 inpatients aged <5 years with culture-confirmed Shigella; study done in India; observation of bloody and mucoid stool by unspecified observer used to indicate dysentery | 192 (165) | 85·9% (80·2–90·5) | |
| Echeverria et al (1990)29 | 1986–87 471 inpatients <5 years with diarrhoea and culture-confirmed Shigella spp, Salmonella spp, Campylobacter spp, diarrhoeagalenic Escherichia coli, or rotavirus; study done in Thailand; observation of bloody stool by unspecified observer used to indicate dysentery | 94 (37) 110 | 39·4% (29·4–50·0) | 80·6% (76·3–84·5) |
| Moalla et al (1994)30 | 1986 170 children aged <6 years presenting with acute diarrhea; study done in Tunisia; unclear definition of dysentery | 14 (8) | 57·1% (28·9–82·3) | |
| Huskins et al (1994)31 | 1984–88 318 inpatients (<15 aged <3 months and 159 aged 1–10 years) with culture-confirmed Shigella spp; study done in Bangladesh; observation of bloody stool by unspecified observer used to indicate dysentery | 318 (117) | 36·8% (28·0–46·2) | |
| Ronsmans et al (1988)32 | 1984 300 community members of all ages, with watery, mucoid, or bloody diarrhoea; study done in Bangladesh; observation of bloody stool by medical assistant or history of bloody stool by caregiver report used to indicate dysentery | 82 (51) 80 | 62·2% (50·8–72·7) | 86·7% (81·5–91·0) |
| Stoll et al (1982)33 | 1979–80 3550 inpatients of all ages with acute diarrhoea containing blood, mucous, or neither; study done in Bangladesh; history of observation of bloody or mucoid stool used to indicate dysentery | 412 (227) 298 | 55·1% (50·2–60·0) | 85·0% (83·7–86·2) |
| Mo-Suwan et al (1979)34 | 1977 144 inpatients (<5 years not specified) with diarrhoea; study done in Thailand; observation of bloody stool by laboratory staff used to indicate dysentery | 5 (2) 9 | 40·0% (5·3–85·3) | 95·0% (89·9–98·0) |

The appendix (p 3) summarises the associated QUADAS assessment. QUADAS=Quality Assessment of Diagnostic Accuracy Studies. WAZ=weight-for-age (1997).36 (Continued from previous page)
with ciprofloxacin (2-day short course vs 5-day long course) to have no effect on clinical or bacteriological efficacy. No differences were found for clinical and bacteriological outcomes in studies of co-trimoxazole versus pivmecillinam, co-trimoxazole versus cefixime (other than diarrhoea on day 4), cefixime versus nalidixic acid, nalidixic acid versus ampicillin, nalidixic acid versus ofloxacin, and low-dose ampicillin versus standard-dose ampicillin. Additionally, no difference was seen between single-dose ampicillin and multiple doses of ampicillin. In one study, azithromycin was bacteriologically but not clinically superior to cefixime. Furazolidone was clinically superior to ampicillin in one study but inferior to nalidixic acid in another. Gentamicin was found to be bacteriologically but not clinically inferior to nalidixic acid; however, norfloxacin was clinically superior to nalidixic acid. One study showed that cefixime was clinically superior to ampicillin plus sulbactam, and another study showed that co-trimoxazole had better clinical, but not bacteriological, outcomes than ampicillin. Finally, one study reported that pivmecillinam was clinically and bacteriologically superior to nalidixic acid when cases with Shigella infections that are resistant to nalidixic acid were included.

