

Pneumococcal disease and vaccination in the Americas: an agenda for accelerated vaccine introduction

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ABSTRACT

This piece summarizes the presentations and discussions at a meeting on pneumococcal disease surveillance in the Americas that was held in Mexico City, Mexico, on 2 November 2004. This meeting was organized by the Pan American Health Organization (PAHO) and the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) of the Global Alliance for Vaccines and Immunization (GAVI). The meeting participants reviewed the status of pneumococcal disease surveillance in the Region of the Americas, estimates of the burden of pneumococcal disease, the distribution of Streptococcus pneumoniae serotypes that cause invasive disease, the status of pneumococcal vaccine introduction, health economic analyses, and financial issues related to vaccine introduction. The meeting participants also worked to identify the next steps for generating the critical information needed to help make decisions on pneumococcal vaccine introduction.

Coordinated pneumococcal disease surveillance for the Region of the Americas dates back to the 1993 establishment by PAHO of the Regional System for Vaccines (RSV) project for surveillance of bacterial meningitis and pneumonia, including pneumococcal disease. Surveillance data from the RSV indicate that the distribution of major serotypes in the Americas has been stable over time (but that antibiotic resistance is increasing), with serotype 14 being the leading serotype isolated in most countries participating in RSV. Based on local serotype data from six of the RSV countries (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay), the 7-valent vaccine would cover 65% of serotypes, the 9-valent vaccine would cover 77%, and the 11-valent vaccine would cover 83%.

Key words

Streptococcus pneumoniae, pneumococcal vaccines, immunization programs, drug costs, Americas.

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A workshop on the status of pneumococcal disease and vaccine introduction in the Region of the Americas, organized by the Pan American Health Organization (PAHO) and the Pneumococcal Vaccines Accelerated Development and Introduction Plan (PneumoADIP) of the Global Alliance for Vaccines and Immunization (GAVI), was held in Mexico City, Mexico, on 2 November 2004 (1). The meeting participants reviewed the current status of pneumococcal disease surveillance in the Region of the Americas, estimates of the burden of pneumococcal disease, the distribution of *Streptococcus pneumoniae* serotypes that cause serious disease, the status of pneumococcal vaccine introduction, health economic analyses, and financial issues related to vaccine introduction. Following formal presentations, the participants discussed the current pneumococcal disease situation in the Region, epidemiological surveillance, and burden of disease estimates. The ultimate objective of the discussion was to identify the next steps for generating the information needed to help make decisions on vaccine introduction. The purpose of this paper is to present the results of the meeting and to outline an agenda of priority activities for accelerating vaccine introduction decisions.

GLOBAL OVERVIEW

The World Health Organization (WHO) estimates that pneumococcal disease causes some 1.6 million deaths annually, of which some 800 000 are among children less than 5 years old (2). Pneumonia is the leading cause of infectious mortality in children—higher than HIV, tuberculosis, or malaria—with pneumococcal deaths exceeding the some 1.1 million deaths from malaria annually. However, recent interviews with global health decisionmakers indicate that awareness of those facts is low. Clearly, more data and better communication of existing data on the importance of pneumococcal diseases are important in en-

suring that pneumococcal vaccine introduction is adequately prioritized.

The epidemiologic pattern of *S. pneumoniae* infections is influenced by several important factors, but all pneumococcal disease begins with colonization of the upper respiratory tract. In many cases, colonization is followed by either localized infection of mucosal surfaces, such as the tympanic membranes or the lungs, or invasion of other sterile body spaces such as the bloodstream, cerebrospinal fluid, or joints (3). Pneumococcal carriage occurs in all age groups. The rates of invasive pneumococcal disease are highest in children aged < 2 years, but disease continues to occur at all ages, with rates among the elderly approaching those seen in young children. In industrialized countries the highest mortality rate from invasive pneumococcal disease is found among the elderly, who may account for 80% or more of the pneumococcal deaths in these nations. Though most pneumococcal deaths are due to invasive disease, otitis media is also a major cause of morbidity as well as economic costs to health systems and families. While most episodes of otitis media resolve on their own, they are still a leading cause of antibiotic use and of missed work for parents. The episodes also have the potential for long-term sequelae such as hearing loss in children. Several risk factors for pneumococcal disease have been described, including attending a child care center, lack of breastfeeding, antecedent use of antibiotics, recurrent/frequent otitis media, and underlying medical conditions such as sickle cell disease, HIV, and nephrotic syndrome.

Antibiotic resistance is another critical issue, with a pattern of increased rates of antibiotics use leading to greater antimicrobial resistance. The resulting use of broad-spectrum and newer antibiotics in turn produces more resistance to these newer antibiotics. The growing resistance to conventional antibiotics substantially increases treatment costs.

