to approximately 0.8 million deaths per year [1]. Most of this burden is concentrated in the developing countries of Asia and Africa.

An important cause of diarrhea in children in the developing world; Cholera is a rapidly dehydrating disease that can be fatal if untreated. Cholera was traditionally not

(ICDDR, B) do not restrict use of antibiotics to only "severe" cases and children with "some dehydration" who continue to pass large volumes of stool, are also candidates for antibiotic therapy [8,9].

Dysentery is a major cause of childhood morbidity and mortality [10] and a variety of pathogens are responsible for it including *Shigella*, *Salmonella*, *E. Coli* and *Cam*, *lobac.e* . Of these, *Shigella* is responsible for most of the dysentery cases in the developing world [11]. The global incidence of *Shigella* is estimated at 80-165 million episodes annually, with 99% of episodes in the developing world [12]. A total of 69% of these episodes and 61% of all deaths attributable to shigellosis involve children under 5 years of age. According to previous estimates, 13.9% of infants and 9.4% of 1 to 4 year olds who are hospitalized with shigellosis die each year [13], while a recent review shows that shigellosis incidence is substantial and similar to the earlier estimate, but the updated death estimate is 98% lower [14]. The WHO recommends treating all cases of bloody diarrhea as suspected shigellosis and recommends treatment of shigellosis with ciprofloxacin and with three second-line antibiotics; pivmecillinam, azithromycin and ceftriaxone [10].

Cryptosporidium is a zoonotic intracellular protozoan parasite, which is an important cause of persistent diarrhea in children. It was included in the WHO Neglected Diseases Initiative in 2004. Cryptosporidium may cause life-threatening disease in people with AIDS and contributes significantly to morbidity among children in developing countries [15]. It may account for up to 20% of childhood diarrhea cases in developing countries and is a potentially fatal complication of AIDS [16]. Cryptosporidium infection in early childhood is also associated with poor cognitive function and failure to thrive [17]. Management of persistent infective diarrhea includes rehydration, adequate diet, micronutrient supplementation and antimicrobials [18]. Of established efficacy in immunocompetent patients, nitazoxanide is also useful for immunocompromised patients [19].

We reviewed the scientific evidence available for the use of antibiotics in the treatment of diarrhea due to Cholera, *Shigella* and *C*, *.o o idi m* in children, as well as differences in the effectiveness of various antibiotics. A Cochrane review [20] has evaluated the effectiveness of antibiotics for *Shigella* in children and adults,

Each study was assessed and graded according to the CHERG adaptation of the GRADE technique [22]. Randomized trials received an initial score of "high". We deducted a grade point for each study design limitation. One- to two-point grade increases were allotted to studies with statistically significant strong levels of association (>80% reduction).

Q

We conducted a meta-analysis for individual studies and pooled statistics were reported as the relative risk (RR) between the experimental and control groups with 95% confidence intervals (CI). Mantel–Haenszel pooled RR and corresponding 95% CI were reported or the DerSimonian–Laird pooled RR and corresponding 95% CI, where there was an unexplained heterogeneity. All analyses were conducted using the software Review Manager 5.1. Heterogeneity was quantified by Chi^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance, a low p-value (less than 0.1) or a large chi-squared statistic relative to its degree of freedom and I^2 values greater than 50% were taken as substantial and high heterogeneity. In situations of high heterogeneity, causes were explored by sensitivity analysis and random effect models were used.

We summarized the evidence by outcome, including qualitative assessments of study quality and quantitative measures, according to the standard guidelines. A grade of "high", "moderate", "low" and "very low" was used for grading the overall evidence indicating the strength of an effect on specific health outcome according to the CHERG Rules for Evidence Review [22].

Results

C

We identified 374 titles from search conducted in all databases. After screening titles and abstracts, we reviewed 21 papers for the identified outcome measures of interest (Figure 1). Only one study reported data exclusively for children aged up to 5 years of age, so we expanded our study population to include children up to 16 years. Nine papers were reviewed and two [23,24] included in the final dataset as only these two studies had a suitable control or placebo group [23,24], whereas all other studies had comparison groups of different antibiotics. Both of the included studies were randomized control trials and were conducted in Bangladesh.