**Discussion**

Our systematic reviews found Shigella infection to be associated with mortality in children presenting with diarrhoea, and that dysentery did not adequately identify

| Population and study characteristics | Intervention | Comparator | N | Outcomes of interest for systematic review | RR, HR, mean difference, or proportion of clinical cure (95% CI) |
|-------------------------------------|--------------|------------|---|------------------------------------------|------------------------------------------------------|
| Alam et al (1994)46 | Inpatients aged 1–8 years with bloody diarrhoea lasting <72 h, >20 erythrocytes and pus cells per high power field, and culture-confirmed Shigella spp; study done in Bangladesh | Pivmecillinam 50 mg/kg per day for 5 days | Nalidixic acid 60 mg/kg per day for 5 days | Proportion with clinical improvement (≥1 formed stool without blood in the previous 24 h, with no fever [rectal temperature <37.8°C] and no abdominal pain or tenderness) on day 5 | RR 1.42 (1.15–1.75); 1.25 (1.00–1.56) |
| Basualdo et al (2003)47 | Inpatients aged 6 months to 5 years with dysenteric diarrhoea per physician’s evaluation (<2 bloody diarrhoeal stools in 24 h or the presence of >20 leucocytes per high power field on microscopy [or both], with fever, and abdominal pain or tenesmus [or both]) with culture-confirmed Shigella spp; study done in Paraguay | Azithromycin 52 mg/kg per day for 1 day, followed by 6 mg/kg per dose for 4 days | Cefixime 8 mg/kg per day for 5 days | Proportion with clinical cure (resolution or substantial improvement of signs and symptoms) at day 5; proportion with bacteriological cure at day 3 | RR 1.39 (0.97–1.47); 0.72 (0.54–0.98) |
| Bhattacharya et al (1997)48 | Inpatients aged 1–10 years with a history of acute bacillary dysentery (>3 stools in 24 h and passage of visible blood and mucus in stool for <3-day duration); study done in India | Norfloxacin 20 mg/kg per day in two-divided doses for 5 days | Nalidixic acid 60 mg/kg in four divided doses for 5 days | Mean duration of diarrhoea after therapy; mean duration of presence of blood in stool | 2–3 days for norfloxacin group vs 3–7 days for nalidixic acid group (difference: 1 day, –1.73 to –0.27); 1–4 days vs 2–4 days (–1, –1.58 to –0.42) |
| Dutta et al (1995)49 | Inpatients aged <5 years diagnosed with dysentery (>3 loose stools per day, in which stool was intimately mixed with blood and mucus, and accompanied by symptoms: fever, abdominal pain, and tenesmus), of less than 3-day duration; patients who received treatments known to be effective against dysentery were excluded, as were children who had <10 bowel movements per day; study done in India | Furazolidone 7.5 mg/kg per day in four divided doses for 5 days | Nalidixic acid 55 mg/kg per day in four divided doses for 5 days | Clinical cure (no blood in stool, no fever, stool semi-solid with frequency <3 times last 24 h or no stool for last 18 h) at day 5 of treatment | 29 (85.3%) of 34 for furazolidone group vs 29 (100%) of 29 for nalidixic acid achieved clinical cure; p=0.039 |
| Gilman et al (1980)50 | Inpatients children with blood, pus, mucus, and mucus in stool, ≥4 stools per day, and culture-confirmed Shigella spp; study done in Bangladesh | Low-dose ampicillin 50 mg/kg per day | Standard dose: ampicillin 150 mg/kg per day | Mortality at day 21; proportion with microbiological failure on day 3 | 0 deaths occurred among 28 children in the low-dose group compared with 2 deaths among the 29 children in the high-dose group (risk difference: –0.07, –0.02 to 0.02); 0 microbiological failures in either group on day 3 |
| Gilman et al (1981)51 | Inpatients adults and children aged 2–10 years passing blood and mucus in stools for <1 month, presence of faecal leucocytes, and culture-confirmed Shigella spp; study done in Bangladesh | Single-dose ampicillin 200 mg/kg | Multiple doses of ampicillin 100 mg/kg per day for 5 days | Proportion clinically failed (persistence of dysentery for 7 hospital days or its recurrence ≥7 days after initiation of therapy and a positive stool culture for Shigella) at day 21; proportion with bacteriological cure on day 21 | RR undefined (risk difference 0.04 [95% CI –0.04 to 0.13]); RR 3.13 (0.38–25.6) |

