



Case management of a multidrug-resistant *Shigella dysenteriae* serotype 1 outbreak in a crisis context in Sierra Leone, 1999–2000

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Summary From December 1999 to the end of February 2000, 4218 cases of dysentery were reported in Kenema district, southeastern Sierra Leone, by a Médecins Sans Frontières team operating in this region. *Shigella dysenteriae* serotype 1 was isolated from the early cases. The overall attack rate was 7.5% but higher among children under 5 years (11.2%) compared to the rest of the population (6.8%) (RR = 1.6; 95% CI 1.5–1.8). The case fatality ratio was 3.1%, and higher for children under 5 years (6.1% vs. 2.1%) (RR = 2.9; 95% CI 2.1–4.1). A case management strategy based on stratification of affected cases was chosen in this resource-poor setting. Patients considered at higher risk of death were treated with a 5 day ciprofloxacin regimen in isolation centres. Five hundred and eighty-three cases were treated with a case fatality ratio of 0.9%. Patients who did not have signs of severity when seen by health workers were given hygiene advice and oral rehydration salts. This strategy was effective in this complex emergency.

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1. Introduction

After centuries as a scourge of underprivileged populations, bacillary dysentery still remains a major health problem in the tropics, causing high

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mortality (Wittenberg, 1999). In 1986, it was estimated that 140 million cases and 580 000 deaths annually were due to *Shigella* infection in children less than 5 years of age, excluding data from China (Keusch and Bennish, 1998). Dysentery bacilli were first demonstrated by Shiga in 1898, and subsequent studies showed that four species (serogroups), *Shigella dysenteriae*, *S. flexneri*, *S. boydii* and *S. sonnei*, were responsible for the disease (Shears, 1996). Later on, the four species of *Shigella* were subclassified by serotype: *S. dysenteriae* 10 serotypes, *S. flexneri* 6, *S. boydii* 18 and *S. sonnei* 1. In the tropics, most infections are due to *Shigella dysenteriae* serotype 1 (*S. dysenteriae* 1) and *S. flexneri*. Infection is by ingestion, the infective dose being as low as 10–100 bacteria for *S. dysenteriae*. Over recent decades *Shigella* species have become resistant to most of the widely used and inexpensive antimicrobials such as sulfonamides, tetracycline, ampicillin, chloramphenicol, trimethoprim–sulfamethoxazole, nalidixic acid (NA) and pivmecillinam (Salam and Bennish, 1991). Intermediate susceptibility or resistance to fluoroquinolones and third-generation cephalosporins has been described but remains uncommon (Anh et al., 2001; Horiuchi et al., 1993; Radice et al., 2001; Sarkar et al., 2003).

Shigella dysenteriae 1 has the ability to cause epidemics with high attack rates and high case fatality ratios (CFR) in all age groups (Bennish and Wojtyniak, 1991; Kotloff et al., 1999). Attack rates in epidemics of *S. dysenteriae* 1 have ranged from 6% in the 1980–1982 epidemic in central Africa to 33% in an epidemic affecting an island in the Bay of Bengal in 1975 (Bennish and Wojtyniak, 1991). Case fatality ratios have ranged from 0.6 to 7.4% in documented epidemics (Bennish and Wojtyniak, 1991) and are often higher in malnourished children (Keusch and Bennish, 1998). Since the beginning of the 1990s, large outbreaks of *S. dysenteriae* 1 have been reported in Central Africa, specifically in Rwanda (Paquet et al., 1995), Burundi (Ries et al., 1994), and the Democratic Republic of Congo (formerly Zaire) (Goma Epidemiology Group, 1995). Epidemics then extended progressively to East and Southern Africa, affecting Kenya (Iversen et al., 1998; Malakooti et al., 1997), Mozambique (Aragon et al., 1995), Malawi (Pitman et al., 1996), Zambia (Tuttle et al., 1995), Zimbabwe (Wittenberg, 1998) and South Africa (Pillay et al., 1997; Rollins et al., 1995). Multiple drug resistance of *S. dysenteriae* 1 strains has become increasingly problematic in case management of outbreaks in the last decades (Shears, 1996). Physicians were forced to abandon commonly employed antibiotics, i.e. ampicillin or chloramphenicol, and had to



Figure 1 Area of intervention by Médecins Sans Frontières, Sierra Leone 1999–2000.

use more costly treatments (Keusch and Bennish, 1998).