A pneumococcal vaccination program has benefits beyond the protec-

tion provided to vaccinated children. Reducing the circulation of bacteria can reduce transmission to and among unvaccinated individuals and thereby provide indirect protection of unvaccinated persons (4). This herd immunity is demonstrated by a reduction in the circulation of serotypes included in the pneumococcal vaccine applied to the entire population. However, a concern has been raised that replacing the currently circulating serotypes could increase the circulation of nonvaccine strains.

Pneumococcal disease is serious, common, and preventable. However, its prevention requires a concerted international effort to make the vaccine available in all countries, including the poorest ones. The poorest nations carry the highest disease burden, yet vaccination is often prohibitively expensive for them. This has been true, for example, with the *Haemophilus influenzae* type b and hepatitis B vaccines, whose introduction in the world's poorest countries has been unacceptably slow.

PNEUMOCOCCAL DISEASE SURVEILLANCE IN THE AMERICAS

Coordinated pneumococcal disease surveillance in the Region of the Americas dates back to the 1993 establishment by PAHO of the Regional System for Vaccines (RSV) project for surveillance of bacterial meningitis and pneumonia, including pneumococcal disease, in six countries of Latin America: Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay (5). The objective of the RSV network was to determine the distribution of pneumococcal serotypes causing severe disease and the prevalence and epidemiology of antimicrobial-resistant pneumococci. Subsequently, RSV was incorporated into the PAHO Special Program for Vaccines and Immunization, which expanded the activities of the network to conduct surveillance for other agents that cause meningitis and pneumonia, such as *Haemophilus influenzae* type b (Hib) and meningococcus.

TABLE 1. *Streptococcus pneumoniae* serotypes causing invasive disease and isolated from children aged < 6 years in six countries of Latin America through the Regional System for Vaccines network, 2000–2003

Serotype	Argentina		Brazil		Chile		Colombia		Mexico		Uruguay		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	41	7.5	81	5.1	6	17.6	30	7.3	6	1.6	33	10.5	197	6.04
3	8	1.5	55	3.5	1	2.9	22	5.4	8	2.2	19	6.1	113	3.46
4	5	0.9	32	2.0	4	11.8	4	1.0	4	1.1	6	1.9	55	1.69
5	69	12.6	66	4.2	0	0.0	26	6.3	0	0.0	37	11.8	198	6.07
6A	9	1.6	71	4.5	2	5.9	27	6.6	15	4.1	8	2.6	132	4.04
6B	40	7.3	156	9.8	1	2.9	47	11.4	41	11.1	16	5.1	301	9.22
7F	21	3.8	39	2.5	1	2.9	6	1.5	5	1.4	10	3.2	82	2.51
9V	17	3.1	41	2.6	0	0.0	17	4.1	12	3.3	11	3.5	98	3.00
14	196	35.7	488	30.7	4	11.8	118	28.7	37	10.0	110	35.1	953	29.2
18C	23	4.2	80	5.0	2	5.9	17	4.1	8	2.2	6	1.9	136	4.17
19A	14	2.6	56	3.5	1	2.9	1	0.2	16	4.3	12	3.8	100	3.06
19F	16	2.9	71	4.5	10	29.4	13	3.2	65	17.6	8	2.6	183	5.61
23F	20	3.6	79	5.0	2	5.9	39	9.5	52	14.1	4	1.3	196	6.00
12F	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	9	2.9	9	0.28
Others	70	12.8	273	17.2	0	0.0	44	10.7	100	27.1	24	7.7	511	15.7
Total	549	100	1 588	100	34	100	411	100	369	100	313	100	3 264	100

The number of participating countries was enlarged to 15 in 1998, and subsequently to 21, including some countries of the English-speaking Caribbean. In addition to the 6 original countries the RSV member countries are: Bolivia, Costa Rica, Cuba, the Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, Nicaragua, Panama, Paraguay, Peru, Trinidad and Tobago, and Venezuela. The RSV network continues to monitor trends in the circulating serotypes and in antimicrobial resistance patterns; this information could help to measure the impact of pneumococcal vaccination in the Americas. In 2000 the RSV network added surveillance for X-ray-proven pneumonia.

Surveillance data from RSV show that the distribution of major serotypes has been stable over time in the six initial RSV countries (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay), but that antibiotic resistance has been increasing. Based on data collected in the six countries, no significant serotype changes occurred between the 1993–1999 period and the 2000–2003 period. In total, over 8 000 isolates were studied in both periods. Serotype 14 was the leading serotype isolated in the six countries. Table 1

shows the distribution, by number and percentage, of the isolates of streptococcus pneumonia, by serogroup and by country, in invasive diseases occurring in children aged < 6 years during the 2000–2003 period in the six countries.

