Epidemic dysentery caused by *Shigella dysenteriae* type 1: a sentinel site surveillance of antimicrobial resistance patterns in Burundi

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Annual epidemics of bacillary dysentery have been a public health problem in Burundi for the last 14 years. Recent civil unrest, resulting in the displacement of large numbers of people into refugee settlements, has aggravated the situation. We report the results of a nationwide, health-centre based, sentinel site survey to check the drug resistance of *Shigella dysenteriae* type 1 (Sd1), the causal organism of such epidemics.

*Shigella* spp. (of which 97% were Sd1) were isolated from 73% of the 126 specimens collected from six main sites around the country. There was no difference in culture results from fresh and frozen stool specimens. Overall Sd1 resistance to commonly available antibiotics (sulfamethoxazole + trimethoprim, ampicillin, tetracycline, and chloramphenicol) varied from 77% to 99% and was fairly uniformly distributed over the country. All Sd1 isolates were susceptible to newer drugs, such as ciprofloxacin and ceftriaxone. Resistance to nalidixic acid, the current first line of treatment for bacillary dysentery in Burundi, varied from 8% to 83% in the different sentinel sites; global resistance was 57%.

**Introduction**

Epidemic peaks of bacillary dysentery have occurred in Burundi between September and March every year for the last 14 years and their magnitude has been increasing. In 1992, 75,741 cases were reported from health centres, 2.5 times the number reported in the previous year. In 1993, 91,179 cases had already been reported by the end of August. The case fatality rate, determined earlier that year, was approximately 7% (1). Civil unrest in the country during the last quarter of 1993 resulted in the displacement of large numbers of people into refugee settlements with inadequate conditions of sanitation and hygiene, further aggravating the situation.

A health-centre-based study, conducted in the central province of Gitega in 1990, identified *Shigella dysenteriae* type 1 (Sd1) to be the most frequently iso-

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**Materials and methods**

**Study design**

The study was conducted from 27 December 1993 to 17 January 1994 at health centres in six sentinel sites in Burundi (Rugombo, Ngozi, Gasorwe, Munanira, ...
Rutovu, and Butezi; see Fig. 1). In Ngozi, two health centres were selected, one near the border with Rwanda (Gatsinda) and one further inland (Mubuga). The centres were chosen according to the following criteria: easy access by road; continuous functioning throughout the period of civil unrest, with health staff present; the presence of a refrigerator in working order; a caseload of at least 20 new patients per day complaining of bloody diarrhoea; and geographically dispersed throughout different regions of the country.

To be included in the study, patients had to report bloody diarrhoea with a duration of 4 days or less, have macroscopically visible blood in their stools, and have received no antibiotic treatment.

Five stool specimens were collected at a health centre in Gatumba on 21 December 1993 in order to test the laboratory procedure. At the main study sites stool specimens were taken (depending on local availability) from approximately 10 patients who fulfilled the criteria on each of two consecutive days.

Fig. 1. Map of Burundi indicating the location of the sentinel sites used in the study and the two provinces where antimicrobial resistance was checked previously.

The name, age, and sex of each patient were recorded. All specimens were taken directly from fresh stool samples, using sterile swabs (two swabs per patient). These were immediately placed in pre-refrigerated Cary–Blair transport medium. At the more peripheral sites (Ngozi, Gasorwe, Munanira, Rutovu and Butezi), specimens taken on the first day were kept frozen overnight at −10 °C to −20 °C. Specimens taken on the second day were kept cool (at 4–8 °C). On the second day, all specimens were transported on ice packs, in insulated boxes, to the national laboratory in Bujumbura. There, the specimens that had been frozen were inoculated immediately onto xylose–lysine–deoxycholate medium and MacConkey agar and the others were kept refrigerated overnight and inoculated the next day.

**Laboratory procedure**

Cultures were examined for *Shigella* spp. according to WHO guidelines. Antibiotic sensitivity was tested using the disc diffusion technique with discs containing 30 μg of nalidixic acid, 10 μg of ampicillin, 15 μg of sulfamethoxazole + trimethoprim, 30 μg of tetracycline, 30 μg of chloramphenicol, 5 μg of ciprofloxacin, or 30 μg of ceftriaxone. Quality control was performed by the Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA; 22 (18%) of the isolated strains were re-examined.

**Data analysis**

Data were processed and analysed using dBase and SPSS software. Differences in the proportions between groups were compared statistically using the χ² test with Yates’ correction and, where the expected cell value was < 5, Fisher’s exact test. All P values are two-tailed.

**Results**

The results are summarized in Table 1.

