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The Fifth Regional Pneumococcal Symposium, held March 5-6, 2013, in São Paulo, brought fresh evidence that pneumococcal vaccines are an increasingly effective tool in disease prevention. Already credited with saving lives and preventing illness through a herd protection effect that extends beyond the immunized populations, presentations at the symposium showed that pneumococcal vaccines have the potential to save many more lives.

There were important discussions focusing on the fact that the burden of pneumococcal disease in groups that have not been the target for immunization—children over five and adults—remains significant. And if expanding pneumococcal immunization to new populations is justifiable.

Maria Deloria-Knoll of the Johns Hopkins University Bloomberg School of Public Health discussed new insights from a project called the Adult Global Estimation of Disease Burden and Distribution of Serotypes of Serious Pneumococcal and Meningococcal Disease (AGEDD). Preliminary estimates suggest that globally, pneumococcal diseases could account for between 250,000 to 400,000 deaths each year in older children and adults.

Her colleague, Dagna Constenla, presented preliminary findings of a study that shows countries in Latin America and the Caribbean are spending about US $622 million each year to treat invasive pneumococcal disease (IPD)—and that’s not including the costs incurred by families or the private sector. Nelson Alvis-Guzmán of the University of Cartagena showed evidence from Colombia that just vaccinating individuals 60 years and older would save the country US $8 million a year.

One of the biggest issues surrounding the expanded use of pneumococcal vaccines is determining how much disease reduction can be achieved in older populations simply by vaccinating only the very young. Jennifer Loo of the US Centers for Disease Control and Prevention (CDC) showed that in the US, between 2000 and 2009, pneumococcal immunizations were credited with saving 19,000 lives and preventing 280,000 illnesses. But almost all of that progress was achieved in older, unvaccinated populations, who benefited from the herd protection generated by immunizing young children.

But Loo’s colleague at the CDC, Tamara Pilishvili, said that despite the enormous gains from the herd protection effect, a large burden of pneumococcal disease remains in adults. She said most of the IPD today in the US is found in adults over 50 years of age. She also said that although herd protection extends to immune-compromised populations, they have a large residual burden of disease.

Adding another potential rationale for immunizing beyond very young children was evidence that preventing pneumococcal infections could be a way to prevent deaths from influenza. Emory University’s Keith Klugman presented evidence from both the 1918 pandemic and the recent outbreak of H1N1 indicating that influenza appears to make people more susceptible to deadly pneumococcal infections. And he discussed a study from Spain that linked pneumococcal vaccination with a sharp reduction in the risk of being hospitalized for influenza.

There was considerable discussion of the pneumococcal conjugate vaccines (PCVs) used in children compared to the pneumococcal polysaccharide vaccines (PPSVs) that many countries offer to older adults.

As Lee Harrison of the University of Pittsburgh noted, PCVs are generally viewed as superior because they induce an immune response in infants—PPSV’s do not—and they reduce carriage of disease in young children, which is the key to generating herd protection. But evidence also was presented indicating that the 23-valent PPSV vaccine can produce a protective immune response in older individuals. And there was discussion about how polysaccharide and conjugate vaccines could be combined to provide a high level of protection in older populations.
There was a general consensus that better surveillance is needed to gain greater insights into the burden of pneumococcal disease in older populations in Latin America, and to understand how much disease is being prevented via childhood immunizations—and thus the cost-effectiveness of targeting older groups.

Sabin’s Ciro de Quadros said he felt the “same vibes” at this meeting as he did eight years ago when discussions were just beginning about introducing pneumococcal vaccines for young children. He was confident that the assembled experts were ready to write a similarly impressive chapter in the increasingly compelling story of pneumococcal immunization.

“It’s very clear that we have a very serious problem with pneumococcal disease in children older than five years of age and in adults,” he said. “And we certainly have vaccines that can help solve it.”

Introduction and Opening Remarks

On March 5, 2013, 155 delegates from 26 countries gathered in São Paulo, Brazil to discuss the potential for vaccines to further reduce the burden of pneumococcal disease in the Americas. It was the fifth meeting on pneumococcal disease held jointly by the Sabin Vaccine Institute (Sabin), the Pan American Health Organization (PAHO), the U.S. Centers for Disease Control and Prevention (CDC), and the Johns Hopkins International Vaccine Access Center (IVAC). But according to Sabin’s Ciro de Quadros, this gathering was breaking new ground. It was the first to “focus especially on older children and adults.”

Carla Domingues of Brazil’s Ministry of Health said it was poignant to be hosting the symposium at a time when Brazil was marking the 40th year of its National Immunization Program. “To be hosting this international event, in São Paulo, in Brazil, is one more indication of the success of our program,” she said.

De Quadros said progress made with immunizations in the Americas in the last 40 years was “incredible.” In just the last two decades alone, he said, countries in the region have introduced vaccines against rotavirus, pertussis, haemophilus influenza, hepatitis B, pneumococcal, and HPV. And all of the studies to date, he added, have shown that “vaccines are the best purchase you can make in the overall health supermarket.”

But de Quadros noted that there is no end to the job of communicating this message to policy makers. While the case for immunizations is clear, each year a new crop of political leaders must be briefed with the most up-to-date information available, as they confront decisions about whether to introduce new vaccines or expand the use of existing ones.
Keynote Address: The Value of Vaccination

Lee Harrison, an infectious disease specialist at the University of Pittsburgh, reviewed the history of pneumococcal vaccines, placing particular emphasis on the impact of the move from the older polysaccharide vaccine to the newer conjugate vaccines. He noted that the conjugate vaccines that are now the mainstay of childhood immunization programs around the world are superior in several respects to the polysaccharide formulation, which is still used in many countries in the Americas to immunize older adults.

“We desperately need data on the direct effects of pneumococcal conjugate vaccines on adult pneumonia.”
~ Lee Harrison, University of Pittsburgh

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Granoff DM, Pelton SI, Harrison LH. Vaccines. 6th ed, in press

“The main issue,” he said, “is that the conjugation process creates a t-cell dependent immune response and that gives it a whole bunch of advantages over the polysaccharide vaccine.”

Perhaps the most important advantage, Harrison said, is that conjugate vaccines are efficacious in infants, whereas polysaccharide vaccines do not induce an adequate immune response in this age group. The protection conferred by conjugate vaccines also lasts longer, he said, and they reduce the carriage of pneumococcal pathogens—a crucial factor in achieving the herd protection that has become a hallmark of the various pneumococcal conjugate vaccines, or PCVs.

Pneumococcal vaccines are typically labeled with a number that refers to the “valents” or disease serotypes targeted by a particular formulation. For example, the 23-valent polysaccharide pneumococcal vaccine, often referred to as PPSV23, is intended to provide protection against 23 different pneumococcal serotypes. Despite the large number of serotypes targeted, PPSV23 has not had the same impact on disease as conjugate vaccines that cover far fewer strains. As Harrison noted, this disparity is caused by PPSV23’s inferior response in infants and its failure to reduce carriage of serotypes in the nasopharynx (the chamber-like area in the back of the nose that harbors pneumococci).
The first pneumococcal conjugate vaccine introduced in the region was a 7-valent formulation (PCV7), which was introduced in the US in 2000 for children under 5 years. It was followed by a 10-valent formulation (PCV10). And in 2010, a 13-valent formulation (PCV13) came on the market. As of March 2013, in the Americas, 26 countries and territories have added a pneumococcal conjugate vaccine to their childhood immunization programs and are currently using either PCV10 or PCV13.

