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# REVIEW ARTICLE
# Comparison of resistance to third-generation cephalosporins in *Shigella* between Europe-America and Asia-Africa from 1998 to 2012

B. GU[1,2]†, M. ZHOU[1,2]†, X. KE[1,2]†, S. PAN[1,2]*, Y. CAO[1,2], Y. HUANG[1,2], L. ZHUANG[3], G. LIU[1,2] AND M. TONG[1,2]

[1] *Department of Laboratory Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China*
[2] *National Key Clinical Department of Laboratory Medicine, Nanjing, China*
[3] *Department of Acute Infectious Disease Prevention and Control, Jiangsu Provincial Center for Disease Prevention and Control, Nanjing, China.*

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## SUMMARY

We conducted a systematic review to compare resistance to third-generation cephalosporins (TGCs) in *Shigella* strains between Europe-America and Asia-Africa from 1998 to 2012 based on a literature search of computerized databases. In Asia-Africa, the prevalence of resistance of total and different subtypes to ceftriaxone, cefotaxime and ceftazidime increased markedly, 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. 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 *S. sonnei*, which even outnumbered *S. flexneri* in some periods. Moreover, 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. These data suggest that monitoring of the drug resistance of *Shigella* strains should be strengthened and that rational use of antibiotics is required.

**Key words**: Cefotaxime, ceftazidime, ceftriaxone, meta-analysis, resistance, *Shigella flexneri*, *Shigella sonnei*.

## INTRODUCTION

As members of the Enterobacteriacae family, *Shigella* species can be classified into four major subtypes based on biochemical and serological characteristics, namely, *S. dysenteriae, S. flexneri, S. boydii* and *S. sonnei*, of which *S. flexneri* and *S. sonnei* are the most common strains [1–4]. Shigellosis is an acute enteric infection caused by *Shigella* species and is manifested by diarrhoea [5]. Acute diarrhoeal disease is a major public health problem throughout the world, with >2 million deaths occurring each year. It primarily affects children aged <5 years in developing countries [6, 7]. About 164·7 million people suffer from bacillary dysentery annually worldwide, causing 0·6 million deaths, of which 60% were in children aged <5 years in developing countries [8–10]. Although shigellosis is a self-limiting disease, antibiotic treatment is recommended because it can shorten the excretion

* Author for correspondence: Dr S. Pan, Department of Laboratory Medicine, the First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, China. (Email: sypan@njmu.edu.cn)
† These authors contributed equally to this work.

time of the pathogen and reduce the duration of transmission rates [11].

However, since the first sulfa-resistant *Shigella* strain was reported in Japan in 1940, antimicrobial resistance has developed from single to multi-drug resistance in recent decades, thus resulting in reduced efficacy of antimicrobial therapies [12, 13]. *Shigella* strains have progressively become resistant to most of the widely used and inexpensive antimicrobials, i.e. sulfonamides, tetracycline, ampicillin, trimethoprim-sulfamethoxazole, nalidixic acid and pivmecillinam, which have all in succession been used as first-line antimicrobial drugs in many parts of the world [12–15]. A significant increasing resistance was seen in quinolones and aminoglycosides, especially in Asia-Africa [16, 17]. Third-generation cephalosporins (TGCs), with their wider antibacterial spectrum and stronger antibacterial activity compared with first- and second-generation cephalosporins, have shown good therapeutic effects against shigellosis. However, sporadic reports concerning resistance to TGCs have appeared [18–22].

The present study aims to analyse the prevalence and distribution of TGC-resistant *Shigella* worldwide using meta-analyses based on systematic review of articles published between January 1998 and December 2012. We also wish to provide recommendations for the empirical antibiotic therapy of shigellosis. Despite the profusion of reports from different parts of the world concerning trends in the antimicrobial resistance of *Shigella*, to the best of our knowledge, these were the first meta-analyses to compare the prevalence of resistance of *Shigella* strains between Europe-America and Asia-Africa and to provide information regarding useful antibiotic treatment for shigellosis.

## METHODS

### Search strategy

Two independent reviewers (B. Gu and M. Zhou) undertook a systematic literature review of potentially relevant studies that reported the prevalence of drug resistance associated with *Shigella* infections. Studies were identified using MEDLINE and EMBASE databases for data in articles reported from January 1998 to December 2012, and the bibliographies of identified articles. Random or fixed effects models were used, based on the *P* value considering the possibility of heterogeneity between studies for meta-analyses. Statistical analyses were undertaken using Stata v. 10.0 (StataCorp, USA). The search strategy used the following terms and connectors: 'bacterial surveillance' OR 'antimicrobial resistance' OR 'bacterial resistance' AND '*Shigella*'. The search was not restricted by language.

### Selection of studies

Studies obtained from the literature search were checked by title and citation. If an article appeared relevant, the abstract was reviewed. Manuscripts with relevant abstracts were examined in full. The criteria for inclusion and exclusion of studies were established by the investigators before the literature was reviewed. Inclusion criteria were: Original article, Short communication, Correspondence or Letter which provided sufficient original data; all strains isolated from stools between 1998 and 2012. Exclusion criteria were: (i) irrelevant studies which focused on resistance mechanism or pathogen identification; (ii) animal or plant experiments; (iii) not isolated from humans; (iv) reviews and case reports; (v) does not include *Shigella* species; (vi) does not cover study drugs; (vii) does not provide specific data on prevalence of resistance ; (viii) not data from 1998 to 2012; (ix) not separated by region or year; (x) does not provide reliable information in full. The studies included were divided into five periods (1998–2000, 2001–2003, 2004–2006, 2007–2009, 2010–2012) for comparison between states and three periods (1998–2000, 2001–2006, 2007–2012) for comparison between countries to allow for analyses of trends based on the year in which shigella were isolated. Before we excluded studies, authors of such studies were contacted in an effort to obtain missing data. Disagreements between the two reviewers regarding standards for inclusion or exclusion were resolved by consensus.