Based on the serotype data from the six countries, the 7-valent vaccine would cover 65% of the serotypes, the 9-valent vaccine would cover 77%, and the 11-valent vaccine would cover 83% (Table 2). As an example of the increasing threat of antibiotic-resistant pneumococcus, RSV surveillance shows that the proportion of pneumococcus that is not susceptible to penicillin increased from 14.7% in 1993 to 30.6% in 1999, and to 39.8% in 2003.

PNEUMOCOCCAL CONJUGATE VACCINE TRIALS

At least eight large randomized, controlled phase III trials of pneumococcal conjugate vaccines have been conducted. Among them have been three trials with the 7-valent vaccine from Wyeth (Prevenar), three with Wyeth's 9-valent vaccine candidate, and one each with a 7-valent vaccine candidate from Merck, an 11-valent vaccine candidate from GlaxoSmith-

Kline (GSK), and an 11-valent vaccine candidate from Aventis. While each of these trials provides important information about the potential for pneumococcal conjugate vaccine to protect children, only the 7-valent vaccine from Wyeth is currently licensed, and the remaining vaccine candidates are likely to be reformulated if they reach commercialization.

One consistent finding of the completed efficacy trials of the 7- and 9-valent conjugate vaccines is a high level of efficacy against invasive disease caused by the serotypes contained in the vaccines (6). The point estimates of efficacy range from 77% to 97%. In HIV-infected children in South Africa, the point estimate of efficacy against vaccine-type invasive disease was 58%. Continued follow-up in South Africa shows that the protection lasts for up to four years following vaccination, even in HIV-infected children.

Pneumonia represents the largest burden of pneumococcal disease, and it constitutes an important cause of childhood mortality in developing countries (7). However, vaccine efficacy against nonbacteremic pneumococcal pneumonia has been difficult to determine because of the lack of a suitable test to make an etiological diagnosis. Efficacy

TABLE 2. Proportion of invasive diseases caused by *Streptococcus pneumoniae* that would be prevented by different polyvalent pneumococcal vaccines in children aged < 6 years, according to isolates found in six countries of Latin America (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay), 2000–2003

Vaccine serotype	11-valent			9-valent			7-valent		
	Number of isolates	%	% cumulated	Number of isolates	%	% cumulated	Number of isolates	%	% cumulated
1	197	6.04	6.04	197	6.04	6.04	NI ^a	—	—
3	113	3.46	9.50	NI	—	—	NI	—	—
4	55	1.69	11.20	55	1.69	7.72	55	1.69	1.69
5	198	6.07	17.20	198	6.07	13.80	NI	—	—
6B	301	9.22	26.50	301	9.22	23.00	301	9.22	10.90
7F	82	2.51	29.00	NI	—	—	NI	—	—
9V	953	29.20	58.20	953	29.20	52.20	953	29.20	40.10
14	301	9.22	67.40	301	9.22	61.40	301	9.22	49.30
18C	136	4.17	71.60	136	4.17	65.60	136	4.17	53.50
19F	183	5.61	77.20	183	5.61	71.20	183	5.61	59.10
23F	196	6.00	83.20	196	6.00	77.20	196	6.00	65.10

^a NI = not included.

trials have focused on measuring the impact of the vaccine against overall clinical or radiological pneumonia. Trials in the state of California (in the United States) (6) and in non-HIV-infected children in South Africa have shown that the vaccine results in a 20%–30% reduction in radiologically confirmed pneumonia (8). However, a trial among the Navajo Indian population in United States did not show a similar effect, according to a presentation that Thomas Cherian made during the November 2004 workshop in Mexico City. Also, Cherian said, data suggest that the vaccine's effect on pneumonia is mainly limited to children less than 24 months of age.

Data from South Africa suggest that measuring the impact of vaccine on radiological pneumonia might underestimate the true impact of the vaccine on pneumonia. The use of alternative definitions, including the use of acute phase reactants, is being evaluated to determine whether they can be used to fully define vaccine impact on pneumonia. One of the unexpected findings in the South African trial (8) was the impact of the vaccine on virus-associated hospitalized pneumonia. Results demonstrated a reduction of approximately 30% in virus-associated pneumonia, suggesting a sizable proportion of hos-

pitalized cases of pneumonia associated with viral infections have dual bacterial and viral infections and are preventable by vaccination.

The 7-valent conjugate vaccine from Wyeth has also been evaluated for efficacy against otitis media, according to information presented at the Mexico City workshop. The vaccine had 57% efficacy against culture-confirmed otitis media that was due to the vaccine serotypes. This reduction, however, was offset by increases in otitis due to nonvaccine serotypes, so that the overall effect on pneumococcal otitis media due to any serotype was 51%. Importantly, the vaccine did show significant reductions in cases of otitis requiring tympanostomy tube placement. Chronic otitis and hearing loss are common in developing countries, and reduction of this morbidity would be an important public health contribution. Further research is warranted.