There also are a few countries in Latin America and the Caribbean (LAC) that have the polysaccharide vaccine (PPSV23) in their arsenal of immunizations. But it is chiefly used in older individuals, those for whom a pneumococcal infection poses particular risk. That group includes people with immune-compromising diseases and individuals over 65 years. LAC countries utilizing PPSV23 are: Argentina, Aruba, Bahamas, Brazil, Colombia, Costa Rica, Ecuador, El Salvador, Panama, Paraguay, Uruguay, and Venezuela.
Harrison said that the capacity of a particular formulation to reduce the burden of pneumococcal disease depends on the mix of serotypes circulating in a given region. For example, PCV7 covered 86 percent of pediatric disease serotypes in the US, but only 60 percent in Latin America, which is why many Latin American countries originally opted for the 10-valent formulation—it covers 81 percent of disease serotypes in the LAC region. The US recently switched to PCV13 because it boosted coverage of disease serotypes to 92 percent. Many other countries in the LAC region have also adopted PCV13.

**Protecting Older Members of the “Herd” by Immunizing the Young**

A major highlight of the pneumococcal conjugate vaccine success story concerns the impact these formulations have had on disease burden beyond the target population. In the US, Harrison said, the effort to vaccinate children under five with conjugate vaccines—starting in 2000—has led to a 37 percent reduction in pneumococcal disease, “among adults of grandparent age.”

“Immunization of children with pneumococcal conjugate vaccines prevents pneumococcal disease in adults,” he said. This herd protection happens because young children are key carriers of pneumococcal infections. And as the conjugate vaccine reduces the overall carriage of disease in young children, fewer older adults are exposed to infections carried by young children.

In fact, disease prevented via herd protection can exceed the amount of disease prevented in the vaccinated group. In 2003 an analysis of herd protection in the US generated by PCV7 showed that immunization of young children prevented 9,140 cases in the vaccinated group while preventing 20,459 cases in the unvaccinated group.

“Over twice as many cases were prevented through the herd effect,” Harrison said.

### Estimated annual cases of PCV7-type invasive pneumococcal disease prevented in the U.S., 2003

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CDC, MMWR 2005,54:893
Harrison said the PCV7 vaccine also was credited with lowering the rate of antibiotic-resistant pneumococcal disease circulating in the US, as some of the serotypes targeted by the vaccine had become difficult to treat.

“When we started immunizing against pneumococcus in young kids, the incidence of disease caused by antibiotic resistant strains really plummeted quite substantially,” he said.

Harrison said the impressive amount of disease that can be prevented in the overall population by immunizing only young children presents an interesting question. When debating the value of extending pneumococcal vaccination to older children and adults, experts could well ask themselves how much disease, particularly pneumococcal pneumonia, would these additional immunizations prevent—in addition to what is being achieved already through herd protection?

“We desperately need data on the direct effects of pneumococcal conjugate vaccines on adult pneumonia,” Harrison said.

Session I: Epidemiology and Surveillance of Pneumococcal Disease

Any effort to implement pneumococcal immunizations for older children and adults will require a better understanding of the epidemiology of disease in LAC populations. PAHO’s Lúcia Helena de Oliveira offered an overview of the current state of pneumococcal disease surveillance in the region.

She noted that it’s widely accepted that pneumococcal diseases are a significant cause of sickness and death worldwide. But a key challenge facing decision makers is the limited amount of information available in the developing world regarding the burden of different types of pneumococcal ailments, chiefly pneumococcal pneumonia and pneumococcal meningitis. Yet introducing any vaccine—or, in this instance, expanding its use into new populations—requires evidence that the burden of disease justifies the investment.

“Surveillance is an essential component to decision-making,” de Oliveira said.

She noted that even when studies are available, data are not always collected in the same way, making it difficult to compile an overall estimate for the burden of disease. Moreover, pneumococcal surveillance ideally should be tracking the prevalence of various disease serotypes in different populations, she said. That way, researchers can more accurately predict the capacity of a particular pneumococcal vaccine formulation to reduce infections in a given population.

Nonetheless, de Oliveira said, there are statistics available that can shed light on the issue. For example, a 2009 study conducted by researchers at Sabin, CDC, and PAHO offered estimates for deaths in the Americas linked to pneumococcal infections in children. Pneumonia was found to cause between 980,000 and 1.5 million deaths, and meningitis caused between 2,600 and 6,800 deaths annually. Of these deaths, the total believed to be caused by pneumococcal infections was between 12,000 and 28,000.
**Picking Spots for Surveillance**

De Oliveira said that most pneumococcal surveillance work in the region involves collecting data on pediatric bacterial pneumonia and bacterial meningitis treated in hospitals. That’s because children under five with bacterial pneumonia are frequently hospitalized. And almost all incidences of meningitis require hospitalization.

There are currently 11 countries regularly reporting data to PAHO from hospital-based surveillance of pneumococcal diseases. It’s complicated work, de Oliveira said. For example, making a diagnosis of pneumonia can be difficult, as is determining whether it is bacterial. Now, adding another challenge, she said, is the desire for increased surveillance of pneumococcal disease in older children and adults, information that will be needed to determine whether PCV immunization should be extended to older populations.

An existing laboratory surveillance network called SIREVA collects data from regional and national laboratories and several hundred sentinel sites across the region. Although SIREVA provides data on pneumococcal disease serotypes in the region, de Oliveira said the data is not sufficient to develop estimates on the burden of disease in older populations. Another challenge to surveillance efforts is that the widespread introduction of pneumococcal conjugate vaccines into childhood immunization programs across the region is changing the epidemiological profile of pneumococcal diseases in all groups.

**Adapting Surveillance to Include Adults**

Despite the many challenges, de Oliveira said there are opportunities to expand existing surveillance systems that now monitor young children in order to gain more insight into the burden of pneumococcal disease in adults.

“We already have significant experience with sentinel sites for surveillance of childhood disease, so we can take this knowledge and to try to adapt it to adult surveillance,” she said.

In addition, influenza surveillance is relatively well established in most countries, de Oliveira said, and it might be possible to modify these efforts to at least assess pneumonia burden in adults. She said there are discussions already underway to incorporate pneumonia surveillance at sites that collect influenza data on adults.

**The laboratory surveillance network in Latin America**

PAHO’s Gloria Rey-Benito further explored data from SIREVA that might shed light on the disease burden in older age groups. She cautioned that while the SIREVA data is improving our understanding of disease trends beyond young children, adults over 60 continue to be poorly represented in the data—although they represent a crucial cohort for the study of pneumococcal disease.

She said surveillance is turning up some interesting insights, including the fact that serotype 12F is more common in older patients than in children.

“12F is perhaps one of the serotypes that seems to be saying: ‘Here I am, and I am affecting mostly the older groups,’ ” Rey-Benito said.