### Validity assessment

Studies were assessed for quality, with only high-quality studies included for analyses. High-quality studies were prospective cohort or retrospective consecutive cohort studies; provided basic data that included study period and area, total number tested and number of resistant strains; conducted a susceptibility test in accordance with guidelines established by the Clinical and Laboratory Standards Institute (CLSI); reported at least one of the three antimicrobials of interest (ceftriaxone, cefotaxime, ceftazidime) with quality control; included individuals who had no other infections except bacillary dysentery. Only one

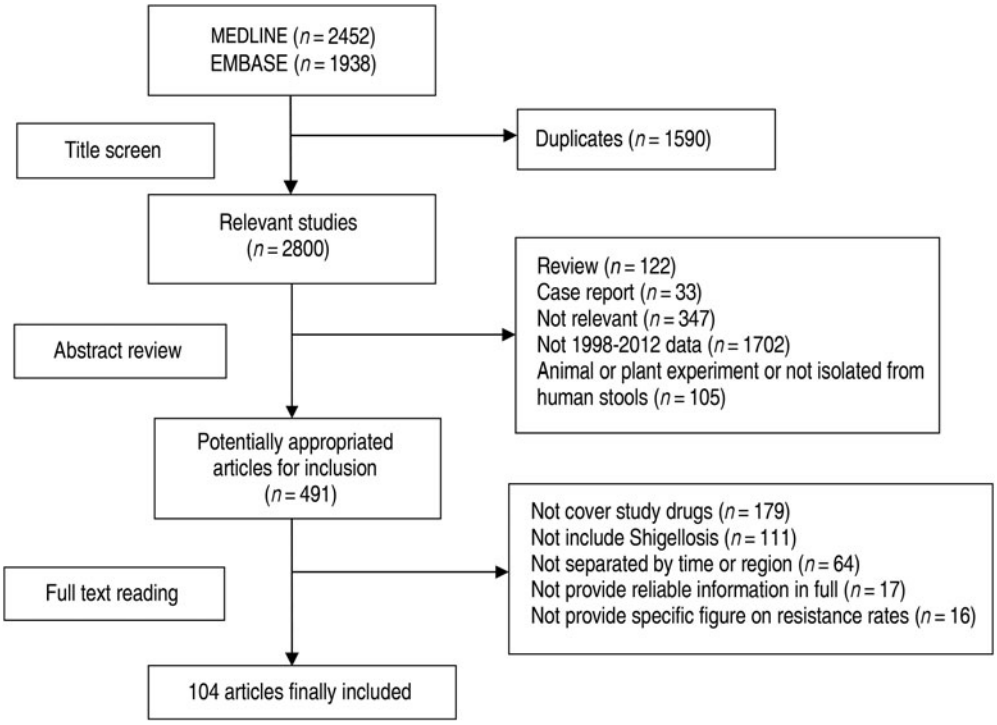


**Fig. 1.** Results of the systematic literature search.

representative case for each outbreak was included unless the isolates had different patterns of antibiotic susceptibility. If studies overlapped, we included the more recent and larger study in the analyses. If the smaller study provided data not reported in the larger study, results were included for that specific variable.

### Data extraction and statistical analyses

Data extraction was performed by two reviewers using a standardized extraction form. If there was disagreement, the relevant article was reviewed and differences resolved by consensus. Microsoft Excel v. 12.0 (Microsoft Corp., USA) was used for the entry and analyses of data. The possibility of significant heterogeneity between studies was tested with the $Q$ test ($P < 0{\cdot}10$ was considered indicative of significant heterogeneity), and random or fixed effects models were chosen according to the $P$ value for meta-analyses. Freeman–Tukey arcsine transformations were performed to stabilize variances and, after the meta-analysis, investigators transformed the summary estimate and the confidence interval (CI) boundaries back to proportion using the sine function; the specific conversion details are given in reference [23]. Data manipulation and statistical analyses were undertaken using Stata v. 10.0.

## RESULTS

### Results of the systematic literature search

We reviewed 4390 publications from MEDLINE and EMBASE databases reported from January 1998 to December 2012. Candidate articles are given in Supplementary Table S1. After scanning of the title and abstract, 491 articles were retrieved for detailed full-text intensive reading. Of these 492 articles, 179 did not cover the study drugs, 111 did not include *Shigella* species, 64 were not separated by time or year, 17 did not have secure sources of information, 16 did not provide specific prevalence of resistance. Finally, 104 studies concerning the resistance data of *Shigella* to TGCs based on inclusion and exclusion criteria (Fig. 1) were included.

### Studies considered for primary analysis

A total of 104 reports were included in the meta-analyses. Analyses were conducted across geographical areas, study years and different subtypes for selected primary endpoints. That is, the resistance of: *Shigella* to ceftriaxone, cefotaxime and ceftazidime; *S. flexneri* to ceftriaxone, cefotaxime and ceftazidime; and *S. sonnei* to ceftriaxone, cefotaxime and ceftazidime (Supplementary Table S1).

Table 1. *Resistance to ceftriaxone, cefotaxime and ceftazidime in* Shigella *spp. collected during 1998–2012*

| | Europe-America | | Asia-Africa | |
|---|---|---|---|---|
| Study period | R% (95% CI) | Weight % | R% (95% CI) | Weight % |
| **Ceftriaxone** | | | | |
| 1998–2000 | 0·2 (0·1–0·5) | 19·4 | 0·8 (0·3–1·6) | 19·5 |
| 2001–2003 | 0·4 (0·1–0·9) | 33·8 | 1·2 (0·7–1·8) | 38·9 |
| 2004–2006 | 0·5 (0·2–1·0) | 32·7 | 3·0 (1·5–5·0) | 25·1 |
| 2007–2009 | 0·2 (0·1–0·5) | 14· 1 | 8·8 (4·9–13·6) | 14·0 |
| 2010–2012 | NR | NR | 14·2 (3·9–29·4) | 2·5 |
| Overall | 0·4 (0·2–0·6) | 100·0 | 2·5 (1·9–3·2) | 100·0 |
| **Cefotaxime** | | | | |
| 1998–2000 | 0·1 (0·0–0·4) | 77·1 | 3·7 (1·4–7·0) | 19·6 |
| 2001–2003 | NR | NR | 0·8 (0·4–1·4) | 34·6 |
| 2004–2006 | 0·2 (0·0–1·0) | 22·3 | 3·0 (1·4–5·2) | 26·4 |
| 2007–2009 | 3·7 (3·1–28·6) | 0·6 | 10·4 (3·7–20·0) | 13·5 |
| 2010–2012 | NR | NR | 22·6 (4·8–48·6) | 5·9 |
| Overall | 0·1 (0·0–0·4) | 100·0 | 3·7 (2·4–5·2) | 100·0 |
| **Ceftazidime** | | | | |
| 1998–2000 | 0·2 (0·0–0·5) | 78·7 | 1·6 (0·1–4·5) | 12·9 |
| 2001–2003 | 0·2 (0·0–1·4) | 14·1 | 1·7 (0·2–8·9) | 25·6 |
| 2004–2006 | 0·5 (0·5–4·4) | 3·6 | 11·0 (2·6–24·4) | 29·4 |
| 2007–2009 | 0·5 (0·5–4·4) | 3·6 | 11·1 (4·5–20·3) | 22·4 |
| 2010–2012 | NR | NR | 6·2 (3·8–9·1) | 9·7 |
| Overall | 0·2 (0·0–0·5) | 100·0 | 6·0 (2·8–10·3) | 100·0 |

R, Resistance; CI, confidence interval; NR, no result.
Weight % refers to how much each row contributes to the 'Overall' row.