(Table 3 continues on next page)
| Population and study characteristics | Intervention | Comparator | N | Outcomes of interest for systematic review | RR, HR, mean difference, or proportion of clinical cure (95% CI) |
|-------------------------------------|--------------|------------|---|------------------------------------------|----------------------------------------------------------------|
| (Continued from previous page)      |              |            |   |                                          |                                                                 |
| Helvaci et al (1998)57              | Inpatients aged 1–13 years with acute bloody mucoid diarrhoea and culture-confirmed Shigella spp; study done in Bangladesh | Cefixime 8 mg/kg per day for 5 days | 65 | Proportion with duration of fever between days 0 and 2; proportion with duration of diarrhoea between days 0 and 2; proportion with time to disappearance of blood in stool between days 0 and 2; mean duration spent in hospital | RR 1·65 (1·01–2·12); 3·56 (1·30–9·78); 2·80 (1·54–5·09); mean duration 3·4 days for the cefixime group vs 5·8 days for the ampicillin plus sulbactam group, difference –2·4 days (–3·20 to –1·60) |
| Islam et al (1994)54                | Outpatients aged 1–8 years with bloody diarrhoea of >72 h duration and <20 pus cells per high power field via stool microscopy, and culture-confirmed Shigella spp; study done in Bangladesh | Gentamicin 30 mg/kg per day orally for 5 days | 71 | Proportion with clinical improvement (<6 stools without visible blood on day 5, with absence of fever (rectal temperature <37°C) and abdominal pain or tenderness) on day 5; proportion with bacteriological cure on day 5 | RR 1·70 (0·85–3·39); 0·55 (0·34–0·87) |
| Moolasart et al (1999)55            | Inpatients aged 6 months to 12 years with acute gastroenteritis (diarrhoea [>3 loose stools or 1 bloody stool in a 24 h period] accompanied by fever, abdominal pain, or vomiting); study done in Thailand | Cefixibuten 5 mg/kg per day for 5 days | 8 | Time to clinical success (no definition given), in children infected with Shigella; proportion with microbiological cure at day 2, in those infected with Shigella | RR 2·3 days for the cefixibuten group vs 2·0 days for the norfloxacin group; RR 3·1% vs 2·0% for the cefixibuten group vs 100% for norfloxacin group |
| Prado et al (1992)56                | Inpatient and outpatient children aged 6 months to 15 years presenting with bloody diarrhoea (grossly or by Haemocult test) or diarrhoea with fever (≥38°C) and presence of polymorphonuclear leukocytes in the stool, in those who had received no treatments; study done in Mexico | Norfloxacin 15 mg/kg per day for 5 days | 28 | Proportion with treatment success at day 6 (absence of watery stools by day 5 plus a negative stool culture on day 6) | 92·3% for the furazolidone group vs 51·3% for the ampicillin group, p < 0·001 |
| Prado et al (1993)57                | Outpatient children aged 6 months to 12 years presenting with acute diarrhoea for <2 days, visible blood in stool and presence of sheets of polymorphonuclear white cells on stool microscopic examination; or acute diarrhoea with presence of sheets of polymorphonuclear white cells on stool microscopic examination and a weight-for-height index >70% according to US National Center for Health Statistics standards; study done in Guatemala and Argentina | Furazolidone 5 mg/kg per day in four divided doses for 5 days | 78 | Mean duration of diarrhoea; mean duration of fever; microbiological cure 2 days after treatment | RR 2·4 days in cefixibuten group vs 3·4 days in co-trimoxazole group (statistical significance not reported); 1·3 days vs 1·2 days (statistical significance not reported); 1·4% and 22·2% (statistical significance not reported); 2 patients in each group had Shigella isolated in stool after treatment |
| Prado et al (1993)58                | Inpatients aged 6 months to 12 years presenting with acute diarrhoea for <2 days, visible blood in stool and presence of sheets of polymorphonuclear leukocytes in the stool, and presence of sheets of polymorphonuclear white cells on stool microscopic examination; or acute diarrhoea with presence of sheets of polymorphonuclear white cells on stool microscopic examination and a weight-for-height index >70% according to US National Center for Health Statistics standards; study done in Guatemala and Argentina | Cefixibuten 4·5 mg/kg twice daily for 5 days | 22 | Treatment failure (persistence of fever or visible blood in stool after 72 h of treatment); duration of isolation of Shigella, diarrhoea, fever, visible blood in stools, occult blood in stools, and pus cells in stools | 5·8 days for the furazolidone group, 2·4 days in ceftibuten group, 3·4 days in co-trimoxazole group (statistical significance not reported); 1·3 days vs 1·2 days (statistical significance not reported); 1·4% and 22·2% (statistical significance not reported); 2 patients in each group had Shigella isolated in stool after treatment |

