Surveillance for *Streptococcus pneumoniae* in Latin American children

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Acute respiratory tract infection (ARI) is a leading cause of morbidity and mortality worldwide. In the developing world, over four million children under age five die each year of this illness (1). Pneumonia accounts for 70% of all ARI deaths (2). While respiratory syncytial virus, parainfluenza, influenza and adenovirus are responsible for most fatal cases of pneumonia in developing countries, *Streptococcus pneumoniae* is the most frequent bacterial cause and accounts for most fatal cases. Besides pulmonary infection, *S pneumoniae* causes morbidity and mortality from meningitis, sinusitis and otitis media.

There are few data describing the epidemiology of invasive *S pneumoniae* in Latin America. Several studies (3,4) confirm it as the most frequent bacterial cause of childhood pneumonia in this region, though its true incidence is likely underestimated. Establishing a diagnosis is difficult; there are no rapid tests for *S pneumoniae* and blood culturing is expensive, lacks sensitivity and is therefore not routinely used. Treatment is usually empirical, and the widespread, unsupervised use of antibiotics further complicates microbiological diagnosis.

The burden of this illness in developing countries and the global emergence of antibiotic resistant pneumococci (5) make prevention of pneumococcal disease by immunization an appealing strategy. Ninety serotypes of *S pneumoniae* have been identified based on differences in antigenic capsular polysaccharides (6). A pneumococcal polysaccharide vaccine containing 23 of these serotypes has been available since 1983. The major limitation of this vaccine is its poor immunogenicity in children who in the developing world are disproportionally affected by pneumococcal disease. The development of a new generation of vaccines is addressing this problem. Bacterial polysaccharides are recognized by T cell independent immune mechanisms and do not induce protective antibody levels in children less than two years of age. Covalently linking the bacterial polysaccharides to carrier proteins transforms them to T cell dependent antigens. These conjugated vaccines recruit T cells to induce high level, protective antibodies in children. They also ensure T cell memory required for booster responses.

The optimal serotype composition of the 23-valent polysaccharide vaccine was based on detailed epidemiological surveillance using sterile site isolates collected mainly in the United States and Europe. Limited data describing serotypes of invasive *S pneumoniae* in developing countries have suggested a different distribution from that in the developed world (7-9). Ideally, any pneumococcal vaccine would be designed to reflect the prevalent serotypes in the region of intended use. Determination of the serotype distribution of *S pneumoniae* in Latin America and assessment of differences among countries are a crucial preface to development and use of any pneumococcal vaccine in this region.

A protein polysaccharide pneumococcal conjugate vaccine, containing serotypes specific to Latin America, promises to be an effective public health intervention. The development of such a region specific vaccine, however, has been hindered by a lack of both baseline epidemiological information and technical infrastructure. Identification of the most prevalent regional serotypes is essential to optimize a pneumococcal conjugate vaccine that will be limited, by cost, to seven to nine serotypes. The epidemiological and laboratory infrastructure required to collect these baseline data, to do large scale phase II to III vaccine trials and then to do phase IV postmarketing surveillance for disease and adverse events needs to be developed in the region. Finally, a protein polysaccharide conjugate vaccine will be comparatively expensive. It is hoped that these

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costs can be minimized by regional production of vaccine achieved through transfer of technology.

To address these issues, the Pan American Health Organization (PAHO) in 1993 launched an initiative called Sistema Regional de Vacunas (Regional System for Vaccines) (SIREVA). Its broad objective is to strengthen scientific and technical cooperation for the development, production, quality control and evaluation of vaccines for several bacterial and viral pathogens in Latin America. SIREVA's specific objectives for *S pneumoniae* are to:

- determine the relative prevalence of capsular types of *S pneumoniae* causing invasive disease, particularly pneumonia, in children less than five years old;
- establish and strengthen regional, laboratory and epidemiological capability for monitoring capsular polysaccharide types and subtypes, and antimicrobial resistance patterns of pneumococci in Latin America;
- create a bank of isolates and specimens with which subtypes of *S pneumoniae* can be identified and diagnostic tests can be evaluated;
- develop the capacity to produce pneumococcal capsular polysaccharide and protein polysaccharide conjugate vaccines in the region.

