Global surveillance of rickettsial diseases: Memorandum from a WHO meeting*

Rickettsial diseases are widely distributed throughout the world and are particularly prevalent in developing countries. An indirect immunofluorescence antibody test and standard protocol for its use have been developed and distributed to laboratories in 37 countries. This Memorandum summarizes the results obtained as well as the conclusions and recommendations made by participants at a WHO meeting on the Global Surveillance of Rickettsial Diseases, held in Oslo on 10 September 1991.

Introduction

The rickettsial diseases of man are widely, though variably distributed throughout the world. Such diseases include the typhus fevers, spotted fevers (tick typhus), scrub typhus, acute and chronic Q fever, rochalisae infections, and ehrlichiosis. Available evidence strongly suggests that these serious and incapacitating diseases constitute a very significant, but often unrecognized, fraction of the acute febrile disease burden in many populations, especially in developing countries. Simple but effective treatments for these diseases are nevertheless available that reduce mortality to very low levels and greatly attenuate morbidity, enabling patients to return quickly to an active life. Such reductions in morbidity and mortality diminish the unnecessary drain on valuable medical resources; preventive/control measures are also available for some of these diseases. Improved global surveillance of rickettsial diseases is urgently required to assess their prevalence, to support the diagnosis and specific treatment of patients, to permit the development and implementation of strategies for their prevention and control, and to provide a sound and credible database to justify requests to funding agencies for support of such strategies.

In 1987, at the WHO Consultation on Laboratory Diagnosis of Rickettsial Diseases, in Palermo, the Directors of the WHO Collaborating Centres for Rickettsial Reference and Research, and other interested participants, developed a strategy for the global surveillance of rickettsial diseases. The immediate objective was to obtain reliable data on the global prevalence and distribution of these diseases and thereby reduce the associated mortality and morbidity. Additional objectives were to identify and characterize strains of pathogenic rickettsiae from various parts of the world, and to transfer existing diagnostic technology to laboratories in developing countries. A diagnostic kit was developed, and the Collaborating Centres produced reagents and distributed materials for serological testing of patient's sera. The indirect fluorescence antibody technique (IFA), which has been extensively field tested, was selected as the preferred diagnostic procedure, because of its sensitivity, specificity, cost, and suitability for use in developing countries. A standard protocol for the procedure was provided. The following were sent to laboratories that requested them: partially purified suspensions of *Rickettsia conorii* and *R. prowazekii* antigen reagents; known positive and negative control sera; fluorescein-labelled antiglobulin for use in the IFA test; and teflon-coated slides. "Hands-on" workshops were also held in Bangladesh, Brazil, India, Nepal and Thailand to familiarize local laboratories with the reagents and their use.

* This Memorandum is based on the report of a WHO meeting that was held in Oslo on 10 September 1991. The participants at the meeting were Dr J. Kazar, Bratislava, Slovak Republic; Dr J.G. Olson (Rapporteur), Atlanta, GA, USA; Dr D. Raoult, Marseilles, France; Dr R. Regnery, Atlanta, GA, USA; Dr F. Segura-Porta, Sabadell, Spain; Dr I. Tarasseyvich, Moscow, Russian Federation; Dr M. Thibon, Paris, France. WHO Secretariat: Dr Y. Pervikov, Division of Communicable Diseases.

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Present study

Laboratories in 37 countries agreed to participate in the surveillance by testing paired sera from patients with pyrexia of unknown origin. These laboratories were also asked to prepare line listings of the name, age and sex of patients, the date of onset of illness, date when serum specimens were collected, and the likely locations of exposure to rickettsial vectors. Titres ≥64 were considered positive. WHO has received data from some of the participating laboratories, as outlined below (see also Table 1).

Results

Region of the Americas

In Brazil, the Fundação Ezequiel Dias, Belo Horizonte, reported evidence of spotted-fever-group infections among 13 (13.9%) of the 93 patients in their test population, mainly from Minas Gerais State; in contrast, the Instituto Adolfo Lutz, São Paulo, found no evidence of rickettsial antibodies in the 82 specimens from their test population. The five samples from Lima, Peru, also contained no antibodies to rickettsial organisms. However, in El Salvador, 8 (20%) of 40 samples were positive for typhus-group rickettsiae and 13 (32.5%) of 40 samples were positive for spotted-fever-group rickettsiae.