(Continued on next page)
### Table 3: Randomised controlled trials of antibiotic treatment for Shigella infections or dysentry, or both

| Population and study characteristics | Intervention | Comparator | N | Outcomes of interest for systematic review | RR, HR, mean difference, or proportion of clinical cure (95% CI) |
|--------------------------------------|--------------|------------|---|-------------------------------------------|----------------------------------------------------------|
| **(Continued from previous page)**   |              |            |   |                                           |                                                          |
| **Salam et al (1988)**               |              |            |   |                                           |                                                          |
| 58 patients in Salam et al (1988)    | Nalidixic acid (55 mg/kg per day for 5 days) | Ampicillin (100 mg/kg per day) for 5 days | 74 | Proportion with clinical cure (no unformed stools and no fever [rectal temperature of ≥39°C] on day 5) | RR 1.05 (0.79–1.39); 1.00 (1.00–1.00)* |
| **Salam et al (1998)**               |              |            |   |                                           |                                                          |
| 58 patients in Salam et al (1988)    | Ciprofloxacin 10 mg/kg twice daily for 3 days | Pimemecillin 15–20 mg/kg three times per day for 5 days | 120 | Proportion with clinical cure (absence of persistent dysentry by day 3 and ≤6 stools by day 6, with no bloody mucoid stools, ≤1 watery stool, and no fever [rectal temperature <37.8°C] on day 6; proportion with bacteriological cure on day 6; proportion with bloody mucoid stool ≥3 days in duration) | RR 1.23 (0.98–1.54); 1.11 (1.02–1.20); 0.64 (0.30–1.37) |
| **Taylor et al (1987)**              |              |            |   |                                           |                                                          |
| 58 patients in Taylor et al (1987)   | Erythromycin 40 mg/kg per day in four divided doses for 5 days | Supportive treatment and co-trimoxazole (trimethoprim 8 mg/kg plus sulfamethoxazole 40 mg/kg) twice daily for 5 days if indicated by clinician | 21 | Proportion with diarrhoea at day 7, in children with Shigella spp initially isolated | 38% for erythromycin group vs 14% for control group (statistical significance not reported) |
| **Vinh et al (2000)**                |              |            |   |                                           |                                                          |
| 66 patients in Vinh et al (2000)     | Daily nalidixic acid 55 mg/kg per day for 5 days | Ofloxacin 7.5 mg/kg twice daily for 1 day | 66 | Proportion with clinical cure (symptoms resolved and absence of new symptoms [relapse] within 5 days of treatment initiation; proportion with microbiological cure (absence of pathogen identified in stool sample from day 5) | 75% for nalidixic acid group vs 90% for ofloxacin group (p=NS); 92% for nalidixic acid group vs 100% for ofloxacin group (p=NS) |
| **Vinh et al (2011)**                |              |            |   |                                           |                                                          |
| 494 patients in Vinh et al (2011)    | Gatifloxacin 10 mg/kg per day for 3 days | Ciprofloxacin 15 mg/kg twice daily for 3 days | 494 | Proportion with clinical failure (presence of fever [defined as ≥37.8°C] or persistence of vomiting, abdominal pain, or tenesmus with or without ≥2 loose stools or with or without bloody, mucous, or both) at day 5; proportion with bacteriological failure at day 3 or more; difference in time to diarrhoea clearance, measured in hours; difference in time to recovery from fever, measured in hours; difference in time to recovery from bloody diarrhoea, measured in hours | RR 1.35 (0.77–2.37); RR 0.66 (0.24–1.82); HR 0.98 (0.82–1.17); HR 1.00 (0.84–1.20); HR 1.11 (0.93–1.32) |
| **Yurus et al (1982)**               |              |            |   |                                           |                                                          |
| 118 patients in Yurus et al (1982)   | Co-trimoxazole (trimethoprim plus sulfamethoxazole) 6 mg/kg per day every 12 h for 5 days | Ampicillin 50 mg/kg per day divided into doses every 6 h to patients ≥15 kg | 118 | Time to negative culture; time to decline of fever; time to clearance of blood in stool; duration of persisting stool mucus; duration of abdominal pain | 2.9 days for co-trimoxazole group vs 3.1 days for ampicillin group (p=NS); 1.3 days vs 1.5 days (p=0.05); 1.5 days vs 2.2 days (p=0.05); 3.3 days vs 4.9 days (p=0.05); 2.8 days vs 3.6 days (p=0.05) |
| **Zimbabwe, Bangladesh, South Africa (Zimbabwe Dysentery study Group (2002)** |              |            |   |                                           |                                                          |
| 253 patients in Zimbabwe, Bangladesh, South Africa (Zimbabwe Dysentery study Group (2002) | Short course ciprofloxacin 15 mg/kg every 12 h for 3 days; 2 days of placebo | Standard course ciprofloxacin 15 mg/kg every 12 h for 5 days | 253 | Proportion with treatment success (either resolution of illness [no bloody mucoid or watery stools and no more than a trace of blood in any stool, and ≤3 stools in the previous day]; or marked improvement [no bloody mucoid stool and at most one watery stool and no more than a trace amount of blood]) at day 6; proportion with bacteriological cure at day 6 | RR 0.94 (0.74–1.20); 1.00 (1.00–1.00)* |

