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A Critical Gap: Investigation of Human Rickettsial Infections in Latin America

Human Rickettsioses in Latin America

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ABSTRACT

The Fifth Latin American Conference on Rickettsial Diseases marks a milestone in the development of rickettsiology in Latin America. The knowledge produced by Latin American rickettsiologists has grown immensely in the last decade. Yet sufficient funding for scientists in rickettsiology has not materialized, as many other scientists and clinicians fail to perceive the importance of rickettsial diseases. To move the field forward, and to gain interest and support from Ministries of Health and funding sources, human studies that establish the incidence and clinical severity of these infections is required. Only studies of human disease can provide these data, which we are unable to determine at present. I propose we close this critical gap by promoting the following:

1. Development of accurate, sensitive, species-specific tests for establishment of the diagnoses of infections caused by Rickettsia, Ehrlichia, and Anaplasma species.
2. Performance of longitudinal, prospective population-based studies of patients utilizing these diagnostic assays to determine the incidence, geographic distribution, seasonality, socioeconomic risk factors, clinical manifestations and severity of illness including mortality.
3. Establishment of knowledge of the human pathophysiology, complications, mechanisms of organ injury, clinical biomarkers of severity and of effective immunity, and mechanisms of protective immunity for rickettsial diseases.
4. Collaboration among scientists investigating human illnesses caused by arboviruses, hantaviruses, leptospirosis, influenza, and other agents of similar syndromes in order to share patient samples, demographic data, and costs and effort of the work.
5. Establishment of human specimen banks for the development of improved diagnostics, investigations of pathogenesis and immunity, and identification of currently unrecognized novel emerging infectious agents.

The critical gap is knowledge of the public health and clinical impact of human infections. Indeed the ultimate purpose for our investigations of rickettsiae and rickettsial diseases is the alleviation of suffering. Only then will patients benefit from our research efforts.

Keywords: Rickettsia, Ehrlichia, Anaplasma, Rickettsioses, Latin America

The Fifth Latin American Conference on Rickettsial Diseases marks a milestone in the development of rickettsiology as a scientific discipline in Latin America. In the chapter on spotted fever rickettsioses in the first edition of Tropical Infectious Diseases: Principles, Pathogens, and Practice published in 1999, I speculated expansively of the likelihood for the presence of rickettsioses as significant clinical diseases in Mexico, Central and South America (1). There were very few data to support this idea. At the First Latin American Conference on Rickettsioses in Ouro Preto, Brazil in 2004, there were 10 oral presentations, a small number of posters, and strong expressions of enthusiasm and excitement (2). At the second congress on rickettsial diseases in Ribeirao Preto, Brazil, there were 10-fold more participants, more presentations, and significant scientific progress (3). Subsequent meetings in Bogota, Colombia (4) and San Jose, Costa Rica (5) enhanced the depth of participation from other countries and witnessed continued advancement of scientific knowledge of these diseases and their agents. The chapter on spotted fever rickettsioses in the third edition of Tropical Infectious Diseases: Principles, Pathogens, and Practice was filled with facts and knowledge produced by Latin American rickettsiologists whose studies have elucidated the natural cycles of Rickettsia rickettsii more extensively than any others of spotted fever rickettsiae anywhere on Earth (6). Yet obtaining sufficient funding for training of scientists in rickettsiology has not been accomplished, mainly because scientists in other areas of microbiology and infectious diseases who review the grant applications do not perceive the importance of rickettsial diseases. They do not rank the need for greater scientific effort in rickettsiology as high as that of dengue, malaria, diarrheal and other diseases. It is unclear whether or not there is sufficient support by Ministries of Health in Latin America for investigation of patients with acute undifferentiated febrile diseases to determine the incidence of infection by Rickettsia, Ehrlichia, Anaplasma, and even Orientia. The best strategy to change the minds of grant application review panels and public health organizations is establishing comprehensive data on the incidence and severity of rickettsial infections in human populations in these countries. Prior to the first Latin American symposium on rickettsial diseases in Ouro Preto, Brazil in 2004, the Pan American Health Organization sponsored an experts' consultation on Rickettsioses in the Americas (2). The recommendations of the consultation included the establishment of an active, prospective epidemiological surveillance network in Latin America, the development and deployment of effective diagnostic tests, promotion of cooperation among countries and developing research capacity. The aim of the Pan-American Health Organization representative to establish WHO Collaborating Centers for Rickettsial Diseases in the Americas was never achieved. Those goals remain important today because insufficient attention is paid to knowledge of spotted fever and typhus rickettsioses, ehrlichioses, and anaplasmosis, which continues to result in misdiagnosis, ineffective treatment, and excess morbidity and mortality. To gain greater attention, performance of human studies that establish the incidence and clinical severity of each of these infections is required. Sufficient public health support and physicians' knowledge of rickettsioses will be obtained only after data are obtained and promulgated regarding the impact of these readily treatable diseases. Funding support for public health measures and research by philanthropy such as the Bill and Melinda Gates Foundation requires convincing data of the importance of the problem calculated in DALYs (disability-adjusted years of life lost). Only studies of human disease can provide these data, which we are unable to determine at present. What do we need to do? I suggest the following:

1.Development of accurate, sensitive, species-specific tests for establishment of the diagnoses of infections caused by Rickettsia rickettsii, R. parkeri, R. typhi, R. prowazekii, R. amblyommii, Ehrlichia chaffeensis, E. ewingii and Anaplasma phagocytophilum.