### Comparison of the resistance of TGCs between Europe-America and Asia-Africa

Table 1 shows the comparison of the resistance of total *Shigella* isolates to ceftriaxone, cefotaxime and ceftazidime between European-American and Asian-African countries. As seen in the table, a lower average prevalence of ceftriaxone resistance was found in Europe-America countries (0·4%, 95% CI 0·2–0·6), with no large fluctuations. Data for 2010–2012 in Europe-America were not found. By contrast, the resistance to ceftriaxone in Asia–Africa during the study years showed an obvious upward trend, especially after 2007, reaching 14·2% (95% CI 3·9–29·4) during 2010–2012, 17·8 times greater than that found in 1998–2000. The average prevalence of resistance in Asia-Africa was 2·5% (95% CI 1·9–3·2), 6·3 times of that found in Europe-America.

Slightly different from ceftriaxone, prevalence resistance to cefotaxime in Europe-America showed a noticeable upward trend after 2007, despite the relatively low total average prevalence of resistance of 0·1% (95% CI 0·0–0·4). The data for 2001–2003 and 2010–2012 in Europe-Africa areas were not found. Nevertheless, the prevalence of resistance to cefotaxime was markedly higher in Asia-Africa than in Europe-America, i.e. 3·7% (95% CI 2·4–5·2), 37·0 times that observed in Europe-America.

Similar to ceftriaxone, the prevalence of resistance to ceftazidime in Europe-America remained at a very low level, with an average prevalence of resistance being 0·2% (95% CI 0·0–0·5). However, there was a mild increasing trend of resistance during the study periods in Europe-America. The data for 2010–2012 in Europe-Africa were not obtained. With regard to Asia-Africa, analogously, resistance to ceftazidime was much more severe than that seen in Europe-America. The total average prevalence of resistance was 6·0% (95% CI 2·8–10·3), 30·0 times higher than that seen in Europe-America.

### Comparison between S. *flexneri* and S. *sonnei*

The resistance patterns of *S. flexneri* and *S. sonnei* to ceftriaxone, cefotaxime and ceftazidime are compared to each other in Table 2. The overall prevalence of resistance of *S. flexneri* to ceftriaxone was 0·6% (95% CI 0·3–1·1) whereas that of *S. sonnei* was only 0·2% (95% CI 0·1–0·4) in Europe-America. However, Asia-Africa

Table 2. *Rates of resistance to ceftriaxone, cefotaxime and cefazidime in* Shigella flexneri *and* S. sonnei *isolated from Europe-America and Asia-Africa during 1998–2012*

| | | *S. flexneri* | | *S. sonnei* | |
|---|---|---|---|---|---|
| District | Study period | R% (95% CI) | Weight % | R% (95% CI) | Weight % |
| **Ceftriaxone** | | | | | |
| Europe-America | 1998–2000 | 0·3 (0·0–1·7) | 12·8 | 0·1 (0·0–0·4) | 9·7 |
| | 2001–2003 | 1·1 (0·2–2·6) | 23·3 | 0·1 (0·0–0·3) | 33·5 |
| | 2004–2006 | 0·6 (0·1–1·4) | 42·9 | 0·4 (0·2–0·7) | 34·4 |
| | 2007–2009 | 0·4 (0·0–1·6) | 21·0 | 0·3 (0·1–0·7) | 22·4 |
| | 2010–2012 | NR | NR | NR | NR |
| | Overall | 0·6 (0·3–1·1) | 100·0 | 0·2 (0·1–0·4) | 100·0 |
| Asia-Africa | 1998–2000 | 0·4 (0·1–0·8) | 22·3 | 1·3 (0·6–2·2) | 25·7 |
| | 2001–2003 | 1·4 (0·7–2·4) | 33·4 | 2·0 (0·9–3·5) | 39·5 |
| | 2004–2006 | 2·8 (1·4–4·8) | 25·7 | 6·2 (2·4–11·5) | 24·2 |
| | 2007–2009 | 10·6 (3·3–21·4) | 14·8 | 15·6 (8·1–25·1) | 9·4 |
| | 2010–2012 | 32·1 (1·1–79·5) | 3·8 | 6·7 (1·0–16·9) | 1·1 |
| | Overall | 3·0 (2·0–4·2) | 100·0 | 3·5 (2·3–5·0) | 100·0 |
| **Cefotaxime** | | | | | |
| Europe-America | 1998–2000 | NR | NR | NR | NR |
| | 2001–2003 | NR | NR | NR | NR |
| | 2004–2006 | 0·6 (0·1–3·2) | 100·0 | 0·2 (0·1–1·6) | 100·0 |
| | 2007–2009 | NR | NR | NR | NR |
| | 2010–2012 | NR | NR | NR | NR |
| | Overall | 0·6 (0·1–3·2) | 100·0 | 0·2 (0·1–1·6) | 100·0 |
| Asia-Africa | 1998–2000 | 4·3 (0·6–11·4) | 24·5 | 0·6 (0·1–1·8) | 30·8 |
| | 2001–2003 | 2·4 (0·8–4·9) | 29·3 | 0·8 (0·3–1·6) | 33·9 |
| | 2004–2006 | 4·0 (1·2–8·4) | 27·9 | 4·8 (0·3–14·6) | 22·5 |
| | 2007–2009 | 21·6 (8·1–39·2) | 11·8 | 13·5 (4·4–26·5) | 7·0 |
| | 2010–2012 | 34·0 (25·5–43·1) | 6·5 | 14·2 (1·7–36·0) | 5·8 |
| | Overall | 6·3 (3·7–9·7) | 100·0 | 2·8 (1·3–4·8) | 100·0 |
| **Ceftazidime** | | | | | |
| Europe-America | 1998–2000 | NR | NR | NR | NR |
| | 2001–2003 | 0·7 (0·1–4·2) | 46·8 | 0·3 (0·1–2·1) | 84·0 |
| | 2004–2006 | 0·7 (0·6–5·7) | 26·6 | 2·1 (1·9–17·3) | 8·0 |
| | 2007–2009 | 0·7 (0·6–5·7) | 26·6 | 2·1 (1·9–17·3) | 8·0 |
| | 2010–2012 | NR | NR | NR | NR |
| | Overall | 0·7 (0·0–2·7) | 100·0 | 0·5 (0·0–2·3) | 100·0 |
| Asia-Africa | 1998–2000 | 1·9 (0·1–9·0) | 11·7 | 0·6 (0·1–3·6) | 10·0 |
| | 2001–2003 | 2·8 (0·3–14·3) | 34·3 | 1·3 (0·0–5·7) | 39·0 |
| | 2004–2006 | 10·4 (0·1–34·3) | 29·6 | 9·5 (1·3–24·0) | 33·5 |
| | 2007–2009 | 16·6 (0·9–46·1) | 19·5 | 17·5 (2·8–73·6) | 11·9 |
| | 2010–2012 | 11·6 (2·8–25·3) | 4·9 | 0·7 (0·6–5·8) | 5·6 |
| | Overall | 7·0 (1·9–14·8) | 100·0 | 4·4 (1·4–9·0) | 100·0 |