The appendix (p 4) summarises the associated GRADE quality assessment. RR=risk ratio. HR=hazard ratio. NS=non-significant. GRADE=Grading of Recommendations Assessment, Development and Evaluation.

*All patients in Salam et al (1988) were bacteriologically cured at day 6. **All patients in the study by the Zimbabwe, Bangladesh, South Africa Dysentery study Group (2002) were bacteriologically cured at day 5.

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**Articles**

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children with *Shigella* infections in many settings. Treatment strategies targeting dysentery-free *Shigella* infections might reduce diarrhoea-associated mortality. Because a range of antibiotics have shown efficacy in treating children with dysentery and *Shigella* infections, antibiotic treatment of high-risk groups of children without dysentery might be an effective addition to the current guidance.

The majority of *Shigella* mortality studies reported a significant association with death when compared with other causes of diarrhoea. The different populations, clinical management strategies, study designs, and enrolment periods resulted in marked heterogeneity in the magnitude of association across the studies. Most studies used standard culture to detect *Shigella* infection, with only one study using molecular methods, which can triple the detection rate by detecting lower-burden infections. Length of follow-up and management practices also varied across studies with all but one study being limited to patients admitted to hospital without post-discharge follow-up. The prevalence of known risk factors for mortality (young age, HIV infection, and severe acute malnutrition) varied across studies, and these subgroups of children might be at highest risk of *Shigella*-associated mortality. Despite these sources of heterogeneity, the pooled association of *Shigella* and mortality suggests that *Shigella* is an important risk factor for death in children with diarrhoea.