South-East Asia Region

India, Mongolia, Nepal, and Thailand reported serological evidence of typhus and/or spotted-fever-group infections. Several provinces in Mongolia reported evidence of rickettsial infections, with 48 (3.9%) of 1229 specimens containing significant antibody titres to spotted-fever-group rickettsiae and 117 (9.5%) of 1229 specimens containing significant levels of antibodies to Q fever. In India, the National Institute of Communicable Diseases, Delhi, detected antibodies to typhus-group rickettsiae in 7 (7.6%) of 92 specimens and to spotted-fever-group rickettsiae in 4 (4.3%) of 92 specimens: the National Institute of Virology, Pune, reported that 2 (16.6%) of 12 specimens had significant antibody levels to spotted-fever-group rickettsiae. In Nepal, 4 (21%) of 19 specimens showed evidence of infection with spotted-fever-group rickettsiae and 5 (26.3%) of 19 showed evidence of infection with scrub typhus rickettsiae. In Thailand, the Health Sciences Research Institute, Nonthaburi, found 25 (25%) of 100 specimens positive for spotted-fever-group rickettsiae, 23 (23%) of 100 specimens positive for typhus-group rickettsiae, and 7 (7%) of 100 positive for antibodies to scrub typhus rickettsiae.

Western Pacific Region

In China eight patients from Shandong Province had significant titres to scrub typhus rickettsiae, as did nine patients from Jinan city.

African Region

The National Research Institute of Health, Addis Ababa, Ethiopia, reported that 31 (16.8%) of 184 persons had diagnostic levels of antibody to typhus-group rickettsiae. In Côte d’Ivoire, the Laboratoire de Bactériologie-Virologie, Abidjan, observed that 16 (17%) of 94 individuals were seropositive to spotted-fever-group rickettsiae and 1 (1%) had a significant titre to typhus-group rickettsiae. In Guinea-Bissau 3 (7.5%) of 40 samples had antibody to typhus and 8 (20%) of 40 samples had antibodies to spotted-fever-group rickettsiae. Of 40 samples from Cape Verde, 3 (7.5%) were positive for antibodies to

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Table 1: Results of the serosurveys for rickettsial antibodies in persons with undiagnosed febrile illnesses

<table>
<thead>
<tr>
<th>Region</th>
<th>No. of specimens tested</th>
<th>No. positive:</th>
<th>Typhus</th>
<th>SFG*</th>
<th>Scrub typhus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Pacific</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>China</td>
<td></td>
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<tr>
<td>South-East Asia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>India</td>
<td>104</td>
<td>7 (7.6)</td>
<td>6 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mongolia</td>
<td>1229</td>
<td>48 (3.9)</td>
<td></td>
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</tr>
<tr>
<td>Nepal</td>
<td>19</td>
<td>4 (21.1)</td>
<td>1 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>100</td>
<td>23 (23.0)</td>
<td>25 (25.0)</td>
<td>7 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>93</td>
<td>0</td>
<td>13 (13.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minas Gerais State</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>São Paulo</td>
<td>82</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>El Salvador</td>
<td>40</td>
<td>8 (20.0)</td>
<td>13 (32.5)</td>
<td></td>
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<tr>
<td>Peru</td>
<td>5</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Eastern Mediterranean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td>40</td>
<td>6 (15.0)</td>
<td>11 (27.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>100</td>
<td>18 (18.0)</td>
<td>13 (13.0)</td>
<td></td>
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<tr>
<td>Syrian Arab Republic</td>
<td></td>
<td>11</td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Tunisia</td>
<td>69</td>
<td>12 (17.4)</td>
<td>27 (39.1)</td>
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</tr>
<tr>
<td>Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cape Verde</td>
<td>40</td>
<td>3 (7.5)</td>
<td>4 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>94</td>
<td>1 (1.1)</td>
<td>16 (17.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>184</td>
<td>31 (16.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guinea-Bissau</td>
<td>40</td>
<td>3 (7.5)</td>
<td>8 (20.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* SFG = spotted-fever group.
* Figures in parentheses are percentages.
typhus and 4 (10.0%) were positive for antibodies to spotted-fever-group rickettsiae.

**Eastern Mediterranean Region**

The National Hospital, Lattakia, Syrian Arab Republic, tested sera from 11 persons and found no antibodies to spotted-fever- or typhus-group rickettsiae. However, evidence of rickettsial diseases was documented in Tunisia and Pakistan. In Tunisia, the Laboratoire Régional de la Santé Publique de Sousse found that 12 (17.4%) of 69 people tested had diagnostic titres to typhus-group rickettsiae and 27 (39.1%) had titres to spotted-fever-group rickettsiae. Results from the Khyber Medical College in the Peshawar region of Pakistan revealed that 18 (18%) of 100 persons had significant titres to typhus-group rickettsiae and 13 (13%) had significant titres to spotted-fever-group rickettsiae. Of 40 samples from Iran, 6 (15.0%) were positive for typhus-group rickettsiae and 11 (27.5%) were positive for spotted-fever-group rickettsiae.