R, Resistance; CI, confidence interval; NR, no result.
Weight % refers to how much each row contributes to the 'Overall' row.

showed a different pattern of resistance in that *S. sonnei* appeared to be more resistant to ceftriaxone than *S. flexneri*, with the respective prevalence of resistance being 3·5% (95% CI 2·3–5·0) *vs.* 3·0% (95% CI 2·0–4·2). With regard to cefotaxime and ceftazidime, *S. flexneri* showed a higher prevalence of resistance than *S. sonnei* in Europe-America and Asia-Africa regardless of regional differences. The overall prevalence of resistance of *S. flexneri* and *S. sonnei* to cefotaxime and ceftazidimewere 0·6% (95% CI 0·1–3·2) *vs.* 0·2% (95% CI 0·1–1·6) and 0·7% (95% CI 0·0–2·7) *vs.* 0·5% (95% CI 0·0–2·3) (Table 2), respectively, in Europe-America, and 6·3% (95% CI 3·7–9·7) *vs.* 2·8% (95% CI 1·3–4·8) and 7·0% (95% CI 1·9–14·8) *vs.* 4·4% (95% CI 1·9–9·0) (Table 2), respectively, in Asia-Africa. Irrespective of

*S. flexneri* or *S. sonnei*, the prevalence of resistances to these three study drugs was greater in Asia-Africa than in Europe-America, especially from 2007 to 2012. Data concerning these three TGCs in Europe-America during 2010–2012 were not found.

### Comparison of the resistance of TGCs between different countries

Comparative analyses of the resistance of *Shigella* isolates against TGCs in different countries are illustrated in descending order in Table 3. First, we can see that the highest average prevalence of resistance to ceftriaxone was in Vietnam, reaching 16·9 (95% CI 13·4–20·7), followed by China, India and Palestine, representing 11·2% (95% CI 10·0–12·4), 9·5% (95% CI 8·1–11·1) and 9·2% (95% CI 2·2–20·2), respectively. Similarly, the first four countries with a high prevalence of resistance to cefotaxime were Nigeria (43·6%, 95% CI 31·7–55·9), China (12·0%, 95% CI 10·5–13·4), Ghana (11·6%, 95% CI 2·8–25·3) and Palestine (5·0%, 95% CI 0·2–15·7). With regard to ceftazidime, Sudan, Iran, Palestine and India had a higher prevalence of resistance, each representing 52·1% (95% CI 37·9–66·1), 10·0 (95% CI 8·4–11·8), 7·9% (95% CI 1·6–18·5% and 6·6% (95% CI 3·4–10·7), respectively. Comparing these three TGCs, ceftazidime had the highest overall prevalence of resistance of 3·8% (95% CI 0·7–4·4) whereas ceftriaxone showed the lowest resistance of 0·9% (95% CI 0·8–1·0). However, one marked similarity was that all the countries that showed a relatively high prevalence of resistance were developing countries in Asia such as Vietnam and China. The extraordinarily high prevalence of resistance for cefotaxime in Nigeria and for ceftazidime in Sudan may have a potential association with the small sample of the data. Second, these figures also provided a tendency of resistance over time. That is, the fastest-rising countries for resistance to ceftriaxone, cefotaxime and ceftazidime were Pakistan, India and Iran from 2007 to 2012, representing a 6·1-, 14·0- and 2·1-fold increase over the last 15 years.

## DISCUSSION

For years, shigellosis has been endemic in many resource-poor countries. This has been primarily because of over-crowding, poor housing, poor sanitation and inadequate water supply facilitating faecal–oral transmission. Any of the four subtypes of *Shigella* (*S. dysenteriae, S. flexneri, S. boydii, S. sonnei*) can cause shigellosis with symptoms ranging from watery diarrhoea to fulminant dysentery [20, 24–26]. Shifts in the prevalent serogroups and changing resistance patterns in antimicrobial susceptibilities in *Shigella* are posing major difficulties in determination of an appropriate drug for the treatment of shigellosis [7, 27]. Moreover, antimicrobial resistance in *Shigella* varies from region to region. Thus, when choosing an appropriate antibiotic to treat shigellosis, an understanding of the local antimicrobial resistance is important. Knowledge regarding the occurrence of different serotypes in different countries and geographical regions may assist in the recognition and tracing of emerging pathogens and in the implementation of correct treatment and control strategies.

