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# Table of Contents

Foreword ...................................................... V

Executive Summary ........................................ vii

Introduction .................................................. 1

Keynote. The Value of Vaccines ............................. 2

**Session I. Global Pneumococcal Epidemiology** ........................ 5
Global Burden of Pneumococcal Disease ...................................... 5
Global Antibiotic Resistance of Pneumococcus ................................ 6

**Session II. Pneumococcal Epidemiology in the Americas** ............... 8
Pneumococcus in Latin America and the Caribbean: Review of the Evidence ........................................ 8
Antibiotic Resistance in Latin America ............................................. 10
SIREVA II: Latin America’s Surveillance Network .............................. 11
Measuring Vaccine Impact in the United States ................................. 12
Discussion ..................................................................... 13

**Session III. Impact of Conjugate Pneumococcal Vaccines: Direct and Indirect Effects** ............... 15
Real-time Impact in the U.S. .................................................. 15
PCV Efficacy Against Invasive Disease and Pneumonia ....................... 18
PCV Impact on Otitis Media .................................................... 19
Discussion ..................................................................... 20

**Session IV. Pneumococcal Vaccine Development: Update & Issues** .......... 22
Serotype Replacement in Perspective ............................................ 22
Wyeth: Existing and Upcoming Vaccines ........................................ 23
GlaxoSmithKline: Two-at-a-Blow ............................................... 24
sanofi pasteur: Protein Vaccine in Hand ........................................ 25
Instituto Butantan: Zeroing in on a Whole Cell Vaccine ...................... 26
Emerging Market Manufacturers: Their Rising Role ............................ 27
Discussion ..................................................................... 28
The Second Regional Pneumococcal Symposium, held in São Paulo, Brazil, in December 2006, followed by two years the First Symposium, held in Mexico City. Participants in Mexico City had noted the urgent need to better understand the burden of pneumococcal disease in Latin America and the Caribbean. For while it was clear that Streptococcus pneumoniae claimed the lives of many children and caused extensive disease, rough estimates of its impact made it difficult for policy makers to make the tough decisions, and commit the resources necessary, for combating the disease.

Over two days in São Paulo, a dramatically different situation emerged. Presentations highlighted the actual burden of disease, its associated costs, and the potential benefits that widespread use of conjugated pneumococcal vaccines would bring to the region. One significant source of this data was a comprehensive report that reviewed all the literature in connection with pneumococcal disease in the region of the Americas. The report was the result of an intense year of work by a team of epidemiologists allied with the Albert B. Sabin Vaccine Institute, working in collaboration with the Pan American Health Organization, GAVI’s PneumoADIP at The Johns Hopkins University, and the United States Centers for Disease Control and Prevention in Atlanta.

Many other contributors, from across the region and the world, brought their unique national and global perspectives to bear as well, collectively presenting an in-depth understanding of the possibilities and challenges ahead in the effort to alleviate the burden of pneumococcus. The Symposium therefore brought to end a chapter of research that lays the basis to accelerate PCV introduction throughout the Americas, while also raising new questions and challenges.

We deeply thank all the researchers, epidemiologists, economists, doctors, public health workers, members of industry, dedicated policy makers, donors and others who participated in shaping this Second Regional Pneumococcal Symposium, and who will truly shape the future of the children in the Americas.
The World Health Organization (WHO) estimates that pneumococcal disease accounts for almost 1.6 million deaths annually. Up to 1 million children under five die from pneumococcal disease every year, and millions more suffer from pneumococcal pneumonia, otitis media (middle ear infections), meningitis, and sepsis (blood poisoning).

While pneumococcal disease can be controlled by antibiotics, they are often not available in developing countries where the vast majority of child deaths occur. And, where antibiotics are used, the emergence of resistant strains of pneumococcus is making treatment more difficult and costly.

Pneumococcal disease is caused by the bacterium Streptococcus pneumoniae, of which there are over 90 serotypes, each characterized by the molecules, called polysaccharides, on its outer coat. Some 23 of these serotypes are the most important human pathogens, and they are included in a vaccine for adults. But the vaccine is useless in children, because of the immaturity of their immune systems. Hence the need for a childhood vaccine attuned to the capabilities of children’s immune responses.

A vaccine for children does exist. It is a pneumococcal conjugate vaccine (PCV), and it has been part of the universal childhood immunization program in the United States since 2000. But this vaccine is still unavailable in most of the world, and is notably absent in poor- and middle-income countries, where the greatest numbers of child deaths and disease occur.

The Second Regional Pneumococcal Symposium, held in São Paulo, Brazil, in December 2006, tackled the myriad of issues necessary to transform this situation, and enable all countries to prevent a huge burden of pneumococcal deaths and disease in children.

Symposium participants discussed a comprehensive review of data on the regional burden of pneumococcal disease and assessments of vaccine cost-effectiveness, evidence of vaccine efficacy in the United States and in clinical trials worldwide, and new ways of assessing the value of vaccines and building political support for vaccination programs.

Participants learned of new vaccine developments by both multinational pharmaceutical companies and emerging market manufacturers. Symposium participants heard the evidence regarding concerns such as serotype replacement and the problems and possible solutions to antibiotic resistant pneumococcus.

Throughout the two days of discussion, presenters and participants addressed recurrent themes of equity, vaccine affordability and accessibility in countries in transition, and the need for targeted communication strategies.

**New Evidence on the Value of Vaccines**

In a keynote address, Dr. David Bloom, an economist with the Harvard School of Public Health, presented new economic data showing that childhood

“Everybody thinks that education is the most powerful instrument of development. What is at stake now is the question of whether we move health up to that same level.”

—DR. DAVID BLOOM
Harvard School of Public Health, US
immunization programs can generate a rate of return ranging from 12% to 21%—making them competitive with investments in primary and secondary education as a stimulus to economic growth.

“Everybody thinks that education is the most powerful instrument of development. What is at stake now is the question of whether we move health up to that same level,” said Bloom.

To do so will require re-analysis of previous economic evaluations of different vaccines, including those for pneumococcus and rotavirus, said Bloom. “We have been shooting ourselves in the foot by leaving out major components of the benefits of vaccines over the years,” he said. These components consist of additional indirect economic benefits generated by vaccination—from the increased savings accrued by a healthier population to children’s improved cognitive abilities and higher earnings later in life.

This deeper understanding of the value of individual vaccines must be communicated to the policymakers who decide on vaccine introductions. Throughout the Symposium, discussion cued back to the importance of targeted communications with ministers of finance, ministers of health, central bank governors, and other policymakers so that they can understand and act on this knowledge.

“With the concrete information we have received this week, we have enough data to start an important defense against pneumococcal disease in all countries,” said Dr. Ciro de Quadros, Director of International Programs of the Albert B. Sabin Vaccine Institute.

Impact in Latin America: Save the Life of One Child Every Hour

“Pneumococcus kills approximately two children every hour in the Americas, or more than 18,000 children every year,” said Dr. Elizabeth Gómez, Director of Epidemiology and Statistics at the Ministry of Health of the Dominican Republic, reporting on the first comprehensive analysis of the burden of pneumococcal disease in Latin America and the Caribbean.

The analysis also found that pneumococcus causes 1.6 million cases of disease. It incurs a total economic cost of US$333 million across the region, and the equivalent of more than 600,000 Disability-Adjusted Life Years.

At the same time, universal vaccination with the current PCV would prevent more than half of the deaths and disease associated with pneumococcus, and be cost effective based on standard WHO measures. This translates into almost one life saved per 1,000 children vaccinated and one case of pneumococcal disease averted per 80 children vaccinated.

The study found that even greater reductions in disease would be possible using vaccine formulations that include additional serotypes.

Other speakers documented the actual impact of PCV7, especially in the United States, where it has been in use since 2000.

Efficacy of PCV

Dr. Cynthia Whitney, an epidemiologist with the U.S. Centers for Disease Control and Prevention, reported that in the U.S. vaccination with PCV7 has led to a 98% reduction of invasive pneumococcal disease (IPD) caused by vaccine serotypes in children under five, a 50% reduction in disease in children too young or too old to be immunized, and an 82% decline in disease in adults aged 65 or older.

“Isn’t it amazing that you can vaccinate children and reduce vaccine-type disease in older adults by almost 82%? I think this is a bigger effect than anyone would have predicted,” Whitney said.
Dr. Lee Harrison of the University of Pittsburgh illuminated the impact of PCVs in four clinical trials, from the United States to the Gambia, showing that vaccination in the Gambia decreased deaths from pneumococcus by 16%, and that efficacy against IPD caused by vaccine serotypes ranged from 97% to 77%. Surprisingly, long-term efficacy against all-serotype IPD was higher in HIV-positive children (45%) than in HIV-negative children (35%).

Meanwhile, Latin American studies show that the current vaccine formulation would have an efficacy of about 60% in the region. As antigens are added for other dominant circulating serotypes, efficacy could rise to 84% for an upcoming 13-valent vaccine, reported Dr. Lucia Oliviera of the Pan American Health Organization.

**Equity, Affordability and Sustainability**

As noted by Bolivia’s Dr. Erick Machicao, vaccination in Latin America has been an instrument of health, equity and development. Many noted that for the conjugate pneumococcal vaccine to serve as the same, it must be affordable over the long run.

Cost-effective analysis took different tacks: some evaluated cost-effectiveness based on the vaccine’s current price of US$53 per dose for a three-dose course; others estimated cost-effectiveness based on a range of prices as low as US$1 per dose. All found the vaccine either cost-effective or highly cost-effective.

However, several of the speakers who presented the on-the-ground challenges of implementing pneumococcal vaccine stated that at its current price, the vaccine would not be sustainable as part of universal childhood vaccination.

“The current price-per-dose of more than US$50 prevents our country from taking a leap to introduce the vaccine in our routine program for universal vaccination,” said Dr. Expedito Luna, Director of the Surveillance and Infectious Disease Control program in Brazil.

As a result, some countries are focusing on vaccinating high-risk and vulnerable populations of children, including those with underlying health conditions.

As noted by Dr. Jon Andrus of the Pan American Health Organization, in the long-run, solutions must come from a combination of innovative financing, the creation of “fiscal space” by national governments, and successful negotiations between PAHO’s Revolving Fund and vaccine manufacturers for the purchase of vaccines in bulk, at a uniform price, for countries across the region.

However, as noted by Dr. Orin Levine, Executive Director of PneumoADIP, there is the “price of inaction, as well as the price of the vaccine.”

And with the price of inaction in mind, Symposium participants endorsed a “Call to Action” on Pneumococcus in the Americas.

In the long-run, solutions must come from a combination of innovative financing.

—DR. JON ANDRUS of the Pan American Health Organization
In light of the burden of pneumococcal disease in the Americas, and the existence of a safe, efficacious vaccine, participants called for:

- The introduction of pneumococcal vaccines wherever feasible;
- The World Health Organization to expedite the prequalification of the existing vaccine for purchase by United Nations agencies;
- Work to raise awareness among the public and policy makers of the burden of pneumococcal disease and the value of vaccination;
- Increased vaccine research and expanded surveillance;
- PAHO and its Revolving Fund for the acquisition of vaccines to work together with national governments, bilateral and multilateral agencies, the GAVI Alliance, and the manufacturers of vaccines to facilitate the introduction of pneumococcal vaccines.

In short, Symposium participants called for "making 2007 the year of action to combat pneumococcal disease in the Americas."

"Isn’t it amazing that you can vaccinate children and reduce vaccine-type disease in older adults by almost 82%? This is a bigger effect than anyone would have predicted."

—DR. CYNTHIA WHITNEY
U.S. Centers for Disease Control and Prevention
Introduction

The Second Regional Pneumococcal Symposium, held 13-14 December 2006, reviewed all the major issues associated with pneumococcal disease globally, and the possibility of its control using safe and effective vaccines in the region of the Americas.

“I do believe that this Symposium will be the beginning of a great job in the region of the Americas to start more efficient control of pneumococcus, which is one of the main diseases contributing to child mortality in the region,” said Dr. Ciro de Quadros of the Albert B. Sabin Vaccine Institute.

The conference built awareness of the:

- Burden of pneumococcal disease in the region,
- Value of vaccines and,
- Processes for evaluating vaccine introduction by country.

Investigators reported on a comprehensive analysis of the regional burden of disease, which found that pneumococcus claims the lives of two children under five every hour—more than 18,000 children a year.

“The deaths of children from pneumococcus in the region of the Americas are the equivalent of four plane crashes of children every month,” de Quadros said. “Why do we allow four crashes every month of airplanes full of children? This social norm has to change.”

The data also showed that widescale immunization with conjugate pneumococcal vaccine could prevent half of the deaths and about half of the 1.6 million cases of disease every year. And economic analysis showed that the vaccine would be highly cost-effective, especially when taking into account the impact of “herd immunity”—the protection extended to members of the community who are not vaccinated, when vaccination of children stops the transmission of disease.

In opening remarks, symposium co-coordinator Dr. Orin Levine of PneumoADIP noted that the Symposium brought together key representatives required for successful collaborative action to reduce the huge burden of pneumococcal disease in the Americas—people from academia, pediatrics, PAHO, the Albert B. Sabin Vaccine Institute, the CDC, the GAVI Alliance, the vaccine industry, and others.

“It has become clear in the last several years that we can make enormous progress against infectious diseases, like pneumococcal disease, but it requires collaborative action,” Levine said.

Dr. Jon Andrus, director of PAHO’s Technical Advisory Committee, noted that immunization in the Americas is at a crossroads. “As we look back from where we have come, we have created, working all together, an umbrella of protection,” he said. The eradication of polio, the elimination of measles, near-elimination of rubella, were all accomplished with relatively inexpensive vaccines, purchased in bulk on behalf of countries for the last thirty years through PAHO’s Revolving Fund.

“But as we look forward we still have amazing public health challenges to confront,” said Andrus, co-coordinator of the Symposium.

Andrus presaged the determination of Symposium participants, ultimately expressed in a Call to Action issued by the Symposium. “We are here to make a difference,” he said. “I would like to leave us with a call for action: To do whatever we can to make that vaccine available and affordable for those who need it most. For us it is an issue of equity.”

“It has become clear in the last several years that we can make enormous progress against infectious diseases, like pneumococcal disease, but it requires collaborative action.”

—DR. ORIN LEVINE
GAVI’s PneumoADIP
Dr. Ciro de Quadros introduced the keynote speaker, Dr. David Bloom, an economist at the Harvard University School of Public Health, with an analogy: “Some few weeks ago,” he said, “there was a terrible accident here in Brazil with a collision of two airplanes, and about 300 people fell in the Amazon region and everybody died. Every day since then, that accident has been in the press here in Brazil. Today we will learn that every hour, two children in this region die from pneumococcal diseases. This is the equivalent of an airplane crash every week. So why do we allow four crashes every month of airplanes full of children? This social norm has to change. If it does not, the inequities between the children that receive new vaccines and the ones that do not will continue to grow. To change this social norm, decision-makers must come to appreciate the value of vaccines.”

**Breakthroughs in Valuing Vaccination**

Dr. David Bloom presented new economic evidence that shows how immunization programs can actually boost the wealth of nations. He reviewed new studies that calculate a rate of return on childhood vaccination programs ranging from 12% to 21%, making them competitive with investments in primary and secondary education as a stimulus to economic growth.

The new analyses demonstrate that public health spending can be justified not only on moral, ethical and human rights grounds, but can also be an instrument of economic growth, Bloom said. The insights come at a time of both great advances and colossal failures in child health.

**Child Health: Great Advances and Colossal Failures**

Bloom noted United Nations data that shows the global rate of infant mortality has declined from 12% of live births in 1960 to just over 5% today—a decline of nearly 60%. In part, the decline reflects the expansion of basic childhood immunization as indicated by the increase in DTP vaccine coverage from about 5-10% of children in 1974 to about 75% by 1990. The rate has been level since 1990, however, as the great advances of the past have been offset by what Bloom called “colossal failures.”

Key among these is the fact that over 10 million children died in 2002 before age five, and six to seven million of those deaths could have been prevented or cured with existing medical knowledge. As a result, children account for about 20% of global deaths, even though they comprise only 10% of the world’s population. Furthermore, infant mortality rates vary across countries by a factor of more than 50—and are increasing in size.

**How Health Begets Wealth**

Bloom said that in the last decade, macroeconomists have begun identifying the many ways that health begets wealth, and those insights are helping to answer an age-old question: What accounts for the vast differences in wealth between nations? “Why is per-capita income in Chile three times what it is in Iran? Why is per capita income in Norway 130 times what it is in Tanzania?” he asked.

The old answer to those questions—that differences among countries can be explained by discrepancies in physical and human capital—has never provided a full explanation. Only once the role

“The bottom line is that population health is an exceedingly robust and powerful predictor of economic growth.”

—DR. DAVID BLOOM
Harvard School of Public Health, US
of health is considered does a more complete answer become possible, Bloom said.

We now know that health creates wealth in a multitude of ways:

- Healthier workforces are more productive;
- Healthier populations invest more in education, a fundamental determinant of economic growth and development;
- Healthier people who expect longer retirements are more likely to save money, an accumulation of capital that leads to economic growth;
- Healthy populations are a magnet for attracting direct foreign investment;
- Health improvements trigger demographic changes that have the potential to spur economic growth if the right policy environment is in place.

