Outbreak of epidemic typhus associated with trench fever in Burundi

Raoul D; Ndihokubwayo, J B; Tissot-Dupont, H; Roux, V; Faugere, B; Abegbinni, R; Birtles, R J

WHO Reference Centre for Rickettsial Diseases, Universite de la Mediterranee, Marseille, France (Prof D Raoul D PhD, H Tissot D Dupont MD, V Roux PhD, R J Birtles PhD); CHU de Bujumbura, Bujumbura, Burundi (J B Ndihokubwayo MD); Hospital Houphouet Boigny, Laboratoire de Parasitologie, Marseille, France (B Faugere MD); and WHO Bujumbura, Burundi (R Abegbinni MD)

Correspondence to: Prof Didier Raoult, Unite des Rickettsies, CNRS UPRESA 6020, WHO Reference Centre for Rickettsial Diseases, Faculte de Medicine, Universite de la Mediterranee, Boulevard Jean Moulin, Marseille, France (e-mail: Didier.Raoult@ medicine.univ-mrs.fr)

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Summary

Background After a 12-year absence, epidemic typhus has re-emerged among the displaced population of Burundi. Following the outbreak of civil war in 1993, over 760 000 people now inhabit refugee camps, under appalling conditions. A typhus outbreak occurred among prisoners in a jail in N'Gozi in 1995. At the time, the disease was not recognised, and was referred to as sutama. Reports of sutama among the civilian population date back to late 1995 and, in association with body-louse infestation, the disease has subsequently swept across the higher and colder regions of the country.

Methods During a field study in February, 1997, 102 refugees with sutama underwent clinical examination and interview. Serum samples were collected and infesting body lice removed. Microbiological analysis included antibody estimations and specific PCRs aimed at diagnosis of Rickettsia prowazekii, Bartonella quintana, and Borrelia recurrentis. Between January and September, 1997, nationwide epidemiological data on the prevalence and distribution of sutama was obtained through liaison with local health services. A second field study in March, 1997, entailed the collection of further serum samples from suspected cases of sutama in different regions of Burundi.

Findings Most of the 102 patients with sutama during initial assessment presented with manifestations similar to those previously described for typhus in Africa, though skin eruptions occurred in only 25 (25%) cases. Microbiological testing revealed evidence of R prowazekii infection in 76 (75%) patients, confirming that most cases of clinically-diagnosed sutama were epidemic typhus, and supporting the reliability of clinical diagnosis as a basis for the nationwide surveillance of the disease. Up to September, 1997, 45 558 typhus cases were clinically diagnosed, most of which occurred in regions at an altitude of over 1500 m. Serological testing of 232 individuals from different regions of Burundi provided microbiological evidence to support clinical diagnoses in seven provinces, confirming the widespread nature of the outbreak. Serum from 13 of the original 102 patients and 19 (8%) of the 232 suspected cases had raised antibody titres against B quintana. A fatality rate of 15% among jail inmates fell to 0.5% after administration of a single dose of 200 mg doxycycline to suspected cases.

Interpretation A gigantic outbreak of R prowazekii-induced typhus and B quintana-induced trench fever is continuing in Burundi. Transmission of both diseases to such a large number of people has followed a widespread epidemic of body-louse infestation. Diagnosis of typhus could be reliably made by means of clinical criteria, and the disease could be efficiently and easily treated by antibiotics. This epidemic highlights the appalling conditions in central-African refugee camps and the failure of public-health programmes to serve their inhabitants. Louse-associated disease remains a major health threat in this and other war-torn regions of the world.

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Introduction

"The incidence of typhus may serve as an indicator of man's follies" [1]

Epidemic, or louse-borne, typhus is caused by the obligate intracellular bacterium Rickettsia prowazekii. Human beings are regarded as the principal reservoir of the disease, since infection is lifelong. However, following initial illness, the infecting bacteria remain latent for a long period and recrudescence, in the form of Brill-Zinsser disease, occurs only once. Brill-Zinsser disease is much milder than epidemic typhus and usually develops when an individual is immunodepressed by severe stress or malnutrition. [2,3]