Sierra Leone is a West African country with an estimated population of 4.7 million inhabitants in 1998 (UNICEF, 2000). Sierra Leone has been devastated by 10 years of civil war. In the World Health Report for 2000, the Sierra Leonean health system was bottom of the list of 191 countries (WHO, 2000). By the end of November 1999, the Médecins Sans Frontières (MSF) team operating in Kenema district, in the southeast of Sierra Leone, reported an increasing number of consultations for bloody diarrhoea in the health posts of the southern part of the district (Figure 1). By the end of December 1999, the National Reference Centre for *Escherichia coli* and *Shigella* (CNRES), Institut Pasteur in Paris, had confirmed the presence of *S. dysenteriae* 1 in stool specimens from patients with bloody diarrhoea. In this article, we describe the investigation and the case management strategy of the outbreak and report the outcome of 583 cases treated with a 5 day regimen of ciprofloxacin.

2. Materials and methods

2.1. Population

The population covered by the investigation was living in six chiefdoms (subdistricts) of south Kenema district: Gegbwema, Kokuru, Gorahun, Mano

Djeibla, Konjo and Tokpombu. No census had been performed recently. The population figures for each public health post area were extrapolated from the number of children under 5 years old attending a polio mass vaccination campaign organized in October–December 1999, assuming a vaccine coverage of 100% and a proportion of children under 5 years old in the population of 17% (UNICEF, 2000). Patients living outside the six chiefdoms were included in the analysis of treatment efficacy but were excluded for the calculations of attack rates.

2.2. Case identification

Active case finding was organized from 22 November 1999 in each chiefdom through mobile teams covering specific areas. A case was defined, following WHO guidelines, as a person living in any of the six chiefdoms, presenting with blood in the stools as observed by a health worker, from December 1999 to the end of February 2000 (WHO, 1995). Mobile teams reported their investigations on a daily basis:

- Cases with signs of severity (dehydration, fever $>38.5^{\circ}\text{C}$, convulsions or seriously ill when first seen), or considered to be at a higher risk of death from dysentery (those less than 5 years old, 50 years of age or older, or obviously malnourished) were referred to a medical facility for treatment (see below).
- Patients who did not meet these criteria when seen by health workers were given hygiene advice and oral rehydration salts (ORS).
- Cases who had died with reported symptoms of bloody diarrhoea at the time of death were registered.

The data were processed and organized so as to describe time, place and person characteristics. The indicators chosen were attack rates and CFR.

2.3. Microbiological investigations

As only limited laboratory facilities were available, microbiological investigations were performed on a small number of cases at the beginning of the intervention in order to confirm the diagnosis. During the follow-up of the investigation, *Shigella* cultures, antibiograms and minimum inhibitory concentration (MIC) were performed on a random sample of cases. Stool samples were transported on Cary Blair transport medium at 4°C and sent within 8 days to Institut Pasteur, Paris. Samples were tested for the presence of the *stx* gene by the PCR system described by Bastian et al. (1998).

PCR-positive isolates were grown on Hektoen agar (Bio-Rad, Marnes la Coquette, France), and identified biochemically (Ewing, 1986), and antigenically by using type-specific sera (Bio-Rad). Strains were initially identified at the Institut Pasteur, Paris, which also determined the MIC for NA and ciprofloxacin of 10 strains of *S. dysenteriae* 1 using the Etest[®] (Biedenbach et al., 1997; Murphy et al., 1997). Subsequently, the national reference laboratory of Freetown, supported by WHO, was provided with equipment to process *Shigella* cultures and antibiograms. MSF also set up a field laboratory in Kenema to perform cultures and antibiograms.