Additional benefits accrue from vaccinating children:

- Healthy children have better records of school attendance, attend school for more years, and have better cognitive development;
- Healthy, educated children grow into more productive workers;
- Parents stay healthier and are more productive, with lower rates of absenteeism and presenteeism, when they have healthy children.

“The bottom line is that population health is an exceedingly robust and powerful predictor of economic growth,” Bloom said. “A 10-year gain in life expectancy translates into as much as one additional percentage point of annual growth of income per capita, which compounds over time.”

In short, improved health has the potential to take nations and individuals out of poverty. “The main asset that the poor have is their labor. And clearly health status determines the value of that labor,” Bloom said.

**Competitive Return on Investment**

To demonstrate how health, and vaccination in particular, creates wealth, Bloom reviewed two recent case studies. One study calculated the rate of return if the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunization) were to extend the use of available and anticipated vaccines to 75 low-income countries from now until 2020 at an estimated cost of US$13 billion. The investment would reduce the child mortality rate in those countries by 1,616 per 1,000 live births by the year 2020.

Bloom calculated the rate of return on this investment by comparing the program’s cost (US$13 billion) to its benefits in economic terms, taking into account worker productivity gains at the individual level. The results: the rate of return would be 12% in 2005, rising to 18% by 2020.

A second study based on longitudinal data from the Philippines encompassed nearly 2,000 children born between May 1983 and April 1984. The data allowed Bloom and his colleagues to relate the children’s immunization experience in the first two years of life to their later cognitive development as measured by their test scores on language, mathematics, and reasoning.

“We actually find a significant positive effect of childhood vaccination on all three test scores,” Bloom said. He then translated those higher test scores into an impact on earnings, and compared the gains in earnings due to vaccination with the program costs. This yielded an estimated rate of return of 21%.

“These estimated rates of return, 12 to 18% on the GAVI program and 21% in the Philippines, compare very favorably with estimated rates of return in the most exalted instrument of development, namely education,” Bloom said.

“Immunization programs make eminently good economic sense because they can be expected to yield an extremely handsome return on investment. And that return is important for economic growth, for poverty reduction, and for reducing global income inequality,” he continued.

Bloom argued that the burden is no longer on the health community to provide arguments in favor of vaccination programs. Rather, “The evidence is so strong that the onus now is on economic leaders and political leaders to say why they are not doing this, because this amounts to what in economic terms is very much a ‘no-brainer’!”
Discussion

Following Bloom’s presentation, questions and comments focused on the importance of communicating the value of vaccines to decision makers, and the most effective ways to do so. Bloom said that to help ministers of finance, central bank governors, and other policymakers to understand and act upon these arguments, the analyses need to be taken down to the level of individual vaccines and countries. He urged economists and epidemiologists to redo all of the previous economic evaluations of different vaccines, including pneumococcal and rotavirus vaccines, applying the new understandings of how to value vaccines.

Bloom noted the need to promote news and articles in publications read by decision makers, such as The Economist and the journal of the International Monetary Fund, as well as the importance of face-to-face briefings for finance ministers, and developing venues to bring together Ministers of Finance and Ministers of Health.

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Harvard School of Public Health, US
Pneumococcal disease is a primary cause of death among children in developing countries and the leading cause of death from infectious disease. Based on current estimates, it accounts for 1.6 million deaths every year, including nearly one million children under the age of five.

During this session, Dr. Lara Wolfson, a scientist in the Initiative for Vaccine Research of the World Health Organization (WHO), reported on a major effort of WHO and its partners to update the data on the global burden of disease imposed by pneumococcus. The project, still underway, uses state-of-the-art knowledge and methods in epidemiology and statistics and will provide a new baseline in the understanding of disease and deaths caused by Streptococcus pneumoniae.

Although a pneumococcal conjugate vaccine (PCV) has recently become available, its use worldwide remains limited. Meanwhile, the public health impact and costs associated with S. pneumoniae continue to grow, fanned by the spread of antibiotic resistant strains of the bacteria. Resistance makes the disease more difficult and costly to treat, and challenges the abilities of public health systems to bring pneumococcal disease under control.

Dr. Keith Klugman, William H. Foege Professor of Global Health at the United States’ Emory University, summarized the risk factors and impact of antibiotic resistant pneumococcus and described global problems of emerging resistant clones.

**Global Pneumococcal Disease Burden**

Dr. Lara Wolfson described the Global Burden of Disease project. Initiated by WHO and its partners, the project’s goal is to estimate the number of cases and deaths caused by Streptococcus pneumoniae and Haemophilus influenzae type B worldwide, regionally, and by country. The project is analyzing three major syndromes: 1) meningitis; 2) pneumonia, and; 3) non-pneumonia, non-meningitis in children under five years of age, with 2000 as the base year.

“One thing we found very consistently,” Wolfson said, “is that everyone is crying out for more and better data, and emphasizing the importance of improving and strengthening surveillance to generate that data.”

Thus far, the project has taken about two and a half years and involved 66 people, as a collaboration among WHO, the PneumoADIP and the Hib Initiative.

Wolfson described the project’s rigorous “four step plus one” process. Its requirements are: a sound database of evidence, peer review of estimates, inclusion of measures of uncertainty, and an independent evaluation of both the data and the methods. WHO’s Evidence and Information for Policy Cluster reviews the analysis and data to ensure consistency with vital registration data, surveillance data, and other disease burden estimates. As a final step, WHO consults with individual countries on their findings.

The literature review searched for data on disease syndromes, data quality, incidence age, stratification by regions and overall child mortality levels, and the impact of HIV. The review initially yielded almost 15,000 citations, of which over 400 ultimately qualified for inclusion. Due to limited data sources, the researchers extrapolated hard data to countries with similar levels of child mortality in the same geographic region.

**Preliminary Findings in Latin America**

While the project is still finalizing disease burden estimates, Wolfson summarized preliminary findings on pneumococcus in Latin America. These included:

- Case fatality rates for Pneumococcal meningitis in Latin America range from about 15% to about 76%, and are heavily driven by access to care.
(because of the high efficacy of antibiotic treatment);

- There were between 900,000 and 1.7 million cases per year of pneumonia, causing between 8,700 and 22,500 deaths per year;

- The case fatality ratio for pneumonia ranged from just under 0.1% to 9.1%, and the overall incidence was between 1,280 and 2,250 cases per 100,000 children under five years of age;

- The majority of pneumococcal deaths are actually from pneumococcal pneumonia, a syndrome that is often not very carefully estimated;

- Pneumococcal meningitis has the highest case fatality ratios;

- For all causes, the case-fatality ratios are closely related to overall mortality rates for children under five years of age.

Wolfson said that the project is nearing completion. An expert committee has reviewed its results, and the country consultation process will soon commence, with plans to have final results in mid 2007.

**Global Antibiotic Resistance of Pneumococcus**

Antibiotic resistance in pneumococcus is a global problem, made worse by the emergence of multiply-resistant bacteria, and "the invasion of the clones," said Dr. Keith Klugman. On the other hand, "There is something that can decrease antibiotic resistance and that is the pneumococcal conjugate vaccine," he said.

**Risks for Antibiotic Resistance**

Factors that increase the risk of antibiotic resistance include young age, hospitalization, and HIV positive status, but the greatest risk of all is antibiotic use, Klugman said. In children, the risk of carrying resistant pneumococci remains elevated for two to three months after receiving antibiotics. Studies have shown, however, that a high dose, short duration course of antibiotics is the best way to minimize risk.

The correlation between antibiotic use and antibiotic resistance is so clear that it can be seen at the country level. For example, in the European Union, both antibiotic use and resistance are lowest in the Netherlands, and highest in Spain.

**Invasion of the Clones**

Klugman noted that the emergence of resistance has been complicated by multiple resistance, in which the bacteria can prevail over more than one class of antibiotic. As an example of how multiple resistance can emerge, Klugman described a study from Canada that shows that the most influential factor in developing penicillin resistance is not penicillin use, but use of the macrolide azithromycin, which is a totally different class of antibiotic. "So the macrolide is selecting strains that have multiple resistances, including penicillin resistance," Klugman said.

High levels of resistance are often due to clones. "What happens is that resistant clones come into the population and replace the susceptible strains of..."
pneumococcus,” Klugman explained.

One CDC study shows that 93% of 144 resistant strains of pneumococcus from across the United States belong to just eight clones. Similarly, one clone was responsible for 50% of the cases of penicillin-resistant pneumococcal meningitis in Salvador, Brazil, and another was responsible for a high level of fluoroquinolone resistance in Hong Kong.

In the United States, however, widescale immunization with pneumococcal conjugate vaccine has dramatically lowered the total number of resistant cases of pneumococcal invasive disease from about 50,000 per annum just prior to vaccine introduction to fewer than 10,000 in 2002.

Since 2002, however, a counter-trend has emerged, Klugman said, as the number of resistant cases of pneumonia is again on the rise, driven by the emergence of resistant clones of pneumococcal serotypes not included in the current vaccine formulation. In particular, a multi-drug resistant serotype 19A clone is “invading the United States...and it is a very worrying trend,” Klugman said. Since 2002, it has increased 2.5 fold in children and 2.6 fold in adults.

In other words, while pneumococcal conjugate vaccines interrupt transmission of multiply resistant vaccine strains, Klugman said that resistance is now emerging in nonvaccine types.

“It is extremely important that vaccines be introduced, and that surveillance continues to monitor where and how resistance is emerging so there can be even newer vaccine formulations to combat these emerging antibiotic resistant strains,” he concluded.

“There is something that can decrease antibiotic resistance and that is the pneumococcal conjugate vaccine.”

— DR. KEITH KLUGMAN
Emory University, US
This session was sweeping in the breadth and depth of data presented on the epidemiology of \textit{S. pneumoniae} in the Americas. Drs. Maria Teresa Valenzuela and Elizabeth Gómez reported the results of a major initiative documenting the extent of pneumococcal disease in Latin America and the Caribbean. Dr. Maria Christina Brandileone reviewed the prevalence of antibiotic resistant pneumococcus in the region, and Dr. Lucia Oliveira updated the extensive work of SIREVA, the pneumococcal surveillance network in Latin America.

In addition, Dr. Brendan Flannery reported on the use of post-vaccination surveillance in the United States for gauging vaccine impact. “I am going to show you something that is quite exciting,” Flannery said. “Using terrible data like we have in the United States, we have been able to demonstrate very important vaccine impact. And that is, perhaps, for decision makers, rather convincing.”

Pneumococcus in Latin American and the Caribbean: Review of the Evidence

Representatives of a multinational team of public health experts released findings from the most comprehensive study ever conducted on the impact of pneumococcal disease in South America and the Caribbean.

“It is important to know that no country in this region has yet introduced the pneumococcal conjugate vaccine to their expanded immunization program,” began Dr. Maria Teresa Valenzuela, Director of the Public Health and Epidemiology Department at the University of the Andes in Santiago, Chile. An important goal of the study, therefore, was to give policymakers the necessary information to decide whether to expand their immunization programs to protect all children against pneumococcal disease.

The Executive Summary of the report, entitled “The Burden of Pneumococcal Disease and the Cost Effectiveness of a Pneumococcal Vaccine in Latin America and the Caribbean: A review of the evidence and an economic analysis” was distributed at the conference. It was written by a team of researchers associated with the Albert B. Sabin Vaccine Institute, working in collaboration with the Pan American Health Organization (PAHO); GAVI’s Pneumococcal Accelerated Development and Introduction Plan (PneumoADIP) at Johns Hopkins University in Baltimore, MD; and the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, GA.

Main Findings

“Pneumococcus kills approximately two children every hour in the Americas, or more than 18,000 children every year,” said Dr. Elizabeth Gómez, Director of Epidemiology and Statistics at the Ministry of Health of the Dominican Republic.

In addition, across Latin America and the Caribbean, the study found that \textit{S. Pneumoniae} causes an estimated 1.6 million cases of disease, including:

- 1.3 million cases of acute middle ear infections that can lead to deafness;
- 327,000 cases of pneumonia;
- 3,900 cases of meningitis (inflammation of the brain);
- 1,200 cases of sepsis (blood infection);

Gómez noted that the total burden of pneumococcal disease in the region amounts to “a total of 600,000 Disability-Adjusted Life Years (DALYs)—an extremely important element in determining cost-effectiveness that we will hear about later today.”
Additional findings included:

- For children under two years there are 51 cases of pneumococcal pneumonia per 100,000 children;
- For every 100,000 children under the age of three, the incidence of pneumococcal bacteremia is 87, and for sepsis the incidence is 2;
- The annual incidence of IPD in children under five is 32 cases per 100,000 children;
- The fatality rate of IPD in children ages zero to two is 12%; in children under five it is 10%;
- The rate of IPD attributed to \textit{S. pneumoniae} is 32%;
- The annual incidence of bacterial meningitis in children under age one is 138 cases per 100,000, and decreases as age increases.

In addition, Gómez said that a review of 13 studies suggests that 43% of the cases of acute otitis media are caused by \textit{Streptococcus pneumoniae}, but she noted that there was a paucity of available information.

\textbf{Methodology}

Valenzuela described the “three pillars” of the study, which included a systematic review of literature; a multi-nation search for other sources of information, including interviews with physicians; and a statistical analysis allowing the scientists to draw conclusions and make recommendations based on the collected data.

An initial comprehensive literature review identified 6,000 publications during the period 1990-2006, which were narrowed down to 143 peer-reviewed papers that were included in the analysis. The team also conducted a survey of health care providers, contacted the ministries of health of each target nation to obtain relevant data, and corresponded with 36 pneumococcal researchers (out of the 46 contacted in 13 countries).

They analyzed the data to calculate incidences, fatality rates, and the ratio of syndromes due to \textit{S. pneumoniae}, which were then applied to the region’s annual newborn population of 11,500,000 live births, followed hypothetically through the first five years of life.

Valenzuela noted that 73% of the epidemiological studies had come from the eight nations in the “Southern Cone,” and that almost 60% of the studies were carried out in just three countries—Brazil, Argentina and Chile. With some exceptions, studies from countries with low under-five mortality rates were overrepresented compared to countries where children were more likely to die from the disease, such as Haiti and the Dominican Republic.

Limitations due to the small number of studies in countries with the highest mortality rates, and the ongoing need for data, led researchers to suggest their results were conservative in estimating the burden of disease. For example, Gómez noted that only two studies provided information on the annual incidence of Invasive Pneumococcal Disease (IPD), but that 12 studies provided information on IPD fatality rates, and 56 contained enough data to allow the researchers to analyze resistance to antibiotics in the region, as well as the most prevalent serotypes.

The report “The Burden of Pneumococcal Disease and the Cost Effectiveness of a Pneumococcal Vaccine in Latin America and the Caribbean: A review of the evidence and an economic analysis,” was prepared by Dagna Constenla, Elizabeth Gómez, Fernando Pio de la Hoz, Rosalyn O’Loughlin, Anushua Sinha, Juan E. Valencia, Maria Teresa Valenzuela.

“It is important to know that no country in this region has yet introduced the pneumococcal conjugate vaccine to their expanded immunization program.”

—DR. MARIA TERESA
Valenzuela, University of the Andes, Chile
Antibiotic Resistance in Latin America

Dr. Maria Cristina C. Brandileone, with the Adolfo Lutz Institute in São Paulo, Brazil summarized the status of antibiotic resistant pneumococcus in Latin America. She noted that, as in North America, Latin America has witnessed an increase of resistance to penicillin over recent years, mainly in connection with two clones of serotype 14.

Brandileone presented data from the SIREVA laboratory surveillance network of 21 countries in Latin America collected between 2000 and 2005. “The specific objectives were to determine the serotype, the antimicrobial resistance of the strains, identify penicillin-resistant clones, and to establish laboratory capture” of the data, she said.

During the study period, the network analyzed approximately 17,500 strains, 11,500 of which were from children younger than six years of age. The largest proportion of strains, 42%, corresponded to a diagnosis of meningitis, 32% to pneumonia, and 26% to others. The higher number of isolates for meningitis, however, is due to its compulsory reporting in Latin America. In contrast, often no biological material is collected in relation to outpatient treatment of pneumonia, Brandileone noted.

Major Findings on Resistant Pneumococcus in Latin America

The preliminary analysis from the study found particularly high resistance associated with serotype 14, which is estimated to comprise 71% of resistant strains, due to dissemination of two serotype 14 clones. Serotype 6B accounts for another 11% of resistant strains. “The two serotypes, 14 and 6B, together account for 82% of the total resistant strains in the region,” Brandileone said.

Brandileone noted that the 7-valent vaccine includes serotype 14, and would, therefore, protect against the resistant serotype 14 clones that have spread through the population.

Reviewing resistance data related to a number of countries, Brandileone pointed out that in the period from 1993 to 1999, compared to 2000 to 2005, intermediate antimicrobial resistance increased from 17% to 24%, while high resistance increased a non-significant 12%. However, the study did find a higher percentage of resistance than expected in children younger than six years.

Resistance rates varied by country. For example, in the Dominican Republic, 33% of the child population had intermediate resistance, and 25% had high resistance. In Venezuela, on the other hand, only 8% had high resistance.

To illustrate the situation on-the-ground, Brandileone reviewed data regarding penicillin-resistant pneumococcal strains in Brazil. Starting in the year 2000, a 20% to 30% increase in resistant pneumococcus in children had occurred. This increase was independent of age, but highest in children younger than five years.

In conclusion, Brandileone stressed the need for a clinical guide on the rational use of antimicrobials in the region, noting that even within one country, Brazil, different regions and different hospitals use various antibiotic drugs. She urged that surveillance data be monitored precisely for changes in serotypes and increases in resistance.