Serotypes 8 and 11A also are “relatively common” in older patients, she said.

The PCV vaccines currently on the market cover none of these serotypes—12F, 8 or 11A—, though the PPSV23 vaccine covers 8 and 11A.

Rey-Benito also noted that testing sometimes fails to identify the serotype and simply classifies it as “other.” She said wider adoption of more sensitive testing could “identify a large amount of these serotypes and reduce the number of references to ‘other serotypes.’”

Overall, she said that when studying serotype prevalence and distribution, it’s important to remember that they can differ country-by-country and that the impact of PCVs on circulating serotypes also can vary from one country to another.

“There are definitely great differences between countries, which leads to the need to maintain surveillance in each country and to improve the integration of clinical, epi and lab data,” she said.
Discussing Surveillance: Challenges in a Post-Vaccination Era

Ciro de Quadros sought to steer the discussion toward challenges posed by surveillance efforts in a post-vaccination era, particularly those that arise when different PCVs are in use throughout the region. He also pointed out that a vaccine’s overall impact on disease would inevitably depend on how widely it’s used.

“Unless I know the vaccine uptake, I cannot really take seriously any surveillance on epidemiology once the vaccination has started,” he said.

De Oliveira agreed that vaccination coverage rates needed to become a part of pneumococcal surveillance data. For example, the impact of pneumococcal immunization on disease rates would be quite different in areas where there is 30 percent coverage versus 80 percent coverage.

Another participant suggested that data on vaccine coverage should also document the type of vaccine involved (PCV10 or 13, or PPSV23) and the number of doses received, as this information can also influence vaccine impact.

Pneumococcal Disease Surveillance and the AGEDD Project

Maria Deloria-Knoll of the Johns Hopkins University Bloomberg School of Public Health discussed an ambitious effort to conduct a systematic review of published and unpublished data and provide global and regional estimates of illness, death, and disease serotypes linked to invasive pneumococcal disease (IPD) in children over five years of age and adults. It’s called the Adult Global Estimation of Disease Burden and Distribution of Serotypes (AGEDD) project. The goal, she said, is to accumulate data that could be used for “advocacy and policy making.”

Researchers involved in the project have looked at published papers, various databases, and surveillance information that many countries now post on the Internet. And they have focused on several of the most “serious pneumococcal diseases”—namely pneumococcal meningitis, pneumococcal bacteremic pneumonia, and pneumococcal non-bacteremic pneumonia.

Deloria-Knoll said the analysis was hampered by a lack of data in different regions for various conditions. For example, she said there were no data on incidence of pneumococcal meningitis in Asia, and no data for Africa or Latin America for estimating the ratio of bacteremic pneumococcal pneumonias to cases of meningitis. The researchers utilized various techniques to develop estimates where data was lacking.

Overall, the AGEDD project found that, globally, pneumococcal diseases account for between 250,000 to 400,000 deaths each year in older children and adults. It concludes, “pneumococci are an important cause of pneumonia and bacterial meningitis in older children and adults, with the highest occurrence in Africa.”

For each region, Deloria-Knoll said that researchers have endeavored to rank the top 13 serotypes for the older age cohorts. There were some serotypes that made the top 13 in one region but not in another. So overall, there were 19 different serotypes represented across the regions.

There were several trends noted in the AGEDD data. Serotypes 3 and 14 were found to be common in every region. Serotype 5 is found in Africa, Asia, and Latin America. Serotype 8 is common in Africa and Europe, and serotype 12F is only common in the Americas and Oceania. Africa has the least variety, with ten serotypes accounting for 70 percent of the isolates in the region. In North America, there were 12 serotypes that covered 70 percent of the isolates; in Europe and Oceania, 13; Asia, 15; and Latin America, 16.

For Latin America, serotype 1 was the top serotype followed by 14 and 3. By comparison, in North America, serotype 14 is dominant.
The data also appear to confirm the greater coverage achieved globally with conjugate vaccines that target more serotypes. PCV7, for example, covers only about 35 percent of the prevailing strains in Latin America for the older age cohort. But the PCV10 and PCV13 offer fairly similar coverage for every region.

Given the large amount of disease in children over five and adults that is caused by serotypes covered by PCV10 and PCV13, Deloria-Knoll said broadening their use could bring a big payoff in terms of lives saved.

"Depending on the case fatality rate, we're going to have a huge impact in terms of the total number of deaths," she said.

Deloria-Knoll said there are multiple qualifications that need to be made in terms of the uncertainties in the estimates generated by analysis. For example, the studies reviewed varied in quality, particularly for Africa. There also were challenges with taking surveillance information available on government web sites and integrating it into a database. But overall, she said, the study likely underestimates both incidence of disease and case fatality rates.

Pneumococcal Disease in Adults in LAC

"This data (on disease serotypes in Latin America) should be interpreted very carefully."
~ Fernando de la Hoz, National University of Colombia

Fernando de la Hoz, of the National University of Colombia, and other experts sought to provide a better understanding of how pneumococcal diseases affect adults and children over five in Latin America and the Caribbean. Like Deloria-Knoll, he cited difficulties in aggregating data from multiple sources. For example, there were instances in which the methodologies employed in some studies were sufficiently different from other approaches that it was not possible to include the information in a meta-analysis. He and his colleagues also found that studies involving small groups of patients—some with as few as 12—tended to show the lowest fatality rate for pneumonia.

Not surprisingly, studies that sought to identify risk factors related to dying from pneumococcal pneumonia frequently found that patients over the age of 65 were at particular risk.

For pneumococcal meningitis, the fatality rates in the studies varied significantly, ranging from 8 percent to 58 percent. The studies of meningitis also tended to be much smaller, de la Hoz said, and had far fewer patients than the studies of pneumonia fatalities.

De la Hoz and his colleagues also examined information on pneumococcal serotypes that had been collected from 2006 to 2011 in the SIREVA database. He said it was important to understand that many samples in the SIREVA data—36 percent—had been isolated from meningitis patients. Brazil has contributed a large number of samples to SIREVA, and most of their isolates are from meningitis patients.

But de la Hoz also said the high proportion of meningitis cases in the database does not reflect the real-world distribution of pneumococcal disease in the population of interest, i.e. people above the age of five. It's important to keep this fact in mind, he said, when comparing the serotypes from the SIREVA data to those covered by the three conjugate vaccines. For example, the data would appear to show that older patients are more likely to harbor serotypes that are not included in the existing conjugate vaccines.

In a study led by the Sabin Vaccine Institute, in collaboration with the Johns Hopkins International Vaccine Access Center (IVAC), the Centers for Disease Control and Prevention (CDC), and the Pan American Health Organization (PAHO), a group of experts performed a systematic review of available epidemiological data on adult pneumococcal disease in Latin America and the Caribbean.
“This data should be interpreted very carefully,” he said, because the rate of non-vaccine serotypes is higher in patients with meningitis compared to those with other pneumococcal syndromes.

The analysis also revealed a decrease in PCV serotypes in people older than five in Brazil and Argentina, after the introduction of universal PCV immunizations for young children—which could be a sign of herd protection. But de la Hoz reiterated the need for caution when drawing any firm conclusions, given the heavy weight of meningitis samples in the serotype data.