Despite the impressive effects of the 7-valent vaccine against invasive pneumococcal disease (IPD) and pneumonia, the price of this vaccine is a significant obstacle to its sustained use in developing countries. Preliminary data suggest that schedules using fewer doses of the conjugate vaccine may be as effective as a three- or four-dose schedule. Studies to evaluate al-

ternative vaccination schedules using fewer doses of the conjugate vaccine, with or without a booster dose of polysaccharide vaccine, are planned.

THE EXPERIENCE IN THE UNITED STATES SINCE THE INTRODUCTION OF A PNEUMOCOCCAL CONJUGATE VACCINE IN 2000

Wyeth's Prevenar, a 7-valent pneumococcal polysaccharide-protein conjugate vaccine, was introduced in the United States in 2000 (4). Although demand for the vaccine has been strong, supply shortages have occurred, limiting the number of doses that children were able to receive. Despite the shortages, active surveillance for invasive pneumococcal disease in sites throughout the country has shown dramatic declines in disease burden in young children. Disease caused by the seven vaccine serotypes has been nearly eliminated among children aged < 2 years, dropping from 158 cases per 100 000 children in 1998–1999 to 6 cases per 100 000 in 2003 (4). Increases in disease caused by nonvaccine serotypes have been observed, but so far they have been small relative to the decreases in vaccine serotype disease.

The Wyeth Prevenar 7-valent vaccine has also reduced transmission of vaccine-type pneumococci, leading to substantial declines in the incidence of vaccine-type invasive disease among unvaccinated children and adults in the United States (4). This herd immunity has resulted in 31% less invasive pneumococcal disease due to vaccine serotypes in persons 65 years old and older, the age group that has the highest remaining burden of disease and suffers the most pneumococcal deaths. The vaccine has also greatly reduced the burden of antibiotic-resistant infections in both vaccinated children and unvaccinated adults. Because this conjugate vaccine almost doubled the cost of the primary series of vaccines for children, continued surveillance is important to demonstrate the vaccine's impact and also to watch for undesired consequences (e.g., increased risk of serious vaccine adverse events). In developing countries, surveillance to measure the vaccine's impact on pneumonia incidence will be even more important.

ISSUES WITH PNEUMOCOCCAL SURVEILLANCE

Pneumococcus is not associated with a single clinical syndrome, but rather produces a variety of diseases, each of which may be caused by any of several other organisms. Therefore, establishment of pneumococcal disease is dependent on laboratory confirmation. However, for pneumonia, which is the disease of greatest public health importance, there are no good tests to determine pneumococcal etiology. The gold standard, isolation of pneumococci from blood cultures, is poorly sensitive. It probably captures less than 10% of all pneumococcal pneumonias, according to information presented at the November 2004 workshop in Mexico City.

Surveillance for pneumococcal disease can be conducted using either the classical methods for surveillance for laboratory-confirmed disease or indirect methods that use pneumonia sur-

veillance and vaccine probe studies. Surveillance for laboratory-confirmed disease will provide data on serotype distribution and antimicrobial susceptibility. If done as prospective community-based surveillance, it will also provide incidence data on IPD. However, a number of factors need to be taken into consideration when interpreting the data. The study setting, prevailing clinical practices, criteria and threshold for obtaining cultures, and community antibiotic use may all influence the data that are generated. These factors must be carefully considered when comparing data collected over different time periods and from different sites. Efforts to standardize these factors may contribute to more interpretable data.

The vaccine probe approach has been a useful method to determine the burden of Hib disease, according to information presented at the November 2004 workshop in Mexico City. With pneumococcal vaccine, determining the disease burden is difficult because of the multiplicity of serotypes that cause disease and the fact that only a few of them are represented in the 7-valent vaccine. However, it is still possible to determine the vaccine-preventable burden of disease. Estimation of pneumonia disease burden using the same outcome definitions as the vaccine trials will allow estimation of vaccine impact even where vaccine trials or probe studies are not possible. However, these studies may need to explore other pneumonia definitions in order to define the vaccine-preventable pneumonia burden more fully.

Finally, national decisionmakers will increasingly need local data in order to decide on vaccine introduction. Prospective disease burden studies are not feasible or even necessary in every country or in all the regions of a large country. A burden assessment tool is under development that will allow rapid estimation of the local burden, using available local data and making adjustments for certain key variables, and using assumptions based on regional or epidemiologically representative data from prospective studies.

PROGRESS OF THE SURVEILLANCE NETWORK OF THE REGIONAL SYSTEM FOR VACCINES

The RSV network was established in 1993 to conduct epidemiological surveillance for vaccine-preventable bacterial disease. As was mentioned earlier, the network initially included 6 countries of Latin America, but later was expanded to 21 nations, including several in the English-speaking Caribbean. The objective of this network is to conduct epidemiological and laboratory surveillance for meningitis, pneumonia, and sepsis due to *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*.