“Pneumococcus kills approximately two children every hour in the Americas or more than 18,000 children every year.”

—DR. ELIZABETH GÓMEZ
Ministry of Health, the Dominican Republic
SIREVA II: Latin America’s Surveillance Network

Dr. Lucia Helena de Oliveira, Regional Advisor for New Vaccines with PAHO, reported on PAHO’s regional surveillance laboratory network of 21 countries in the Americas that was founded in 1993, known as SIREVA. The network aims to help epidemiologists link laboratory data with necessary epidemiological and clinical data, to more accurately characterize the human and financial burden of pneumococcal disease in the region.

SIREVA work is guided by the recommendations of PAHO’s Technical Advisory Committee (TAC) and its Directing Council, composed of the Ministers of Health of the Americas Region. The TAC has focused on strengthening the clinical and epidemiological components of pneumococcal surveillance and the conduct of burden of disease and economic studies. A 2006 meeting of the Directing Council emphasized the role of immunization in reducing child mortality in accordance with the Global Immunization Vision and Strategy and the Millennium Development Goals.

Serotype Surveillance and Vaccine Coverage

De Oliveira summarized SIREVA’s serotype prevalence data, comparing the periods from 1993-1999 and 2000-2004. She reported that the prevalence of individual serotypes had not changed dramatically, with the most important serotype being 14, followed by 6, 5, and 1.

De Oliveira used the data to estimate the potential impact of different vaccine formulations on serotype coverage in Latin America:

- Seven-valent vaccine would cover almost 59% of serotypes;
- Nine-valent vaccine would cover 71%;
- Eleven-valent vaccine would cover 77%;
- The upcoming 10-valent vaccine would cover 74.5%;
- The upcoming 13-valent vaccine would cover 84%.

Current Work and Future Plans

De Oliveira reported that PAHO is collaborating with countries to implement surveillance in sentinel hospitals, maintain the capacity and quality of the laboratory network, standardize case definitions for pneumonia and meningitis cases, collect epidemiological data from all patients meeting those definitions, and analyze and publish the data. In addition, PAHO is working with countries to determine the incidence of disease using population-based studies and conducting cost-effectiveness studies to help guide decisions regarding vaccine introduction. Through 2007, SIREVA intends to support 10 countries in strengthening surveillance.

Key to the surveillance effort is use of a standardized case definition across all countries, and SIREVA defines pneumonia based on a chest X-ray showing a pneumonia-compatible radiological pattern. The definition is used in a new PAHO guide for bacterial pneumonia and meningitis surveillance.

“The U.S. findings suggest that 20% of the otitis media visits in young children... might be preventable with pneumococcal vaccine.”

—DR. BRENDAN FLANNERY
U.S. Centers for Disease Control and Prevention

Proceedings of the Second Regional Pneumococcal Symposium
in children younger than five years. The guide will be reviewed on December 15-16, 2006, at a regional meeting of representatives from 25 countries of Epidemiological Surveillance Systems. “During the meeting, we intend to validate this guide to publish it in March 2007,” de Oliveira said.

Measuring Vaccine Impact in the United States

Dr. Brendan Flannery, an epidemiologist with the U.S. Centers for Disease Control and Prevention (CDC), described how pneumococcal disease surveillance data has been used to demonstrate vaccine impact in the United States. He demonstrated that, despite concerns with the quality of surveillance, it is possible to monitor trends that gauge vaccine impact.

Two studies—one using a sentinel surveillance system at eight pediatric hospitals across the country, and another using population-based surveillance—both showed large declines in invasive pneumococcal disease after the vaccine’s introduction in 2000, with the greatest reductions among children under two years.

Flannery noted that in children under two years, X-ray confirmed pneumonia has declined by almost 50% compared to the years before vaccine introduction.
In addition, a study of outpatient visits in the United States found a significant reduction in all visits for otitis media, albeit with wide confidence intervals. “The U.S. findings suggest that 20% of the otitis media episodes among children younger than two years old...were prevented with pneumococcal vaccine,” Flannery said. This would mean two million fewer visits per year for ear infections in this age group alone.

Meanwhile, hospital discharge data show that invasive pneumococcal disease has also decreased among persons 65 years and older.

Flannery emphasized the value of including X-ray data on pneumonia. For example, studies in Uruguay and Chile that did so showed rates of disease that were approximately 100 times higher than the measured incidence of invasive pneumococcal disease. Further, in Chile the measured rate was tripled by adding ambulatory patients.

He noted that comparisons of disease surveillance results before and after the introduction of pneumococcal vaccine can provide a clearer idea of the proportion of disease due specifically to S. pneumoniae, which will ultimately allow far more accurate estimates of the burden and cost of pneumococcal vaccine.

Discussion

During a wide-ranging discussion led by Dr. Ciro de Quadros, members of the audience asked the researchers to elaborate on a number of topics.

Rates of Morbidity and Mortality in Latin America and the Caribbean

QUESTION: Xavier Sáez-Llorens from Panama questioned the data regarding the death toll attributed to pneumococcal pneumonia, arguing, “Obviously, at least in Central America or in some other countries, the rate is well below this mortality.” Conversely, he added that the incidence of acute otitis media seemed much too low, which he blamed on “significant underreporting,” particularly for children under 12 months. He suggested breaking down the data by region in order to “capture more information.”

QUESTION: Antonio Arbo from Paraguay questioned the incidence for meningitis, suggesting there may be underreporting reflected in the data. He recommended the researchers indicate whether cases have been confirmed with cultures. Commenting on the death rate for pneumococcal pneumonia (for sick children under the age of two), he noted the scarcity of studies might have led to conclusions that, “do not reflect the situation in the countries.” “If we consider that eight out of 100 die, we are overestimating...it is important to clarify these limitations,” he added.

RESPONSE: Gómez said that the fatality rate for meningitis represented one of the most solid pieces of data in the report. “This information summarizes 18 papers representing the three sub-regions,” she said. Among the countries contributing data were Chile, Brazil, Colombia, Venezuela, Guatemala, Mexico, the Dominican Republic, and Cuba. Additionally, the data on pneumococcal meningitis included only events that had been confirmed by “isolation of the etiological agent.”

Gómez conceded the number of studies was indeed small, but noted that her team had been conservative in estimating burden of disease. “The same methodological limitations that we briefly presented allowed us to see very clearly that there is important underestimation of the magnitude of the problem,” Gómez said.

Valenzuela noted that cases of otitis media are under-reported. Many of the conclusions regarding the role of S. pneumoniae in causing acute otitis media were extrapolated from the work of Dr. Adriano Arguedas of Costa Rica, Valenzuela said. She added that Dr. Arguedas’ work clearly supports the finding that S. pneumoniae is the causal agent in 43% of all cases of acute otitis media in the region. Valenzuela also noted that the research team had a particularly hard time identifying population-based data on acute otitis media.

Antibiotic Resistance and Serotype 14 in Latin America

QUESTION: Antonio Arbo asked for the total number of serotype 14 strains examined for the study. He noted that if it is the most widely represented serotype, it would be logical that the frequency of resistance would be higher as well.
RESPONSE: Brandileone noted that her data included about 9,000 samples of all strains from eight countries, but she did not have the specific number of serotype 14. “What you suggest is logical, but it is interesting to see that the proportion of resistant serotype 14 strains has increased with time,” she said.

QUESTION: Raúl Ruvinsky commented that, in Argentina, serotype 14 accounts for 34% out of 2,100 isolates—a percentage similar to those found in the other countries. It is the one with the highest resistance, as compared to all other serotypes.

RESPONSE: Brandileone said that unpublished data show that clone Spain of serotype 14 began increasing regionally starting in 1997, when it had almost no presence. For example, in Brazil, the clone initially was only located in the state of São Paulo. Today, it has spread to all the regions in the country.

COMMENT: Dagan noted that if the vaccine introduced seven years ago had not already contained type 14, its recent meteoric rise would now be considered a replacement strain.

The Definition of Pneumonia Used by SIREVA

QUESTION: Gustavo Aristizabal from Bogota, Colombia, Greta Miño from Ecuador, and others questioned the definition of pneumonia used by SIREVA. Some felt X-ray-compatible pneumonia was too restrictive. Another person suggested that blood counts and quantitative PCR be used.

RESPONSE: De Oliveira replied, “I am an epidemiologist, as were most of the individuals who worked on this guide. When we think in terms of public health, we have to balance sensitivity and specificity in case definition. It is completely different when a doctor looks at the patient from the clinical point of view. We are going to have false negative cases and false positive cases, but we need to strike that balance. We know that it is not a perfect case definition but it is a definition to work with in public health.” She emphasized that there would be an opportunity to validate the guide with a large number of individuals from the Ministries of Health at a meeting that directly followed this one.

COMMENT: There is a tool available on the WHO website for standardization of the interpretation of X-ray confirmed pneumonia. There is a paper by Dr. Thomas Cherian in the WHO Bulletin, and a paper in Spanish by Dr. Rosanna Lagos that explains the surveillance in Latin America.
Three presentations captured the stunning array of “direct and indirect effects” of the pneumococcal conjugate vaccine (PCV). The direct effects are experienced by the children vaccinated: lives saved, illnesses averted and nights at home in bed rather than in emergency rooms or local clinics. Indirect effects are health benefits experienced by the vaccinated child’s younger and older siblings, parents, friends, grandparents, teachers as well as children not yet vaccinated—in short, the community at large.

The reason for these indirect effects is “herd immunity,” which occurs when vaccination in the target population stops transmission of pneumococcus in the larger “herd.” In the United States, the impact of herd immunity since vaccine introduction in 2000 has proven to be greater than anyone anticipated, according to Dr. Cynthia Whitney of the U.S. Centers for Disease Control and Prevention (CDC).

A presentation by Dr. Lee Harrison illuminated the impact of PCVs in four clinical trials, from the United States to the Gambia, showing that the introduction of PCV will bring large public health benefits to developing as well as developed nations.

A third presentation by Dr. Ron Dagan addressed the vaccine’s impact on otitis media (OM), or middle ear infection, of which there are 24 million cases a year in the U.S. alone.

**Real-Time Impact in the U.S.**

Dr. Cynthia Whitney of the U.S. CDC shared the U.S. experience with PCV7, which was licensed in 2000. The government recommended that the vaccine be given to all children under 2 years and to certain high-risk children aged 2 to 4 years. By 2005, about 83% of children aged 19-35 months had received three or four doses.

“Disease caused by the vaccine types has dropped dramatically in young children following conjugate introduction, and herd immunity appears to be protecting unvaccinated kids,” Whitney said.

The U.S. experience with PCV7 includes a 98% reduction in IPD caused by strains covered by the vaccine in children under 5 years, a 50% reduction in disease in children either too young or too old to be immunized, and an 82% decline in disease in adults aged 65 or older.

Whitney reviewed highlights of post-introduction data based on the CDC’s Active Bacterial Core (ABC) surveillance system, which operates in 10 states and tracks invasive pneumococcal disease in a population of about 20 million people.

Summarizing the major effects of pneumococcal vaccination, Whitney reported that the rate of vaccine type invasive pneumococcal disease (IPD) in children under five dropped from about 80 cases per 100,000 children at baseline in 1999 to 1.5 cases per 100,000 children in 2005—a 98% reduction in IPD.

A case control study conducted in the surveillance areas demonstrated that efficacy against individual vaccine serotypes ranged from a low of 87% against 19F to a high of 100% against 9V. The vaccine extended some cross-protection against vaccine-related strain 6A, but it did not afford similar protection against vaccine-related strain 19A.

Whitney also reviewed the effect of various vaccine schedules, and reported that even a single dose given to infants before the age of seven months exhibited 73% effectiveness, although protection did not persist more than 6 months after a single dose. Schedules of two, three, or four doses all had 95%-100% effectiveness and protection lasted. “This is good news in that there is some flexibility for vaccine schedules for countries that introduce pneumococcal conjugate vaccine. I think a variety of different three-dose schedules would probably always be effective,” she said.
Herd Effects in Children and Adults

When enough of the susceptible population is vaccinated, transmission of disease can be reduced, thus protecting other members of the population, or “herd.” Epidemiologists have found strong evidence of such “herd immunity” from pneumococcal conjugate vaccine in the U.S., Whitney said.

In children, this evidence includes a drop in vaccine-type disease in children who are either too young or too old to have received pneumococcal conjugate vaccine: a 50% disease reduction in infants under two months of age (when the first dose is given) and a similar drop in children aged 5-17 years.

In adults ages 65 and older, disease rates have fallen from about 60 per 100,000 to about 45—a 34% decline—since vaccine introduction. For vaccine serotypes only, disease rates have fallen “a whopping 82%,” Whitney said. At the same time, nonvaccine type disease has gone up a relatively small amount, compared to the magnitude of the decline.

“Now isn’t that amazing that you can vaccinate children and reduce disease in older adults by almost 82%? I think this is a bigger effect than anyone would have predicted,” Whitney said.

Other Findings in the U.S.

Whitney reported on a number of other important findings based on the nearly 6 years of PCV7 use in the United States. Among them:

- **Impact on Adults Living with HIV:** A study by Dr. Brendan Flannery demonstrated that the childhood pneumococcal vaccine is extending protection to adults with HIV/AIDS. From 1999 and 2004, overall (all serotypes) invasive disease rates dropped by 37% in adults between 18 and 64 years of age who are living with HIV, including a 62% drop in disease caused by vaccine types. The drop in disease caused by vaccine serotypes was similar to the drop experienced by adults not infected with HIV. Unlike healthy adults, however, adults with HIV/AIDS had a 43% increase in disease caused by nonvaccine serotypes.

- **Replacement:** “There are 90 pneumococcal vaccine serotypes and this vaccine is taking away seven of them. Will some of the other ones take over?” Whitney asked. Post-licensure data show a large drop in vaccine-type disease in children under 2 years, from 160 cases per 100,000 children to 2 cases per 100,000. However, one nonvaccine serotype has countered this trend. Serotype 19A increased from five cases per 100,000 children at baseline, to 15 per 100,000 in 2005. “The magnitude of this replacement disease has been very small compared to the vaccine benefit,” Whitney emphasized.

- **Penicillin resistance:** The vaccine has greatly reduced the amount of penicillin-resistant S. pneumoniae. After having increased dramatically in the decade before the vaccine was introduced, the number of infections caused by penicillin-resistant strains has since plummeted. This is because serotypes that were most resistant were also included in the vaccine. “As predicted, you take those strains out of circulation with the vaccine, and we see this nice drop in resistant disease,” Whitney said.

In summary, Whitney said the widespread use of
Pneumococcal conjugate vaccine has led to large declines in invasive disease rates in young children, a herd benefit in unvaccinated children and adults, an indirect benefit to highly susceptible adults (particularly those living with HIV/AIDS), and fewer resistant infections. At the same time, but to a limited extent, replacement disease reduces benefit in some highly susceptible groups, such as those living with HIV/AIDS.

“The main question now is: How can we encourage introduction of conjugate vaccines in more places?” said Whitney.

**Vaccine-Type Invasive Disease in Children <5 Years**

**ABCs 1998–2005**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases/100,000 population</th>
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98% reduction

CDC unpublished data and MMWR Sep 16, 2005

**Herd Effect in Adults**

**Invasive Pneumococcal Disease Rates Over Time**

**ABCs, 1998-2005**

- 65+ years: -34%
- 40-64 years: -16%
- 18-39 years: -48%

2005 vs. baseline

Lexau et al. JAMA 2004 and unpublished data

The take home message today is that use of conjugate vaccine in children has been very effective for disease prevention in adults. And here are the data to show it.
**PCV Efficacy Against Invasive Disease and Pneumonia**

Dr. Lee Harrison, of the University of Pittsburgh, reported efficacy data from four clinical trials conducted in different settings. All data suggested that the introduction of pneumococcal conjugate vaccines will have a huge positive public health impact in both developed and developing countries.

The four trials took place in 1) Northern California in the United States; 2) among American Navajo and Apache Indians in the United States; 3) Soweto, South Africa; and 4) the Gambia. They evaluated the efficacy of PCV against IPD and pneumonia. Efficacy against IPD caused by vaccine serotypes ranged from 97% in the California trial, to 77% in both the American Indian and Gambian trials.

Among the most impressive findings was a 16% reduction in deaths caused by pneumococcus in the Gambia, as well as higher long-term efficacy against pneumococcal disease in HIV-infected children than in uninfected children in South Africa.

The U.S. trials used the 7-serotype vaccine, later known as Prevnar, while the South African and Gambian trials used CPV9 (Prevnar plus serotypes 1 and 5). The Northern California Kaiser Permanente trial ultimately served as the basis for licensure of PCV7 in the United States in 2000, “and it now is an integral part of our immunization schedule given at two, four and six months, with a booster at 12 to 15 months,” Harrison said.

The Northern California Kaiser Permanente trial vaccinated 38,000 infants with a three-dose schedule plus a booster. There were 39 vaccine-serotype cases in the control group, and one in the vaccinated group. The efficacy for IPD against vaccine serotypes was 97%, and against all serotypes was close to 90%. Efficacy for first radiographic pneumonia was a more modest 30%.

A breakdown by serotype showed that efficacy ranged from about 85% for 19F and 6B to 100% for four others (there were no serotype 4 cases, so efficacy could not be determined).