Various factors can contribute to the emergence and dissemination of multidrug-resistant (MDR) strains of *Shigella*. The most decisive factor is selection of MDR strains harbouring certain resistance mechanisms because of overuse or misuse of drugs in certain geographical areas. TGCs are used for treating infections caused by MDR *Shigella* [19, 28]. As part of the $\beta$-lactam family of drugs, TGCs have advantages over the other agents: i.e. a wider spectrum of activity, stronger germicidal activity, fewer allergic reactions, and stablility against $\beta$-lactamase. The activity of $\beta$-lactams is in combination with penicillin-binding proteins and inhibition of cytoderm synthesis, thereby restraining the proliferation of bacteria. Reports regarding resistance by *Shigella* to TGCs have been published, but they are relatively uncommon [20, 29, 30]. However, resistance to TGCs due to extended-spectrum $\beta$-lactamases (ESBLs), which confer resistance to all $\beta$-lactamases except cephamycins and carbapenems, has emerged as a new problem. ESBLs, are enzymes usually derived from the widespread broad-spectrum $\beta$-lactamase TEM-1 and SHV-1, able to hydrolyse and cause resistance to oxyimino-cephalosporins and aztrenman, There are also new families of ESBLs, including the CTX-M and OXA-type enzymes as well as novel, unrelated $\beta$-lactamases [31].

Comparing the prevalence resistance to these three study drugs, the first conclusion we can make is that, to all appearances, in Europe-America, there were few large changes in the prevalence of resistance of the three study drugs during the study years, maintaining a level of <0·1%. However Asia-Africa had a much greater prevalence of resistance with an increasing upward trend year by year. Although no upward

Table 3. *Resistance to ceftriaxone, cefotaxime and cefazidime in* Shigella *spp. in different countries during 1998–2012*

| Country | 1998–2000 R% (95% CI) | Weight % | 2001–2006 R% (95% CI) | Weight % | 2007–2012 R% (95% CI) | Weight % | 1998–2012 R% (95% CI) | Weight % |
|---|---|---|---|---|---|---|---|---|
| **Ceftriaxone** | | | | | | | | |
| Vietnam | 3·8 (1·3–7·5) | 2·9 | 6·8 (3·6–10·9) | 0·9 | 22·2 (17·5–27·4) | 5·6 | 16·9 (13·4–20·7) | 1·4 |
| China | 4·7 (3·2–7·5) | 5·4 | 10·9 (9·4–12·5) | 7·6 | 14·5 (11·9–17·3) | 13·8 | 11·2 (10·0–12·4) | 10·1 |
| India | 0·7 (0·7–6·3) | 0·7 | 6·1 (4·4–8·0) | 3·3 | 13·2 (10·9–15·7) | 15·4 | 9·5 (8·1–11·1) | 5·0 |
| Palestine | 5·0 (0·2–15·7) | 0·6 | 9·2 (2·2–20·2) | 0·2 | NR | NR | 9·2 (2·2–20·2) | 0·2 |
| South Africa | NR | NR | 8·6 (2·6–17·7) | 0·3 | NR | NR | 5·2 (1·6–10·9) | 0·2 |
| Ghana | NR | NR | 4·4 (3·6–32·9) | 0·0 | NR | NR | 4·4 (3·6–32·9) | 0·0 |
| Greek | NR | NR | NR | NR | 3·7 (3·1–28·6) | 0·2 | 3·7 (3·1–28·6) | 0·0 |
| Pakistan | 0·1 (0·1–1·0) | 4·6 | 2·3 (1·6–3·2) | 6·4 | 14·0 (9·5–19·1) | 4·1 | 3·3 (2·5–4·2) | 6·0 |
| Egypt | 2·5 (0·1–7·9) | 1·2 | NR | NR | NR | NR | 2·5 (0·1–7·9) | 0·2 |
| Peru | NR | NR | 2·5 (1·3–4·1) | 2·4 | NR | NR | 2·5 (1·3–4·1) | 1·7 |
| Iran | 0·6 (0·6–5·3) | 0·8 | 2·2 (1·5–3·1) | 6·8 | 4·5 (1·7–8·4) | 3·0 | 2·2 (1·3–3·1) | 4·9 |
| Korea | 1·1 (0·9–8·9) | 0·5 | 3·3 (0·1–10·6) | 0·2 | 3·7 (3·1–28·6) | 0·2 | 2·0 (0·1–6·4) | 0·3 |
| Turkey | NR | NR | 2·2 (0·7–4·8) | 1·0 | NR | NR | 2·0 (0·7–4·8) | 0·7 |
| Tanzania | NR | NR | 1·6 (1·4–13·2) | 0·1 | NR | NR | 1·6 (1·4–13·2) | 0·1 |
| Bangladesh | 0·1 (0·1–0·5) | 9·0 | 1·1 (0·5–1·9) | 4·2 | NR | NR | 0·9 (0·4–1·6) | 3·6 |
| Malaysia | NR | NR | 1·0 (0·0–3·4) | 0·7 | 1·0 (0·0–3·4) | 2·9 | 0·8 (0·0–3·4) | 0·5 |
| Argentina | NR | NR | 0·8 (0·7–6·7) | 0·2 | NR | NR | 0·8 (0·7–6·7) | 0·1 |
| Kuwait | NR | NR | 0·6 (0·5–5·0) | 0·2 | NR | NR | 0·6 (0·5–5·0) | 0·2 |
| Brazil | 0·7 (0·1–1·9) | 7·0 | 0·5 (0·1–1·4) | 2·2 | 0·9 (0·8–7·9) | 0·6 | 0·5 (0·2–1·1) | 2·9 |
| Uruguay | NR | NR | 0·5 (0·5–4·3) | 0·2 | 0·5 (0·5–4·3) | 1·0 | 0·5 (0·5–4·3) | 0·2 |
| Canada | 0·3 (0·0–0·9) | 11·3 | 0·6 (0·1–1·6) | 2·0 | 0·6 (0·1–1·6) | 8·6 | 0·4 (0·1–0·8) | 3·4 |
| Japan | NR | NR | 0·4 (0·4–3·7) | 0·3 | NR | NR | 0·4 (0·4–3·7) | 0·2 |
| Ethiopia | NR | NR | 0·3 (0·2–2·4) | 0·4 | NR | 1·9 | 0·3 (0·2–2·4) | 0·3 |
| Arabia Saudi | 0·5 (0·4–4·2) | 1·1 | 0·4 (0·4–3·6) | 0·3 | NR | NR | 0·2 (0·2–2·0) | 0·4 |
| Chile | NR | NR | 0·2 (0·2–1·6) | 0·7 | NR | NR | 0·2 (0·2–1·6) | 0·5 |
| Mozambique | NR | NR | 0·2 (0·2–2·0) | 0·5 | NR | NR | 0·2 (0·2–2·0) | 0·4 |
| United Arab Emirates | NR | NR | 0·2 (0·2–2·2) | 0·5 | NR | NR | 0·2 (0·2–2·2) | 0·4 |
| USA | 0·0 (0·0–0·3) | 16·7 | 0·2 (0·1–0·4) | 16·7 | 0·2 (0·0–0·4) | 41·5 | 0·2 (0·1–0·3) | 21·7 |
| Finland | NR | NR | 0·1 (0·1–1·0) | 1·1 | NR | NR | 0·1 (0·1–1·0) | 0·8 |
| Indonesia | 0·0 (0·0–0·3) | 15·6 | 0·1 (0·0–0·3) | 7·2 | 0·4 (0·4–3·7) | 1·2 | 0·1 (0·0–0·2) | 8·0 |
| Israel | 0·2 (0·0–0·8) | 12·5 | 0·1 (0·1–0·2) | 27·0 | NR | NR | 0·1 (0·1–0·2) | 19·4 |
| Nepal | NR | NR | 0·1 (0·1–1·0) | 1·1 | NR | NR | 0·1 (0·1–1·0) | 0·8 |
| Yemen | NR | NR | 0·1 (0·1–1·1) | 0·5 | NR | NR | 0·1 (0·1–2·1) | 0·4 |
| Bahrain | 0·0 (0·0–0·4) | 10·3 | 0·2 (0·2–1·8) | 0·6 | NR | NR | 0·0 (0·0–0·4) | 1·8 |
| England | NR | NR | 0·0 (0·0–0·2) | 4·2 | NR | NR | 0·0 (0·0–0·2) | 3·2 |
| Overall | 0·3 (0·1–0·4) | 100·0 | 0·9 (0·8–1·0) | 100·0 | 3·6 (3·1–4·2) | 100·0 | 0·9 (0·8–1·0) | 100·0 |