De la Hoz said if labs used urine tests instead of blood and sputum cultures it might be possible to gain a more reliable estimate of the pneumococcal disease burden in the region, as well as serotype distribution. He said there are urine tests available that probe for disease antigens and detect far more cases of pneumococcal pneumonia than other methods. And he noted that new methods have been developed to “detect not only a pneumococcal infection in urine” but also the presence of 14 disease serotypes.

De la Hoz wants to learn more about the non-vaccine serotypes found in the SIREVA samples. In reports published on the PAHO website, he said the non-vaccine serotypes are usually lumped into a single category. They need to be disaggregated, he said, so researchers can see which ones “are the most frequent in the region.”

Data on Disease Burden: How Much Is Enough?

David Fedson acknowledged the need for more surveillance, but said the lingering question is: how much is enough for making public health decisions? For example, he said, authorities in the US and Europe will justify adoption of pneumococcal vaccines for seniors and certain high-risk groups based only on “reasonable surveillance data for invasive pneumococcal disease,” coupled with analysis of cost-effectiveness.

“Some surveillance is interesting,” he said, “but it is not necessary to have data on some of these endpoints in order to make a public health decision.”

Ron Dagan of the Ben-Grurion University, added that some types of surveillance data can be more confusing than clarifying. And Deloria-Knoll agreed that the focus should be on better, not necessarily broader, surveillance.

Another participant raised questions about the difficulty in distinguishing the proportion of pneumonia cases that are tied to pneumococcal infections.

Deloria-Knoll acknowledged that it’s a challenge. She said the work of the AGEDD team generated estimates that about 25 percent of all pneumonias are pneumococcal pneumonias. Another participant noted that a recent study in the UK found that in older youth and adults, that number was 40 percent.

There was also a question regarding whether seeking data on such a broad population—people over five years of age—obscures the burden of pneumococcal diseases in people older than 50 or older than 65.

De la Hoz acknowledged that most of the Latin American studies looked at a large range of ages—from five to 70 years of age, or five to 81. The problem, he said, is that most of the published data is aggregated, and it may not be possible to break it down into narrower age groupings.

Dagan said given all of the uncertainties and qualifications swirling around various efforts to understand disease burden and serotype distribution in children over the age of five and adults, it could be useful to break down the challenges into specific categories:

- Where do I have the answers?
- Where do I not have the answers?
- Where are my answers possibly misleading?

He said such an exercise could be important because people tend to focus on the final numbers, not all of the methodological headaches involved in generating them.
Deadly Duo: Influenza and Pneumococcal Disease

"It seems like our immune response is able to deal with influenza alone—generally if not always. And it can deal with pneumococcus alone. But when the two come together, it's a problem."

~ Keith Klugman, Emory University

Emory University’s Keith Klugman discussed the latest evidence on the interaction between pneumococcal disease and influenza. He showed data from a study using mice that offered a dramatic example of how the two diseases together form a particularly lethal combination.

When one group of mice was exposed to influenza alone, none died. Another group was exposed to pneumococcus alone (serotype 3), one in ten died. But when a group of mice was exposed to influenza and, seven days later, to pneumococcus, all of them died. A final twist for the mouse study: when the exposures were reversed—the mice were given pneumococcus first and then influenza seven days later—all survived.

Klugman also showed how monkeys with influenza who were exposed to pneumococcus ended up with a much higher blood concentration of pneumococci than did monkeys exposed to the pathogen who were not suffering from influenza: 30,000 per mL in the flu group versus just 55 per mL in the non-flu group.

“To make a story simple, it seems like our immune response is able to deal with influenza alone—generally if not always—and it can deal with pneumococcus alone,” he said. “But when the two come together, it’s a problem.”

The big question is the extent to which pneumococcal infections account for fatalities during an outbreak of influenza—chiefly pneumococcal pneumonia—and thus how deaths attributed to influenza could be reduced by pneumococcal vaccination.

Klugman said there is intriguing data on this topic from the 1918 influenza pandemic. For example, a 2008 study of 58 lung specimens taken from victims of the pandemic noted that all of the specimens had indications of bacterial disease. However, he said it’s not clear whether the specimens were kept precisely because they had a bacterial infection or whether they were a random sample of influenza victims.

Another study of blood cultures taken from influenza patients during the pandemic found that in patients without pneumonia, there was no evidence of pneumococci. But 16 to 25 percent of patients who had influenza complicated by pneumonia had evidence of pneumococci in their blood. Also, an analysis of 285 lung cultures in pandemic influenza victims suffering from pneumonia found disease-related bacteria in 80 percent, with pneumococcus being the predominant organism.

Looking at the 2009 H1N1 pandemic, Klugman discussed a study of cultures taken from children who succumbed to the disease. It found about one third of the children were suffering from a “bacterial super infection.” And in Brazil, a study of patients whose deaths were attributed to H1N1 found 38 percent had a bacterial infection. Also, a study in Argentina found that H1N1 deaths in patients not associated with a high-risk group—they were neither very old nor very young—may have been associated with a bacterial infection. In addition, a study in France found that during the 2009 pandemic, a large portion of H1N1 fatalities in elderly patients involved a bacterial co-infection.

Klugman also presented H1N1 data compiled in 2013 by the CDC. It shows that, with the exception of children under five years of age, who probably received a pneumococcal vaccinations, “there was a significant excess of invasive pneumococcal pneumonia in the months of the pandemic compared to those months in previous years.”

“So, in summary, then, there’s significant evidence that the majority of deaths during the 1918 pandemic were associated with a synergistic lethality of bacterial infections, which were mainly pneumococci,” he said. “For 2009, bacterial
Fifth Regional PNEUMOCOCCAL SYMPOSIUM • 5 – 6 March, 2013 • São Paulo Brazil • FOCUSING ON OLDER CHILDREN AND ADULTS

pathogens played a role in at least a third of deaths, and there was an increase in bacterial pneumonia hospital admissions and invasive pneumococcal pneumonia hospital admissions.”

David Fedson referred to a study conducted in 2004 where mice were exposed to pneumococcus 14 days after they had been infected with influenza. That should have been enough time for the flu virus to clear from their systems, he said. And yet they died within two days.

“There was some fundamental alteration in the host response that has to do with innate and adaptive immunity,” he said.

Fedson also noted that while a third of patients in some studies who died from influenza had evidence of a bacterial pneumonia, two thirds did not. So he said influenza alone can be a proficient killer even absent a co-infection.

Klugman responded that while it’s true that influenza can be deadly all by itself, the data from various studies indicate that the combination of a viral and bacterial infection severely impairs the body’s ability to mount an effective response.

“It doesn’t mean you can’t die of influenza alone,” he said. “It doesn’t mean you can’t die of pneumococcus alone. But the interaction is responsible for a significant fraction of the mortality.”

Klugman also said that the overall estimate that co-infections were present in about one third of the 2009 pandemic influenza fatalities likely undercounts the problem, given the sensitivity of the tests.

Klugman also noted that influenza vaccination, if successful in providing protection from an influenza infection “can prevent the whole problem” associated with co-infections. The challenge, he said, is that influenza vaccination is required every year and it is not equally effective in all age groups. Also, in the case of pandemic influenza, which by definition involves a novel strain of the disease, there will be a delay in formulating and manufacturing a vaccine.