The American Indian trial was a group-randomized double-blind trial of PCV7 versus meningococcal C conjugate. It enrolled about 8,000 Navajo and White Mountain Apache children who were randomized into 38 different units, either in communities or combinations of communities. “The potential advantage of this design is that it measures the direct effects plus the indirect effect of herd immunity,” Harrison said.

The trial was stopped early, however, because of the U.S. licensure of Prevnar. Results, therefore, were based on a small sample size. They showed efficacy for IPD against vaccine serotypes of 77%, with a very wide confidence interval, Harrison said. Efficacy for all serotypes was about 54%.

The South-African trial, conducted by Dr. Keith Klugman, immunized nearly 20,000 infants with three doses, and no booster dose.

The study included both HIV-negative and HIV-positive children. The results: for HIV-negative children, the efficacy against IPD with vaccine serotypes was 85%, and against first radiographic pneumonia was 25%. In HIV-positive children, the efficacy against IPD

“Unexpectedly, long-term efficacy against all serotype disease was higher in the HIV-infected than the HIV-uninfected.”

—DR. LEE HARRISON
University of Pittsburgh, US
with vaccine serotypes was 65%, and against first radiographic pneumonia was 13%. In neither case was there a significant reduction in mortality.

A follow-up study looked at efficacy beyond the 2.3 years of the initial trial. Following children for 6.2 years, the study showed long-term efficacy against all-serotype IPD was 35% in HIV-negative children, and 46% in HIV-positive children, with efficacy waning much more quickly among the latter group.

“For me, unexpectedly, long-term efficacy against all serotype disease was higher in the HIV-infected than in the HIV-uninfected,” Harrison said. And, because of the huge increased risk of IPD in HIV positive children, the vaccine prevented a burden of invasive disease that was 59 times higher than that prevented in HIV-negative children. “This gives you a sense of the public health impact of the vaccine in HIV-positives,” he added.

The Gambian trial vaccinated more than 17,000 infants with three doses of vaccine, without a booster.

It found that immunization reduced mortality by 16%, with an absolute mortality reduction close to five deaths per 1,000 child years. “This suggests that future trials should look at mortality as an endpoint,” Harrison said.

The study found 37% efficacy against first radiographic pneumonia, 7% against clinical pneumonia, 77% against vaccine-serotype IPD, 50% against all-serotype IPD, and 15% against admissions to the hospital.

In conclusion, Harrison said, “Given the burden of pneumococcal disease in developing countries, the introduction of pneumococcal conjugate vaccines will have a huge positive public health impact.”

PCV Impact on Otitis Media

Dr. Ron Dagan, Professor of Pediatrics and Infectious Diseases at the Ben-Gurion University of the Negev in Beer-Sheva, Israel, summarized the impact of vaccination on otitis media (OM), an infection of the middle ear. OM is the most common bacterial infection in children under five for which antibiotic treatment is prescribed worldwide. In the United States alone, there are 24 million cases of otitis media every year.

Dagan addressed four questions about the vaccine: whether it would reduce the incidence of OM; whether it would reduce associated sequelae; whether it could be used therapeutically; and what impact it would have on antibiotic resistant cases of OM.

Does PCV Reduce Otitis Media or Just Alter its Bacteriology?

The answer is “both.” Some studies show that vaccination somewhat reduces the incidence of OM, according to Dagan. For example, a study in a daycare center showed that administering a 9-valent vaccine led to a 26% reduction in prescription for antibiotics to treat OM. United States data collected after the introduction of PCV7 showed that OM visits declined by 20% in children less than two years. He noted, however, that the downward trend in visits had begun before vaccine introduction, leaving open the question of causality. The question is whether the trend will persist.

But vaccination also modifies the bacteriology of OM. It not only changes the serotypes involved in OM, but also leads to an increasing proportion of OM cases caused by other pathogens, especially nontypable Haemophilus influenzae and Moraxella catarrhalis.

For example, four studies conducted in the U.S., Finland, and the Czech Republic showed an efficacy against vaccine-type strains of S. pneumoniae of between 56% and 67%. At the same time, in one of those studies, OM caused by nonvaccine serotypes, as well as by H. influenzae and M. catarrhalis increased, yielding a non-significant vaccine efficacy of just 6% against OM.

This phenomenon raises a new question: whether the planned 10-valent vaccine that will be conjugated with an outer protein of H. influenzae may even more effectively reduce OM. Indeed, initial tests show this may be the case, Dagan said.

Does Vaccination Reduce Antibiotic Resistance in OM?

Yes, said Dagan, but this reduction can be complicated by replacement with other nonvaccine serotypes, especially when antibiotics are used.

He noted that the current PCV7 vaccine includes the most resistant serotypes found in the U.S. and in many parts of the world. Preventing disease by those serotypes, therefore, also prevents drug-resistant disease. But continuing exposure to antibiotics may work against the effects of the vaccine, as seen in one
French study. It found that children who were vaccinated and did not receive antibiotics had less risk of carrying resistant pneumococci while experiencing OM than did children who were vaccinated and who did receive antibiotics.

The use of antibiotics, “in the presence of a little bit of replacement, may attenuate the whole effect of the vaccine,” Dagan said.

**Does the Vaccine Reduce Sequelae Associated with OM?**

Somewhat, according to Dagan. For instance, in California, vaccination was associated with a greater than 50% drop in the cases of children who sought treatment for OM in six or more clinic visits. “So it might be that early vaccination reduces complex otitis media,” Dagan said, and this could reduce the need for ear tubes. In both Finland and the United States, vaccination did, indeed, reduce the need to ventilate the ears by an impressive 40% and 20%, respectively.

**Does PCV Work as a Therapeutic Vaccine?**

No, said Dagan. Studies among children in Belgium and the Netherlands tested whether vaccinating children who already have recurrent OM would prevent its further recurrence. The result: “Children who received the vaccine have a little bit more, not a little bit less otitis media. So it is not a good idea to take a conjugate pneumococcal vaccine and give it to reduce cases in already established, recurrent otitis media.” Dagan cautioned that when people try to give the vaccine therapeutically, it may do more harm than good.

Dagan concluded by noting that PCV exhibits some efficacy against otitis media, but it is “definitely less impressive than what you get with invasive infection, pneumonia, and meningitis.” He said the evaluation, however, is complex and far from conclusive. Future studies are needed on the reduction of disease burden, the modification of pathogens causing OM, vaccine effects on antibiotic use and antibiotic resistance, and on the potential additional benefits of other pneumococcal vaccines such as the 10-valent.

**Discussion**

Questions were directed to Drs. Lee Harrison, Ron Dagan and Cynthia Whitney.

**Two or Three Doses**

**COMMENT:** Adriano Arguedas noted that the U.S. data regarding the two doses plus a booster method is similar to data collected from Hib vaccine trials in
Finland. He said it is very important data for Latin American countries where the main reason the vaccine is not used is the cost.

**RESPONSE:** Whitney said that there are also immunogenicity studies with pneumococcus suggesting that two doses in the first six months of life provide antibody levels that are nearly as good as three doses. “We now have the case control studies showing that the 2-plus-1 schedule is highly effective,” she said. That schedule was just introduced in the United Kingdom and is now being used in Quebec, Canada. Preliminary data show that their disease rates are plummeting.

**COMMENT:** Dagan voiced “a bit of a less super-optimistic view on this.” He explained that the dosage studies have measured impact on IPD, but the bigger burden of death in the world is from pneumococcal pneumonia, and the biggest associated burden of disease is OM. “And so a lower number of doses may give very good protection from invasive disease, but may also significantly lower protection for pneumococcal pneumonia,” he said. It may also alter the post-vaccination carriage rate and lower the impact of herd immunity. He suggested further investigation and caution regarding the 2-plus-1 vaccine schedule.

**Revaccination**

**QUESTION:** Telma Carvalhanas, Brazil, inquired about the panelists views of revaccination, especially among those older than 60.

**RESPONSE:** Whitney replied that there are not good data on how long the pneumococcal polysaccharide vaccine, the 23-valent vaccine, lasts. Some studies suggest that antibodies decline after approximately five to eight years, and if you revaccinate after about five years, antibodies go up again, but not as high as the first time. As a result, there is concern that immune tolerance may be developing. Revaccination in older adults, however, is being considered in the U.S.

**Serotype 1 in the U.S.**

**QUESTION:** De Oliveira asked about a report published on the increase of emphysema due to serotype 1 in the United States.

**RESPONSE:** Klugman replied that there is not a lot of evidence, although studies in HIV-infected kids are now looking at the impact of early retroviral therapy versus later therapy, and how this changes the response to the vaccine. In adults, evidence shows that the burden of pneumococcal disease has greatly decreased in the antiretroviral era, but still remains several-fold higher than in HIV-free comparable adults.

**Antibiotic Use, Vaccination, and Otitis Media**

**COMMENT:** Xavier Sáez-Llorens questioned whether the recent reduction in antibiotic use for OM is the result of reduced disease due to vaccination or to other factors, such as new clinical guidelines on antibiotic use, and the fact that OM caused by Haemophilus and Moraxella probably resolve spontaneously more frequently than does pneumococcus.
The development and licensing of the world’s first pneumococcal vaccine for children was a watershed moment for public health. But, according to presenters in this session, it was the beginning, not the end, of the fight against pneumococcus.

Industry is gearing up to fill the large and growing demand for a childhood pneumococcal vaccine. Multinational companies have some 25 vaccines in development, and emerging suppliers have about seven, according to Dr. Akira Homma.

Representatives of both multinational companies and emerging suppliers updated the Symposium on their vaccine development plans.

Even as new vaccines move through development, the scientific community is tracking another phenomenon, known as serotype replacement: the post-vaccination phenomenon of nonvaccine serotypes replacing vaccine serotypes in carriage and in disease. Dr. Ron Dagan summarized what is known about replacement related to pneumococcal vaccines, concluding that, “The overall benefit from vaccination exceeds by far any increase by replacement disease.”

**Serotype Replacement in Perspective**

Dr. Ron Dagan, of Ben-Gurion University, Beer-Sheva, Israel, began by acknowledging that “Serotype replacement is probably one of the most complex and problematic issues because we do not yet know everything, but we know a lot is going on.”

Dagan discussed serotype replacement in relationship to the overall effect of the vaccine in reducing disease, the possible effect of antibiotic use, and the natural changes occurring in serotype distribution.

He pointed to one study by the U.S. Centers for Disease Control and Prevention that showed a projected annual reduction of IPD in children under age 5 of more than 12,500 cases, compared to an increase of fewer than 1,000 cases due to nonvaccine serotypes.

Dagan said that while we know the net effect of the vaccine, we do not always know to what extent serotype replacement might be mitigating its impact. This is especially true for disease syndromes, such as pneumonia, in which the starting bacteriology is unknown. However, Dagan emphasized that we do know the vaccine’s overall impact is to reduce pneumonia. “We don’t know whether a reduction of 20% is actually reduction of 40%, with 20% replacement, or if it is no replacement at all,” he said.

Dagan reported that replacement definitely occurs in the carriage of pneumococcal serotypes, as well as in otitis media, in which there is significant replacement disease.

Replacement is possibly more of a problem in adults than in children, according to Dagan. Because children transmit replacement serotypes to adults, who may be more susceptible to them. In fact, replacement serotypes have been a problem for people living with HIV, particularly for women and African Americans with HIV, Dagan said.

**Replacement with Antibiotic-Resistant Serotypes**

Other studies have shown the rise in some antibiotic-resistant nonvaccine serotypes. However, “They tend to go up even before vaccination because they may have more virulence factors and they tend to be clonal,” Dagan said. He noted that this makes it more difficult to tease out the actual effects of vaccination. In addition, “vaccination does not mean that we reduce antibiotic use,” meaning that the predominant factor driving antibiotic resistance—use of antibiotics—is still in place.

In the case of serotype 19A, an antibiotic-resistant clone that rose threefold in the United States in the four years following vaccine introduction, Dagan
argued that “the vaccine may have played a role but antibiotics played another role.” In addition, multidrug resistant nonvaccine serotypes are increasing in regions in which the vaccine is not used. This includes a multidrug resistant 19A in Korea and a multidrug resistant 14 in Brazil and other parts of Latin America.

In conclusion, Dagan noted: “We have to understand that things occur with vaccination, and without vaccination...but don’t blame anything on the vaccine.” Saying that replacement is a real phenomenon, Dagan called on the need for more surveillance. “And so far, in my opinion, the overall benefit from vaccination exceeds by far any increase of disease replacement,” he said.

**Wyeth: Existing and Upcoming Vaccines**

“There is now a vaccine available, the 7-valent vaccine, which is effective against the most serious disease,” said Dr. Peter Paradiso, Vice President of Wyeth Vaccines. In addition, “The unanticipated, indirect effects of this vaccine add a dimension of value that we could not have anticipated.”

Wyeth’s vaccine is known as Prevnar in the United States, where it is now part of the universal childhood vaccination schedule. Known as Prevenar elsewhere, the vaccine has been launched in 73 different countries, with more than 125 million doses distributed.

Prevnar was designed to cover the most prevalent serotypes globally, and includes serotypes 4, 6B, 9V, 14, 19F, 18C and 23F. But the vaccine isn’t perfect, according to Paradiso. At the time of licensure, Paradiso said Wyeth had hoped the vaccine would provide cross-protection to other serogroups, particularly 6A and 19A. And, while researchers found that the vaccine afforded some cross-protection against 6A, it was not enough to generate herd immunity—and there was no cross-protection against 19A.

**Future Vaccines**

Wyeth is now focusing its pneumococcal vaccine development on a 13-valent candidate that builds Prevnar. Paradiso explained that one key to successfully expanding serotype coverage is to not negatively affect the serotypes that are already there. The 13-valent conjugate pneumococcal vaccine (13v PnC) contains the original seven serotypes, plus 6A, 7F, 3, 1, 5, and 19A. Serotypes 1 and 5 are important in many parts of the world, and 19A is responsible for an increased burden of disease in the United States since Prevnar’s introduction, Paradiso said.

Development and testing of 13v PnC faces another challenge: placebo-controlled trials cannot be conducted in most populations, especially for invasive disease, because an effective vaccine is already available. Therefore, Paradiso said that they will gauge efficacy through using a correlate of immunity specified by WHO guidelines, namely the proportion of infants achieving a concentration of

“Serotype replacement is probably one of the most complex and problematic issues because we do not yet know everything, but we know a lot is going on.”

—DR. RON DAGAN  
Ben-Gurion University, Israel
anticapsular antibody of 0.35 \( \text{g/mL} \) within one month of immunization.

Wyeth recently concluded a Phase II proof-of-concept trial for 13v PnC. “We demonstrated with more power than we had expected that this vaccine is going to be able to induce a good protective response to all 13 serotypes,” Paradiso said.

Wyeth is now conducting Phase III trials, working toward licensure, and building manufacturing facilities to accommodate the new serotypes.

**GlaxoSmithKline: Two-at-a-Blow**

William Hausdorff with GlaxoSmithKline (GSK) described the development of a vaccine that targets two major bacterial respiratory pathogens, *S. pneumoniae* and *H. influenzae*. He showed data indicating that *H. influenzae* represents 22-56% of bacterial AOM in several studies, including 34% in a Chilean study.

The vaccine, known as PHiD-CV (for Pneumococcal *Haemophilus influenzae* Protein D-Conjugate Vaccine) contains a conserved *H. influenzae* protein, which is a pathogenicity factor in otitis media and is immunogenic in humans. PHiD-CV contains the same seven pneumococcal serotypes found in Prevnar, as well as serotypes 1, 5, and 7F.

“In addition to accounting for quite a large number of cases of invasive disease, these serotypes have other very interesting properties, such as the ability to cause outbreaks of meningitis in Africa,” said Hausdorff. Serotypes 1, 5, and 7F are also prevalent in Latin America, representing from 17-32% of all IPD in children under six in Argentina, Brazil, Chile, Colombia, and Uruguay. Taken together, the 10 serogroups in the vaccine are responsible for approximately 85% of invasive pneumococcal disease in children worldwide.

The precursor to PHiD-CV was an 11-valent conjugate that also included serotype 3, and GSK tested this vaccine in a clinical trial dubbed POET—the Pneumococcal Otitis Media Efficacy Trial—conducted in the Czech Republic as a double-blind, randomized controlled study comparing the 11-valent conjugate vaccine with the control vaccine, Havrix (a vaccine for hepatitis A). Two years of surveillance tracked the occurrence of otitis media.

The results, published in *The Lancet*, showed efficacy of 58% against pneumococcal otitis media caused by the vaccine serotypes. All serotypes appeared efficacious, with the sole exception of serotype 3, which “was good for nothing,” and was therefore removed from the subsequent vaccine formulation. Efficacy against *Haemophilus*-caused otitis media was 35%. “At the end, the effect was 42% regarding all bacterial AOM cases,” Hausdorff said. However, he noted that the magnitude of the effect on all bacterial AOM would likely vary depending on the starting epidemiology. In Finland, for example, where *Moraxella* causes a good proportion of otitis media, the vaccine impact would be predicted to be lower, but still potentially prevent 28% of all bacterial AOM cases.

Thus far, more than 10,000 children have received the PHiD-CV vaccine or its precursor, the 11- valent vaccine. GSK anticipates licensure of this vaccine by the end of 2008 and plans to submit the vaccine for prequalification to WHO in 2008. In addition, GSK will carry out a double-blind, randomized efficacy trial for otitis media and pneumonia in 24,000 children in Argentina and Panama.