This meta-analysis found that *Shigella* infection had a stronger association with mortality than did dysentery. Only a single study, published in the 1980s, found a significant association between dysentery and mortality. However, children with *Shigella* infection and dysentery do have higher-burden infections. Also, *Shigella* dysentery, through its association with shiga-toxin production and very severe diarrhoea, is associated with severe complications such as haemolytic uraemic syndrome and severe hyponatraemia. Given the established consequences of dysentery, the near absence of an association between dysentery and mortality in studies is likely to be the consequence of effective management strategies, including the administration of antibiotics.

Although *Shigella* infection was strongly associated with dysentery in all the included studies, dysentery was not a reliable tool for identifying *Shigella* infection. In other words, *Shigella* is common in children with dysentery, but most children infected with *Shigella* do not present with dysentery. The sensitivity of dysentery for identifying *Shigella* appears to have declined over time, although a subset of recent studies found dysentery to be fairly sensitive. Differences in the sensitivity of dysentery for *Shigella* infection across studies might be due to variability in *Shigella* species, such as the global

| N       | Shigella-infected cases | Weight* (%) | OR (95% CI) |
|---------|-------------------------|-------------|-------------|
| Islam et al (1986) | 3251 | 109 | 12.90 | 1.9 (0.8–4.6) |
| Kodloff et al (2013) | 1146 | 42 | 14.86 | 0.9 (0.4–1.8) |
| O’Reilly et al (2012) | 400 | 21 | 10.42 | 4.2 (1.8–8.5) |
| Uysal et al (2000) | 184 | 24 | 12.83 | 5.1 (3.3–16.2) |
| Teka et al (1996) | 380 | 53 | 15.18 | 5.6 (2.3–13.8) |
| Dutta et al (1995) | 3205 | 485 | 14.98 | 5.4 (1.7–16.6) |
| Islam et al (1986) | 1146 | 67 | 18.83 | 1.6 (1.2–2.1) |
| Overall | 3251 | 436 | 100.00% | 2.8 (1.6–4.8) |

Test for overall effect: p = 0.000

![Figure 2](image_url)

**Figure 2:** Individual and pooled effect estimate comparing the odds of death between children with and without laboratory-confirmed *Shigella* infection

| N       | Dysentery cases | Weight* (%) | OR (95% CI) |
|---------|----------------|-------------|-------------|
| Islam et al (1986) | 671 | 74 | 13.00 | 1.4 (0.5–4.3) |
| O’Reilly et al (2012) | 1146 | 96 | 17.77 | 1.1 (0.5–2.3) |
| van den Broek et al (2009) | 200 | 66 | 18.43 | 0.6 (0.4–1.2) |
| Uysal et al (2000) | 400 | NA | 8.04 | 0.6 (0.3–1.2) |
| Dutta et al (1995) | 380 | 75 | 18.88 | 17.0 (8.8–33.3) |
| Rozman et al (1998) | 46607 | 17953 | 23.87 | 2.6 (0.9–7.3) |
| Overall | 400 | 66 | 100.00% | 1.3 (0.7–2.3) |

Test for overall effect: p = 0.002

![Figure 3](image_url)

**Figure 3:** Individual and pooled effect estimates of studies comparing the odds of death in children with and without dysentery