Of the 126 specimens collected, 92 (73%) were positive for *Shigella* spp. Of these, 89 (97%) were identified as Sd1, 2 (2%) as *S. flexneri* and 1 (1%) as *S. dysenteriae* type 2. Isolation rates varied from 35% (Butezi) to 100% (Gatumba). In the sites where both methods of conservation were used by the local health personnel (Ngozi, Gasorwe, Rutovu and Butezi), overall isolation rates were 63% for frozen specimens and 68% for non-frozen specimens; the difference was not statistically significant (χ² = 0.029, P > 0.05). Overall isolation rates were 84% for specimens collected by doctors but only 53% for

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Table 1: Results of sentinel site surveillance of *Shigella dysenteriae* type 1 (Sd1) drug resistance in Burundi, December 1993 to January 1994

<table>
<thead>
<tr>
<th>Site</th>
<th>Rutovu</th>
<th>Rugombo</th>
<th>Ngozi*</th>
<th>Munanira</th>
<th>Butezi</th>
<th>Gasorwe</th>
<th>Gatumba</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of samples</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>21</td>
<td>26</td>
<td>23</td>
<td>17</td>
<td>20</td>
<td>5</td>
<td>126</td>
</tr>
<tr>
<td>Yielding Sd1</td>
<td>10</td>
<td>18</td>
<td>21</td>
<td>18</td>
<td>5</td>
<td>13</td>
<td>4</td>
<td>89</td>
</tr>
<tr>
<td>Yielding other <em>Shigella</em> spp.</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Isolation rate (all <em>Shigella</em> spp.) (%)</td>
<td>71.4</td>
<td>90.5</td>
<td>80.8</td>
<td>78.3</td>
<td>35.3</td>
<td>65.0</td>
<td>100.0</td>
<td>73.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>% Resistance of Sd1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalidixic acid</td>
<td>80.0 83.4 81.1 38.9 20.0 7.7 50.0 56.7</td>
</tr>
<tr>
<td>Sulfamethoxazole + trimethoprim</td>
<td>100 77.8 76.2 72.7 80.0 76.9 75.0 76.7</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>100 100 95.2 94.4 60.0 84.6 100 93.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>100 100 100 100 100 92.3 100 98.9</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>100 100 100 94.1 100 100 100 98.9</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0 0 0 0 0 0 0 0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0 0 0 0 0 0 0 0</td>
</tr>
</tbody>
</table>

* Data are for two centres combined.

The laboratory in Burundi correctly identified the *Shigella* spp. in 100% of isolates (22/22). The sensitivity of the local laboratory to identify correctly isolates demonstrating antibiotic resistance was as follows: 100% (22/22) for nalidixic acid, tetracycline, and chloramphenicol; 95% (21/22) for ampicillin; and 73% (16/22) for sulfamethoxazole + trimethoprim.

**Discussion**

The study confirmed previous findings that Sd1 is the most frequently isolated cause of dysentery during the epidemic period in Burundi, and was identified in 71% of all specimens. Apart from the results for Butezi, the isolation rates for *Shigella* spp. were the highest to have been reported for Burundi or elsewhere (1, 2, 4–7).

The isolation rates of *Shigella* spp. were significantly higher for samples selected by highly qualified medical personnel than for those selected by intermediate-level health staff; it is possible that better trained health personnel applied the case definition more carefully. In the study, the proportion of patients who attended a health centre with complaints of bloody diarrhoea and who were not able to produce a stool specimen on the spot or did not have macroscopically visible blood in their stools was as high as 30% in some centres. The collection of specimens from fresh stool samples offers advantages over the taking of rectal swabs, because it allows a visual check for microscopic blood.

In contrast, the method used to conserve the specimens (freezing or chilling) did not seem to influence the isolation rates. It was not possible to check objectively the influence of duration of transport (which was always <4 hours), but isolation rates tended to be lower in samples from the most peripheral sentinel sites (Gasorwe and Butezi); however, in these sites all specimens were taken by the local staff (medical assistants). The lack of visible blood in some of the specimens collected from centres such as Butezi appears to indicate that careless selection of cases was the major reason for the low rates obtained.

Quality control at CDC indicated that the national laboratory in Bujumbura performed well, in the sense that the essential data on drug resistance were reliable. The results obtained for sulfamethoxazole +
trimethoprim did not affect any decision regarding national antibiotic treatment policy.

Our findings also confirm that Sd1 remains resistant to the commonly available antibiotics in Burundi — sulfamethoxazole + trimethoprim, ampicillin, tetracycline, and chloramphenicol. The resistance pattern of Sd1 to nalidixic acid varied substantially between different regions in the country. Results obtained from the two health centres in the Ngozi area indicate that similar variations can also occur at a more local level; it is not generally recognized that resistance patterns can vary so considerably within a small geographical area during the same epidemic.