Although a single case of Brill-Zinsser disease can act as the source of an outbreak, widespread epidemic typhus cannot occur unless social conditions also provoke widespread body-louse infestation. However, the predisposing factors to ectoparasite infestation are often the same as those for Brill-Zinsser disease. The body louse is a fastidious parasite, specific to human beings and requiring daily blood meals and body warmth to survive; infestation only occurs, therefore, if clothes are not changed or washed regularly. [2] R prowazekii is pathogenic for lice, and infection leads to death within about 3 weeks. [2] Body lice also act as vectors for Bartonella quintana, the agent of trench fever, and Borrelia recurrentis the agent of relapsing fever. [2,4,5]

Only a few foci of epidemic typhus have been reported during the 1990s, with cases occurring in
Ethiopia, Nigeria, and Peru. [3,6] Before the outbreak reported in this study, the most recent case described in Burundi occurred in 1984. [7] In December, 1995, a Swiss nurse who had been working with inmates of a prison in N'Gozi in northern Burundi was diagnosed as having typhus on her return to Switzerland, and typhus was subsequently diagnosed among prisoners. [8,9] In December, 1996, the detection of R prowazekii antibodies in serum samples collected from civilians confirmed that an outbreak was taking place among the general population (unpublished observations). In January, 1997, an outbreak-investigation team was assembled to monitor the extent and progress of the outbreak, to implement specific diagnostic methods, and to assess and oversee suitable antibiotic prescription.

**Methods**

At the time of this study, the social situation in Burundi significantly impeded investigation and management of the outbreak. Civil war, together with blockades imposed by surrounding countries, led to the suspension of all non-military aeroplane flights and a severe petrol shortage.

In February, 1997, the national refugee population was estimated to be over 700 000 (unpublished observations). At least 28 large camps had been established and, in most, no health care was available. Since most camps were set up in remote areas away from towns that were in strategic positions in the war, patients had to travel substantial distances for medical help. Most refugees had arrived at the camps with little more than their clothes, and, probably because ambient temperatures were low, the clothes were seldom changed or washed. Unsurprisingly, infestation by body lice had been prevalent in the populations of refugee camps since 1994 (unpublished observations). Cases of unexplained fever began to be recorded as early as August, 1995, in the provinces of Muramvya, Gitega, and Kayanza (unpublished observations; Figure 1). The fever was often accompanied by severe headache and painful myalgia, and was generally referred to as sutama, which translates as "crouching", since this was the preferred position of patients who found standing upright uncomfortable (unpublished observations).
Clinical investigation of sutama

Two members of the investigation team (DR and JBN) visited the health centres that served seven refugee camps in Muramvya and Kayanza in February, 1997 (Figure 1 and Figure 2). At each centre, inpatients and visiting outpatients with suspected sutama underwent physical examination, gave a blood sample, and were asked to collect and hand over infesting body lice. Our initial goal was to investigate whether sutama was indeed epidemic typhus, and, if so, to use the most common clinical manifestations of sutama as a clinical definition of the disease. Typhus could then be monitored on a nationwide scale by the collation of data submitted by local health workers in different regions of the country.
Figure 2. Monthly prevalence of sutaama between January and September, 1997, in refugee camps in three central highland provinces of Burundi. Administration of doxycycline began in late March, 1997, and insecticide treatment was available from August.

**Antibody estimations**

Serum was tested with a microimmunofluorescence test. [10] We incorporated three antigens into the assay. R prowazekii (Brein 1) and R typhi (Wilmington) were cocultivated with Vero cells and purified. [10] B quintana (Oklahoma) was grown in ECV-304 cells, and purified. [11] The cut-off titre for this assay for diagnosis of rickettsiosis has been previously established as 1/128 for IgG, and 1/64 for IgM. [12,13] A cut-off titre of 1/128 has also been established for diagnosis of B quintana. [4] A series of 150 serum samples, collected from all provinces of Burundi during 1990 as part of a study into the seroprevalence of HIV-1 (unpublished data), was used as a control group.

**Western blotting and adsorption of serum**

Antigens of both R prowazekii and R typhi resolved by SDS-PAGE. [12] After resolution, proteins were transferred to nitrocellulose membranes and blotted with patients’ serum. [12]

To elucidate the specificity of cross-reacting antigens, five serum samples were adsorbed [14] with either R prowazekii or R typhi before their incorporation into either microimmunofluorescence tests or western blots.