Table 3 (*cont.*)

| Country | 1998–2000 R% (95% CI) | Weight % | 2001–2006 R% (95% CI) | Weight % | 2007–2012 R% (95% CI) | Weight % | 1998–2012 R% (95% CI) | Weight % |
|---|---|---|---|---|---|---|---|---|
| **Cefotaxime** | | | | | | | | |
| Nigeria | 43·6 (31·7–55·9) | 2·5 | NR | NR | NR | NR | 43·6 (31·7–55·9) | 0·7 |
| China | 0·4 (0·4–3·5) | 2·4 | 6·7 (5·4–8·1) | 26·9 | 23·0 (19·8–26·3) | 43·6 | 12·0 (10·5–13·4) | 27·3 |
| Ghana | NR | NR | 11·6 (2·8–25·3) | 0·6 | NR | NR | 11·6 (2·8–25·3) | 0·3 |
| Palestine | 5·0 (0·2–15·7) | 1·1 | 5·0 (0·2–15·7) | 0·6 | NR | NR | 5·0 (0·2–15·7) | 0·3 |
| India | 9·2 (5·5–13·7) | 7·1 | 1·6 (0·8–2·7) | 14·4 | 7·1 (3·7–11·6) | 10·9 | 4·7 (3·4–6·0) | 13·6 |
| Greece | NR | NR | NR | NR | 3·7 (3·1–28·6) | 0·5 | 3·7 (3·1–28·6) | 0·1 |
| Turkey | 3·7 (2·4–5·4) | 23·6 | 3·3 (2·2–4·6) | 16·4 | 3·7 (2·4–5·4) | 41·1 | 3·3 (2·1–4·6) | 10·7 |
| Egypt | 2·5 (0·1–7·9) | 2·3 | NR | NR | NR | NR | 2·5 (0·1–7·9) | 0·8 |
| Iran | NR | NR | 1·6 (0·8–2·8) | 13·0 | 22·4 (10·7–36·8) | 2·6 | 1·6 (0·8–2·8) | 8·5 |
| Tunisia | NR | NR | NR | NR | 1·5 (1·3–12·4) | 1·2 | 1·5 (1·3–12·4) | 0·2 |
| Yemen | 7·7 (1·2–19·3) | 1·3 | 0·1 (0·1–1·1) | 4·2 | NR | NR | 1·1 (0·2–2·7) | 1·5 |
| Central African Republic | NR | NR | 0·9 (0·0–3·0) | 3·2 | NR | NR | 0·9 (0·0–3·0) | 2·1 |
| Argentina | NR | NR | 0·8 (0·7–6·7) | 0·7 | NR | NR | 0·8 (0·7–6·7) | 0·4 |
| South Africa | NR | NR | 0·7 (0·6–6·1) | 0·7 | NR | NR | 0·7 (0·6–6·1) | 0·5 |
| Kuwait | NR | NR | 0·6 (0·5–5·0) | 0·9 | NR | NR | 0·6 (0·5–5·0) | 0·6 |
| Nepal | NR | NR | 0·4 (0·3–3·2) | 1·4 | NR | NR | 0·4 (0·3–3·2) | 0·9 |
| Arabia Saudi | 0·5 (0·4–4·2) | 2 | 0·4 (0·4–3·6) | 1·2 | NR | NR | 0·2 (0·2–2·0) | 1·5 |
| United Arab Emirates | NR | NR | 0·2 90·2–2·2) | 2·1 | NR | NR | 0·2 (0·2–2·2) | 1·4 |
| Finland | NR | NR | 0·1 (0·1–1·0) | 4·7 | NR | NR | 0·1 (0·1–1·0) | 3·1 |
| Senegal | 0·4 (0·4–3·5) | 2·4 | 0·1 (0·1–0·7) | 6·6 | NR | NR | 0·1 (0·1–0·6) | 5·1 |
| Bahrain | 0·0 (0·0–0·4) | 19·9 | 0·2 (0·2–1·8) | 2·4 | NR | NR | 0·0 (0·0–0·3) | 8·4 |
| Canada | 0·0 (0·0–0·2) | 35·1 | NR | NR | NR | | 0·0 (0·0–0·2) | 12·0 |
| Overall | 1·2 (0·8–1·7) | 100·0 | 2·1 (1·7–2·5) | 100·0 | 11·3 (9·7–13·0) | 100·0 | 3·0 (2·6–3·4) | 100·0 |
| **Ceftazidime** | | | | | | | | |
| Sudan | NR | NR | 52·1 (37·9–66·1) | 2·5 | 52·1 (37·9–66·1) | 5·3 | 52·1 (37·9–66·1) | 1·3 |
| Iran | NR | NR | 10·0 (8·4–11·8) | 61·3 | NR | NR | 10·0 (8·4–11·8) | 33·6 |
| Palestine | 5·0 (0·2–15·7) | 2·4 | 9·2 (2·2–20·2) | 2·0 | NR | NR | 7·9 (1·6–18·5) | 1·1 |
| India | 0·7 (0·7–6·3) | 2·9 | 5·3 (2·0–9·9) | 6·4 | 11·3 (5·9–18·1) | 11·6 | 6·6 (3·4–10·7) | 5·0 |
| Ghana | NR | NR | 4·4 (3·6–32·9) | 0·3 | NR | NR | 4·4 (3·6–32·9) | 0·2 |
| China | 0·4 (0·4–3·5) | 5·2 | 3·4 (1·7–5·6) | 17·5 | 4·2 (2·8–5·8) | 77·4 | 4·0 (2·8–5·5) | 22·9 |
| Uruguay | NR | NR | 0·5 (0·5–4·3) | 2·6 | 0·5 (0·5–4·3) | 5·7 | 0·5 (0·5–4·3) | 0·4 |
| Brazil | NR | NR | 0·2 (0·2–1·5) | 7·4 | NR | NR | 0·2 (0·2–1·5) | 4·1 |
| Canada | 0·1 (0·0–0·4) | 89·5 | NR | NR | NR | NR | 0·1 (0·0–0·4) | 30·4 |
| Overall | 0·2 (0·0–0·5) | 100·0 | 7·5 (6·3–11·7) | 100·0 | 5·9 (4·5–7·6) | 100·0 | 3·8 (0·7–4·4) | 100·0 |