2.4. Treatment strategy

A case management strategy was based on stratification of affected cases. Curative activities focused on the patients at a higher risk of death, according to previous studies (Huskins et al., 1994; Legros et al., 1999; Nathoo et al., 1998). These were persons with bloody diarrhoea aged under 5 years or over 50 years, or malnourished, or those in whom the illness was severe (defined by dehydration, temperature $>38.5^{\circ}\text{C}$, convulsions or coma). Such patients were hospitalized in temporary isolation centres and received a 5 day course of ciprofloxacin (500 mg orally every 12 hours for adults and 15 mg/kg every 12 hours for children) (WHO, 1995). Severe dehydration was treated parentally. They remained hospitalized for the entire duration of the treatment. Health care workers directly observed the treatment. Any death of a patient in the isolation wards was attributed to dysentery. Pregnant women were treated conservatively (rehydration, supplementary feeding) because of the contraindication of ciprofloxacin in that group. A 5 day treatment with ceftriaxone (1 g/day) was available if their condition deteriorated. Each patient received a food ration equivalent to 2300 kcal per day. After discharge, a supplementary ration of 1300 kcal per day was given for one month regardless of the nutritional status on admission. Hygiene, control of access and sanitation measures implemented in the isolation centres were based on standards for cholera treatment centres (WHO, 1997). National personnel were in charge of the isolation centres (nurses, nurses' assistants, and logisticians) and each centre was visited and supervised every second day by MSF doctors. In the isolation centres, patients' charts included demographic and clinical data.

Patients who did not have signs of severity when seen by health workers were given hygiene advice, ORS and information about where to get treatment if their condition deteriorated.

2.5. Environmental investigation

Health workers assessed water sources in the visited villages, and basic hygiene advice was given to the population as well as recommendations to boil drinking water. No environmental samples were taken due to difficulties in handling specimens in this complex setting.

2.6. Statistical analysis

Data were collected from registers kept by mobile teams, health posts and isolation wards. Statistical analysis was done with EpiInfo version 6 (CDC, Atlanta, GA, USA) and SPSS 10.0 (SPSS Inc., Illinois, USA). Proportions were compared using the χ^2 test. Point estimates are presented with 95% confidence interval.

3. Results

3.1. Description of the outbreak

From the six chiefdoms considered, 4218 cases of bloody diarrhoea were reported from 22 November 1999 to 27 February 2000. The outbreak peaked during the last weeks of December 1999 and then slowly decreased (Figure 2). The estimated population in this area was 55 875, giving an overall attack rate of 7.5%. The attack rates varied somewhat between the six chiefdoms (Figure 3). However, some of this variation may be due to uncertain denominators, as attendance at the health post in each chiefdom was not linked to the administrative area of the chiefdom. The sex ratio (M/F) was 1.02

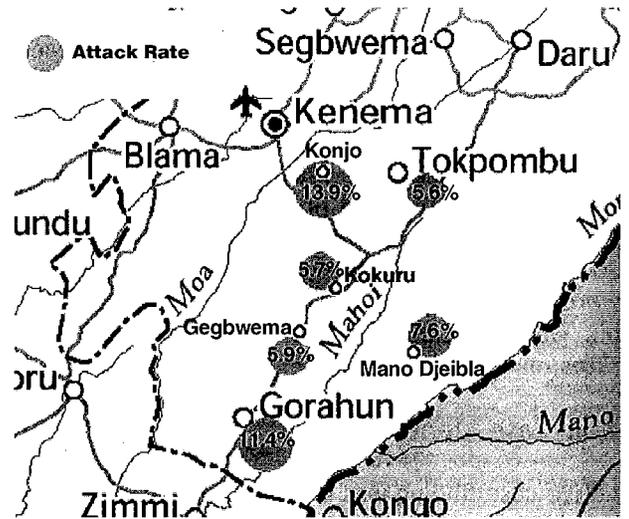


Figure 3 Attack rate by location in the south eastern part of Kenema province, Sierra Leone, November 1999–February 2000.

and distribution by age group showed an overrepresentation of children under 5 years old (Table 1) (data excluding Gegbwema chiefdom). The attack rate in the population under 5 years old was 11.2% (1060/9499), higher than the 6.8% for those over 5 years old (3158/46 376; RR = 1.6, 95% CI 1.5–1.8).