**Nucleic-acid extraction, PCR amplification, and base-sequence assessment**

Body lice collected from Russia were used as negative controls for R prowazekii and Borella recurrentis amplifications. We used ants, collected in Marseille, France, as negative controls for B quintana amplifications, since previous examinations of several series of body lice had always revealed some to be infected with B quintana (unpublished observations). These controls were processed concurrently with body lice collected from Burundi. DNA extracts, suitable for use as templates in PCRs, were prepared from lice by means of the reagents of the QIAamp tissue kit (Qiagen, Hilden, Germany). We assessed the effectiveness of the extraction and the absence of PCR inhibitors by PCRs incorporating broad-range 18S rRNA gene primers. [15]

The PCR we used to detect R prowazekii DNA incorporated the primer pair CS877p/CS1273r. [16,17]
allowing amplification of a citrate synthase gene (gltA) fragment. We used two PCRs for detection of B. quintana DNA: the first incorporated the broad range primer pair 16Sf/23Sf, allowing amplification of the entire intragenic spacer region between the 16S and 23S rRNA genes; the second incorporated the primers CS443[1][CS979] (tgc atg att ttg gca cgt gg), allowing amplification of a gltA fragment (unpublished data). The PCR used for detection of Bo rickettsii, B. elizabethae, and Bo burgdorferi, respectively. Reaction mixes for all PCRs included 5 [micro sign]L DNA extract, 5 pmol of each primer, 200 [micro sign]M each of dNTP, 0.75 U Taq DNA polymerase, and 5 [micro sign]L of 10X PCR buffer, made up to 50 [micro sign]L with sterile distilled H2O (all reagents from Boehringer Mannheim Biochemicals, Indianapolis, IN, USA). Amplifications were done in a peltier thermal cycler PTC-200 (MJ Research Inc, Watertown, MA, USA) with an initial denaturation step at 95[degree sign]C followed by 40 cycles of denaturation at 95[degree sign]C for 30 s, annealing at T_95 for 30 s, extension at 68[degree sign]C for 60 s. The cycle was completed by a 7 min step at 72[degree sign]C to allow complete extension of all products. The T_95 of primers was 46[degree sign]C with the exception of CS440/CS979 and Bf1/Brl, which required a T_95 of 55[degree sign]C. When this higher T_95 was used, the extension temperature was raised to 72[degree sign]C. We measured the success of each PCR by ultra-violet illumination of ethidium bromide stained 1% w/v agarose gels on which products had been resolved by electrophoresis.

The identities of PCR products derived from gltA-fragment amplification were established by base-sequence assessment. We purified products using the QIAquick PCR purification kit (QiaGen). Sequencing reaction mixes were prepared with the Amplicycle sequencing kit (Perkin-Elmer Corporation, Foster City, CA, USA); we used the fluorescein-endlabelled forms of the primers used for amplifications to prime sequencing reactions. Electrophoretic resolution of the products of these reactions was done with an ALF DNA sequencer (Pharmacia LKB, Uppsala, Sweden), incorporating 6% denaturing polyacrylamide gels, in accordance with the manufacturer's protocol.

Surveillance
We carried out a second field study in March, 1997, to provide microbiological evidence to support the clinically-based assumption that typhus was now widespread in Burundi. Two members of the investigation team (BF and JBN) collected 222 serum samples from febrile patients attending the health centres, which served 28 refugee camps situated in nine provinces of Burundi. Owing to logistical difficulties, the time available for sample collection at each site was very limited; serum was thus taken by convenience sampling of patients present at the health centres at the time of the visit.

Between January and September, 1997, district health workers monitored the prevalence of epidemic typhus among health-centre attendees. Cases were identified as patients complaining of sputum, and by a fever exceeding 39[degree sign]C accompanied by severe headaches. Each week, data was collated at a regional, then national, level. Since, during this time, most of the population had been displaced to refugee camps, estimates of baseline population numbers were derived by the combination of estimates of the number of inhabitants of each refugee camp in the region.