The RSV network conducts surveillance of pneumococcus serotypes and antimicrobial susceptibility of strains isolated from children aged < 6 years suffering from invasive pneumococcal disease. Since the beginning, quality control has been strict, with support coming from the National Centre for Streptococcus in Edmonton, Canada. The network has strengthened its quality control by adding two subregional reference centers: the *Instituto Adolfo Lutz*, which is in the city of São Paulo, Brazil, and the *Instituto Nacional de Salud* (National Institute of Health), which is in the city of Bogotá, Colombia.

Based on 4 876 isolates from the 1999–2002 period from the six initial RSV countries (Argentina, Brazil, Chile, Colombia, Mexico, and Uruguay), the *S. pneumoniae* serotypes found, ranked by frequency, were: 14, 6A/B, 1, 18C, 5, 23F, 19F, 19A, 7F, 9V, 3, and 12F, according to information presented at the November 2004 workshop in Mexico City. However, there are distribution differences among countries, as well as differences in antimicrobial susceptibility patterns.

The RSV network has entered a new stage that will require better coordination and management of all activities. The goals in the new stage include:

- increasing funding to PAHO in order to strengthen coordination in the Region of the Americas

- implementing and maintaining a quality management system within the framework of the ISO 9000 norms that certify the quality management system of an institution
- standardizing laboratory techniques following criteria used by the National Committee for Clinical Laboratory Standards
- strengthening the RSV program by conducting external evaluations of performance in the 21 participating countries
- conducting supervisory and quality assurance activities for national and local laboratories, using standardized tools
- having laboratory researchers from the RSV group publish at least four scientific articles during 2005–2006
- conducting training workshops to improve the diagnostic capacity in all the RSV laboratories
- acquiring reagents to identify and serotype pneumococcus, haemophilus, and meningococcus and to determine sensitivity patterns in the participating countries
- creating a Web site for the countries in the Region of the Americas to input up-to-date data and also to disseminate information to the local, national, and Regional level that will guide the decision-making process

In 2000, surveillance of radiological pneumonia was initiated by selected countries, including Argentina, Brazil, Colombia, Costa Rica, Chile, Nicaragua, Panama, Paraguay, and Uruguay. Pneumonia is recognized as an important cause of childhood morbidity and mortality, and Hib and pneumococcal conjugate vaccines will significantly reduce this burden. To establish radiological pneumonia surveillance within the RSV network, it was essential that methods used to interpret chest radiographs be standardized. In 2001 a WHO-sponsored working group defined a constellation of criteria that was most likely to represent bacterial pneumonia, including a process of standardization and calibration (9). To facilitate the standardized use of these definitions, an external quality assurance and

self-assessment and training program was also developed by an ad-hoc group of experts at the request of PAHO.

PROJECTED ECONOMIC IMPACT OF PNEUMOCOCCAL VACCINATION IN DEVELOPING COUNTRIES

Conjugate pneumococcal vaccines hold the promise of reducing pneumococcal disease deaths and disability, but costs of introduction, vaccine price, and cost-effectiveness need to be considered when implementing vaccine policy. Various economic analyses have been conducted, including using data from a middle-income sub-Saharan Africa country to model a three-dose schedule of a 9-valent vaccine. For that model, inputs were derived from published literature, unpublished data, and opinions from a panel of experts. The base-case estimate of a pneumococcal conjugate vaccine's incremental cost-effectiveness ratio (CER) was US\$ 508/disability-adjusted life year averted, according to information in a presentation by Anushua Sinha at the November 2004 workshop in Mexico City. This CER was most sensitive to three data inputs: vaccine efficacy against fatal pneumonia, proportion of under-five deaths due to acute respiratory infection, and vaccine price.

COMMUNICATIONS

Experiences with the introduction of other vaccines and other health interventions highlight the importance of an effective communications strategy. The collection of data for publication in scientific journals or for presentation at technical meetings is not sufficient to assure that policymakers are aware of and understand the data. Research, surveillance, and economic data need to be presented in ways that policymakers can understand.

Introducing a safe, affordable pneumococcal vaccine will require a wider network of partners and advocates who will support changes in national immu-

nization policy. For purposes of advocacy development it will be important to tailor messages based on the best scientific data available. Effective channels for disseminating the messages include scientific publications, reports at scientific meetings, and the news media. Approaches to communication will need to be evaluated periodically, and modifications made when appropriate.

THE EXPERIENCES OF SIX COUNTRIES IN LATIN AMERICA

As described below, the experiences of six countries in Latin America were reviewed in presentations given by experts during the November 2004 workshop in Mexico City.