“We are currently in negotiations with international public health groups to ensure availability of the vaccine for all children in need,” he concluded.
sanofi pasteur: Protein Vaccine in Hand

Robert Hopfer, of sanofi pasteur, dedicated his talk to the memory of his friend and colleague, Jim Maleckar, who passed away suddenly in July 2006. Hopfer said that Jim had worked in the vaccine industry for more than 15 years, the last seven with sanofi pasteur at Swiftwater, where he was the leader of research and development for the pneumococcal and meningococcal product franchise. “We miss him very much, as does the entire pneumococcal vaccine community,” Hopfer said.

Sanofi pasteur currently produces a 23-valent pneumococcal polysaccharide vaccine for adults that is licensed in more than 70 countries, and is working on developing both conjugate vaccines and protein antigen vaccines, Hopfer said.

“The global demand for pneumococcal vaccine is unmet,” Hopfer said. “The huge overall demand for a pediatric vaccine will only be met by multiple suppliers.”

In the past, sanofi pasteur worked on an 11-valent pneumococcal polysaccharide vaccine, but its complex formulation coupled with low yields made industrialization unfeasible. Therefore, we are not pursuing further development of this vaccine,” Hopfer said.

Protein Antigen Vaccines

Hopfer emphasized the potential of protein antigen vaccines, and noted that the company is “at the threshold of starting a Phase I study” of one such vaccine. Such vaccines are based on highly conserved proteins that are common to most, if not all, pneumococcal serotypes. Hopfer said that sanofi pasteur is in the process of conducting a comprehensive evaluation of potential protein antigen candidates—of which there are more than 2,400.

A number of challenges exist for protein antigen vaccines, including the need to establish proof-of-concept for the approach, and to develop alternatives to efficacy trials, given that the current correlates of protection are based on glycoconjugate vaccines.

The company previously worked on a Pneumococcal Surface Protein A (PspA) candidate that went through Phase I clinical trials. PspA, a conserved surface protein, is a virulence factor that interferes with activation of complement within the immune system. While the trial showed that PspA was safe and immunogenic in adults, most individuals in the Phase 1 study demonstrated pre-existing anti-cardiac myosin antibody levels prior to vaccination, and some individuals who received the antigen developed an increase within 30 days post-vaccination. These responses were transient and there was no indication of clinical significance even after intense clinical and laboratory investigations. However, this experience prompted the company to pursue development of alternative pneumococcal protein antigens, Hopfer explained.

Sanofi pasteur aims to develop a multivalent protein vaccine that would protect against different stages of disease, provide greater serotype coverage than conjugate vaccines, require a less complex manufacturing process, and offer opportunities to explore synergy between polysaccharide antigens and additional pneumococcal protein antigens “and ultimately provide a long-term contribution to global reduction of pneumococcal disease,” Hopfer concluded.

“We are currently in negotiations with international public health groups to ensure availability of the vaccine for all children in need.”

—DR. WILLIAM HAUSDORFF
GlaxoSmithKline

Proceedings of the Second Regional Pneumococcal Symposium
Instituto Butantan: Zeroing in on Whole Cell Vaccine

Dr. Luciana Cerqueira, Director for Investigation and Development at Brazil’s Instituto Butantan, summarized the institute’s work on pneumococcal vaccine development. She noted that the studies at Instituto Butantan were catalyzed by PAHO and SIREVA, which began conducting surveillance of serotype prevalence in Latin America in 1993. The finding that serotype prevalence in Latin America differed from that in Europe and the United States catalyzed additional research into alternatives to the 7-valent vaccine, which covered only about 60% of the serotypes in Brazil, Cerqueira said.

Butantan initially worked on production of polysaccharide 23F in fermenters as part of a coordinated effort with other centers to develop a multivalent polysaccharide conjugate vaccine, but later concluded that such a vaccine process would be too complex. They soon began examining protein alternatives, especially two well-characterized surface-exposed proteins, and pneumolysin proteins. Butantan has since worked on development of recombinant protein vaccines, recombinant Lactobacillus vaccines, DNA vaccines, and conjugation of polysaccharide with PspA recombinant protein.

More recently, Dr. Richard Malley of Children’s Hospital Boston proposed that the Institute produce a whole cell pneumococcal vaccine under good manufacturing practices (GMP) conditions for clinical trials. Malley and Dr. Porter Anderson at the University of Rochester, New York, had found that a whole cell pneumococcal vaccine reduced carriage of pneumococcus and provided cell-mediated protection.

Butantan began work on the project, changing the culture medium and improving yield, Cerqueira said. They also developed an alternative adjuvant that succeeded in getting protection against intranasal challenge. Butantan has set up a fermentation laboratory and a GMP pilot plant for the project, with plans to start GMP production in 2007, Cerqueira reported. A Phase I clinical trial is planned for Sweden, followed by trials in Brazil and South Africa.

The project is now supported by the nongovernmental organization PATH, “so we should have the resources to take this project to completion,” she said. The intranasally administered whole cell vaccine is Butantan’s first priority. “If the whole cell vaccine works as well in humans as in mice...it would provide very cheap and broad ranging nonserotype specific protection,” she said.
Emerging Market Manufacturers: Their Rising Role

“The rich countries have already spoken, and now the developing countries will say something,” began Dr. Akira Homma, President of the Developing Country Vaccine Manufacturers Network (DCVMN).

Formally organized in July 2005, the DCVMN was formed to provide quality vaccines at affordable prices to the developing world, and to obtain recognition of the essential role of developing country vaccine producers in assuring the availability of vaccines to immunize every child, said Homma.

Homma highlighted the size of the potential pneumococcal vaccine market: an annual 43 million doses in high-income countries; 131 million doses in middle-income countries; and 178 million doses in low-income countries, for a total global market of 352 million doses worth US$5.3 billion annually. This leaves a current production capacity deficit of some 250 million doses, Homma said. But whereas multinational companies have some 25 vaccines in development, emerging suppliers have only about 7 in development and are 6 to 10 years from reaching the market, he said.

Full membership in DCVMN requires WHO prequalification. The DCVMN member list now includes seven laboratories, with another five associate members who are in the process of prequalification. (See box of DCVM members.)

DCVMN members are approaching pneumococcal vaccine development from a variety of perspectives and technologies, Homma said. These include development of a polysaccharide vaccine by Bio-Manguinhos/Fiocruz, a nonencapsulated vaccine by Indian Immunobiologics, a regional approach to vaccine serotypes by BioVac Institute, and a possible protein technology by Shanta Biotechnics Ltd.

Insufficient funding remains a major issue for vaccine development by DCVMN members. And, Homma pointed out that while DCVMN members now provide 80% of the vaccines needed to supply

### DCVMN Members

| 1. Bharat Biotech | 10. Institut Pasteur, Senegal* |
| 2. Biological E | 11. Kangtai |
| 5. Birmex | 14. Razi Institute |
| 6. Butantan | 15. Serum Institute of India* |
| 7. Chengdu Institute of Biological Products | 16. Shantha Biotech* |
| 8. CIGB* | 17. VACSERA |
| | 19. LG Lifesciences* |

* WHO Pre-qualified full members.
“The price will only come down when new manufacturers enter into the market and equilibrate demand and supply.”

—DR. AKIRA HOMMA
Developing Country Vaccine Manufacturers Network

UNICEF and PAHO’s Revolving Fund, “We don’t have 80% of the money, because all of these vaccines have a low price, very few pennies...and are not new vaccines with high-aggregate values.”

Finally, Homma challenged the idea that the main reason for delay in getting new vaccines to developing countries (23 years in the case of HepB) is that the price of a vaccine must remain high in its early stages of marketing for the manufacturer to earn its cost of research and development. Rather, Homma said, “The price will only come down when new manufacturers enter into the market and equilibrate demand and supply. Then the price will come down and we will make it possible for all the countries to benefit from pneumococcal vaccines.”

Discussion

The Ethics of Trials for New Pneumococcal Vaccines

**QUESTION:** A participant asked GSK’s Hausdorff about the ethics of conducting a placebo-controlled trial in Panama and Argentina when a vaccine is already available.

**RESPONSE:** Hausdorff said that the study, designed in collaboration with public health officials in the region, will aim to understand the magnitude of the impact on pneumonia of a conjugate pneumococcal vaccine with a global formulation in Latin America. “We have data from sub-Saharan Africa and from the United States, but the lack of data from Latin America is helping to slow down introduction of conjugate pneumococcal vaccines. That is the question that we were asked by Latin American public health officials and that we want to be able to answer.”

Co-investigator Dr. Xavier Sáez-Llorens added that the inclusion of a placebo group is “not only ethical, but is also key for several reasons.” He pointed out that the vaccine differs from others now on the market because, in addition to pneumococcus, it introduces potential protection against nontypeable Haemophilus. Additionally, he said that the Government of Panama is not considering the public-sector introduction of Prevnar in the upcoming years because it considers rotavirus and hepatitis to be higher vaccine priorities. Finally, he said that the study is designed only to evaluate prevention of otitis media and pneumonia, not invasive disease, which is the principal target of Prevnar.

**Which Proteins?**

**QUESTION:** Another participant asked sanofi pasteur’s Hopfer which proteins are being used in the vaccine about to enter Phase I clinical trial.

Hopfer declined to answer.

**Why Not a 23-Valent PCV?**

**QUESTION:** Klugman noted that there is accumulating evidence that conjugate vaccines in the elderly may offer some advantage over the polysaccharide vaccine. He asked, therefore, why Wyeth wasn’t thinking in terms of a 23-valent conjugate or a 20-valent conjugate.
RESPONSE: Rather than develop a 23-valent conjugate, Paradiso said Wyeth might think in terms of formulating vaccines targeted regionally or for an adult population, including a possible 13-valent vaccine for adults. He noted that studies with Prevnar in adults over 70 have already shown good results. Regarding infant vaccines, “We cannot take every vaccine through the kind of clinical trials we are going through with 13-valent,” he said. Therefore, they would need to develop a consensus with regulatory authorities on how to streamline the regulatory process.

What Do Suppliers Want from the Public Sector?

QUESTION: Orin Levine asked, “If the public sector were Santa Claus and the private sector had a wish list of what it wants from us in order to help spur that collaborative action to get pneumococcal vaccines out, what would that short wish list be?”

RESPONSE: Paradiso said that he would want to know how much vaccines the public sector needs and when. “We are interested in supplying the vaccine. We need to understand what the demand will be beyond 2010 so that we can build for that demand. We have the knowledge and the capacity, but if we are going to build it we have to know somebody is going to be there to use it in the end.”

RESPONSE: Hopfer said they would like to know the epidemiological data and surveillance data from countries where the number of isolates has been low, to help define a formulation that will truly be global for a very long term.
Opportunities and Challenges for PCV Introductions

It is widely acknowledged that the new conjugate vaccines, including those for pneumococcus, will be more expensive than the older vaccines that were simpler to develop and manufacture. Decisions about introducing the new vaccines therefore depend, in part, on an assessment of their "cost-effectiveness" compared to other health interventions. “Cost-effective” interventions provide a health benefit but cost, rather than save, money.

Economists and epidemiologists around the world are therefore conducting cost-effectiveness studies on PCVs. This session reported on such studies in some of the worlds’ wealthiest and poorest nations, as well as in the transitional economies of Latin America. In most cases, the results pointed toward a vaccine that was cost-effective to highly cost-effective.

Significantly, when the vaccine’s herd effect was considered in the wealthiest nations, the conjugate pneumococcal vaccines were catapulted into the highly cost-effective category. In the United States, for example, incorporating herd effects drops the cost-per-life-year-saved from US$80,000 to US$7,500, according to Mr. Tom Ray, a health services analyst with Kaiser Permanente.

The studies used similar approaches to determine cost-effectiveness. They estimated the costs and benefits of the vaccine, and translated this into a common measure: the number of disability-adjusted life years or DALYs averted, and the cost per DALY averted.

According to WHO thresholds, highly cost-effective interventions have a per DALY cost of no more than one times the per capita GNI; cost-effective interventions have a per DALY cost of between one to three times the GNI; and more costly interventions are not cost-effective.

Elements comprising vaccine cost typically included the price of the vaccine itself, the number of

![](Cost Effectiveness of PCV7.png)

G. Thomas Ray PIDJ 2006
“If the experience in the United States is any indication, then the herd effect could have a significant impact on the cost-effectiveness of PCV in other countries.”

—MR. TOM RAY
Kaiser Permanente, US

doses, and the administration costs. Offsetting these were medical savings derived from the cases of pneumococcal disease prevented and nonmedical savings, mainly based on the prevention of lost work time by parents. As seen in Dr. David Bloom’s earlier presentation, this was a very conservative measure of nonmedical savings.

Following the cost-effectiveness presentations, speakers gave three perspectives on vaccine financing, those of the World Bank, the PneumoADIP, and PAHO.

Cost-Effectiveness in High-Income Countries

“Conjugate pneumococcal vaccine is a very expensive vaccine compared to other routinely used infant vaccines, and the question is, ‘Is it worth it?’” began Tom Ray, a health services analyst with Kaiser Permanente.

To answer the question, Ray reviewed fourteen cost-effectiveness studies conducted in high-income countries in Australia, Europe, and the United States.

Results

The studies estimated the number of cases of disease and hospitalizations that would be prevented per 1,000 children vaccinated. A study conducted in Germany estimated that 600 cases of otitis media and 60 cases of pneumonia would be prevented, whereas another study conducted in Norway estimated that fewer than 50 cases of otitis media and fewer than 5 cases of pneumonia would be prevented through the vaccine. Based on all 14 studies, 4.5 deaths could be prevented for every 100,000 children vaccinated.

An estimate of the savings associated with vaccination showed that about 53% were related to savings in medical costs, and about 47% were in nonmedical costs. “So in these high-income countries, non-medical costs have a significant impact on cost-effectiveness,” Ray said.

In most of the studies, the cost-per-life-year-saved ranged from US$30,000 to US$160,000. In general, Ray noted that in high income countries, health interventions that cost less than US$50,000 per-life-year-saved are considered cost-effective; between US$50,000-US$100,000 are borderline; and over US$100,000 are not very cost-effective.

The Herd Effect

In the U.S. study, the incorporation of herd effects dropped the cost-per-life-year-saved from US$86,000 to US$7,500. Another U.S. study showed that in persons older than 65, the rates of invasive pneumococcal disease dropped 30-35% after PCV introduction in children. In fact, “Most of the cases of invasive disease that were prevented by the vaccine were actually in non-vaccinated people,” he said.

“If the experience in the United States is any indication, then the herd effect could have a significant impact on the cost-effectiveness of PCV in other countries,” Ray said. He cautioned, however, that a number of factors could affect the impact of the herd effect. For example, an altered vaccine schedule or the vaccine’s coverage rate could make a difference. The U.S. results reflected a 70% coverage rate in children. “If only 30% of the children are vaccinated, there will be less of a herd effect,” he pointed out.
“As we vary vaccine dose costs and vaccine efficacy in this analysis, it is hard to make this vaccine not look highly cost-effective,”

—DR. ANUSHUA SINHA
New Jersey Medical School, US

Cost-Effectiveness in the World’s Poorest Countries

Dr. Anushua Sinha, Assistant Professor of Preventive Medicine and Community Health, UMDNJ — New Jersey Medical School, USA reviewed a study of the cost-effectiveness of PCV in 72 GAVI-eligible countries, in which per capita income is under $1,000.

“We pooled results in terms of cost of vaccination, disease costs and health benefits gained across 72 countries,” Sinha explained. The study considered costs to the health system, to families, and to members of society.

In terms of costs, Sinha said that the model assumed a vaccine cost of US$5 per dose, based both on price projection, but also on the assumption that public market funding in GAVI-eligible countries would be very different from the current private market price US$53 per dose, Sinha said. The study based its assumption of vaccine efficacy on the results of a clinical trial in The Gambia of the 9-valent vaccine.

Results

The study found that vaccination in the 72 countries would save from 262,000 to 470,000 lives per year, with the larger number factoring in a strong herd effect. Vaccination would avert from 8.3 million to 15 million disability-adjusted life years; and the cost per DALY averted would range from $22 to $100 (in international dollars). This is less than one times the countries’ average GNI of $450, making the vaccine highly cost-effective based on WHO standards, Sinha said.

The model considered vaccine prices from $1 to $10 per dose. “As we vary vaccine dose costs and vaccine efficacy in this analysis, it is hard to make this vaccine not look highly cost-effective,” Sinha said.

Economic Burden of Pneumococcal Disease in Latin America and the Caribbean

Dr. Dagna Constenla, independent consultant, summarized the findings of the cost-of-burden analysis from the new report on PCV in Latin America and the Caribbean. (See Session II for related findings regarding the burden of pneumococcal disease in Latin America).

Findings on the economic burden of pneumococcal disease were based primarily on data from 10 countries: Argentina, Brazil, Chile, Colombia, the Dominican Republic, Honduras, Mexico, Panama, Uruguay, and Venezuela.

In conducting the study, the researchers estimated the costs incurred for a variety of medical services. For instance, the cost of pneumococcal disease ranged from $82 per patient for a case of acute otitis media to $1,792 to provide inpatient care to a child with pneumococcal meningitis. The study estimated the total economic burden of pneumococcus by multiplying the number of expected disease events by the mean cost per event.