A multicentre surveillance study was begun in 1993 to achieve some of these objectives. It involves national reference laboratories in Argentina, Brazil, Chile, Colombia, Mexico and Uruguay. Two agencies of Health Canada have participated: the National Centre for Streptococcus (NCS), in Edmonton, Alberta, and the Bureau of Infectious Diseases (formerly the Bureau of Communicable Disease Epidemiology) at the Laboratory Centre for Disease Control (LCDC). Before the study began, the NCS held a workshop in Edmonton that was attended by representatives from each of the national reference laboratories. This extremely successful meeting provided 'hands on' training in serotyping and antimicrobial sensitivity testing of *S pneumoniae.* Participants were then able to transfer this expertise to their own laboratory personnel and to other laboratories in their respective countries. The development of personal and professional relationships among participants from different countries has led to the creation of a regional laboratory network with expertise in serotyping and antimicrobial susceptibility testing of *S pneumoniae.*

The development of this laboratory expertise in Latin America paved the way for the *S pneumoniae* surveillance study. Under the direction of the regional laboratory coordinators, clinicians in over 65 hospitals in 23 cities from the six participating countries began to collect isolates of *S pneumoniae* according to uniform study criteria. All children five years old and younger are enrolled if they present with meningitis, sepsis, arthritis, peritonitis or with the World Health Organization clinical criteria for pneumonia (10). Children presenting with inclusion criteria have appropriate cultures taken. Only isolates from sterile body sites, including blood, cerebrospinal fluid, pleural, peritoneal or joint fluid, are accepted. Specimens positive for *S pneumoniae* are forwarded to respective national reference laboratories for serotyping and antimicrobial sensitivity testing. The NCS is acting as a reference laboratory and provides regular quality control.

The study is also collecting epidemiological information about culture positive cases. We helped to create a standardized data collection form and computerized database for use in all study centres. Data entered locally are sent to the LCDC bimonthly from each country. They are collated, analyzed and a quarterly report is generated and distributed to all study participants. Laboratory personnel in participating countries were trained to manage computerized data and to write programs that summarize and analyze that country's results. The LCDC has also worked closely with local clinicians and microbiologists to recruit participants, clarify study definitions and troubleshoot problems that arose as the study progressed.

As of January 1, 1996, over 1400 invasive isolates of *S pneumoniae* have been collected. These isolates have been well distributed throughout the region, with 18% coming from Argentina, 27% from Brazil, 10% from Chile, 22% from Colombia, 11% from Mexico and 12% from Uruguay.

Sixty-four per cent have been isolated from children less than two years old, underscoring the need for an effective vaccine in this age group. The data have confirmed the unique serotype distribution of pneumococcus in the developing world, especially the high prevalence of serogroups 1 and 5. Clearly, these would need to be included in any pneumococcal vaccine for use in Latin America. Investigators have been successful in isolating pneumococcus from children with respiratory disease, with 47% of all isolates coming from children with pneumonia. Forty-seven per cent of all isolates have come from blood, 29% from cerebrospinal fluid and 16% from pleural fluid. The study has also provided interesting data about penicillin resistance. The prevalence of pneumococcus with decreased susceptibility to penicillin varies by country, but overall, 10% of isolates have shown intermediate susceptibility (minimum inhibitory concentration [MIC] 0.12 to 1.0 μg/mL) and 6% have shown resistance (MIC 2.0 μg/mL or more).

Besides the *S pneumoniae* serotype distribution study, scheduled to finish this spring, the LCDC has been involved in several related activities. These include the development of a regional network of epidemiologists with expertise and experience in vaccine evaluation and the expansion of the newly created laboratory network to evaluate other diseases such as *Haemophilus influenzae* b infections. PAHO is also exploring the feasability of purified pneumococcal capsular polysaccharide production in the region as a step towards eventual protein polysaccharide conjugate vaccine production in Latin America.

The SIREVA *S pneumoniae* study is an example of successful cooperation between the North and the South, governmental and nongovernmental organizations and among microbiologists, epidemiologists and clinicians. It is the first multicoun-

try, systematic surveillance for *S pneumoniae* in the developing world, and has collected important epidemiological data about invasive S *pneumoniae* in anticipation of a new generation of conjugate vaccines. Most important, it has created a strong network of regional and international expertise that may be used to study both existing and emerging infectious diseases.

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