Mexico

Beginning in February 2002, Mexican health authorities conducted an evaluation of the impact of the conjugated 7-valent vaccine among 185 children initially aged < 1 year. The vaccine was administered using a vaccination schedule of three doses, with an interval of 6 months between each dose and a booster for children initially aged 2 to 6 months, and two doses and a booster for children initially aged 7 to 11 months. All children were followed up after vaccination, up to 2 years of age.

Nasopharyngeal samples were taken from all the children prior to vaccination in order to perform a pneumococcal colonization study. In the study, 59 of the children (32%) were found to be carriers of *S. pneumoniae*. Six of the seven serotypes contained in the 7-valent vaccine were isolated from children in both of the age groups: 4, 6B, 14, 18C, 19F, and 23F.

Guatemala

In 1996 a surveillance network for pneumococcal disease was established in Guatemala. This network included the three public reference hospitals in the area of the capital, which together

serve approximately 85% of the city's population. A surveillance protocol, including case definitions for meningitis, sepsis, pneumonia, and other invasive diseases, was standardized. In the three participating hospitals' laboratories, the agars used for bacterial isolation were improved, the latex agglutination test was implemented, and automatic systems to detect bacterial growth in blood cultures were progressively introduced. These improvements in the laboratories resulted in an increase in the rate of isolation of *S. pneumoniae* and *H. influenzae* type b, from 0.6% to 18.7%, from cultures of specimens collected from suspected cases.

From October 1996 to June 2004, 301 confirmed cases of invasive pneumococcal disease were detected using conventional bacterial culture, latex agglutination, or both methodologies to confirm the diagnosis. Fifty-seven cases (19.0%) were confirmed by culture alone, 79 (26.2%) by latex agglutination alone, and 165 (54.8%) by both methodologies. Of these 301 cases, 152 (50.5%) were meningitis, 140 (46.5%) were pneumonias, and the other 9 (3.0%) corresponded to sepsis and septic arthritis. The peak of invasive pneumococcal disease occurred among children aged 2 to 7 months, and meningitis was the most common diagnosis in this age group. Mortality from pneumococcal meningitis was 40%, and 7% for severe pneumonia (defined as pneumonias with bacteremia and/or pleural effusion).

Of the cases detected using latex agglutination that would not have been detected using conventional bacterial culture, 33 were cases of meningitis (21.7% of all meningitis), and 46 were cases of pneumonia (32.8% of all pneumonias).

Epidemiological surveillance has detected the serotypes 1, 2, and 5 as causative agents for severe invasive pneumococcal disease.

Colombia

In Colombia the Microbiology Group of the National Institute of Health has coordinated surveillance.

In 1993, surveillance began with the participation of 9 hospitals located in 3 cities of the country. The network now includes 21 public health laboratories serving 88 sentinel hospitals in 41 cities in the country network for acute bacterial meningitis and acute respiratory infection. Results have been validated with international external quality control coordinated by the National Centre for Streptococcus in Canada.

From January 1994 through October 2004, 1 167 *S. pneumoniae* isolates were collected in children < 5 years old. Of the 1 167 positive isolates, meningitis was diagnosed in 548 cases (47.0%), pneumonia in 468 cases (40.1%), sepsis in 97 cases (8.3%), and other infections in 54 cases (4.6%).

Of all the 90 *S. pneumoniae* capsular serotypes, 41 were characterized by serotyping. The most frequent was serotype 14, followed, in descending order, by 6B, 23F, 1, 5, 19F, 6A, 18C, 9V, and 4.

In 394 (33.8%) of the 1 167 isolates, resistance to penicillin was determined. Of these 1 167, in 151 of them (12.9%) there was intermediate resistance (minimal inhibitory concentration (MIC) = 0.125–1 µg/mL) to penicillin, and in 244 (20.9%) there was high resistance to penicillin (MIC ≥ 2 µg/mL). Lower susceptibility to penicillin was found more frequently in the 23F, 14, 19F, 6B, and 9V capsular subtypes. Intermediate resistance to ceftriaxone was found in 179 (15.3%) of the 1 167 isolates, and high resistance to this drug in 65 (5.6%) of the isolates. All the isolates were susceptible to vancomycin.

Dominican Republic

The Microbiology Institute of the Robert Reid Cabral Children's Hospital is the main sentinel laboratory of the Dominican Republic, and it coordinates the laboratory network for bacterial resistance surveillance in the country. From 2000 to 2003 this laboratory processed 10 442 blood cultures, of which 1 534 (14.7%) were positive for bacte-

rial isolates; of these 1 534, 101 of them (6.6%) were positive for *S. pneumoniae*.