The study found that pneumococcal disease incurs a cost of $333.4 million in the 10 countries, or the equivalent to US$28 per child born in the region by age five. It includes US$293 in direct medical costs.
Out-of-pocket expenses for families add another US$40 million in costs. When translated into disability-adjusted life years lost, the annual cost of pneumococcal disease in the region is more than 600,000 DALYs.

Cost-Effectiveness of CPV in Latin America and the Caribbean

Dr. Juan Esteban Valencia, Health Economist and Professor, CES University in Medellín, Colombia, summarized the findings of the cost-effectiveness analysis. The study weighed the costs of the disease against the potential benefits of vaccination, determined on the basis of vaccine efficacy. It found that region-wide vaccination with PCV7 would prevent:

- 9,478 child deaths, or 53% of deaths due to \(S.\ pneumoniae\);
- 680,000 cases of acute otitis media;
- 176,000 cases of clinical and chest X-ray positive pneumonia;
- 2,768 cases of invasive pneumococcal disease.

From an economic standpoint, this would save US$180 million, and avert 321,876 DALYs annually, Valencia said.

They next factored in the cost of the vaccine, assuming three-doses per child. At US$53 per dose (the price paid by the Revolving Fund), the total regional direct cost of the vaccine was $1.83 billion. They calculated the vaccine cost at various prices, the lowest being $5 per dose. At this price, the regional direct cost of vaccine came to US$200 million.

The cost per DALY averted ranged from US$5,106 with a vaccine price of US$53 per dose, to US$62 per DALY with a vaccine price of US$5 per dose, Valencia reported. The cost per life saved would range from a high of US$171,130 to a low of US$2,110.

Based on a standard formula for cost-effectiveness, Valencia concluded that the vaccine would be considered cost-effective. And, as the price of the vaccine drops, its cost-effectiveness increases, because the value of the DALY drops in kind.

Valencia noted that neither the herd effect nor a loss in quality of life resulting from disease were included in the analysis, making it a conservative estimate of cost-effectiveness.

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<th>Cases of Pneumococcal Disease</th>
<th>Total Events Annually</th>
<th>Number of Events Annually/1,000 Children</th>
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<tr>
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Vaccine Financing Perspectives

Representatives of the World Bank, the PneumoADIP and PAHO each presented their organization’s views regarding financing of conjugate pneumococcal vaccines. Major themes revolved around the need for countries to create “fiscal space” for vaccine purchases, as well as the importance of developing sustainable financing mechanisms that enhance equity within countries.

World Bank Perspective on Vaccine Financing

Santiago Cornejo of the World Bank outlined three things needed to help mobilize resources for the new, more expensive vaccines coming available:

- Countries need to create “fiscal space”;  
- The public health community needs to show the evidence that will lay the basis to prioritize spending on vaccines, and;  
- Communications must be tailored to reach the national decision makers.

While the World Bank is a decentralized institution, with no single policy, Cornejo said that it is a strong supporter of immunization. “We believe immunization is a cornerstone of health systems and we often use the immunization coverage rate as an indicator of performance on our disbursements. So that shows how relevant we think it,” he said.

The World Bank lends support to vaccines in situations of crisis management and provides time-limited support, such as loans for polio vaccines for disease eradication, Cornejo said. However, it tends not to extend many loans for ongoing vaccination programs, as that is not a sustainable way to finance the recurring costs of such programs. “If you are going to take a loan with high interest in order to finance your vaccine you should be very careful,” he said.

The Bank has helped design innovative mechanisms to finance new vaccines on a global level. These include Advance Market Commitments (or AMCs) and IDA “buy-downs.” As an example of the latter, an initial loan with high interest rates given for polio immunization could be converted to an IDA—a loan with better interest and repayment terms.

Conclusions of Cost-Effectiveness of a Pneumococcal Vaccine

<table>
<thead>
<tr>
<th>US$/DALY</th>
<th>GDP L. A. US$/4,404</th>
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<tbody>
<tr>
<td>US$/5</td>
<td>581</td>
</tr>
<tr>
<td>US$/10</td>
<td>1,619</td>
</tr>
<tr>
<td>US$/20</td>
<td>3,691</td>
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<tr>
<td>US$/40</td>
<td>&lt; per capita GDP</td>
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Cost – Effectiveness ratio (US$/DALY) less 1 per capita GDP is Highly Cost effective (WHO Report 2002).
terms—if the country reaches certain performance levels, Cornejo said. Donors can also help pay off the debt.

Affordability and Sustainability. Cornejo stressed the importance of affordability and sustainability. “In order to be affordable, the price will need to be decreased. But, we need to realize that most of these new vaccines are going to be more expensive than the traditional vaccines,” he said.

Two other issues affect affordability and sustainability, according to Cornejo. First is the fact that many countries will be considering the introduction of more than one higher-priced new vaccine. These include vaccines for pneumococcus, rotavirus and HPV.

Secondly, vaccine price is just one aspect of the total cost of vaccine introduction. “Nonvaccine costs can be extremely high, for example the impact of rotavirus on cold chain,” he said.

Create Fiscal Space. Cornejo said that new resources for vaccine introduction could be mobilized by either obtaining new donor financing or creating “fiscal space” in national budgets. Cornejo noted a number of options that create fiscal space: 1) redirecting resources, for instance by reducing defense spending or freeing up funds from other health interventions; 2) reducing wastage in existing programs; and 3) enacting new earmarked taxes.

“But whatever mechanism we use to finance immunization, for the Bank it is an issue of equity,” Cornejo said. “We must make sure that those with lower resources within the country have the ability to access these new vaccines.”

Provide Evidence and Communicate with Decision makers. Cornejo noted that advocacy for pneumococcal vaccines at the global level is well ahead of advocacy at the country level, especially in comparison to HIV/AIDS and malaria. Cornejo said that the difficulty is due, in part, “to our success” with immunization, especially in Latin America where coverage rates are high; the disease burden is low, and cheap vaccines are available.

“So we have been on a kind of cruise-control mode,” he said. “But now we are living in a brand-new era that will require mobilization of more and new resources for vaccines. Therefore, it is very important that we improve our advocacy message in order to mobilize these resources for vaccines.”

To do this, he urged the development of tailored, country-specific advocacy plans, with messages tailored for people that do not have a background in immunization. He also stressed the importance of finding champions outside the immunization arena who could effectively communicate the issue.

The GAVI Investment Case for Pneumococcal Vaccine

Dr. Orin Levine, Executive Director of GAVI’s PneumoADIP, described the ADIP, the work of the GAVI Alliance, and the recently approved global “Investment Case” for pneumococcal vaccine presented to GAVI. “About one in 10 child deaths is due to pneumococcal disease,” Levine said. “But a challenge we have faced is that many people did not recognize pneumococcal disease, in part because of the difficulty of diagnosis.”

“It is very important that we improve our advocacy message in order to mobilize these resources for vaccines.”

—MR. SANTIAGO CORNEJO
the World Bank

Proceedings of the Second Regional Pneumococcal Symposium
“The whole idea is to use evidence to generate the political will to appropriately prioritize disease prevention and vaccine introduction.”

—DR. ORIN LEVINE
GAVI’s PneumoADIP

PneumoADIP: Finding Pneumo. The mission of GAVI’s PneumoADIP is to improve child health and survival by accelerating the evaluation of and access to new life-saving pneumococcal vaccines for the world’s children. Created in 2003 with an award to Johns Hopkins University of US$30 million, the PneumoADIP is organized around three main areas: establishing the value of the vaccine; communicating its value; and delivering that value. It supports activities in more than 56 countries, and is helping to re-energize the SIREVA network in Latin America, Levine said.

“The whole idea is to use evidence to generate the political will to appropriately prioritize disease prevention and vaccine introduction,” Levine said. “All of our work is designed to try to ensure a reliable supply of affordable vaccine and ensure financing.”

He stressed that reaching the Millennium Development Goal #4 of improving child survival requires pneumonia prevention, and pneumococcal disease is an especially important target.

The GAVI Alliance. PneumoADIP is a program supported by the GAVI Alliance, which includes the major international institutions involved in global health such as the World Bank, WHO and UNICEF. It also includes public and private sector donors, bilateral donors from industrialized country governments, the Bill and Melinda Gates Foundation, and manufacturers based in both industrialized and developing countries.

“The GAVI Alliance comes together to agree on a common set of objectives and they have collectively been able to mobilize financial resources,” Levine said. “Between 2006 and 2015, they have 10 year commitments for the 72 GAVI countries on the order of US$6 billion...and that is definitely a major improvement over what we have had in the past.”

Global Investment Case for PCV. To maximize the impact of these resources, the GAVI Alliance utilizes “investment cases” that argue for the financing of different new vaccines. The PneumoADIP recently presented an investment case for PCV to the GAVI Board.

“Its objective is, quite simply, to accelerate pneumococcal vaccine use in the world’s 72 poorest countries by 15 years over historical precedence. In the process, we estimate that we will prevent 3.9 million child deaths by 2025,” Levine said.

The investment case emphasized that widescale prevention of pneumococcal disease in GAVI countries would translate into almost a 10% reduction in all mortality in children under five.

In addition, “Pneumococcal disease is a problem that is getting worse, not better,” Levine said. “HIV increases the risk of pneumococcal disease by 20-40 fold. Antibiotic resistance complicates treatment and pneumococcal pneumonia is a common partner of pandemic influenza—it would add on the order of almost half a million deaths in children should a pandemic hit GAVI countries.”

The investment case also stressed that the time was right for financing PCV: its safety, efficacy and cost-effectiveness has been established, and current and upcoming vaccine formulations would provide an adequate supply to GAVI countries through 2011. In addition, investment now would contribute over
time to the development of sustainable and affordable pricing.

Costs to GAVI for both the vaccine and strategic and technical costs were forecast to be between US$127-189 million between 2007 and 2010, and an additional US$440-951 million between 2011 and 2015. Country co-financing would contribute additional funds, totaling perhaps US$21-31 million dollars from 2007-2015.

The pneumococcal vaccine investment case was made in tandem with a similar case for accelerating rotavirus vaccination, and a requested grant of US$200 million to support price negotiations and the strategic and technical activities needed for rollout.

The GAVI Board approved all three. “We have taken an historic step to shorten the time lag that we have always had with new vaccines,” Dr. Levine said.

**PAHO Perspective**

“This is a new era of immunization,” said Dr. Jon Andrus of the Pan American Health Organization (PAHO). “There are new vaccines, new targets, new supply paradigms, new challenges... We can use the success of the Revolving Fund ...to make a difference in the Americas with pneumococcal disease.”

**Optimizing Use of the Revolving Fund.**

Underpinning past advances in disease reduction throughout much of the Americas has been PAHO’s Revolving Fund, which bulk purchases vaccines on behalf of countries. PAHO has tallied up successes in fighting disease: the eradication of polio, reduction of *Haemophilus influenzae b*, measles elimination, and near-elimination of rubella.

Both capitalization of the Fund and expenditures have increased over time, and dramatically so since the introduction of MMR vaccine in 1997. Today, the Revolving Fund delivers 14 antigens on a routine basis, and 37 countries in the Americas use the Fund, with only a handful of exceptions, including Canada, the U.S., Chile, and Mexico.

Key to these successes has been:

- Country-based interagency coordinating committees,
- A policy of rapid deployment of vaccine to susceptible populations,
- Assured supply and work with a diversity of suppliers,
- National immunization managers overlooking their country’s plan of action, and,
- Budget line items for vaccination.

In the Americas, 26 countries have laws regarding vaccination, with proposed legislation in another three. Andrus noted that a line item in the national budget for vaccine purchase has been essential. But, counterintuitively, laws that prohibit import taxes on vaccines can indirectly increase the vaccine cost by up to one-third by cutting off the revenue stream provided by import taxes.

The Revolving Fund’s ability to negotiate a uniform price has also been critical to past successes. Andrus said that uniform pricing of a vaccine has allowed the development of health equity, low transaction costs, and rapid deployment.

Today, however, many countries have recognized that continued improvement in public health and achievement of the Millennium Development Goals (MDGs) will require introduction of pneumococcal and rotavirus vaccines.

Andrus identified two challenges in making the new vaccines affordable: the Revolving Fund’s ability

**PAHO has tallied up successes in fighting disease:**

the eradication of polio, reduction of *Haemophilus influenzae b*, measles elimination, and near-elimination of rubella.
to negotiate an affordable price and the ability of countries to create the necessary fiscal space and improved vaccine laws that will ensure sustainability.

**Creating Fiscal Space.** PAHO is working on the supply side to create fiscal space, Andrus said. The organization is critically reviewing its management of the Revolving Fund. “We think we can reduce costs, make more efficient use of resources, and improve the service to countries,” Andrus said. It is working to assure supply chain efficiency from the costs of vaccine acquisition to the costs of supply processing, inventory, and distribution. “At each link, we can analyze where we at PAHO can improve services to the countries,” Andrus said.

At the same time, an independent assessment of the Fund’s work determined that 60% of the problems in efficiency are at the country level. “For example, if a vaccine stays at a central supply and is not picked up, costs are incurred. We need to work more closely with the countries in tackling the challenges that would reduce costs,” he said.

**Defining the Vision.** In September 2006, PAHO’s Directing Council, composed of all the ministers of health from the Latin American and Caribbean countries, issued a resolution that articulated three principles for immunization:

- Sustaining the development of national immunization programs in the context of the overall health objectives, and accelerating the uptake of priority new vaccines;
- Closing equity gaps and contributing to the achievement of the MDGs and the goals of the WHO’s Global Immunization Vision and Strategy;
- Continuing to build health systems and infrastructure within the Americas.

To realize the vision, PAHO is strengthening operational preparedness and national capacities for decision making. It is working with countries to revitalize national plans of action for immunization, which are especially important now that multiple new vaccines are becoming available. One planning tool is Pro-Vac, a PAHO initiative that combines economic analysis, disease surveillance, and epidemiological studies. Strongly evidence-based, it provides programs, expertise and training to guide decision-making.

To enhance sustainability of its immunization programs, PAHO is also transitioning from a childhood immunization program to a family immunization program in order to enable the delivery of vaccines for influenza, HPV and HIV when they become available. “We are moving from sustainability of just vaccines to the sustainability of the overall immunization program that can reach out and deliver more services to more people,” Andrus emphasized.

“This is a new era of immunization. There are new vaccines, new targets, new supply paradigms, new challenges... We can use the success of the Revolving Fund ... to make a difference in the Americas with pneumococcal disease.”

— DR. JON ANDRUS
Pan American Health Organization
Public health officials described the pneumococcal burden of disease and vaccination programs in three Latin American countries: Brazil, Mexico and Chile. Although none of the three has universal vaccination with PCV, Mexico initiated a vaccination campaign in nine Mexican states in 2006, with plans to continue to expand that program; Brazil has a program to vaccinate high-risk children; and Chilean researchers are documenting the epidemiologic evidence needed by decision makers. Chile’s Dr. Rosanna Lagos said the data will lead to the inevitable conclusion that the “7-valent vaccine currently available should be implemented immediately in children with higher-risk conditions.”

All three country representatives noted both the opportunities represented by conjugate pneumococcal vaccine to control disease and the economic challenges of expanding the universal vaccination schedule.

Lagos noted the ethical urgency of addressing the situation in which wealthier citizens can buy vaccines that are not yet available to the majority of the population. She noted that countries in transition face particular challenges in resolving this dilemma. “In the developed world, we know that these diseases impose an important economic burden and that mobilizes decisions for the use of vaccines,” she said. And in the poorest countries, immediate introduction is motivated by the urgent need to save many lives. However, Lagos said that although the childhood mortality rate in countries like Chile is comparable to the United States, “We don’t have the resources that would allow us to easily disburse funds in long-term immunization programs.” For instance, immunizing all Chilean infants against pneumococcus would cost the same as current State spending per capita on health.

Brazil

Dr. Expedito Luna, Director of the Surveillance and Infectious Disease Control program at the Ministry of Health in Brazil, noted that the country’s public health system serves 80% of the population, while the remaining 20% use private providers. This system has had marked success in vaccination. As noted later by Dr. Luna, Brazil has wide immunization coverage delivered through over 100 vaccination facilities countrywide. The coverage for polio and measles immunization is close to 100%. Most recently, the oral rotavirus vaccine was introduced in the universal vaccination program. Brazil works not only on childhood vaccination, but also on vaccine schedules for adolescents, adults, and the indigenous population. Overall, there is high vaccine coverage and historically low levels of vaccine-preventable disease.

This success has enabled the strong promotion of vaccination in Brazil’s health funding: the vaccine budget has increased nine times in the past decade, to a 2006 level of $350 million U.S. dollars, Luna said.

Burden of Disease

Brazil does not currently have a national system for tracking pneumococcal disease. However, there are several other forms of surveillance that “give us some clues on the behavior of these diseases here in our country,” said Luna. These include: epidemiological surveillance on meningitis conducted in Brazil since 1975; a good record of hospitalizations in the public health system; a national mortality information system; and Brazil’s participation in SIREVA.

Data from 2005 shows that all-cause pneumonia was the second leading reason for hospitalizations (behind childbirth). It accounted for almost 10% of hospitalizations, and constituted the primary cause of hospitalizations in the elderly and those ages one to four.

