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Authors
Horwitz, Marcus
Marston, Barbara
Broome, Claire
et al.

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EDITORS:

James M. Barbaree
Botany and Microbiology Department
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Cincinnati, Ohio

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American Society for Microbiology

Prospects for Vaccine Development

MARCUS A. HORWITZ, BARBARA J. MARSTON, CLAIRE V. BROOME, AND ROBERT F. BREIMAN

UCLA School of Medicine, Los Angeles, California 90024, and Centers for Disease Control and Prevention, Atlanta, Georgia 30333

Participants in the session on Prospects for Vaccine Development discussed a broad range of topics relevant to vaccination against Legionnaires disease, including clinical, epidemiologic, immunologic, feasibility, safety, and cost-benefit considerations.

With respect to clinical considerations, the participants fully appreciated that Legionnaires disease is a relatively common, serious, and frequently fatal disease that often requires very expensive hospitalization. The participants also understood that Legionnaires disease is an important cause of nosocomial pneumonia and death. Thus, the participants felt that prevention of Legionnaires disease by immunization merits serious consideration.

Central to the topic of vaccination is an assessment of the risk of acquiring vaccine-preventable disease. Unfortunately, accurate information on the incidence of Legionnaires disease is extremely limited. Estimates of the incidence of Legionnaires disease have ranged from 10,000 to 100,000 cases annually in the United States. However, the scientific basis for these estimates is not clear. Cases reported to the Centers for Disease Control via the usual reporting mechanisms are unquestionably a minute fraction of the total that occur. Consequently, accurate estimates of incidence are likely to derive instead from carefully conducted epidemiologic studies. In this regard, the study presented at this conference by Barbara Marston and her colleagues on the incidence of community-acquired pneumonia in Ohio has provided data on hospitalized cases of Legionnaires disease. If extrapolated to the United States as a whole, which may or may not be a valid exercise, the Ohio incidence data yield an estimate of 11,000 hospitalized cases of Legionnaires disease annually in the United States. This estimate does not include cases of serious pneumonia not leading to hospitalization.

A vaccine against Legionnaires disease might be targeted against high-risk groups, i.e., smokers; persons with chronic cardiopulmonary disease, chronic renal disease, and diabetes mellitus; the elderly; transplant recipients; alcoholics; immunocompromised patients; and persons on corticosteroid medications, etc. In addition to data on overall incidence of Legionnaires disease, more information is needed on the incidence of Legionnaires disease in high-risk groups.

With respect to immunologic considerations and feasibility, four prototypic vaccines have been reported that induce protective immunity in the guinea pig model of Legionnaires disease: an avirulent mutant *Legionella pneumophila strain; L. pneumophila* membranes; the major secretory protein of *L. pneumophila*; and the major cytoplasmic membrane protein of *L. pneumophila*, a genus-common antigen and member of the Hsp60 family of heat shock proteins. In the guinea pig model, animals infected with aerosolized *L. pneumophila* develop a pneumonic illness that mimics Legionnaires disease in humans both clinically and pathologically, and thus this animal model is a superb one for studies of vaccine efficacy. All of the reported prototypic vaccines induce cell-mediated immunity, which is generally believed to play a central role in host defense against Legionnaires disease in humans. Since immunocompromised patients are among those at high risk for Legionnaires disease and many of these persons may have diminished cell-mediated immune responses, some participants in this session felt that an evaluation of the efficacy of prototypic vaccines in an immunocompromised animal model would be useful. Once promising vaccine candidates are identified, investigators must address production of the material in a form acceptable for clinical studies.

Studies on the efficacy of vaccines in the human population would probably need to focus on high-risk groups. Accurate estimates of disease incidence will be crucial to determine the sample size needed for a vaccine efficacy study. A multicenter trial would likely be required to enroll a sufficiently large study population.

With respect to safety, a successful vaccine would obviously need to be safe as well as effective. A vaccine consisting of one or a few molecules would seem less likely to cause toxic or other adverse reactions than one consisting of a whole organism or large multimolecular components of an organism.

With respect to cost-benefit considerations, the lack of good epidemiologic data on the incidence of Legionnaires disease in high-risk groups renders accurate cost-benefit analysis very difficult. Nevertheless, it seems likely from available infor-

mation that a safe, effective, and moderately priced vaccine targeted against high-risk groups, e.g., renal transplant recipients or patients with chronic renal disease, would be extremely cost-beneficial.

A vaccine against Legionnaires disease might be combined with other vaccines targeted against diseases such as influenza, for use with high-risk groups that overlap with those at risk for Legionnaires disease. This should favorably affect the cost-benefit ratio.

In summary, the participants of this session felt that Legionnaires disease is a serious and highly fatal disease with a relatively high incidence, and that development of a vaccine to prevent Legionnaires disease is desirable. Given the success of prototypic vaccines in an animal model, a safe and effective vaccine against Legionnaires disease in humans seems feasible. Development and use of a safe and effective vaccine against Legionnaires disease would likely result in substantial reductions in mortality, morbidity, and medical expenditures; however, additional epidemiologic studies will need to be conducted to optimally target risk populations and define cost-benefit ratios.