R, Resistance; CI, confidence interval; NR, no result.
Weight % refers to how much each row contributes to the 'Overall' row.

trend was showing in Europe-America, some studies have reported that certain MDR strains of *Shigella* have been transmitted by travellers in Europe-America [32–35]. Furthermore, resistance rates to ceftriaxone, cefotaxime and ceftazidime were up to 14·2% (95% CI 3·9–29·4), 22·6% (95% CI 4·8–48·6) and 6·2% (95% CI 3·8–9·1), respectively (Table 1) during 2010–2012 in Asia-Africa which should attract immediate attention. Several explanations could account for this phenomenon. First, regional differences which directly determine the socioeconomic status are the root cause. People living in relatively developed areas (Europe-America) tend to obtain better treatment after infection than people in less developed countries (Asia-Africa). Second, deficiencies in medical systems and facilities also play an important part. Asian-African countries such as Pakistan lack the infrastructure to monitor antimicrobial resistance at the national level [36, 37]. In addition, inexpensive antibiotics are available from numerous licensed and non-licensed sources in many Asian-African countries, making drug abuse a common problem, leading to a high prevalence of resistance [5, 27]. Third, poor hygiene and sanitation with limited access to safe drinking water contributes to the spread of MDR strains of *Shigella.* Underlying conditions, such as malnutrition, which increase the risk of contracting diarrhoea, are also common in Asian-African countries [27].

Upon comparison of the prevalence of resistance between *S. flexneri* and *S. sonnei*, the former showed a notable increase in resistance to these three antibiotics in Asia-Africa. Values for resistance in 2010–2012 reached 32·1% (95% CI 1·1–79·5) and 34·0% (95% CI 25·5–43·1) (Table 2) for ceftriaxone and cefotaxime, respectively, suggesting that prescription of these antibiotics should be considered very carefully. With regard to *S. sonnei*, the increase was also very fast although lower than that for *S. flexneri*, each representing <20% in 2010–2012. Similar trends were found in the prevalence of resistance of *S. flexneri* and *S. sonnei* in Europe-America to the study drugs although the total average resistance remained at a low level (<1·0). Information about the prevalence of resistance by *Shigella* to cefotaxime was only seen in 2004–2006 in Europe-America, which stresses the need for continuous surveillance of resistance in those countries. When explaining the appreciable difference between the prevalence of resistance of *S. flexneri* and *S. sonnei*, several studies have demonstrated that integrons have a key role in the development of drug resistance in bacteria, especially Gram-negative bacteria [38–40]. In *Shigella* species, antimicrobial resistance is often associated with class 1 and class 2 integrons that contain resistance gene cassettes. These gene cassettes are mobile and can be transferred from one bacterium to another. Antibiotic resistance gene cassettes may provide 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. The distribution of integrons varies according to the species and resistance phenotype. *S. sonnei* and *S. boydii* strains contain a single class 2 integron, whereas *S. flexneri* and *S. dysenteriae* strains carry a class 1 integron, either alone or in association with a class 2 integron [41]. Harbouring two types of integrons therefore increases the probability of dissemination of MDR strains of *Shigella*.

Another noteworthy finding in these meta-analyses was that certain countries both in Europe-America and Asia-Africa, had a rapid rising trend in the prevalence of resistance of *S. sonnei* which, even outnumbered that of *S. flexneri* in some periods. For instance, the total prevalence of resistance of *S. sonnei* to ceftriaxone was higher than that for *S. flexneri* in Asia-Africa (Table 2). The years 2007–2009 also witnessed a greater prevalence of resistance to ceftazidime in *S. sonnei* than *S. flexneri* in Europe-America and Asia-Africa. For example, the results for *S. sonnei* against ceftazidime were three times higher than that for *S. flexneri* in Europe-America (Table 2). Historically, *S. sonnei* has been predominantly responsible for dysentery in developed countries, but is now emerging as a problem in the developing world, apparently substituting for the more diverse *S. flexneri* in areas undergoing economic development and improvements in water quality [4, 8, 42]. When pursuing the root cause of this phenomenon, it is easy to associate the differences between the mechanisms of infection of *S. sonnei* and *S. flexneri. S. sonnei* are often reported to be associated with schools, care facilities, contaminated food and insects acting as transmission vehicles between faecal waste and food preparation areas whereas *S. flexneri* is associated with waterborne transmission [43–45]. More direct and diverse mechanisms of transmission could explain the persistence of *S. sonnei* even if the infrastructure of water supply is improved [46]. Our results showed that, in the near future, *S. sonnei* may take the place of *S. flexneri* as the main strain resistant to TGCs. All these data emphasize the fact that monitoring of

emerging resistance in *Shigella* isolates is essential for timely and appropriate recommendations of antimicrobial therapy. Fortunately, all ***S. sonnei*** strains share a single O antigen that has proven to be a successful vaccine target; a suitable vaccine is an achievable solution for prevention and medication [47, 48].