NA = not available. *Weights are from random-effects analysis. †Number of children with dysentery not reported.
| Enrolment dates | Population and study characteristics | Shigella dysenteriae type 1 | Other S dysenteriae | Shigella flexneri | Shigella sonnei | Shigella boydii |
|----------------|--------------------------------------|---------------------------|------------------|-----------------|----------------|----------------|
|                |                                       | n/N | Case fatality (95% CI) | n/N | Case fatality (95% CI) | n/N | Case fatality (95% CI) | n/N | Case fatality (95% CI) |
| Bennish et al (1990)* | Inpatients of all ages with diarrhoea and culture-confirmed Shigella spp; study done in Bangladesh; deaths ascertained during hospital admission for presenting diarrhoea | 22/219/780 6.7% (5.3–7.8) | 374/9780 8.2% (5.5–11.3) | 6001/9780 10% (9.3–10.8) | 445/9780 10.3% (7.7–13.5) | 739/9780 8.4% (6.4–10.5) |
| Khan et al (2013)f | Inpatients aged <15 years with diarrhoea and culture-confirmed Shigella spp; study done in Bangladesh; deaths ascertained during hospital admission for presenting diarrhoea | 15/792 10.8% (6.4–16.8) | 24/792 4.2% (0.1–21.1) | 504/9792 10.5% (8.0–13.5) | 30/792 13.3% (3.8–30.7) | 77/792 10.4% (0.1–19.0) |
| O'Reilly et al (2012)l | Inpatients aged <5 years with watery, mucoid, or bloody diarrhoea; study done in Kenya; dysentery defined as visible bloody stool; Shigella spp detected by culture; deaths ascertained during hospital admission for presenting diarrhoea | – – 4/42 50.0% (6.8–93.2) | 30/42 23.3% (13.2–52.9) | 6/42† 6.9% (0.8–22.8) | 5/42 0% (0–52.2) | 2/42 50.0% (12.6–98.7) |
| van den Broek et al (2005)TU | Severely malnourished inpatients* aged <4 years with diarrhoea; study done in Bangladesh; unclear definition of dysentery; Shigella spp detected by culture; deaths ascertained during hospital admission for presenting diarrhoea | 38/200 47.3% (31.0–64.2) | – – 162/200 50.6% (42.6–58.6) | – – – – | – – – – |
| de Widderspach-Thor et al (2002)U | All inpatients had culture-confirmed Shigella spp; study done in Djibouti; deaths ascertained during hospital admission for presenting diarrhoea | 6/42† 16.7% (0.4–64.1)† | 6/42† 16.7% (0.4–64.1)† | 23/42 6.9% (0.8–22.8) | 5/42 0% (0–52.2) | 2/42 50.0% (12.6–98.7) |
| Zaman et al (1991)TU | All admissions had culture-confirmed Shigella spp; study done in Bangladesh; deaths ascertained during hospital admission for presenting diarrhoea | 935/3440 0.9% (0.4–1.7) | – – 1834/3440 0.0% (0.7–2.7) | – – – – | – – – – |

Data are Shigella species (n)/total Shigella species (N). The appendix (p 2) summarises the associated GRADE quality assessment. 98 cases of other S dysenteriae, 194 S sonnei, and 379 S boydii are reported; however, no case-fatality rates are given for these serotypes in Zaman et al (1991). *GRADE=Grading of Recommendations Assessment, Development and Evaluation. WAZ=weight-for-age Z score. †Severe malnutrition was defined using Gomez classification WAZ <60% of National Center for Health Statistics median. ‡All S dysenteriae cases combined.

Table 4: Studies of case-fatality rates associated with specific Shigella species
Shigella less likely to develop dysentery after infection were done among children with dysentery. Declining prevalence of dysentery in different regions and across different eras, and cases. Few differences were observed in clinical efficacy of placebo-controlled studies limits conclusions about the overall effectiveness of different antibiotics for the treatment of dysentery. However, given the accepted benefits of treating dysentery with antibiotics, placebo-controlled trials of dysenteric Shigella do not have equipoise. Because Shigella infection, irrespective of dysentery status, appears to be associated with death, antibiotics might play a role in the treatment of non-dysenteric Shigella infection. However, antibiotic resistance develops quickly in Shigella infections and will need to be weighed against increased antibiotic use. The development and use of a rapid diagnostic test for Shigella detection, and ideally a rapid diagnostic test for resistance to commonly used antibiotics, could be used to target treatment and minimise community-wide resistance.