Of a total of 3 360 cerebrospinal fluid (CSF) specimens, 499 (14.9%) were positive for bacterial isolates; of the 499, 145 of them (29.1%) were positive for *S. pneumoniae*.

Of 946 cultures processed from pleural fluids, *S. pneumoniae* was isolated in 149 cases. Of a total of 197 *S. pneumoniae* isolated in blood and pleural fluid of patients with pneumonia, 83 isolates (42.1%) were sensitive to penicillin, 64 (32.5%) were intermediately resistant, and 50 (25.4%) were highly resistant. Of the 180 isolates tested for cefotaxime resistance, 168 (93.3%) were sensitive, 11 (6.1%) had intermediate resistance, and 1 (0.6%) was highly resistant.

Of the 145 *S. pneumoniae* isolated from CSF, 80 (55.2%) were sensitive to penicillin, 44 (30.3%) had intermediate resistance, and 21 (14.5%) were highly resistant. Of 131 isolates tested for cefotaxime resistance, 107 (81.7%) were sensitive, 16 (12.2%) were intermediately resistant, and 8 (6.1%) were highly resistant.

The six most frequent serotypes isolated in meningitis and pneumonia cases were 14, 6A/6B, 23/23F, 1, 18/18A, and 19/19A.

Argentina

In Argentina, researchers have analyzed data from ongoing population-based studies in order to determine the incidence of pneumococcal disease. Over the three years from December 1999 through November 2002 in the city of Córdoba, 28 787 children less than 2 years old with fever or signs suggestive of bacterial diseases were enrolled in a surveillance study of invasive pneumococcal disease and consolidated pneumonia.

Blood cultures were obtained from all children presenting with a fever ≥ 39 °C during the 24 hours prior to presentation. Children who presented with signs compatible with meningitis, pneumonia with or without pleural effusion, or another invasive disease had

samples cultured from blood and other appropriate sterile sites. Chest radiographs were obtained from all children suspected of having pneumonia, and they were read by an independent radiologist. The overall incidence per year of culture-proven invasive pneumococcal disease was 212.2 per 100 000 children aged < 2 years, the incidence of pneumococcal pneumonia was 99.7 per 100 000, and the incidence of meningitis was 8.0 per 100 000.

The estimated rate of febrile bacteremia was 98.5 per 100 000 children per year. The peak incidence of pneumococcal disease was at 6 to 17 months of age. From all *S. pneumoniae* isolated, 60% were from ambulatory patients. The most common serotypes were 14, 6A, 6B, 5, 1, 18C, 7F, 19F, and 9V.

Preliminary results are also available from ongoing studies in Concordia and Paraná (which are cities in the province of Entre Ríos) and in Pilar (which is a city in the province of Buenos Aires). The total population of Concordia is 141 980 inhabitants, of which 16 148 are children aged < 5 years old. Paraná has a total population of 275 000 inhabitants, of which 28 744 are children aged < 5 years old, for a total of 44 892 children aged < 5 years old in the two cities. Pilar has a total population of 232 463 inhabitants, of which 27 209 are children aged < 5 years old.

From 1 November 2002 to 30 April 2004 in Paraná and Concordia a total of 1 000 acute lower respiratory infection cases with a chest radiograph were included in the study; 509 (50.9%) were considered probable bacterial pneumonia.

In children < 5 years old in the three cities the incidence of X-ray-confirmed pneumonia with consolidation ranged from 709 cases per 100 000 to 1 189 cases per 100 000.

From the group of 509 children with consolidation in Paraná and Concordia, 304 cultures were obtained, mostly from blood, CSF, and pleural fluids. The bacteria isolated were *S. pneumoniae* (17 of the cultures, or 5.6%) and *Staphylococcus aureus* (1 of the cultures, 0.3%). Three *S. pneumoniae* were isolated from specimens obtained from other fluid spaces.

In the city of Pilar a total of 567 acute lower respiratory infection cases were included in the study, and a chest radiograph was performed on 525 of the cases (92.6%). Of those 525 with a chest radiograph, 294 of them (56.0%) were considered consolidated pneumonia, that is, probable bacterial pneumonia. In children < 5 years old in the three cities, the incidence of X-ray-confirmed pneumonia with consolidation ranged from 963 cases per 100 000 to 1 189 cases per 100 000.

Of the 130 cultures obtained in Pilar from the 294 children with radiological consolidation, the bacteria isolated were *S. pneumoniae* (6 cases, or 4.6%), *S. aureus* (4 cases, 3.1%), and β -hemolytic streptococci (2 cases, 1.5%).

Uruguay

In 2004, supported by PAHO, Uruguay conducted a cost-effectiveness study of introducing pneumococcal vaccine. Data were collected on the incidence of pneumococcal disease during the 1997–2001 period, opportunity costs, possible effectiveness of the conjugated vaccine, and the cost of an immunization program. The incidence of pneumococcal meningitis during the period of the study among infants aged under 1 year of age was 22.4 per 10 000, with a case-fatality rate of 38.5%.