Meningitis surveillance shows that pneumococcal meningitis infections have remained relatively constant in Brazil since 1998, while “meningitis due to Haemophilus influenzae practically disappeared upon the introduction of the vaccine in 1999,” notes Luna.
**Surveillance**

One of Brazil’s goals is to enhance the detection of *S. pneumoniae* isolates; at present, the public health laboratories only detect between 300 and 350 isolates per year. Therefore, Brazil plans to implement a surveillance system, as part of a PAHO network, for X-ray confirmed bacterial pneumonia in children under age five and adults over age 60.

The new surveillance system, which may begin operating in 2007, will be implemented in five of the 27 Brazilian states, with each state representing one of the five geographic regions of Brazil, stretching from the Amazon to the south. In Parana, a state with 10 million inhabitants and a highly organized health network, there will be an additional population study as part of SIREVA II.

**Status of Vaccination for Pneumococcus**

At present, there is no universal pneumococcal vaccination in Brazil. However, since 1999, there has been an annual campaign to vaccinate the institutionalized elderly with the 23-valent vaccine. And since 2002, the national network of Reference Centers for Special Immunobiologicals has offered PCV7 only to at-risk children.

In 2005, Brazil purchased 291,000 doses of both vaccines at a cost of approximately 55 million US dollars. But less than 10% of the elderly have been vaccinated, and, regarding high-risk children, the coverage remains low as well. “The current price per dose of more than $50 US dollars,” says Luna, “prevents our country from taking a leap to introduce the vaccine in our routine program for universal vaccination.” Universal pneumococcal vaccination of the 3,200,000 children born each year in Brazil would require more than doubling the national budget for vaccines.

Brazil’s strategy, therefore, is to develop national production of the vaccine, with production initiatives currently ongoing at the Instituto Butantan and at Fiocruz in Rio de Janeiro. Luna concludes, “We hope that these initiatives have good sustainability and that this also leads all international producers to reduce prices.”

**Mexico**

Dr. Norma Matias, of the National Center for the Health of Infants and Adolescents, discussed the introduction of the conjugated 7-valent pneumococcal vaccine in Mexico.

**Burden of Disease and Surveillance**

How heavy is the pneumococcal disease burden in Mexico? One study in 32 daycare centers in two Mexican states showed that 30% of 2,777 children under the age of seven were colonized by pneumococcus. The most frequent serotypes were 19F, 6B, 6A, 23F and 11A. Some 56% of the isolated serotypes are included in the 7-valent vaccine. Another study at Children’s Hospital showed that of hospitalizations for invasive pneumococcal disease, 62.5% of the serotypes were penicillin-resistant, with 23F, 19F and 14 being the most frequently-resistant serotypes.

Now, one of Mexico’s most important objectives is to improve current epidemiological surveillance in order to better assess the vaccine’s impact, Matias...
“Given the vaccine cost, it was not going to be possible to vaccinate every child universally. As part of the strategy to introduce the vaccine to susceptible children, we had to define the population that was going to benefit most.”

—DR. NORMA MATIAS
National Center for the Health of Infants and Adolescents, Mexico

says. The National Center for the Health of Infants and Adolescents is working with Boston University on this objective. The researchers plan to measure the immunobiological response to three doses of the vaccine in Mexican children, and they will track any changes in serotypes and antimicrobial resistance.

**Status of Vaccination for Pneumococcus**

“Given the vaccine cost, it was not going to be possible to vaccinate every child universally,” said Matias. “As part of the strategy to introduce the vaccine to susceptible children, we had to define the population that was going to benefit most.” In determining which children should get the vaccine, researchers looked at which Mexican states had the highest incidence of death from lower respiratory infections, the greatest poverty, the highest percentage of indigenous population, and the lowest rate of economic growth.

The first vaccination campaign took place during the first National Health Week in February of 2006, in a total of 41,143 children under the age of two years, in nine Mexican states. In August of that year, the campaign broadened to 228,777 children in 14 states. In 2007, Mexico expects to vaccinate 326,506 children against pneumococcal disease. Children receive three doses: at two months, four months and 12 months. Children over the age of one year receive two doses spaced six months apart.

Meanwhile, the national vaccine schedule in Mexico, as elsewhere, has been expanding and becoming more costly. In 2007, the government will introduce the acellular pertussis and inactivated polio vaccine, as well as the hepatitis B vaccine at birth. “This, plus the introduction of the last two vaccines, conjugated pneumococcal vaccine and rotavirus vaccine, will take the vaccination schedule for a child to over $193,” said Matias.

Nevertheless, Mexico is determined to reduce their infant mortality, which declined greatly in the 1980s and 1990s, but has since plateaued. “We hope that this plateau decreases with the new intervention measures underway in public health,” Matias said.

**Chile**

Dr. Rosanna Lagos, Coordinator for the Center of Experimental Vaccines, a research arm of Chile’s Ministry of Health, reported that Chile does not yet have a national vaccination program for pneumococcal disease. However, researchers have been working to “generate evidence for public health decisions that are impossible to avoid regarding the use of conjugated vaccines.”

**Surveillance**

Starting in 1994, Chilean public health officials began recording the isolates of invasive *S. pneumoniae* and other clinical information on children hospitalized with pneumococcal disease. Since then, improvements in the standardization of data and laboratory procedures have strengthened the ability to identify pneumococcal disease in febrile children in emergency rooms. Some 40% to 50% of the invasive pneumococcal disease is now detected in
this setting, leading to a near-tripling of the reported incidence of the disease in children under age five in the metropolitan regions of Chile.

The most frequent serotypes in this population are 14, 5, 1 and 6B. Certain serotypes were closely associated with variations in disease incidence in particular age groups. Notes Lagos, “A serotype study of one-to-two years may be insufficient to know the real coverage to be offered by these vaccines.”

The fatality rate in children without high-risk conditions was about 4%, and about 8.2% in those with risk factors. Notes Lagos, “the incidence of invasive disease exceeds 200 cases per 100,000 for children with chronic illness, which results in a relative risk seven times higher than children not carrying these conditions.”

**Call to Action**

Lagos asserted that the conjugate vaccine could prevent a great proportion of invasive infections and pneumonia in all children. “From my modest point of view,” concludes Lagos, “pneumonia prevention...is a highly powerful public health reason to implement the routine use of conjugated pneumococcal vaccines with enhanced antigenic spectrum.”

“From my modest point of view, pneumonia prevention...is a highly powerful public health reason to implement the routine use of conjugated pneumococcal vaccines with enhanced antigenic spectrum.”

—DR. ROSANNA LAGOS
Center of Experimental Vaccines, Chile
Noting that pneumococcal vaccine can be an instrument of health, equity and development, presenters infused this session with a sense of urgency: the objective being to accelerate the introduction of conjugate pneumococcal vaccines, rather than simply proceed with business as usual. A series of presentations in two Round Table Discussions illuminated on-the-ground realities as countries evaluate their needs and begin the process of vaccine introductions. The session concluded with a resounding Call to Action on pneumococcal disease and vaccine introduction in Latin America and the Caribbean.

**Round Table: Immunizations in High Risk and Vulnerable Populations**

Countries with limited resources are evaluating the potential use of conjugate pneumococcal vaccine for their most at-risk populations. In Brazil, government programs extend the safety net of vaccines to high-risk populations including children with numerous health conditions, the elderly, and indigenous and remote populations.

In Bolivia, one of the poorest countries in South America, where six out of 10 Bolivians live below the poverty line, the immunization program has been an “instrument of equality,” said Erick Machicao. Presentations enumerated the success and challenges as these efforts move forward.

**Brazil**

Dr. Expedito Luna, Director of the Surveillance and Infectious Disease Control program, presented Brazil’s progress in immunizing vulnerable and high risk populations. Robust funding of vaccination has allowed Brazil to “create strategies for population groups that would not be contemplated in the universal childhood vaccination,” said Luna. Programs were created to reach those over age 60; indigenous communities and those who live in remote areas; those at high-risk because of health condition; and pilot initiatives for quilombos (isolated communities formed by fugitive slaves), sex workers, inmates, and adolescents.

As a result, for example, some 33.5 million people over the age of 60 are vaccinated with a variety of biologicals, covering influenza, tetanus, diphtheria, and pneumococcus. However, Luna said that serious challenges remain to increasing vaccine access and coverage for high-risk populations.

The indigenous population is composed of 300 ethnic groups and 400,000 individuals spread throughout Brazil, often in small, remote communities. To reach remote populations, Brazil developed Operation Gota (“Operation Drops”—named after the oral polio vaccine), an alliance between the Ministry of Health and the Brazilian Air Force and Army. It serves 80,000 inhabitants in more than 1,500 small communities in eight Brazilian states, located either in the Amazon jungle or in the pantanal—a remote swamp area on the border with Paraguay and Bolivia. The sites are served by helicopter and sometimes by boat, at a cost of $1.5 million per year.

Thus far, indigenous populations receive the 23-valent pneumococcal vaccine, but not the conjugated vaccine, notes Luna, and retention of doctors and nurses remains a challenge.

Those at high risk because of health issues are vaccinated through 38 Reference Centers for Special Immunobiologicals around the country. These are centers within hospitals that offer vaccines that are not part of the universal vaccination program. They include the 23-valent pneumococcal vaccine for adults and PCV7 for children. These are offered to people with health indications such as chronic pulmonary disease, childhood cancer, insulin-dependent diabetes, and HIV/AIDS.

However, Luna noted that the number of Reference Centers for Special Immunobiologicals...
needs to be increased, as many people with chronic conditions live far from any center. In addition, outreach for the vaccine programs needs to extend beyond the Centers’ regular patient base. For instance, Luna said that the number of people vaccinated with the 23-valent pneumococcal vaccine is much lower than the number of new patients who register with the HIV/AIDS program, suggesting that referrals for vaccination are inconsistent.

**Economic Costs**

Better coverage, of course, entails greater cost. At present, the Reference Centers’ vaccine program accounts for almost 7% of the value of the national vaccine purchasing program, while serving relatively few people. Luna noted that further enhancement of these strategies “will bring a sustainability problem in connection with costs.”

Finally, for Brazil, there is concern about the impact of new vaccines on the national vaccine production program, and whether the large number of products entering the market may overwhelm the national public sector of vaccine producers. “We want to guarantee scientific and technological development in our country and the sustainability of our immunization program in the long term,” said Luna.

**Bolivia**

Dr. Erick Machicao, National Expanded Program on Immunization Manager of Bolivia, described the vaccination strategies for high risk and vulnerable populations in Bolivia, which is one of the poorest countries in South America. Vulnerable populations include those in the remote Amazon jungle, those in the remote highlands, and internal migrants in and around the cities. Access to healthcare is extremely variable, depending on income, education, and geographic location.

**Components of Success.** In the face of great disparities in wealth and access to healthcare, Bolivia’s Expanded Program on Immunization is an “instrument of equality,” says Machicao. Bolivia has been able to achieve universal coverage for several vaccines. Machicao credits Bolivia’s experience in the eradication of polio and smallpox with building the capacity to achieve wide vaccine coverage. Recently, Bolivia attained 95% coverage of the adult population in a rubella vaccination campaign, and brought yellow fever under control.

Machicao described some of the components of Bolivia’s successful vaccine strategy:

- Advance planning and adequate resources;
- A strong and well-monitored cold chain;
- Committed staff that follows children through their complete vaccine schedules;
- Commitment on national, department and local levels, and strategic interagency alliances;
- Local resources contributed through municipal hydrocarbon taxes;
- Effective communications; and
- Participation by farmers, neighborhood associations, the armed forces, the police forces, and businessmen and businesswomen.

“We want to guarantee scientific and technological development in our country and the sustainability of our immunization program in the long term.”

—DR. EXPEDITO LUNA
Ministry of Health, Brazil
“We have a national development plan and a sectoral health plan to allow us to have much more equity in these vaccination and epidemiological surveillance activities,” says Machicao. The plans underscore the importance of community organization, cross-cultural communication, social inclusion, and the right to health for all. In addition to promoting disease prevention, work on the community level allows for “timely detection in the community for patients suspected of having diseases which are immune-preventable.”

At a recent yellow fever vaccination conference in Bolivia, urban neighborhood organizations and rural farmers were both represented. Their message, says Machiao, was: “we want to be an active part in planning, monitoring and evaluating vaccination activities.” Machiao concludes, “Bolivia is a country with incredible challenges, but vaccination of populations at risk is feasible.”

“Bolivia is a country with incredible challenges, but vaccination of populations at risk is feasible.”

—DR. ERICK MACHICAO
Ministry of Health, Bolivia
Implementation Issues

Dr. José Ignacio Santos, Director of Hospital Infantil de Mexico Federico Gómez, presented an overview of considerations that middle-income countries must inevitably weigh as they consider implementing new conjugate vaccines. He noted that public health authorities must balance questions regarding the value of the vaccines, the burden of disease, affordability and cost-effectiveness, and the necessity of covering the basic health needs of large populations.

With similar concerns in mind, Dr. Ida B. Molina, National Expanded Program on Immunization Manager of Honduras, presented a blueprint for vaccine introduction and implementation, outlining basic processes that are typically necessary to accomplish such changes.

Dr. Maria Belén Jaimes Sanabria, with the Colombian Ministry of Health, detailed the considerations of one country as it assesses the possibility of adopting a conjugate vaccine against S. pneumoniae.

Dr. Santos dedicated his talk to Dr. Jean La Montagne, “one of the pioneers and founders of the childhood vaccination programs in the United States.” He noted that Montagne was born in Mexico, and died there suddenly while attending a global forum on health. “I believe that, two years after his death, it is important to remember those who have made the application of vaccines feasible for many children in the world,” Santos said.

Recent History with Conjugate Vaccines

Conjugated vaccines have been in existence for the last 20 years, Santos said, noting, for example, that children in the industrialized world and in nations throughout the Americas have benefited from a vaccine against Haemophilus influenzae (Hib). “This has been feasible due to the development and distribution of safe, effective and affordable, but not inexpensive, vaccines,” Santos said.

In the last ten years, Santos said, many nations in the Americas have rapidly introduced new vaccines, including the Hib vaccine, the hepatitis B vaccine and the viral MMR, which has replaced the old measles vaccine. Success with introducing the Hib vaccine in the region was built on the experiences of a few countries that went first, including the United States, Canada, Uruguay and Chile. “Remember that Hib was sold as a vaccine against meningitis, but the true value added was against pneumonia,” Santos said. He emphasized the positive role of PAHO’s Technical Advisory Group in aiding vaccine introductions, as well as that of its Revolving Fund, which buys in bulk to reduce costs.

Now, the introduction in the United States of a new conjugated vaccine containing seven serotypes of Streptococcus pneumoniae has led to a significant decrease in illness and death, Santos said, including through an unforeseen outcome—herd immunity among individuals who were not vaccinated.

This raises a critical question: “How can we ensure that the poorest have access to this new biological?” he asked.

Implementation Issues for S. pneumoniae in Latin America

Santos noted the importance of having solid information on the burden of the disease, a goal made difficult by the fact that S. pneumoniae is only one of the causes of pneumonia, meningitis, sepsis and acute media otitis. Nonetheless, “I am very positively surprised by all the information presented here, with the support of the Sabin Institute, so as to get at least an approximate burden of disease,” he said.

Most significant is the finding that two children die per hour in Latin America and the Caribbean due to S. pneumoniae. Therefore, “Being able to include this biological in our schedules, as well as other biologicals now in the pipeline, would allow us to reduce the number of deaths due to this microorganism and also, undoubtedly, help many countries fulfill the Millennium Development Goals, in particular goal number 4 to reduce childhood mortality by two-thirds, between 1990 and 2015,” he said.
Santos stressed the importance of cost-effectiveness studies, and a determination of the vaccine’s affordability in relation to the gross domestic product of a country. “The most important aspect is economic commitment within the countries to ensure program sustainability,” he said.

He noted the major dilemma facing “sandwich countries,” transitional economies that are neither rich nor poor enough to be considered “GAVI countries.” Only seven nations in the Americas are eligible for support from the GAVI Alliance, and “seven countries represent less than 16% of the 11.7 million children born every year in this region,” Santos said. “The other countries are left with a vaccine that costs US$53 a dose.”

In addition to illustrating the issues of cost-effectiveness and affordability, Santos noted that successful implementation requires sufficient infrastructure and a robust epidemiological surveillance program that can evaluate vaccine impact.

**Unresolved Issues**

Santos pointed to conflicts that are inherent in efforts to introduce new vaccines, including between the private and public sectors and potential opposition on the part of parents to multiple additional injections, with the possibility that anti-vaccine constituencies would grow in influence.

Efficacy may also be a concern, Santos said, as it is only about 60% in the region. However, “given the severity of the disease and the mortality risk, the vaccine clearly would be justified with a 40% efficacy,” he argued. Meanwhile, data for a 10-valent vaccine, expected to be licensed in 2008, indicates it would provide greater coverage of the specific serotypes identified in the region, Santos said. He also noted concerns about serotype replacement, urging that they not be used as a basis to reject the vaccine.

In the final analysis, history has taught us that success in vaccination programs depends on “decisions that are made with unquestionable scientific rigor,” said Santos.

**Blueprint for Implementation**

Dr. Ida B. Molina outlined three main stages of vaccine introduction and implementation: the pre-introduction stage that ends with a decision regarding introduction; the operational stage, guided by an introduction plan; and impact measurement.

**Pre-introduction and Criteria.** Although both political and technical considerations enter into the pre-introduction stage and decision-making, the decision should be clearly driven by public health priorities, Molina said.