This review had several limitations, most notably the heterogeneity in all analyses. This finding is unsurprising given the diverse populations, comorbidities, and Shigella species covered by this review. Many studies of dysentery epidemics were excluded because they presented only dysentery case fatality without a comparison population, prohibiting a calculation of an OR. These epidemic reports reinforce the importance of S dysenteriae type 1 to public health, documenting very high incidence and case-fatality rates of 1–11%. Data from South America and Africa were under-represented, which limits our findings' generalisability but highlights the need for further research in these regions. There was also substantial heterogeneity in the definition of dysentery. Most studies defined dysentery as bloody stool, but there was varied use of caregiver reports or provider observation for classification. Previous studies have shown that caregiver report of dysentery classifies up to five times more children as having dysentery than does laboratory-observed blood in stool. Mortality studies did not detail the causes of death, highlighting the need for highly characterised prospective cohorts to better understand mechanisms leading to death. Finally, included studies primarily used stool culture for Shigella identification, a less sensitive method than molecular methods. As a result, some children with Shigella infections could have been misclassified as not having Shigella. However, molecular techniques are unable to differentiate Shigella species and Shigella-like bacteria, such as enteroinvasive E coli, which complicates the attribution of diarrhoea and mortality to Shigella. These methods also do not have the ability to ascribe antimicrobial susceptibility patterns to individual pathogens, limiting the clinical use of molecular techniques.

In conclusion, Shigella infection is associated with an increased risk of mortality. Prevention of Shigella infections through vaccination or improvements in safe drinking water and sanitation will be the long-term solution to Shigella-associated mortality. In the meantime, effective Shigella identification and treatment strategies are needed. In most resource-limited settings, where bacterial culture is unavailable, reliance on dysentery for identifying children with Shigella might inadequately identify those at risk of death. Together, these findings suggest that clinicians should continue to aggressively manage dysentery, but should be aware that the absence of dysentery does not indicate a low risk of death and does not exclude Shigella as a cause of diarrhoea. It might be advisable to use pathogen-directed treatment when available, have a lower threshold for inpatient observation, or increase follow-up frequency in particularly vulnerable children with non-dysenteric diarrhoea, such as those younger than 2 years or those with malnutrition. There is an urgent need to reduce Shigella-associated morbidity.

Figure 4: Sensitivity of dysentery for the detection of Shigella infection over time

### Figure 4

| Year | Sensitivity (%) |
|------|----------------|
| 1975 | 80            |
| 1985 | 70            |
| 1995 | 60            |
| 2005 | 50            |
| 2015 | 40            |

Note: Error bars are 95% CI. Line of best fit is weighted to the inverse of the standard error for each estimate. Error bars are calculated by the Senbarr Stata package and therefore differ slightly to those displayed in table 2. 1=Mo-Suwan et al (1979). 2=Stoll et al (1982). 3=Romans et al (1988). 4=Huskins et al (1994). 5=Moalla et al (1994). 6=Echeverria et al (1991). 7=Dutta et al (1992). 8=Kagalwalla et al (1992). 9=Ahmed et al (1997). 10=Khan et al (2013). 11=Sebel et al (2004). 12=Mathan et al (1991). 13=Nakano et al (1998). 14=Youssef et al (2000). 15=Sowmano et al (1997). 16=van den Broek et al (2005). 17=von Seidlein et al (2006). 18=Ozmert et al (2010). 19=Jafari et al (2005). 20=El Shabrawi et al (2015). 21=Debas et al (2011). 22=Oidoko et al (2014). 23=Hegde et al (2013). 24=Eseigbe et al (2013). 25=Aggarwal et al (2016). 26=Perica et al (2016). 27=Pavlinac et al (2016).
and mortality, but the current evidence to support guideline development is inadequate and of low-to-moderate quality. Robust clinical trials to evaluate alternative interventional approaches to Shigellosis in children without dysentery are needed.

Contributors
KDT, RLB, HEA, and PBP were responsible for the design, data collection, and data analysis. JMP, JLW, and PBP provided expert opinion in the study design and were integral to writing and editing this paper.

Declaration of interests
JMP is the recipient of a research Early Career Award from the Hamilton Health Sciences Foundation. All other authors declare no competing interests.

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