The Mechanics of Herd Protection

The CDC’s Jennifer Loo explored the phenomena of herd protection via immunization, or how vaccination against a certain organism can make the spread of that infectious organism less likely, and thus reduce the risk of disease in unvaccinated individuals.

It happens in two ways, she said.

There is herd protection when immunization of one group can reduce carriage of an infectious organism and therefore, reduce transmission of disease in the broader population, which is how pneumococcal vaccination of young children provides herd protection for older groups.

Herd protection can also occur if immunization is carried out with a vaccine that induces immunity through a weakened (attenuated) form of the organism. In this instance, immunity is achieved by the attenuated strain passing from vaccinated individuals to unvaccinated individuals. This type of herd protection—the only type that can be accurately referred to as herd immunity—can happen with oral polio vaccination (OPV), which utilizes a live-attenuated strain of the virus.

Session II: Current Status and Prospects for Disease Prevention

“Routine use of PCV7 has significantly reduced the burden of IPD in both children targeted to receive the vaccine and in unvaccinated adults. The overall decline in disease burden across all age groups (in the US) translates to 280,000 cases averted and 19,000 deaths prevented.”

~ Jennifer Loo, US Centers for Disease Control and Prevention
Many factors can affect herd protection and the magnitude of impact of a vaccine, Loo said. They include vaccination coverage rates, effectiveness of the vaccine, and underlying medical conditions in unvaccinated populations.

The impact of pediatric pneumococcal vaccination in the US on non-vaccinated groups provides good evidence of herd protection. Loo described how, by 2009, overall rates of invasive pneumococcal disease or IPD in children under five—the vaccinated group—had declined by 76 percent compared to the pre-vaccination baseline. For IPD caused by the seven serotypes in the PCV7 vaccine, the numbers dropped even more dramatically: from 80 cases per 100,000 to less than one case per 100,000 seven years after introduction.

During this time there also were steady declines among age groups of unvaccinated adult populations, with rates of IPD caused by the PCV7 vaccine serotypes falling by at least 90 percent.

"Routine use of PCV7 has significantly reduced the burden of IPD in both children targeted to receive the vaccine and in unvaccinated adults," she said. “The overall decline in disease burden across all age groups translates to 280,000 cases averted and 19,000 deaths prevented.”

In fact, the cases and deaths prevented in those 5 years of age and older have been greater than those among children less than 5 years of age. There have been cost benefits from PCV7 introduction as well. Accounting for only the IPD cases and deaths avoided in the vaccinated population, Loo said, PCV7 immunizations cost the US $33,000 per IPD case avoided, and $112,000 per life year saved. But add in the illness prevented and lives saved via herd protection, and those costs plummet to $5,500 and $7,500 respectively.

More recently, researchers have begun to analyze the impact of PCV13, which replaced PCV7 in the US in 2010. Data from 2012, Loo said, suggested a decline in the cumulative case-counts for IPD caused by the five additional serotypes included in the PCV13 vaccine (PCV7 vaccine is believed to provide some cross protection for the sixth additional serotype in PCV13—6A.) And just as with PCV7, the amount of vaccine-type IPD prevented in older age groups via herd protection appeared to exceed what had been achieved in the vaccinated group.
“In the Active Bacterial Core Surveillance area, of IPD cases caused by the additional serotypes in PCV13, 75 percent of averted cases were prevented in adults 18 years of age and older,” Loo said.

She added that other studies in the US have found similar declines in IPD rates after PCV7 introduction, suggesting herd protection from PCV7 among HIV-infected adults and infants too young to be vaccinated.

Loo cautioned that a number of factors can affect the degree of herd protection achieved more broadly by immunizing young children. These include vaccine coverage rates; the susceptibility of a given population; the proportion of disease caused by the serotypes the vaccine covers; the presence or absence of catch-up campaigns for immunizing children who were missed the first time; and the number of years since vaccine introduction.

“As more countries introduce PCV10 or PCV13 into their national immunization programs, there is a need to evaluate herd protection in a variety of settings,” Loo said.

Monitoring Serotype Mix, Post-Immunization

“A key issue for public health authorities is the need to monitor for pneumococcal serotypes that are not included in the vaccine deployed in a particular country. these non-vaccine serotypes can become more common and cause more illness in the wake of immunization, as the presence of serotypes covered by the vaccine declines. This is termed replacement disease.

Ron Dagan of the Ben-Gurion University, cautioned that, when assessing the potential for replacement disease to occur, it is important to understand that not all pneumococcal serotypes are equally capable of causing illness. Just because they replace vaccine serotypes in the nasopharynx does not mean they are equally capable of making people sick, he said. Studies show that after vaccination, “at the level of the nasopharynx, we see new bugs coming in,” but “carriage,” Dagan said, does not equate with “disease.”

Dagan divided serotypes into roughly three categories:

- “First league” serotypes, “the stars, the ones that really get bad;”
- “Second league” serotypes, which see action only if the stars are gone, but are not as likely to cause disease; and
- Serotypes in a “league of their own:” they are not commonly carried and also not likely to cause replacement at the nasopharynx level after vaccination, but they are very invasive, once they are acquired.

“In many countries that have been using widely PCV7 and in the presence of high antibiotic use, you can see that 19A becomes the number one problem in children because it is multi-resistant, it is virulent, and it is the only “prime league” pneumococcus that is not reduced by PCV7.”

~ Ron Dagan, Ben-Gurion University
In the wake of PCV7 introduction in the US and Europe, Dagan reported on the emergence of a “first league” serotype. Known as “19A,” the serotype was not covered by the vaccine, and it became more common following widespread immunization with PCV7.

“In the United States and other countries you got a huge increase,” Dagan said. But Dagan cautioned that the PCV7 vaccine might not have been solely responsible for the ascendancy of 19A. It turns out this same serotype had developed resistance to antibiotics.

“In many countries that have been using widely PCV7 and in the presence of high antibiotic use, you can see that 19A becomes the number one problem in children because it is multi-resistant, it is virulent, and it is the only “first league” pneumococcus that is not reduced by PCV7,” Dagan said.

But Dagan said there is evidence from the UK that 19A “was starting to jump up even before the introduction” of the PCV7 vaccine. The key point, he said, is that a pneumococcal vaccine may not be the only factor affecting the mix of pneumococcal serotypes in circulation. For example, he noted, after the introduction of PCV7, researchers saw a drop in 12F, a non-vaccine serotype. But no one suggested, “that this was because of the vaccine.” Yet when the non-vaccine serotype 35F increased, he said, “everyone talked about it as happening because of the vaccine.” This calls for caution before before vaccine is “accused’ to be the only factor responsible for replacement.

Dagan said it is important for disease surveillance activities to consider the many factors that can affect the distribution of serotypes in a particular population. For example, he said that while countries using PCV7 universally saw other disease serotypes fill in the void created in the nasopharynx, the mix of replacement serotypes varied.