In a population-based study conducted from June 2001 to May 2004 in the cities of Salto and Paysandu, the annual incidence of consolidated pneumonia in hospitalized children under 5 years of age was significantly higher in children < 1 year old or 12 to 23 months old than it was in those 24–35 months old or 36–59 months old.

The direct average medical cost for one episode of consolidated pneumonia hospitalized in a public health institution was estimated to be US\$ 569. The components that had the highest weight in the cost were the hospitalization (76%) and the surgical procedures as the result of complications (12%).

Microbiological surveillance in children hospitalized for pneumococcal invasive disease at the national pediatric

hospital in Montevideo during the 1994–2003 period found that serotype 14 was the most commonly isolated serotype (30.8%), followed by serotype 5 (18.9%) and serotype 1 (14.4%).

For a 9-valent pneumococcal vaccine, among children aged 1 to 2 years, the expected protection coverage against the most frequent circulating pneumococcal serotypes would be 91% for serotypes causing pneumonias and 83% for serotypes causing meningitis.

The sensitivity analysis of the cost-effectiveness study showed that the variables that influenced the model the most were disease incidence, cost of treatment, and the price of the vaccine. Nevertheless, introduction of a pneumococcal vaccine should not be based solely on costs. Other, qualitative factors related to preventing death and disease and achieving equity in health should also be considered.

RECOMMENDATIONS FOR VACCINE INTRODUCTION IN LATIN AMERICA AND THE CARIBBEAN

The Working Group members at the Mexico City meeting recommended that the countries of Latin America and the Caribbean strive to introduce the pneumococcal vaccine when it becomes affordable. In the meantime, surveillance should be enhanced in order to prepare the way for the vaccine's introduction.

The members of the Working Group recognized the importance of PAHO's coordinating role with RSV. They also indicated that PAHO will need ongoing financial support to assist with the following activities: (1) strengthening laboratory capacity; (2) strengthening the clinical and epidemiological components of surveillance; (3) at key surveillance centers, conducting one or more of the following: economic studies, surveillance for adult pneumococcal disease, and population-based estimates of disease incidence; and (4) supervisory site visits and management meetings.

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RESUMEN

Enfermedad neumocócica y vacunación antineumocócica en las Américas: programa de acción para la introducción acelerada de una vacuna

Este trabajo resume las presentaciones y los debates que hubo en una reunión sobre la vigilancia de las enfermedades neumocócicas en las Américas, celebrada en la ciudad de México, México, el 2 de noviembre de 2004. La reunión la habían organizado la Organización Panamericana de la Salud (OPS) y el Plan para el Desarrollo Acelerado y la Introducción de Vacunas Antineumocócicas (PneumoADIP, por *Pneumococcal Vaccines and Accelerated Development and Introduction Plan*) de la Alianza Mundial para Vacunas e Inmunización (GAVI, por *Global Alliance for Vaccines and Immunization*). Las personas que participaron en la reunión revisaron el estado de la vigilancia de las enfermedades neumocócicas en la Región de las Américas, así como cálculos de la carga de enfermedades neumocócicas, la distribución de serotipos de *Streptococcus pneumoniae* que provocan enfermedad invasora, el estado de la introducción de vacunas antineumocócicas, análisis económicos sanitarios, y aspectos económicos de la introducción de la vacuna. Los participantes de la reunión también se dedicaron a identificar los próximos pasos necesarios para generar la información esencial que hace falta para facilitar la toma de decisiones en torno a la introducción de una vacuna antineumocócica.

La vigilancia coordinada de las enfermedades neumocócicas en la Región de las Américas se remonta a 1993, cuando la OPS estableció el proyecto conocido por *Sistema Regional de Vacunas (SRV)*, dedicado a la vigilancia de la meningitis y la neumonía por bacterias, incluido el neumococo.

Los datos obtenidos mediante las actividades de vigilancia del SRV indican que la distribución de los principales serotipos en las Américas ha sido estable a lo largo del tiempo (pero que la resistencia a los antibióticos va en aumento), siendo el serotipo 14 el que más se aísla en la mayoría de los países que participan en el SRV. Según se deduce de los datos sobre serotipos procedentes de seis de los países abarcados por el SRV (Argentina, Brasil, Chile, Colombia, México y Uruguay), la vacuna septavalente cubriría a alrededor de 65% de los serotipos, la nonavalente cubriría a más de 77% y la undecavalente cubriría a más de 83%.

Palabras clave

Streptococcus pneumoniae, vacunas antineumocócicas, programas de inmunización, costo de los medicamentos, Américas.