When taking a small sample of data into consideration, the prevalence of resistance rates in different countries suggests that the severest problem regarding resistance to these three TGCs appeared in Vietnam (especially for ceftriaxone), China (especially for cefotaxime) and Iran (especially for ceftazidime). It is not unexpected to see that these three countries are developing Asian countries. Apart from some generalities in most developing countries in Asia such as socioeconomic status and medical systems, individualized factors are also important. For instance, in Vietnam, the average prevalence of resistance for ceftriaxone during the study years was 16·9% (95% CI 13·4–20·7) and the resistance in 2007–2012 increased to 22·2% (95% CI 17·5–27·4) (Table 3), 5·8 times greater than that reported in 1998–2000. Between May 2007 and January 2008, 11 cases of childhood shigellosis caused by ceftriaxone-resistant organisms isolated in South Vietnam were reported for the first time [21]. In Vietnam, nalidixic acid is no longer used therapeutically, and fluoroquinolones are recommended for the treatment of *Shigella* infections. However, if a patient does not respond to fluoroquinolone treatment, ceftriaxone is used as an alternative [8, 21]. Thus increases in resistance to older antimicrobial therapies which eventually lead to uncontrolled use of ceftriaxone in this setting may speed the spread of MDR organisms. Moreover, due to the miscellaneous nature of *Shigella* it is likely that resistant genes are transferred regularly to and from other enteric bacteria and could be advantageous in an evolutionary sense. One study suggests that the pattern of infection could be related to the rainy season in Vietnam. That study showed that increased ground water could account for this pattern because a longer distance to a water source was found to be associated with a higher risk of shigellosis [8]. With regard to China, the overall prevalence of resistance showed a progressively upward trend, especially for cefotaxime [average prevalence of resistance, 11·2% (95% CI 10·0–12·4)] (Table 3). These data highlight the socioeconomic development of China but in turn complicate the selection of empirical antibiotics for the treatment of shigellosis. As a result, to control the spread of resistance in *Shigella*, continuous monitoring of resistance patterns at national and international levels is the top priority.

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-Africa. By comparison, ceftazidime, while showing good *in vitro* activity against *Shigella*, is better known for treating *Pseudomonas* infections. We encourage general practitioners to avoid empirical treatment and conduct susceptibility testing in order to select the most appropriate antimicrobial for treatment.

Second, the two main subtypes, *S. flexneri* and *S. sonnei* remain the major strains isolated from patients with shigellosis, showing a gradual increase in resistance, particularly in Asia-Africa. Broadly speaking, attention should be given to not only *S. flexneri* (which has been predominant in the past) but also to *S. sonnei* (which could be a major resistant bacterial strain in the near future). Drug-sensitive tests are needed before prescribing because of strain variations. Vaccines might be a good choice for treatment [49–52].

However, all the data collected are reliant on published reports of *Shigella* species. This is based on the assumption that what is occurring in the community is reflected by what is published. The rate at which resistance is reported may not be directly related to the prevalence of resistance to *Shigella* infection. Although a considerable *Shigella* burden was detected, the actual burden caused by shigellosis may be underestimated for two reasons. First, when passive surveillance is used for case detection, reported rates depend on the healthcare-seeking behaviour of individual patients, some of whom may purchase drugs from pharmacies (known as over the counter; OTC) without medical consultation, have a mild form of the disease that does not prompt them to seek care, or fail to provide a faecal sample. Both appropriate and inappropriate use of antibiotics is a key driver of antibiotic resistance development. However, overuse or misuse of antibiotics provides an avoidable additional pressure leading to more antibiotic resistance. OTC sales of antibiotics without a prescription remains a major problem around the world. OTC availability increased the total quantity

of TGCs supplied in primary care. As an alternative, active surveillance would have provided a more complete detection of all diarrhoeal episodes, at the risk of capturing trivial episodes that do not require medical care [53].

Second, *Shigella* species are highly fastidious organisms that die rapidly in an unsuitable environment, including the unavoidable temperature fluctuations encountered during transport. Therefore, a significant number of cases may have been missed and the actual *Shigella* infection rate may be much higher than we reported. Meanwhile, it is very interesting that collection bias may cause overestimation of drug resistance of *Shigella* isolates, because individuals infected with resistant strains who failed empirical treatment are more likely to be investigated with stool culture for continued diarrhoea than individuals infected with susceptible strains who respond to empirical therapy [16].

In summary, our meta-analyses enabled us to summarize information concerning the prevalence of resistance to TGCs in *Shigella* between Europe-America and Asia-Africa and comparisons between different subtypes and different countries are also provided. Admittedly, missing data during certain years could be a deficiency in this research, which may have some influences on the final results. Naturally, this study just gives the full picture of the situation in the various destination countries. Physicians in these regions should be aware of this point and perform susceptibility testing on all clinical isolates, changing the empirical antibiotic accordingly. The serious problem of shigellosis and antimicrobial resistance may become worse if no effective measure is taken to deal with it. Government and non-governmental organizations have a significant role to play in changing the emergent situation. To slow down the development of TGC resistance, an important control strategy is to reduce the inappropriate use of antibiotics in both community and hospital settings. Although changing these practices is challenging, we have some suggestions. Suggested areas of improvement are enforcement of regulations and pricing policies, and educational programmes to increase the knowledge of drug sellers as well as to increase community awareness to reduce demand pressure for drug sellers to dispense antibiotics inappropriately. The irrational overuse of antibiotics should be minimized as it drives the development of antibiotic resistance, but a better understanding is needed of practices and economic incentives for antibiotic dispensing in order to design effective interventions to reduce inappropriate use of TGCs [54, 55].

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268814003446.

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## DECLARATION OF INTEREST

None.

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