**Conclusions and recommendations**

Unfortunately, limited demographic data were supplied by the participating laboratories. Little new information was obtained about the geographical distribution of rickettsiae, since rickettsial diseases were known to be endemic in the reporting countries. However, the documentation of spotted-fever- and typhus-group infections in Côte d'Ivoire is significant because it confirms previous findings. An isolate from a patient with São Paulo fever was made at the Instituto Adolpho Lutz, Brazil. Molecular characterization at the Centers for Disease Control, USA, revealed that it was identical to *Rickettsia rickettsii*, which causes Rocky Mountain spotted fever.

In the USA, Rocky Mountain spotted fever is a notifiable disease, and, on average, 600–650 cases are reported each year. The majority of such cases have been from the south-eastern and west-south-central states, with the onset of symptoms occurring during May–August. A total of 54.2% of cases have reported a tick bite within 14 days of the appearance of symptoms; the highest incidences are among 5–9-years-olds. The overall case-fatality ratio is 5.2%; however, it is highest among persons aged >40 years (8.2%).

*Ehrlichia chaffeensis*, a new species associated with human disease in the USA, has been identified; approximately 300 cases of illness caused by *E. chaffeensis* have been documented. Cases have also been identified in Portugal and Mali. A new species of *Rochalimaea, R. henselae*, has been isolated from a febrile man who was seropositive for human immunodeficiency virus (HIV). Based on a wide variety of epidemiological and laboratory evidence, including isolation, polymerase chain reaction and serology, *R. henselae* is most certainly the cause of bacillary angiomatosis, peliosis hepatitis and bacteriemia in immuno-compromised patients, and cat scratch disease in persons with healthy immune systems.

In the Russian Federation approximately 1500 cases of tick-borne typhus are reported annually from central and eastern Siberia. Also, more than 1800 cases of Q fever were reported between 1989 and 1991. Cases of Brill–Zinsser disease have steadily decreased over the years, but pediculosis is prevalent, with 0.5–0.7 persons per 100 000 being infected. In Mongolia, foci have been identified where there are greater than expected prevalences of antibody to *R. sibirica* and *Coxiella burnetii*.

Although these findings do not necessarily identify new foci of rickettsioses, they indicate that countries are beginning to identify specific regions that are endemic for rickettsial diseases. The network of surveillance laboratories was established in order to facilitate the proliferation of appropriate diagnostic technology at country and regional levels. An increased awareness of rickettsioses may encourage local physicians to consider a diagnosis of rickettsial diseases and to start prompt antibiotic treatment. A decrease in morbidity and mortality from these diseases should then occur. Considerable effort is still required to make the surveillance system effective; this is justified by the potential gains.

The participants at the meeting made the recommendations outlined below.

- A continual supply of *R. conorii, R. prowazekii,* and *C. burnetii* antigens as well as fluorescein-label- led antihuman immunoglobulin must be provided. It would be advisable to prepare antigens to *R. tsutsugamushi* for distribution to laboratories on request.
- Action should be taken to develop alternative simple diagnostic tests that would be suitable for use in laboratories where no facilities for the immunofluorescence technique are available.
- Interchange of sera (both positive and negative) and information between laboratories must be encouraged in order to promote quality control. The sera should be sent periodically to reference laboratories to maintain diagnostic quality.
- Further training for all the participating laboratories should be encouraged. This is particularly important for laboratories without experience in immunofluorescence techniques.
- WHO should collect and disseminate information on the surveillance of rickettsial diseases throughout the world.
Memorandum

Acknowledgement
Dr J.E. McDade (Centers for Disease Control, Atlanta, GA, USA) is thanked for his valuable contributions to the WHO Project on Global Surveillance of Rickettsial Diseases.

Annex
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Countries participating in the WHO Project on Global Surveillance of Rickettsial Diseases

African Region. Cape Verde, Côte d’Ivoire, Ethiopia, Gabon, Guinea-Bissau.

Region of the Americas. Bolivia, Brazil, Colombia, Costa Rica, Ecuador, El Salvador, Guatemala, Mexico, Peru, Uruguay, USA.

South-East Asia Region. Bangladesh, India, Indonesia, Mongolia, Myanmar, Nepal, Sri Lanka, Thailand.

European Region. Former Czechoslovakia, France, Greece, Italy, Russian Federation, Switzerland.

Eastern Mediterranean Region. Egypt, Iran, Iraq, Pakistan, Syrian Arab Republic, Tunisia.

Western Pacific Region. China.