“That is something we need to be thinking about,” he said. “Are our populations the same? Are we using the same antibiotics? Is the group of 60-plus in my country the same as 60-plus in his country? Maybe in my one country the average age of those who are 60+ group is 82 but in another country it is 63.”

Overall, he noted that moving on to the PCV10 and then the PCV13 vaccine, “most of the bad guys”—particularly 19A, which is covered by PCV13 formulation—are taken care of, and “most of the leftovers after that are not as strong.” He said research is showing that non-vaccine serotypes arising in the wake of immunization with PCV13 are likely to be a threat mainly to immune-compromised patients.

In the discussion after the presentations on herd protection, Loo was asked about the coverage rates Latin American countries will need to achieve before they can see the kind of herd effects documented in the US, where vaccine coverage is at about 90 percent. She said it’s hard to predict what those rates would need to be, but noted that Spain, with less than 50 percent coverage, did not see an impact in
adults on IPD caused by vaccine serotypes. Still, Loo said it might be possible to achieve herd protection nationwide at rates below 90 percent.

Dagan said that, from another perspective, one might assert that any level of vaccine coverage is likely to provide some type of herd protection. He pointed to a study that found unvaccinated infant siblings of vaccinated children carried fewer strains of antibiotic-resistant pneumococci, even before widespread vaccination takes place. “So one vaccine is already enough to have herd protection, in close contacts” he said. However, at the population level, one must cover a fairly large proportion of children with vaccination to observe a significant herd protection.

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Pneumococcal Vaccination in Adults

“Indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from immune-compromised adults.”

~ Tamara Pilishvili,
US Centers for Disease Control & Prevention

Despite the protective benefits gained from vaccinating children, a large burden of pneumococcal disease continues to affect adults in the US, according to the CDC’s Tamara Pilishvili. Most of the 44,000 cases of IPD diagnosed annually are found in adults over 50, she said, as are the majority of IPD deaths.

Pilishvili cited recent decisions by the US Advisory Committee on Immunization Practices (ACIP) to recommend immune-compromised adults be immunized with PCV13, as well as with PPSV23; and that immune-compromised children and youth between the ages of six and 17 be immunized with PCV13.
As of 2010, most of the disease found in adults over 65 involved three serotypes that were missing from PCV7 but included in PCV13, Pilishvili said—19A, 7F, and 3. Although the 6A antigen in the PCV13 vaccine may be providing some cross-protection against 6C, one of the other serotypes causing disease in adults, Pilishvili said that as of late 2012, there was not sufficient evidence to recommend routine immunization of all older adults with PCV13.

And evidence has started to accumulate that immunizing children with PCV13 is extending herd protection to adults against disease caused by serotypes 19A, 7F, and 3, thus reducing the need for direct immunization.

“The picture is similar to what we saw after the 7-valent vaccine introduction,” Pilishvili said.

But the herd effect appears to be insufficient to protect individuals with immune-compromising conditions. “Indirect effects of PCV13 use in children are unlikely to eliminate PCV13 serotypes from immune-compromised adults,” she said.

In addition, studies indicate that 21 percent of the invasive pneumococcal disease found in immune-compromised adults involves serotypes that are not in the PCV13 vaccine. But they are covered by PPSV23. So the recommendation is to give immune-compromised adults both vaccines, Pilishvili said.

Ideally, the dosing schedule would involve starting with PCV13 first, followed in at least eight weeks by PPSV23. A second dose of PPSV23 would be given five years later. For those adults who already have received the PPSV23 vaccine, the recommendation is to follow with a PCV13 one year (or more) later.

Snapshots of PCV Vaccination in Latin America: Brazil and Uruguay

“We are finding that the vaccine is going to have an important impact on the public health of our country.”
~ Carla Domingues, Brazil Ministry of Health

Brazil

Carla Domingues, of Brazil’s Ministry of Health, discussed the impact of adding PCV10 to the country’s childhood immunization schedule. Starting in 2010, Brazil recommended that children receive three doses at two, four, and six months of age, followed by a fourth dose at 12 months. Health officials also recommended that unvaccinated children 12 to 23 months have at least one dose of the vaccine. Vaccine coverage in the first year reached 80 percent, though the goal is to hit 95 percent.

Preliminary data from post-vaccine surveillance efforts show that the vaccine appears to have been 87 percent effective against vaccine serotypes and 72 percent effective against, “all types of IPD.” For children over one year of age targeted for a “catch-up” vaccination with a single dose, the vaccine was 66 percent against disease overall, and 85 percent against vaccine serotypes.
Domingues also presented results from a study indicating the vaccine has prompted a 23 to 28 percent reduction in pneumonia in general among children nationwide.

“We are finding that the vaccine is going to have an important impact on the public health of our country,” she said.

**Uruguay**

Gabriela García Gabarrot of Uruguay’s Ministry of Public Health said her country introduced PCV7 in March of 2008, with doses administered at 2, 4 and 12 months and a catch-up of two doses for unvaccinated children at 15 and 17 months. In 2010, PCV7 was replaced by PCV10 with the same immunization schedule. Post-vaccination surveillance has revealed a decrease in PCV7 serotypes, as well as a decrease, albeit a slower one, for PCV13 serotypes.

Overall, she said that surveillance studies showed that “for one or more doses, we had an effectiveness percentage of 91.3, and for two or more doses, it was 94.8 percent effective.”

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**Summary of Day One: Exploring the Expansion of Coverage**

For Ciro de Quadros, a key issue from the first day of presentations was the need to improve surveillance work, despite the fact that surveillance for pneumococcal disease poses particularly tough challenges. But, he said, the evidence available thus far is provocative.

“It’s very clear that we have a very serious problem with pneumococcal disease in children older than five years of age and in adults,” he said. “And we certainly have vaccines that can help solve it.”

He said his “back of the envelope calculations,” based on the data presented, is that “we have more or less two deaths per hour due to pneumococcal disease in children over five years of age, and adults.”

De Quadros said countries in the region might be spending an estimated US $300 million annually to treat about half the cases of pneumococcal disease. And with that amount of money, he said, “we could vaccinate the entire Latin American cohort, all of them.”

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**Results: PCV10 Efficacy**

<table>
<thead>
<tr>
<th>Efficacy with ≥ 1 dose of PCV10</th>
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</tr>
</thead>
<tbody>
<tr>
<td>• For IPD</td>
<td>72% (CI 95%: 52 to 83)</td>
</tr>
<tr>
<td>• For IPD vaccine serotypes</td>
<td>87% (CI 95%: 69 to 94)</td>
</tr>
<tr>
<td>• For all IPD in the cohort eligible for catch-up</td>
<td>66% (CI 95%: 11 to 90)</td>
</tr>
<tr>
<td>• For the IPD vaccine serotypes within the cohort eligible for catch-up:</td>
<td>85% (CI 95%: 28 to 97)</td>
</tr>
</tbody>
</table>

“It’s very clear that we have a very serious problem with pneumococcal disease in children older than five years of age and in adults.”

~ Ciro de Quadros, Sabin Vaccine Institute
Vaccine Developers Offer Their Perspective

Representatives from several pharmaceutical companies offered an overview of their work with pneumococcal vaccines, including new products under development.