In March 1993, there was no Sd1 resistance to nalidixic acid in Muramvya province (1); the resistance that we found therefore developed over the course of 10 months. Widespread use of the drug and inappropriate case management practices may have contributed to the rapid change in resistance patterns. In addition, cross-border movement of the population may have allowed new resistant strains of Sd1 to be introduced (8).

The overall level of 57% resistance to nalidixic acid has to be interpreted with care. The different sentinel sites are unequally represented in the total sample, with the areas having least resistance to nalidixic acid being underrepresented. The public impact of documented Sd1 resistance to nalidixic acid in different regions is uncertain since data on dysentery mortality rates in Burundi during the study period are not available. It is probable that cases treated with an ineffective antimicrobial were more likely to develop serious complications and therefore that dysentery mortality was elevated in areas with high levels of Sd1 resistance to nalidixic acid.

Conclusions and recommendations

The study shows that good results can be obtained by transporting stool specimens from sentinel surveillance sites to a single national reference laboratory with well-trained local staff for analysis. This makes a strong case for establishing national reference laboratories for the routine surveillance of antimicrobial resistance patterns of Sd1 in Africa. The considerable differences in such patterns between regions make sentinel surveillance with laboratory support the technique of choice for following this resistance over time. The high Sd1 isolation rates make the technique operationally feasible. The ideal frequency for routine surveillance remains controversial. To ensure timely implementation of any necessary changes in national treatment policy, a survey at the end of each dysentery epidemic season appears to be indicated. However, as changes in resistance patterns can occur rapidly, confirmation by the beginning of the following season is recommended.

The regional differences in antimicrobial sensitivity also raise further questions regarding national policies of antibiotic treatment for dysentery. So far, nalidixic acid has been maintained as the first line of treatment for bacillary dysentery in Burundi, however, the rapid development of antimicrobial resistance will probably limit the effectiveness of all available antibiotics against dysentery in the future. As previously stated by Ries et al. (2), public health policies that delay the development of resistance are needed. Priority should be given to improving the case management of dysentery by training health care workers and to closer monitoring of antibiotic treatment in primary health care services. If less affordable new-generation antibiotics have to be introduced, it is advisable to target antibiotic therapy to those patients who have the highest risk of mortality and to place more emphasis on supportive treatment. Strategies for preventing dysentery should also be further investigated, and prevention programmes should be implemented.

Acknowledgements

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Résumé

La dysenterie épidémique due à Shigella dysenteriae type 1: surveillance de la pharmacorésistance au travers des centres de santé sentinelles au Burundi

Des épidémies de dysenterie bacillaire causée par Shigella dysenteriae type 1 (Sd1) sévissent chaque année entre septembre et mars et sont un problème de santé publique au Burundi depuis 14 ans. La récente insécurité civile qui a entraîné un grand nombre de concentrations de personnes déplacées, vivant dans des conditions d'hygiène précaires, a encore aggravé ce problème. Une enquête a été effectuée dans six centres de santé sentinelles répartis sur l’ensemble du pays, afin de déterminer le taux de pharmacorésistance de Sd1 et d'adapter la stratégie nationale en matière
d'antibiothérapie. Au total, 126 prélèvements ont été recueillis; 73% d'entre eux contenaient des espèces de *Shigella*, dont 97% de Sd1. Ces forts taux de récupération sont à attribuer à une bonne sélection des cas. En effet, ni la méthode de conservation des échantillons ( congélation ou simple réfrigération), ni la durée du transport ne les influençaient de façon significative. La plupart des souches de Sd1 isolées étaient résistantes aux antibiotiques couramment utilisés dans les services de santé de base comme l'ampicilline, la tétracycline et le chloramphénicol; 77% étaient résistantes au cotrimoxazole et 57% à l'acide nalidixique. Le degré de résistance à l'acide nalidixique était très différent d'un site à l'autre et variait de 8% à 83%. Toutes les souches étaient sensibles aux antibiotiques plus récents comme la ciprofloxacine ou la ceftriaxone. La comparaison entre la taille de l’échantillon, différente d’un site à l’autre, et la proportion de la morbidité due à la dysenterie dans chaque site (qui reflète l’étendue de l’épidémie dans la région avoisinante), laisse à penser que le chiffre global de 57% de résistance à l’acide nalidixique est sans doute surévalué par rapport à la réalité sur le terrain. Pour cette raison, l’acide nalidixique a été maintenu comme traitement de choix pour la dysenterie bacillaire au Burundi. Néanmoins, afin de retarder le développement d’une antibiorésistance généralisée, il est conseillé d’améliorer l’application de la stratégie de diagnostic/traitement dans les services de santé de base et de limiter le traitement antibiologique aux groupes à risque. D’une façon générale, la politique nationale de prise en charge des cas de dysenterie bacillaire doit mettre l’accent sur la prévention et le traitement de soutien, à la place du recours systématique aux antibiotiques.

**References**