Typhus was also monitored by use of the criteria described earlier among inmates of the jails in N'Gozi, Gitega, and Bururi (Figure 1). In each jail, because the size of the inmate population was known and was stable, estimates of the rates for prevalence, attack, and death could be generated and compared. Since health workers attending Gitega jail had access to antibiotics—whereas those in N'Gozi and Bururi did not—comparison of these variables was used to assess the effectiveness of antibiotic treatment for typhus. All epidemiological data were collated by use of EPI-INFO 6. The significance of results was assessed with Fisher's exact test and Student's t test.
Treatment
A nationwide treatment programme was initiated in March, 1997, with the administration of doxycycline (single dose 200 mg orally) to all cases and suspected cases. Distribution of antilouse insecticides began 3 months later after petrol became more widely available and blockades were removed. The inhabitants of refugee camps were treated with permethrin (1%) dusting powder according to WHO guidelines. [6]

Results
Clinical observations
The clinical manifestations of 102 sutama patients examined during the first field study are given in Table 1. In general, the presentation of the syndrome was similar to that previously seen in African typhus patients. [3] However, only 25 patients had a rash, which, in 11 cases, was purpuric. The prevalence of a rash was significantly lower in patients examined before the third day after onset of symptoms (11.6%), compared with those examined later (34.5%, p<0.01). Most patients had a cough, though very few chest radiographs were done. When radiographs were taken, typhus pneumonia was evident. Unusual complications occurred in several cases among jail inmates, notably patients with gangrene of the fingers or toes and patients with hemiplegia.

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutama</td>
<td>102</td>
</tr>
<tr>
<td>Fever &gt;39°C</td>
<td>102</td>
</tr>
<tr>
<td>Headache</td>
<td>102</td>
</tr>
<tr>
<td>Rash</td>
<td>25</td>
</tr>
<tr>
<td>Purpuric rash</td>
<td>11</td>
</tr>
<tr>
<td>Delirium</td>
<td>81</td>
</tr>
<tr>
<td>Coma</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>57</td>
</tr>
<tr>
<td>Cough</td>
<td>70</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>8</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 1. Clinical findings related to 102 cases of sutama in February, 1997

Estimation of R prowazekii prevalence by antibody estimation and PCR-based detection in lice
Serum was obtained from all 102 clinically diagnosed patients and, when tested with the indirect fluorescent antibody test, 76 (75%) showed significant titres against R prowazekii. The mean delay between onset of symptoms and sampling was 6.75 (SD 4.24) days for these 76 patients, and 2.08 (2.25) for those with a negative serology.

All serum that reacted strongly with R prowazekii also reacted strongly with R typhi antigen; in 47 patients the strength of the IgG reaction was within one dilution of that for R prowazekii, and for all patients the IgM titres against both antigens were within one dilution of each other. Absorption of five serum samples with R prowazekii led to the removal of all detectable antibodies with both antigens, but when absorbed with R typhi, high concentrations of specific anti-R prowazekii antibodies remained (Table 2). These results were confirmed by western blotting (results not shown).
Table 2. Serological cross-reactivity between suitama-patient serum and R prowazekii and R typhi antigens before and after adsorption tests

<table>
<thead>
<tr>
<th>Patient</th>
<th>Antigen</th>
<th>Titre when serum was unadsorbed (IgM/IgG)</th>
<th>Titre when serum was absorbed with R prowazekii (IgM/IgG)</th>
<th>Titre when serum adsorbed with R typhi (IgM/IgG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R prowazekii</td>
<td>2048/1024</td>
<td>0/0</td>
<td>256/128</td>
</tr>
<tr>
<td></td>
<td>R typhi</td>
<td>512/512</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>R prowazekii</td>
<td>128/512</td>
<td>0/0</td>
<td>128/0</td>
</tr>
<tr>
<td></td>
<td>R typhi</td>
<td>64/512</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>3</td>
<td>R prowazekii</td>
<td>1024/1024</td>
<td>0/0</td>
<td>512/0</td>
</tr>
<tr>
<td></td>
<td>R typhi</td>
<td>512/512</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>4</td>
<td>R prowazekii</td>
<td>32/256</td>
<td>0/0</td>
<td>32/128</td>
</tr>
<tr>
<td></td>
<td>R typhi</td>
<td>32/256</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>5</td>
<td>R prowazekii</td>
<td>64/1024</td>
<td>0/0</td>
<td>128/128</td>
</tr>
<tr>
<td></td>
<td>R typhi</td>
<td>64/1024</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

We obtained 63 lice from 44 of the 102 patients examined during the first field study. 16 patients were infected with one or more lice in which R prowazekii DNA was detected. Serum from three of these patients did not yield detectable concentrations of anti-R prowazekii antibodies. Thus, in total, 79 of the 102 clinically diagnosed suitama patients had positive serology or were infested with an infected louse, or both, confirming that most cases of suitama were indeed epidemic typhus and supporting the reliability of clinical diagnosis as a basis for the nationwide surveillance of the disease.