R L ST

Table 2 Quality assessment of trials of antibiotics for the treatment of Shigella

Q	A				S	F	
	D		N				
N	D	L	C	G	G	I	C	R R (95%CI)
Clinical Failure (Antibiotic): Moderate Occurrence Quality							
03 [25-27]	RCT	No Control or placebo group, so used treatment failure rates	All suggest benefit	All studies were conducted in developing countries	Hospital based	50		**0.18 (0.1, 0.33)**
Bacteriological Failure (Antibiotic): Low Occurrence Quality							
04 [25-28]	RCT	No Control or placebo group, so used treatment failure rates	All suggest benefit	All studies except one were conducted in developing countries	Hospital based	09		**0.04 (0.01, 0.12)**

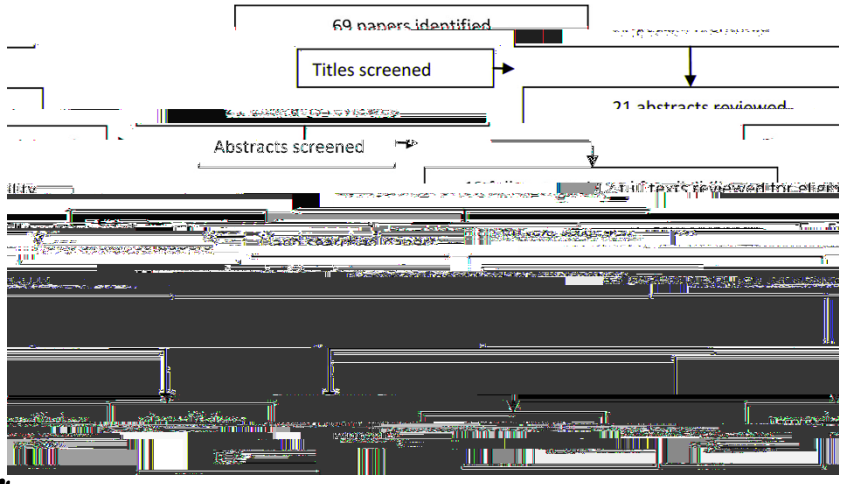

Figure 3 Search strategy flow chart for antibiotic treatment of *Cryptosporidium* diarrhea

Table 3 Quality assessment of trials of antibiotics for the treatment of cryptosporidium

Q	A				S	F	
	D		N				
N	D	L	C	G	G	I	C	R R (95%CI)
Malignancy – All Cause (Antibiotic, Placebo): Low Occurrence Quality							
02 [30,32]	RCT	One studied nitazoxanide while one used spiramycin	All studies suggested benefit	All studies were conducted in developing countr	Hospital based	1	6	**0.24 [0.04, 1.45]**
Clinical Failure (Antibiotic, Placebo): Moderate Occurrence Quality							
02 [30,31]	RCT		Both studied nitazoxanide and suggested benefit	All studies were conducted in developing countr	Hospital based	14	32	**0.48 (0.30, 0.75)**
Parasitological Failure (Antibiotic, Placebo): Moderate Occurrence Quality							
03 [30-32]							

results in an 82% reduction in diarrhea mortality due to *Shigella* (Figure 5). For cryptosporidiosis; there was data on all-cause mortality but the evidence was weak as there were only seven events hence we used clinical failure rates as a proxy for mortality to estimate that antimicrobial treatment of diarrhea due to cryptosporidiosis results in a 54% reduction in mortality (Figure 6).

Discussion

This systematic review concludes that antibiotics when given for Cholera reduce the clinical and bacteriological failure rates; however the evidence for reducing morbidity in children is insufficient to recommend antibiotic use in all cases. It should also be noted that the studies included in our review are more than a decade old and

were nitazoxanide and spiramycin and we conclude that

diarrhea. We have identified a need for further research in this field and recommend that more clinical trials should be conducted to evaluate efficacy and safety of first- and second- line drugs currently in use for treatment for diarrhea in both developing and developed countries to strengthen the evidence of the recommended antibiotics.

C[illegible]

The a thors declare no conflict of interests.

A[illegible]

Dr ZAB as responsible for designing the re ie and co-ordinating the re ie . JKD, AA and RAS ere responsible for: data collection, screening the search res lts, screening retrie ed papers against incl sion criteria, appraising q alit of papers, abstracting data from papers, entering data into Re Man, anal sis and interpretation of data and riting the re ie . ZAB and JKD criticall re ie ed and modified the man script.

A[illegible]

This ork as s pported in part b a grant to the US F nd for UNICEF from the Bill & Melinda Gates Fo ndation (OPP1004060) to e idence-based landscape anal sis on childhood diarrheal disorders and de elopment of global consens s on priorities for research and inter entions.

D[illegible]

The p blication costs for this s pplement ere f nded b a grant from the Bill & Melinda Gates Fo ndation to the US F nd for UNICEF (grant 43386 to "Promote e idence-based decision making in designing maternal, neonatal, and child health inter entions in lo - and middle-income co ntries"). The S pplement Editor is the principal in estigator and lead in the de elopment of the Li es Sa ed Tool (LiST), s pported b grant 43386. He declares that he has no competing interests.
This article has been p blished as part of *BMC [illegible] H[illegible]* Vol me 13 S pplement 3, 2013: The Li es Sa ed Tool in 2013: ne capabilities and applications. The f ll contents of the s pplement are a ailable online at http:// [illegible].biomedcentral.com/bmcp blichealth/s pplements/13/S3.

A[illegible]

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