Approaches to development of such tests include identification of species-specific antigens/epitopes for serologic assays and collaboration with bioengineers to develop low cost point-of-care self-contained devices that detect small quantities of rickettsial DNA in cutaneous lesions or ehrlichial DNA in peripheral blood. The species-specific antigens could determine whether the antibodies are directed against R. amblyommii or a severe pathogen such as R. rickettsii. Indeed quantitative evaluation of acute and convalescent sera could determine whether antibodies against R. amblyommii were preexistent and were unrelated to the acute febrile illness (no rise in antibody titer) or R. amblyommii actually caused the patient's illness (a four-fold or greater rise in antibody titer to species-specific antigen). Current methods that detect antibodies to spotted fever group rickettsiae cannot distinguish whether the illness was caused by R. rickettsii, R. parkeri, R. massiliae, R. amblyommii, R. monacensis, R. conorii, or R .andanae. Polymerase chain reaction amplification of DNA from human samples could determine the precise etiologic agent, for example, distinguishing Ehrlichia chaffeensis, E. ewingii, E. canis and Anaplasma phagocytophilum, which represent a variety of epidemiologic risks and potential severity. Ultimately meaningful human studies require hard on-the-ground efforts to obtain convalescent sera, a task that health promoters rather than scientists can more successfully achieve. A major achievement that we scientists can contribute is isolation of the etiologic agent from patients' samples. There is no stronger evidence that can be provided than, for example, the isolation of R. massiliae, E. canis, or Orientia to alert public health authorities of the reality of an unrecognized threat to health.

2. Performance of longitudinal, prospective population-based studies of patients utilizing these diagnostic assays to determine the age- and gender-specific incidence, geographic distribution, seasonality, socioeconomic risk factors, clinical manifestations and severity of illness including mortality in order to calculate the DALYs and risk factors for infection and for severity for each disease. Knowledge of the occurrence and incidence of a particular infection in defined populations will document a population that would serve as a test bed for future vaccine trials.

3. Establishment of knowledge of the human pathophysiology, complications, mechanisms of organ injury, clinical biomarkers of severity and of effective immunity, and mechanisms of protective immunity for rickettsial diseases – facts that can only be approached by human studies. Our knowledge that regulatory T cells suppress immunity in severe illness of mice experimentally infected with spotted fever rickettsiae or that tumor necrosis factor alpha and interleukin-10 mediate severe monocytotropic ehrlichiosis in mice could be evaluated for their occurrence in humans.

4.Collaboration in performance of investigations of acute undifferentiated febrile illnesses among scientists investigating human illnesses caused by arboviruses, hantaviruses, leptospirosis, influenza, and other agents of similar syndromes in order to share patient samples, demographic data, and costs and effort of the work. The undiagnosed patients entering the studies may have any of these infections, and studies focused on only one etiologic agent or category of disease waste the opportunity to contribute clinical samples and data for investigation of the other infections. Sharing and collaborations are key factors in developing synergy to achieve scientific progress

5. Establishment of human specimen banks for future development of improved diagnostics, investigations of pathogenesis and immunity, and identification of currently unrecognized novel emerging infectious agents. These specimen banks could include sera, blood, buffy coat, cryopreserved cells, extracted RNA and DNA, biopsies and necropsy tissues.

Many investigations have focused on ticks and healthy persons. Studies of ticks and other arthropods by polymerase chain reaction can identify prevalent, even novel, organisms but cannot assess their public health impact. Human serosurveys cannot evaluate subclinical versus symptomatic infections and do not distinguish

among agents that share antigens including those of nonpathogenic organisms. Thus, it is time for us to shift our focus toward studies of infected persons.

The critical gap is knowledge of the public health and clinical impact of human infections. Indeed the ultimate purpose for our investigations of rickettsiae and rickettsial diseases is the alleviation of disease and suffering. The reductions in productivity would also apply to veterinary infections caused by vector-borne obligately intracellular bacteria.

Another important goal that would be advanced by effective human studies of rickettsial diseases would be enhanced physician awareness of rickettsial diseases. Patients with rickettsioses will be treated promptly and appropriately when these diseases are at the forefront of knowledge and thinking of general physicians at the front line of patient encounters. Promulgation of this knowledge will depend on the existence of strong data and its embedding deeply throughout the preclinical and clinical curricula of medical education. Only then will patients benefit from our research efforts.

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