Estimation of B quintana prevalence by antibody estimation and PCR-based detection in lice
13 (13%) of the 102 patients examined during the first field study showed significant antibody titres against B quintana. 11 of these also had significant titres against R prowazekii. We detected B quintana DNA in five lice, one of which also yielded R prowazekii DNA. Three of the B quintana-infected lice were collected from patients who had no detectible anti-B quintana antibodies. We were unable to discern any specific clinical symptoms associated with B quintana infection.

PCR-based detection of Bo recurrentis in lice
All Bo recurrentis-specific PCRs on lice were negative.

Negative controls
None of the 150 serum samples from negative controls had antibodies at titre of 128 or more against any of the three antigens. We did not detect R prowazekii DNA in any of the lice collected from Russia, and none of the PCRs incorporating DNA extracts prepared from ants gave amplification products.

Surveillance of typhus among refugees
Results of the nationwide surveillance programme between January and September, 1997, are shown in Table 3 and in Figure 2. 44 667 cases of suitama were recorded. The outbreak most affected refugees in camps in Gitega, Kayanza, and Muramvya-three provinces in the central highlands of Burundi. The extent of the outbreak appeared to diminish after May, 1997 (Figure 2). Estimation of other
epidemiological variables among sutama patients within the refugee population was not feasible because our estimates of numbers of cases were based solely on health-centre attendees and not on surveillance of entire refugee-camp populations. For example, profoundly ill patients were probably incapable of leaving their refugee camps, and were thus unable to get to health centres. Only cases diagnosed from January, 1997, were included in our estimates, furthermore, we have clear evidence that typhus was extant at least 1 year beforehand.

<table>
<thead>
<tr>
<th>Province in Burundi</th>
<th>Number of refugees</th>
<th>Number of cases diagnosed*</th>
<th>Serum collected from febrile (number of samples from each town/camp)</th>
<th>R prowazekii antibodies detected in serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bubanza</td>
<td>40 557</td>
<td>0</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Bujumbura</td>
<td>23 308</td>
<td>951</td>
<td>Yes (34)</td>
<td>Yes</td>
</tr>
<tr>
<td>Bururi</td>
<td>8889</td>
<td>0</td>
<td>Yes (25)</td>
<td>No</td>
</tr>
<tr>
<td>Cankuso</td>
<td>1900</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cibitoke</td>
<td>97 758</td>
<td>289</td>
<td>Yes (7)</td>
<td>Yes</td>
</tr>
<tr>
<td>Gitega</td>
<td>66 464</td>
<td>10 441</td>
<td>Yes (28)</td>
<td>Yes</td>
</tr>
<tr>
<td>Karuzi</td>
<td>98 763</td>
<td>1205</td>
<td>Yes (10)</td>
<td>Yes</td>
</tr>
<tr>
<td>Kayanza</td>
<td>99 244</td>
<td>14 866</td>
<td>Yes (21+30)†</td>
<td>Yes</td>
</tr>
<tr>
<td>Kirundo</td>
<td>232 157</td>
<td>0</td>
<td>Yes (15)</td>
<td>No</td>
</tr>
<tr>
<td>Makamba</td>
<td>5000</td>
<td>204</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Muramvyva</td>
<td>47 885</td>
<td>15 170</td>
<td>Yes (80+76)†</td>
<td>Yes</td>
</tr>
<tr>
<td>Muyinga</td>
<td>30 296</td>
<td>314</td>
<td>Yes (7)</td>
<td>Yes</td>
</tr>
<tr>
<td>N'Gozi</td>
<td>2869</td>
<td>531</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Rutana</td>
<td>744</td>
<td>0</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Ruyigi</td>
<td>8500</td>
<td>0</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>764 334</td>
<td>43 971</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients presenting to local health centres with sutama and with fever >39°C and severe headache. †Number of serum samples collected during first and second field studies, respectively.