A total of 131 deaths due to bloody diarrhoea was recorded during the outbreak period, giving an overall CFR of 3.1%. The CFR in children under 5 years old (6.1%, $n = 65$) was higher than for the population over 5 years old (2.1%, $n = 66$; RR = 2.9, 95% CI 2.1–4.1). When comparing the number of deaths to the number of cases, we see a clear reduction in the number of cases after introduction of the

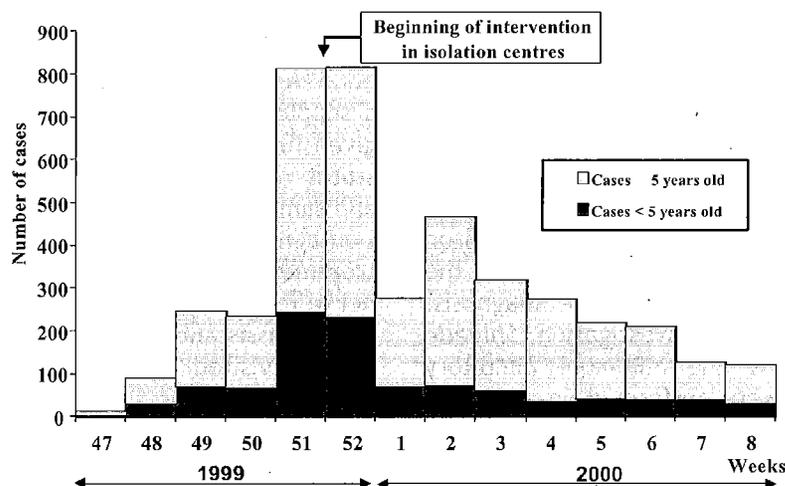


Figure 2 Cases of bloody diarrhoea reported per week by age group in South Kenema district, Sierra Leone, November 1999–February 2000.

Table 1 Age and sex distribution of bloody diarrhoea cases (data for December 1999 to mid-February 2000, missing for Gegbwema chiefdom), Sierra Leone

Age group	Male n (%)	Female n (%)	Total n (%)
<5	344 (28.2)	317 (26.7)	661 (27.5)
5–14	273 (22.4)	198 (16.6)	471 (19.5)
15–49	424 (34.8)	483 (40.6)	907 (37.7)
>49	177 (14.6)	191 (16.1)	368 (15.3)
Total	1218 (100.0)	1189 (100.0)	2407 (100.0)

full-scale intervention, i.e. the last week of December 1999, when most severe cases were treated in isolation centres with ciprofloxacin (Figure 4). The CFR was 5.1% (113/2214) in the period before January 1 and 1.2% (25/2004) in the period after this date (RR = 4.1, 95% CI 2.6–6.5). Among cases not referred to the facilities after the start of the intervention ($n=1421$), the CFR was 1.4% (20/1421).

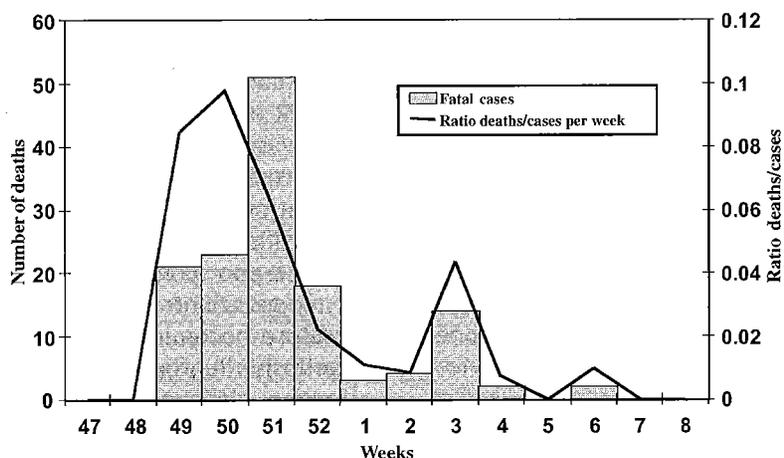
3.2. Isolation centre activities

A total of 583 patients was treated in the isolation centres from 1 January 2000 to 27 February 2000. Of them, 511 (87.7%) came from the six areas where MSF mobile teams operated, and 72 patients, referred by other non-governmental organizations (NGOs), came from other areas. The number of admissions peaked during the third week of January 2000. The median age of cases hospitalized was 25 years (range 4 months to 90 years). Seventeen percent (99) were under 5 years old, 15% (88) between 5 and 14 years, 45% (262) between

15 and 49 years, and 23% (134) over 49 years. The male to female sex ratio was 1.2. The median duration of symptoms before admission was 3 days and not significantly different among age groups. Thirty percent of cases admitted in the isolation centre had axillary temperatures $>38^{\circ}\text{C}$. Only 6% of the case had temperatures $>38.5^{\circ}\text{C}$. No clinical case suggesting haemolytic-uraemic syndrome was recorded. No joint effusion or arthropathy in children was reported. Of 583 patients, 581 completed their treatment (compliance of 99.7%) while two defaulted on day 3. The overall CFR in isolation centres was 0.9% (5/583), higher among children under 5 years old (2.0%, 2/99) than in those over 5 years (0.6%, 3/484), although the difference was not statistically significant (RR = 3.2, 95% CI 0.5–19.0). No pregnant women needed to receive antibiotherapy.