GlaxoSmithKline

Otávio Cintra, of GlaxoSmithKline, discussed his company’s 10-valent PCV, known as Synflorix, noting strong evidence of the vaccine’s efficacy against targeted serotypes and in reducing overall incidence of disease. For example, a study in Finland found an 88 percent reduction in invasive pneumococcal disease in children under the age of six months. Data from Brazil showed 85 percent efficacy against the vaccine’s serotypes and 71 percent efficacy against pneumococcal disease overall.

“Synflorix vaccine has demonstrated impact and effectiveness against invasive pneumococcal disease,” he said. Cintra also noted there is evidence post-vaccination of a drop in hospitalizations due to pneumonia in several Brazilian cities.

Pfizer

Pfizer’s Luis Jodar discussed his company’s experience with its 13-valent vaccine. He argued that since the introduction of PCV13 into National immunization programs around the world, effectiveness has been documented for all clinical outcomes (IPD, pneumonia, otitis media and nasopharyngeal carriage) when used in either the 3+1 or 2+1 dosing schedules.

“Herd effects from PCV13 have been documented much more rapidly than what we originally expected,” he said.

Significant serotype specific reductions on IPD and nasopharyngeal carriage have been observed for serotypes 1, 6A, 7F and 19A. As yet, there has not been enough serotype 5 cases to document an effect. Whereas there has been substantial numerical reductions in serotype 3 cases from several countries, no effectiveness has yet been demonstrated and no impact on NP carriage against this serotype.

“It’s a bit premature to make a definite conclusion and we’ll have to wait a bit longer to determine the impact of PCV13 in reducing serotype 3 pneumococcal disease,” he said.

Beyond infants and children, the disease burden of pneumococcal disease is very high in adults. In many countries, Jodar noted, PCV13 has been licensed against IPD and pneumococcal pneumonia in individuals 50 years and older. PCV13 has the potential overcome the limitations attributed to the 23-valent plain polysaccharide vaccine (PPV23).

Pneumococcal conjugate vaccines, for example, have shown capable of inducing T-cell dependent immune response and thus immunological memory, do not induce hyporesponsiveness after repeated administration, have a profound impact in acquisition of carriage and have demonstrated to be efficacious against pneumococcal pneumonia in infants and young children. An ongoing double-blinded placebo-controlled randomized efficacy trial (CAPITA) conducted in the Netherlands and that has enrolled more than 85,000 individuals 65 years an older will determine the efficacy of PCV13 against Community Acquired Pneumonia in this population.

Jodar argued that a major question is whether “in countries with very high vaccination uptake where PCVs have been introduced into routine infant immunization programs and where herd effects have been profound, is there enough disease to justify the direct vaccination of adults”. The indirect effects of pneumococcal conjugate vaccines implementation on rates of vaccine-type IPD in adults have been profound. However, Jodar mentioned that the most frequent presentation of pneumococcal disease in adults is non-invasive pneumococcal pneumonia, and drawing firm conclusions regarding the magnitude of indirect effects in adults for pneumonia is more difficult. Jodar presented data emerging from studies of CAP in the US, which utilize a validated serotype-specific urinary antigen detection assay, suggesting that the PCV7 serotypes remain a notable cause of CAP in US adults even 10 to 12 years post-introduction of PCV7. Therefore, indirect effects
alone may not be sufficient to tackle this significant public health burden in older adults even in settings of high uptake of conjugate vaccine in the pediatric population.

**Merck**

Merck's Barbara Homeier discussed her company’s vision for reducing the burden of pneumococcal disease and its progress toward developing a 15-valent pneumococcal conjugate vaccine or PCV15.

She said Merck's overall goal is to "provide the broadest coverage for children and adults." She said Merck seeks to do this by maintaining a "robust" global supply of Pneumovax, its 23-valent-polysaccharide vaccine, for adults while developing PCV15 for pediatric populations.

Homeier said Merck sees a future "where not only do PCVs reign, but where we can have a symbiotic relationship with polysaccharides."

Homeier said Merck has pursued a 15-valent vaccine that covers two additional serotypes, 22F and 33F, because "we have seen sustained increase over the last five years in 22F and 33F." She cited data showing these serotypes account for "about 10 percent of IPD cases" in adults in the US.

The Polysaccharide Vaccine

"Don't let anybody tell you the pneumococcal polysaccharide vaccine doesn't prevent pneumococcal pneumonia."

~ David Fedson, formerly of the University of Virginia and Aventis Pasteur

David Fedson, a former professor of medicine at the University of Virginia and formerly with Aventis Pasteur, offered something of a defense for the 23-valent pneumococcal polysaccharide vaccine, or PPSV23. He referred to a "classic study" published in 1976 that found an experimental version of a 13-valent polysaccharide vaccine administered to gold miners in South Africa achieved an 82 percent reduction in pneumococcal bacteremia and a 78 percent reduction in pneumococcal pneumonia.

"Don't let anybody tell you the pneumococcal polysaccharide vaccine doesn't prevent pneumococcal pneumonia," he said.

Fedson acknowledged evidence that antibodies generated by the vaccine rise during the first month following immunization, but then “fall off substantially.” However, he said they continue to "persist at a level which some would regard as low, but which is about twice as high” as pre-immunization.

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**Primary PPV23 Vaccination Of Older Adults Induces Immunity That Last For At Least 10 Years**

- 444 ambulatory adults ≥ 50 years of age
- PPV23 naive and no previous history of invasive pneumococcal disease
- Received one dose of PPV23
- IgG antibodies evaluated in 308 subjects at 5 yrs; 72 subjects at 10 yrs

Fedson noted that there has been much discussion about the potential of PPSV23 to produce "hyporesponsiveness" and that this issue has been used to call into question the value of polysaccharide vaccination. The concern is that it could presage an impaired immune response to a pneumococcal pathogen. But Fedson claimed, "We don't know that, if hyporesponsiveness does occur, whether it has any clinically important consequences."

"The laboratory data are important and they help support certain opinions, certain views, but let's look at what happens in people before we make final decisions," he said.

Fedson cited a 2009 study that looked at the response to PCV7 and PPSV23 in adults 50 to 80 years old. The study concludes that "either vaccine can be administered within the sixth and eighth decade with a similar resultant concentration of IgG antibodies.

Fedson said cost must be considered when comparing adult immunization with polysaccharide versus conjugate vaccines. Fedson noted that if one assumes PPSV23 is about 50 percent effective at preventing IPD, and the PCV13 is about 75 percent effective, then there would be a cut-off after which a higher price for the PCV13 vaccine would not be justified.

"If PCV13 is expensive, it might be better to increase coverage with a polysaccharide vaccine as opposed to spending money on the conjugate vaccine," he said.

Fedson expressed skepticism concerning the potential value of using PCV13 in older adults in countries that are immunizing young children with the vaccine. He believes that as herd protection asserts itself, "there will be very little PCV13 serotype pneumococcal disease to prevent."

"These considerations are certainly behind the decision recently made in the UK not to introduce PCV13 in adult populations," he said.

Peter Paradiso raised an issue that is causing concerns in the US about the continued use of the polysaccharide vaccine: the percentage of disease in people over 65 years of age caused by the serotypes contained in the vaccine has hardly changed even as vaccination rates have climbed over 60 percent.