To reach a decision, several main criteria need to be evaluated:

- The burden of disease based on surveillance;
- Technical feasibility, such as cold chain requirements;
- The efficacy, immunogenicity, and safety of the vaccine, based on clinical trial data;
- Comparison of the vaccine to other possible public health interventions to determine the best intervention;
- Assessment of the security of the vaccine supply;
- Analysis of the vaccine’s cost-effectiveness and cost-benefit.

“The most important aspect [of vaccine implementation] is economic commitment within the countries to ensure program sustainability.”

—DR. JOSÉ IGNACIO SANTOS
Hospital Infantil de Mexico Federico Gómez, Mexico
“If the costs of vaccines are not affordable, greater inequalities among the populations and their vaccine schedules will be generated.”

—DR. IDA B. MOLINA
Ministry of Health, Honduras

Like Santos, Molina emphasized the key role cost-effectiveness analysis plays in decision-making, and highlighted equity concerns. She said two things must be evaluated: the impact of vaccine introduction on the national budget and its ongoing financial sustainability.

“In my country, Honduras, we are facing vaccines whose cost is five times higher than the total cost of all the current vaccines in the program,” she pointed out. “If the costs of vaccines are not affordable, greater inequalities among the populations and their vaccination schedules will be generated.”

At the end of this pre-introduction stage, however, “we need to make a decision and this is an individual decision in each country,” Molina said.

An Introduction Plan. Once a vaccine is approved for introduction, health authorities must develop national plans of action that can be integrated into each country’s National Immunization Program and National Health Plan.

Plans should be “viewed as instruments for resource mobilization,” that take into account financing of existing immunizations, laws that favor financing and sustainability, and resource options. These include national funds, funds of the Strategy for the Reduction of Poverty and the Millennium Account, and private sector and donors’ support.

Plans should specify objectives and goals, target populations and areas, target dates, harmonization activities, vaccine supply, training, communications and information systems upgrades, strengthening of epidemiological surveillance, and costs. And, after implementation, Molina noted the importance of measuring impact.

In conclusion, “It is fundamental to develop a plan for the introduction and implementation that guarantees sustainability,” said Molina. She noted that the Revolving Fund continues to be a mechanism to ensure a regular flow of quality vaccines at affordable prices, offering security and confidence to the countries.

Colombia: One Country’s Experience

Colombia has a national commitment to achieving Millennium Development Goal #4 and reducing child mortality by 60% by the year 2015, said Jaimes Sanabri of the Ministry of Health in Colombia. “To that end, Colombia has proposed to reduce deaths in children younger than 5 years of age to 17 deaths per 1,000 live births, taking into account that the baseline for 1990 was 37 deaths per 1,000,” she said.

Progress is being made: in 2002 the child mortality rate was 28 deaths per 1,000.

To continue that progress, Colombia is updating its Expanded Programme on Immunization (EPI) and adding new vaccines, she said. And, it is in this context that public health authorities are assessing the possible introduction of a conjugate pneumococcal vaccine.

Though the burden of pneumococcal disease has not been fully confirmed, data from the Ministry of Social Protection, the National University and the
National Department of Statistics in Colombia has found that:

- Pneumonia is the third leading cause of death in children younger than 1 year of age, and the second in children between the ages of 1 and 4,
- An estimated 1,200 children under five die of pneumonia every year,
- Pneumococcal pneumonia is estimated to kill between 250 and 900 children every year,
- There are 470,000 to 1.4 million cases of pneumonia in children under five every year,
- The total incidence of pneumococcal meningitis has been estimated in 850 to 1,600 cases a year in children under five.

The existing vaccine could therefore save the lives of a significant number of children. Jaimes Sanabria supported her conclusions with an initial analysis of the serotypes present among children hospitalized with pneumococcal diseases.

An analysis of 2,022 serotypes isolated from 137 hospitals in Colombia in 1994 revealed that 64% of the serotypes correspond to those in CVP7, and that the vaccine would have a “potential effectiveness in Colombia of 62%,” she said.

However, a determination of cost-effectiveness of the new vaccine is still needed. As Dr. Martha Patricia Velandia, National EPI Coordinator of Colombia, later noted, “The cost of the pneumococcal vaccination schedule accounts for what the Colombian state gives to each person in health during a month. Therefore, data is needed for making a decision,” she said.

For now, Colombia has decided to introduce PCV7 for the youngest of its most vulnerable children: those with HIV, congenital heart disease, bronchial asthma, cancer, and other life-threatening conditions. The nation’s Public Health Surveillance System is studying the cost-effectiveness of a pneumococcal vaccine for children in that population under the age of two.

Two other cost-effectiveness studies—of vaccines for rotavirus and hepatitis A—are also in the works.

Jaimes Sanabria noted that the cost of implementing the rotavirus vaccine alone would cost the country almost US$14 million, and that the country’s current budget for EPI is US$50 million.

Meanwhile, one other relatively new vaccine has already had an impact on child mortality: the Hib vaccine has greatly reduced the cases of Hib-associated meningitis.

As the country strives to implement new programs and raise its overall coverage of basic EPI vaccines from 92% to 95%, Jaimes Sanabria noted that there are many challenges. Among them are the need to strengthen management and infrastructure, as well as the information system, the cold chain, and the surveillance of vaccine-preventable diseases.

Discussion

Discussion revolved around questions of vaccine efficacy in Latin America, the role of various leadership bodies, and political and technical considerations in decisions about vaccine introductions.

Surveillance and Vaccine Efficacy

COMMENT: Miguel Tregnaghi of Argentina noted that while it is extremely important to have a solid assessment of both vaccine efficacy and burden of disease, those findings vary greatly depending on the study and the type of surveillance conducted. He emphasized that ongoing surveillance will yield future data that will help us make decisions.

Efficacy in High-Risk Populations

COMMENT: Lucia Bricks of Brazil noted that PCV is a very important vaccine, but that efficacy in high-risk groups where the vaccine is becoming available is expected to be much lower than 60%. This includes populations with unconventional risk factors, such as premature babies which account for 10% of the population at high risk of pneumococcal disease. In addition, she said, serotype replacement problems could be larger in high-risk groups that are immunosuppressed, she said.
How Much Information Is Enough?

COMMENT: Xavier Sáez-Llorens of Panama questioned “whether we need in fact more data for the introduction of the vaccine.” He suggested that Mexico’s plan to “spectacularly update” its vaccination program is driven more by political than technical considerations. He also urged that countries not “reinvent the wheel.” “If Costa Rica and Colombia, which neighbor Panama, have a lot of rotavirus, why is our country going to be completely different?” he asked, noting that sometimes asking for more data delays the introduction of effective vaccines.

Sáez-Llorens also disagreed with Santos’ characterization of Hib and HepB vaccine introductions in the Americas as rapid. “I would say it is the opposite. Their introductions were extremely slow—10 to 12 years. I wonder: who takes responsibility for those deaths and sequelae in the 10 to 12 years that the introduction of the Haemophilus vaccine was delayed in the Americas?”

RESPONSE: Santos replied that in his experience, after Hib was first introduced in Latin America in 1999, by 2002 it was in almost all Latin American countries. “The following year the hepatitis B vaccine was ready and the following year we were already working on a campaign to eradicate congenital rubella syndrome,” he said. Regarding the value of the vaccine, he noted that worldwide, almost 90% of the deaths due to pneumococci occur in other parts of the world, specifically in Africa and South East Asia. “How many deaths are too many? I believe that one death is too much,” he said. Definitely, there are local, regional and national differences. That is why information is important even though it might be limited information, he added.

PAHO’s Role

COMMENT: Xavier Sáez-Llorens argued that PAHO has received unjustified credit for the introduction of vaccines in the Americas—even though the Revolving Fund has been an excellent initiative because it helps to reduce prices. “The introduction of vaccines in many of our countries has been related more to persons than to power groups,” he said.

RESPONSE: Santos emphasized PAHO’s positive role. “The Americas were the first to eradicate smallpox, the first in eliminating polio, and the first in controlling measles. I think this speaks to something more than personal or political decisions by the countries,” he said, noting that those advances were made by the member countries of PAHO.

Dr. Molina added, “There is no doubt that the Revolving Fund has been an extraordinary support mechanism for maintaining immunization programs in our countries.”
“With the concrete information we have received this week, we have enough data to start an important defense against pneumococcal disease in all countries,” said Dr. Ciro de Quadros.

Conference organizers presented a Call to Action that was discussed and approved by Symposium participants. (See addendum.) Given that, in Latin America, pneumococcal disease kills two children per hour, and causes at least 1.6 million cases of disease every year, and that there is a safe and effective vaccine for children, the Call to Action agreed to “promote adaptation of pneumococcal vaccines wherever feasible,” and to “make 2007 the year of action.”

Presentations by Dr. Jon Andrus from PAHO, Dr. Orin Levine from PneumoADIP, Ms. Lisa Jacob from GAVI, and Dr. Ciro de Quadros from the Albert B. Sabin Vaccine Institute all highlighted the need for concerted action. The following are highlights from their talks.

Dr. Jon Andrus, PAHO

Since the first regional meeting on pneumococcus in Mexico City, in November 2004, much has been done, but we still have much to do. We have the data, we have the vaccine, but it is the same situation: We don’t have a vaccine at a price that all the countries can afford to introduce to reduce mortality.

Therefore, PAHO will continue to push the agenda at the highest political levels, and, most importantly, will continue to use the Revolving Fund and to improve its effectiveness. We will maintain our team of international field consultants working with the countries and communicating with the Revolving Fund as countries continue to develop the fiscal space for new vaccines.

Dr. Orin Levine, GAVI’s PneumoADIP

We are going to need collaborative action to be successful, and this Call to Action is an example of that. We have heard today about country experiences and ways in which countries have been very successful in taking evidence, and using it to generate political will, support for introduction of new vaccines.

We have discussed today the price of the vaccine and the substantial challenges ahead in implementation. But, as a community of people who take care of children with pneumococcal disease and who intimately know the value of the vaccine, it is important for us to also make apparent the price of inaction, as well as the price of the vaccine. The challenge ahead is to find that balance and to urge the forces of inaction to the side on the basis of evidence, so that we can have the kind of impact that has been projected.

We have been very successful in generating funding and focusing a new level of attention on health and immunizations. Our success has been based on the promise that these vaccines will deliver the kinds of returns that David Bloom and others have shown are possible. We need to deliver on those promises.

Ms. Lisa Jacobs, the GAVI Alliance Secretariat

We very much support this Call to Action on pneumococcal vaccines. GAVI already has acted, and we will continue to act. Pneumococcal vaccine has been one of our priority new vaccines since 2000. Many factors influenced the recent decision by the GAVI Board to support the purchase and introduction of the vaccine: the PneumoADIP’s investment case, the evidence of disease burden, the introduction of the vaccine in the U.S. with its demonstrated herd immunity, and the very positive dialog that has emerged with manufacturers.

GAVI has been blessed with some very public commitments. Most recently the International Finance Facility for Immunization sold its first bond issue for US$1 billion dollars. Another US$2.2 billion have been fully committed. And, Brazil and South Africa have committed to join the next bond issue. The other very exciting new innovation is the Advance Market Commitment (AMC) mechanism, with its profound implications for speeding access to that vaccine.
GAVI has also enacted a country co-financing policy that will apply to the new pneumococcal and rotavirus vaccines. It asks countries to put up a little funding and is meant to open a budget line that would gradually increase. That way, by the time GAVI support stops, countries will have the resources to continue paying for the vaccine.

Six countries in the Latin American region are eligible for GAVI support: Nicaragua, Cuba, Honduras, Haiti, Guyana and Bolivia. Our plan is to finalize the guidelines for applications for these new vaccines in May of 2007, make those available to countries, and solicit applications for review by autumn. We hope for pre-qualification of both Prevnar and the rotavirus vaccine by the end of 2007.

Dr. Ciro de Quadros, The Albert B. Sabin Vaccine Institute

After all the information and enthusiasm generated by this meeting, there is momentum that facilitates the introduction of the vaccine by governments. There have been more than 34 articles in the newspapers and news agencies from yesterday to today. There is unprecedented communication in Latin America about pneumococcus, the burden of disease, and prevention. Through social communication, these issues are all over the region of the Americas. We have something very important ahead of us.

There are no doubts that the birth of GAVI was very important for vaccination programs all over the world. Progress in the poorest countries has been extraordinary. But, it is clear that for Latin America, in particular, the target population of GAVI is relatively small. However, GAVI could actively participate in the region of the Americas through other mechanisms; they could make a donation to the Revolving Fund. The Fund will have a US$70 million deficit by 2015. If GAVI contributed US$20-30 million to the Revolving Fund, it would greatly facilitate the purchase of new vaccines.

Therefore, We Agree to:

- Support immunization as a common public good, an economic necessity and a vital political priority...
- Request that the World Health Organization expedite the prequalification of the existing vaccine...
- Promote adaptation of pneumococcal vaccines wherever feasible...
- Work to raise awareness...
# Call to Action

By Participants of the Second Regional Pneumococcal Symposium  
São Paulo, Brazil  
14 December 2006

**Considering that:**

- Pneumococcal disease kills up to one million children worldwide every year, with 90% of deaths in developing countries;
- In Latin America, pneumococcal disease kills 18,000 children every year — two every hour — and causes at least 1.6 million cases of disease;
- These include such deadly conditions as pneumonia, bloodstream infections and meningitis, as well as ear infections that can lead to hearing loss;
- While appropriate treatment, including wise use of antibiotics and good nutrition, lowers the incidence of pneumococcal disease, vaccines are the most efficacious way of preventing it;
- Latin America suffers a high economic burden from pneumococcal disease, with direct medical costs estimated to surpass US$293 million per year, and families bearing more than US$40 million in additional costs;
- There is a solution. An existing pneumococcal conjugate vaccine dramatically reduces disease, disability and deaths from pneumococcal disease;
- Adding the current pneumococcal conjugate vaccine to childhood immunization schedules can begin saving lives and preventing disease now;
- New vaccines that promise even greater impact in Latin America are expected to become available over the next two to four years;
- Prevention and control of pneumococcal disease requires collaborative action by governments, industry, health organizations and international agencies.

**Therefore, We Agree to:**

- Continue to support immunization as a common public good in the region, an economic necessity and a vital political priority;
- Request that the World Health Organization expedite the prequalification of the existing vaccine for purchase by United Nations agencies as soon as possible;
- Promote adaptation of pneumococcal vaccines wherever feasible;
- Work to raise awareness among the public and policy makers of the burden of pneumococcal disease and the value of vaccination;
- Encourage increased vaccine research and expanded surveillance;
- Call upon PAHO and its Revolving Fund for the acquisition of vaccines to work together with national governments, bilateral and multilateral agencies, the GAVI Alliance, and the manufacturers of vaccines to facilitate the introduction of pneumococcal vaccines;
- Make 2007 the year of action to combat pneumococcal disease in the Americas.
Dr. Ciro de Quadros introduced Dr. María Luisa Ávila, the Minister of Health of Costa Rica and Dr. Roberto Tapia, Vice-Minister of Prevention & Protection of Health.

Ministry of Health, Mexico, to deliver the closing remarks.

“In Costa Rica, we consider vaccines part of the human development necessary for each nation,” said Dr. María Luisa Ávila, “It is completely unfair that, in a country such as ours, some children are vaccinated with all the possible immunobiologics while another group of the population receives only the basic schedule.”

Thanking the Pan American Health Organization for its help in the development of Costa Rica’s vaccination programs, Ávila emphasized her country’s commitment to updating its vaccination schedule.

However, she noted a challenge beyond technical feasibility or cost. “Unfortunately, there are other obstacles... people who believe that pneumococcus is not an important disease in the country... So, in addition to having to fight against economic constraints, we have to fight against the mental constraints, which may be worse,” she said.

“I hope that our countries move forward toward a shared goal and that the introduction of new biologicals becomes a prompt and effective situation,” Ávila concluded.

Dr. Roberto Tapia, asked, “Taking this plan of action, what else needs to be done? For it to work, he said, “The most critical task is to build political support. And this can be done by promoting the understanding of vaccines as a key pillar to achieving health, equity and economic development.”

He urged promoting this message not only to politicians, but also to the community. He urged that actions be taken to:

- Update countries’ legal mandates to vaccinate, and do so in a way that helps develop new means of financing. He noted that many national vaccination laws address the old framework of vaccine schedules;

- “Give a thrust to justice” and consider vulnerable groups a priority. Vaccination for those in rural areas, prisons, and many marginalized circumstances would assure that people receive a preventive intervention;

- Design a financing scheme for countries with intermediate economies;

- Increase advocacy. Tapia noted that at the country level, HIV/AIDS and malaria have made significant progress because of the advocacy of civil organization. “With pneumococcus we have no civil organizations that are similarly striving,” he said;

- Build a national consensus. When all contribute to decision making, “The barrier of fear and individualized criticism is interrupted, and the decision-making process is accelerated.”
Tapia stressed the importance of a communication strategy built by all the stakeholders, and which, “above all, empowers individuals to be informed and to make the decision to request the vaccine.”

For vaccine introduction, Tapia emphasized the “element of mysticism—meaning passion and pride.” “This must not get lost, because it is the engine that keeps the machinery working,” Tapia concluded. “We have to convey this ‘mysticism’ to the population. The understanding of society is the best sustainability.”

“The understanding of society is the best sustainability.”

— DR. ROBERTO TAPIA
Ministry of Health, Mexico

**Millennium Development Goal #4**

Reduce the under-five child mortality rate by two-thirds, between 1990 and 2015.