Table 3. Nationwide surveillance and serological findings among sutama patients between January and September, 1997

A further 232 serum samples were collected in March, 1997, from febrile refugees encountered in health centres serving camps in nine of the 15 provinces of Burundi (Table 3). We confirmed R prowazekii infection serologically in serum collected from refugees in seven provinces (Table 3). In all seven provinces, typhus had already been widely diagnosed by means of clinical criteria. In the two provinces in which there was no serological evidence of typhus among refugees, there were no clinically diagnosed cases either. In addition to these findings, about 8% of these serum samples contained significant concentrations of antibodies against B quintana. We found evidence of infections among refugees in the provinces of Bujumbura (six of 34 serum samples tested), Karuzi (one of ten), Kayanza (two of 30), Kirudo (five of 15), and Muramvyva (five of 76).

Surveillance of typhus among prisoners and estimation of epidemiological variables of outbreak.
Results of the surveillance programme of prisoners in three jails in Burundi between January and September, 1997, are shown in Table 4. We were also able to calculate estimates of attack rates and death rates (Table 4). In Gitega, all except one of the patients were treated successfully, and the patient who refused treatment died. Ten of the patients had coma, and five presented with hemiplegia. Five (2.5%) patients relapsed 8 days after receiving treatment, but recovered fully after administration of chloramphenicol (2 g per day for 3 weeks). In the jails at Ngozi and Bururi, attack rates were significantly higher than in Gitega (p<10^{-7}), with about half the inmates contracting typhus. The death rate at N'Gozi, furthermore, was also significantly higher (p<10^{-6}) than at Gitega. We also found serological evidence of B quintana infection among the inmates of N'Gozi (two of eight serum samples tested) and Bururi jail (two of 18), but not of Gitega jail (none of 20).

<table>
<thead>
<tr>
<th>Jail</th>
<th>Number of prisoners/number of typhus cases (attack rate)</th>
<th>Number of deaths among typhus patients (death rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gitega</td>
<td>1300/213 (16.4%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>N'Gozi</td>
<td>1200/696 (58.0%)</td>
<td>84 (12.1%)</td>
</tr>
<tr>
<td>Bururi</td>
<td>1400/678 (48.4%)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 4. Comparison of attack rates and death rates for sutama among inmates of three jails in Burundi

Discussion

As in other central-African countries, foci of typhus in Burundi have remained extant following World War II. [3,6] Although the large-scale outbreaks of 1969-71 and 1974-75 overshadowed other years, about 100 cases per annum were reported until WHO ceased estimations in 1984. [6,20-22] Despite the lack of a reliable diagnostic and reporting infrastructure since this time, to the best of our knowledge or that of the health workers in Burundi, there was very little extant typhus in the country in the years immediately before the outbreak. A nationwide serosurvey in 1990 did not show up any evidence for current or recent exposure to R prowazekii (unpublished data).

To differentiate the clinical signs of epidemic typhus from those of other infections is not easy. Typhus is usually exanthematic, and previous clinical studies record the presence of a rash in more than 50% of cases. [2,3] Identification of the rash on dark skin, however, is particularly difficult. Compared with typhoid, diarrhoea rarely occurs with typhus, and splenomegaly, which is common among malaria patients, is seldom found among those with typhus. Other pertinent symptoms are neurological complications such as seizures, coma, and mental confusion. [2,3] Pulmonary symptoms also commonly occur. [3]

Although clinical diagnosis of individual cases is complicated, a cluster of sudden-onset severe pyrexia among louse-infected people living in cold, crowded, and unhygienic conditions should immediately alert the clinician to typhus. [3] The central highlands of Burundi are particularly remote, and sanitation is generally poor. In the colder regions, inhabitants wear several layers of clothing all year round, leading to a high prevalence of body-louse infestation; according to one estimate, as many as two in three people nationwide are infested. [21] Living conditions in refugee camps are particularly difficult, and virtually all inhabitants are likely to have lice. The stressful, deprived conditions that lead to widespread louse infestation also provoke recrudescence of typhus. [3] The fact that a single case of Brill-Zinsser disease can initiate a typhus outbreak is daunting. However, what we do not know is whether the nationwide outbreak originated from a single source or resulted from the combination of more localised independent outbreaks.
We used two approaches to confirm microbiological that most cases of sutama were caused by R prowazekii infection, namely antibody estimates and PCR-based amplification of specific DNA. The high concentrations of both IgG and IgM titres in all our patients probably indicated recent infection, since, although IgG titres can remain raised for a long period after recovery from typhus, IgM concentrations fall rapidly. The absence of any detectable antibodies in serum from patients in our control group, furthermore, suggests that typhus was not prevalent in 1990. Since R prowazekii is pathogenic towards lice and infection usually leads to rapid death, detection of rickettsial DNA in lice can indicate extant human typhus. The durability of lice heightens their potential as diagnostic indicators for typhus; lice collected from suspected cases or during routine survey can easily be transported or posted to laboratories for analysis.