3.3. Microbiological results

CNRES (Institut Pasteur, Paris) first isolated *S. dysenteriae* 1 and detected pathogenicity genes (shigatoxin 1) by PCR on 23 December 1999 in six stool specimens out of 19 samples from Kenema district. By February, the national reference laboratory in Freetown and the field laboratory of Kenema district were performing strain isolation and faeces cultures. Twenty strains of *S. dysenteriae* 1 were isolated from 69 samples in the different laboratories. All were resistant to amoxicillin, amoxicillin–clavulanic acid, tetracycline, trimethoprim–sulfamethoxazole and chloramphenicol. They were sensitive to gentamicin, amikacin, NA, ciprofloxacin, ofloxacin, cefixim and ceftriaxone. None of the samples

**Figure 4** Total number of reported fatal cases of bloody diarrhoea per week and ratio of deaths per reported cases per week in South Kenema district, Sierra Leone, November 1999–February 2000.

collected showed *Escherichia coli* to be the cause of the dysentery. Institut Pasteur (Unité des Agents Antibacteriens) determined the MIC for 10 isolates of *S. dysenteriae* 1. The MIC of NA and ciprofloxacin were respectively 0.032 mg/l and 0.004 to 0.006 mg/l.

4. Discussion

To our knowledge, this is the largest reported outbreak of *S. dysenteriae* 1 in West Africa (Guerin et al., 2003). Diallo et al. (2001) reported a *Shigella* outbreak in Senegal in 1999, but mainly due to *S. flexneri*, *S. dysenteriae* 1 being reported in few cases. From December 1999 to the end of February 2000, 4218 cases of dysentery were reported in Kenema district with an overall attack rate of 7.5%.

Population figures used during the investigation were roughly estimated. Our extrapolation assumed a proportion of 17% for the population under 5 years old, based on UNICEF data. However, the structure of the population has probably changed after 10 years of civil war and this may have biased our estimations of the attack rates.

Members of mobile teams were recruited in the community and therefore had a good knowledge of the region. The outbreak exploded in a situation where this population had not seen a relief agency for years. The community, scared by the rapid spread of the disease, was extremely responsive and willing to collaborate. Therefore, under-reporting of cases during community visits was unlikely to occur in significant numbers.

Isolation of *S. dysenteriae* 1 was only performed in a small number of cases, because access to laboratory facilities was limited and long transport delays reduced the proportion of positive *S. dysenteriae* 1 isolates among stool samples taken. Other organisms could have caused bloody diarrhoea, such as other *Shigella* species, *Campylobacter jejuni*, enteroinvasive *Escherichia coli*, *Salmonella* or *Entamoeba histolytica*. However, only enterohaemorrhagic *Escherichia coli* has caused large outbreaks of bloody diarrhoea mimicking *S. dysenteriae* 1 outbreaks (Dalton et al., 1999; Karch et al., 1999), and this organism was not isolated in Kenema. We can therefore assume that most of bloody diarrhoea cases reported were caused by *S. dysenteriae* 1.

Overall, the CFR observed in Kenema was relatively low (3.1%) compared to the outbreaks of 1993–1995 in Central Africa in refugee situations (3.8 to 7.2%) (Paquet et al., 1995). The CFR of 5.1% before the start of our intervention is, however,

more in agreement with the other outbreaks. We believe that part of the low case fatality observed later in the epidemic can be attributed to effective antibiotic treatment of the most severe cases. Other factors should also be considered such as supportive treatment added to the antibiotherapy (food supplementation) and better nutritional status of the Sierra Leonean population compared to the refugee populations of Central Africa in which many of the *S. dysenteriae* 1 outbreaks occurred. Indeed, in 1994, the Goma Epidemiology Group (1995) reported prevalence of acute malnutrition of 17.7 to 23.1% in refugee camps (below - 2 Z scores weight-for-height in the population of children under 5 years old), while a nutritional survey done by the NGO Merlin in Kenema in December 1999 found a prevalence of malnutrition of 5.7% (same indicator) among children under 5 years old (Merlin [Medical Emergency Relief International], London, Nutritional survey in Blama and Kenema district, Sierra Leone, August 2000, unpublished data). Poor sanitation, i.e. unprotected sources of water and poor hygiene, was observed in the population and has certainly contributed to the spread of the outbreak. Health workers promoted conventional hygienic measures that most likely helped to curtail the epidemic by reducing transmission.