Once sutama was established as epidemic typhus, and since knowledge of the syndrome was widespread, the disease could be monitored by health workers throughout Burundi. The outbreak was affecting mainly the refugee camps within the three highland provinces of the country (90% of cases), but did not significantly spread outside this region. Although almost 1000 cases were also diagnosed in the lowland province of Bujumbura, these cases were thought to have resulted from the migration of infected people from the highlands into Burundi's capital city. Typhus was also rife in all three jails studied, irrespective of their geographical location.

The treatment of typhus is easy and inexpensive—a single dose of 200 mg doxycycline will usually cure patients. In this study, the usefulness of doxycycline regimen in the treatment of patients and the reduction of the spread of disease was underlined by comparison of the outcome of outbreaks in the three jails. In Gitega jail, where treatment was administered, both the attack rate and the fatality rate were significantly lower than those in N'Gozi jail and Bururi jail, where no such treatment was available.

The general applicability of insecticides to the immediate control of epidemic typhus was established during the first N'Gozi jail outbreak in 1996, and a standard treatment protocol with 1% permethrin has been produced by WHO. Because treatment should be repeated every 6 weeks, a total of 3-5 tonnes of powder are required to treat 100 000 people on one occasion; 1 year's supply is therefore ten times this figure. In practice, over-reliance on insecticides may be foolhardy; the severe limitations imposed by the war on Burundi's distribution and communication infrastructures prevented the widespread availability of such quantities of insecticides until July, 1997-6 months after the scale of the outbreak was first recognised. The transient nature of the camps' populations also presented logistical difficulties, since several delousing stations were required to ensure treatment was continued every 6 weeks.

There are substantially fewer drawbacks associated with the administration of doxycycline than with delousing. Antibiotics not only cure current infection, but also ease logistical difficulties, since transport of 100 000 doxycycline tablets is easier than the shipping of 50 tonnes of insecticides. However, although effective treatment can be administered in only a single visit to each camp, which removes the source of further infection from non-immune individuals, infected lice remain. Thus, the optimum control strategy against typhus must be delousing combined with antibiotic treatment, as emphasised in existing WHO guidelines for the control and prevention of louse-borne diseases. In addition, we stress that effective prevention also requires the provision of basic sanitation and hygiene to allow for changes of clothing, washing, and bathing, together with the establishment of effective surveillance programmes. Clearly, the availability of an effective vaccine would circumvent these difficulties, and should a suitable vaccine be produced a small team of health workers could vaccinate all refugees in Burundi within 2 months. A vaccination programme for typhus would, without doubt, remove an enormous threat to the health of people in central Africa.

The study also provided evidence of trench fever among refugees and their infesting lice. However, the clinical presentation of trench fever is not specific. So widespread clinical diagnosis was therefore not possible. Still, B quintana is likely to represent a significant health threat to camp inhabitants.
Given the relapsing nature of this infection, 2.5% of sutama patients who were not cured by single dose of doxycycline, may in fact have been concurrently suffering from trench fever. Such speculation clearly needs further investigation. Unlike R prowazekii, B quintana infection of lice is thought to be long term, [4] so infestation with infected lice cannot be deemed indicative of infection.

This epidemic should serve to highlight the appalling conditions in refugee camps in central Africa, and its existence represent represents a failure of national and international public-health-surveillance and emergency-response programmes. The outbreak also presents an enormous threat to the future health of the population of the region, since a very large reservoir of R prowazekii has now been established. Long-term prevention and control strategies that address the underlying preconditions of this outbreak are needed.

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