For the treatment regimen, there was a choice between NA and ciprofloxacin. For bacillary dysentery, a four times daily regime with NA is recommended (WHO, 1995). Adherence to this regimen is generally poor (50% on day 5 in Central Africa in 1993–94) (Paquet et al., 1995). This facilitates the emergence of resistance to NA, which is the first step in the acquisition of resistance to ciprofloxacin (Hooper, 2000; Rahman et al., 1994). The CFR of patients treated with 5 days NA is reportedly high: 13% in the outbreak described by Chopra et al. (1997) in South Africa with a strain sensitive to NA. Ciprofloxacin provides a more effective care of patients than NA (Vinh et al., 2000). The CFR observed with 5 days ciprofloxacin treatment was 1.2% in the outbreak in Rwanda with a strain resistant to NA (Laureillard et al., 1998). In addition, costs of fluoroquinolones, especially of ciprofloxacin, should no longer be a limit in resource-poor contexts as patent rights are expiring in most countries and ciprofloxacin treatment is therefore becoming cheaper. For use in childhood shigellosis, fluoroquinolones have proved safe and effective, although not yet approved for paediatric use (Alghasham and Nahata, 2000; Bethell et al., 1996; Bhattacharya et al., 1997; Leibovitz et al., 2000; Salam et al., 1998; Schaad, 1993; Tupasi, 1999; Vinh et al., 2000). In co-operation with the

Sierra Leonean Ministry of Health, we therefore decided to use ciprofloxacin as first-line treatment under strict supervision. With high compliance (99.7%) and low CFR (0.9% among hospitalized patients) indicating high effectiveness, our experience using ciprofloxacin in this setting was good. Active case finding in villages with mobile teams and referral systems to treatment centres have facilitated the identification and the treatment with ciprofloxacin of the most serious cases. Oral rehydration, together with health and sanitation education for cases and their families not presenting 'high risk' criteria, seems to be an alternative measure to implement in a complex emergency such as in Sierra Leone, as indicated by the low number of fatal cases after the introduction of our intervention.

A case management strategy based on stratification of affected cases was effective in this complex crisis context. The alternative of a large distribution of treatments for all cases would not have allowed direct observation of treatment, and was in any case not practically possible. The need to use antibiotherapy prudently, and therefore selectively, in order to control the risk of developing resistance has been stressed by different authors (Tuttle and Tauxe, 1993).

Since this outbreak, results of investigations of shorter treatment regimes (3 days) for *S. dysenteriae* 1 dysentery with fluoroquinolones have shown positive outcomes and have become an alternative therapeutic recommendation (Dysentery Study Group, 2002; WHO, 2003). Therapeutic combinations should be considered for research, given the risk of antibiotic resistance developing.

This outbreak is the first large epidemic caused by *S. dysenteriae* 1 reported in West Africa. Up to 1999, *S. dysenteriae* 1 was endemic in Central, East and South Africa, but for unknown reasons had not been reported to cause large epidemics in West Africa. *Shigella dysenteriae* 1 may in the future be responsible for more outbreaks in the subregion, where population movements and also concentrations of people are common and favour the emergence of outbreaks. Public health authorities of West African countries should be aware of and well prepared for potential new outbreaks of *S. dysenteriae* 1. Capacity to isolate and identify *Shigella* strains should be available in reference laboratories of all countries. Monitoring antimicrobial resistance in *S. dysenteriae* 1 strains should be a priority, in order to make timely adjustments to the therapeutic recommendation.

Directly observed therapy with 5 days ciprofloxacin was highly effective. The current treatment recommended by WHO in case of *S. dysenteriae* 1

outbreaks in West Africa is NA. In the light of our results and other published data, the choice of antibiotic treatment of *S. dysenteriae* 1 patients in a context of outbreak in this region should be carefully considered.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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