Fedson said he also shares this concern, but he wondered to what extent it is caused by a failure to vaccinate more than once. He noted as well "people getting invasive pneumococcal disease and dying are often over 75 years old:"

"We have never bothered to say: 'Well, look, antibodies levels go down in five years so let's revaccinate every five years, and let's do that three or four times in a row," he said, "So by the time somebody reaches the age of 80, they have had four doses of the pneumococcal vaccine given every five years.' Then let's see what it does."

De Quadros said that one of the most interesting things about the arrival of conjugate vaccines is the "renewed interest in the polysaccharide vaccine." He said he finds it disturbing to consider the potential impact of any failure to administer more than one dose of the polysaccharide vaccine.

**The Future of Pneumococcal Vaccines**

"If we could use pneumococcal proteins as conjugates, that would be exciting."

~ Keith Klugman, Emory University

Emory University's Keith Klugman began his discussion of the future of pneumococcal vaccine development by revisiting evidence that there are deadly interactions between influenza and pneumococcal disease. He noted that in 1917, researchers prepared what they considered a vaccine against influenza that was in fact a vaccine that actually contained killed pneumococci.

He said while the vaccine did nothing against influenza—because the virus had yet to be isolated—a retrospective meta-analysis of studies from the period found that it provided "significant protection against hospitalization for pneumonia," and from death as well.

The vaccine was retired about 80 years ago, but Klugman wonders whether "perhaps it was discarded too soon."
Klugman also cited more recent evidence linking vaccination against pneumococcal disease to a reduction in influenza-related hospitalizations. A double-blind study in the 1980s in South Africa of an experimental 9-valent pneumococcal conjugate vaccine found a 45 percent drop in influenza hospitalizations for vaccinated subjects versus unvaccinated controls. He said the results suggest that pneumococcal diseases alone can contribute to about half the hospitalizations for influenza.

“We think the vaccine was preventing pneumococcal super-infection and therefore reducing the burden of hospitalization from influenza,” he said.

Klugman presented a model showing that pneumococcal infections during bouts of influenza are much more likely when there is a lot of pneumococcus circulating in young adult populations. Thus, reducing the pneumococcus carriage rate via immunization should lessen the overall number of influenza related hospitalizations.

Taking this hypothesis one step further, Klugman speculated as to whether the dramatic reduction in the carriage of pneumococcus in young adults over the last century, from around 40 percent in 1918 to around five percent today, could explain why the latest flu pandemic caused so few hospitalizations for pneumonia relative to the 1918 pandemic. The incidence of pneumococcal pneumonia hospitalizations associated with influenza dropped from about 11.7 per thousand in 1918 to less than one per thousand in the 2009 pandemic.

Klugman also noted a study in Spain in which “receipt of PCV was associated with a 48 percent reduction” in hospitalization from the H1N1 2009 pandemic influenza.

Meanwhile, Klugman and his colleagues decided to look at hospitalization trends in 10 states in the US as PCV vaccination was being rolled out. They found that as PCV vaccination rates increased, influenza hospitalizations declined. Even in years when overall influenza hospitalization rates rose, “states that had the highest level of coverage, about 80 percent, had far fewer influenza hospitalizations when compared to states with lower coverage.”

“This is not prevention of influenza in the community, this is all hospitalizations with flu,” he said.

Klugman noted that given the benefits that are flowing from PCVs—the herd protection, the intriguing evidence of the effect on influenza hospitalizations and mortality—there could be justification for exploring new types of PCV vaccination that could target the remaining reservoirs of disease.

He said looking to the future, it might be possible to push pneumococcal disease rates even lower by exploring the potential of vaccines formulated with killed pneumococci and conjugate vaccines that use pneumococcal proteins.

“If we could use pneumococcal proteins as conjugates, that would be exciting,” he said.
Assessing the Cost-Effectiveness of Immunizing Older Groups

Anushua Sinha with the New Jersey Medical School discussed studies that shed light on the cost-effectiveness of giving pneumococcal vaccinations to older children and adults. She reviewed a study from the US that modeled different vaccination strategies, including PPSV23 by itself, PCV13 by itself, and strategies that combine the two.

The most striking statistic, she said, was for pneumonia prevention that showed two doses of PCV13 achieving the best results. Also, strategies that included PPSV23 appeared to prevent more cases of IPD.

In terms of cost-effectiveness, “all strategies had very favorable cost-effectiveness rations.” But she noted that the value of adult vaccination depends on the level of herd protection generated by vaccinating children: As herd protection increases, the value of adult vaccination declines. Conversely, if it turns out that herd protection is lower than current estimates, then the value of adult vaccinations increases.

“The degree of herd protection that results from childhood vaccination is critical,” she said.

Sinha also offered an overview of the literature emerging in Latin America regarding the cost effectiveness of adult pneumococcal vaccination. She said there are methodological differences among the various studies that make it difficult to conduct a meta-analysis. But she said evidence is accruing regarding the costs associated with various pneumococcal diseases.
Sinha focused on a study in the São Paulo state of Brazil that found immunizing adults over 60 years of age with PPSV23 is cost-effective.

She said that overall, decision makers in Latin America need more information on all of the core issues related to vaccine introduction: disease burden, economic burden, vaccine effectiveness, and program costs.

“A pipeline of information is emerging to meet the need for evidence, but it exists primarily in the abstract and pre-publication stage,” she said.

The good news, she said, is that early indications from studies within Latin America and from elsewhere in the world support the notion that “pneumococcal vaccination of older adults saves lives and is an efficient use of health care dollars.”

**Economic Burden of Pneumococcal Disease in Older Age Groups**

<table>
<thead>
<tr>
<th>Country</th>
<th>Age (yrs)</th>
<th>Pneumonia</th>
<th>Meningitis</th>
<th>Bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>≥ 18</td>
<td>—</td>
<td>—</td>
<td>Public: $10,996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Private: $10,677</td>
</tr>
<tr>
<td>Brazil</td>
<td>≥ 60</td>
<td>Public: $1,236*</td>
<td>—</td>
<td>—</td>
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<td></td>
<td></td>
<td>Private: $7,044*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>0-10</td>
<td>$6,718**</td>
<td>$23,307</td>
<td>$9,740</td>
</tr>
<tr>
<td>Mexico</td>
<td>≥ 50</td>
<td>$4,270**</td>
<td>$10,921</td>
<td>$7,867</td>
</tr>
<tr>
<td>Multi-Country</td>
<td>≥ 50 (assigning dollar value to years of life lost)</td>
<td>Argentinan: $34,111, Brazil: $31,166, Chile: $28,498, Colombia: $25,028, Mexico: $22,237, Venezuela: $23,843</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* bacteremic pneumonia  ** inpatient pneumonia

Constenla D and Garcia C, unpublished data

Dagna Constenla of the Johns Hopkins University International Vaccine Access Center presented preliminary findings from an analysis of the economic burden of invasive pneumococcal diseases in older children, adults, and the elderly in Latin America and the Caribbean. Constenla led the analysis in collaboration with the Sabin Vaccine Institute, IVAC, the Centers for Disease Control and Prevention (CDC), and the Pan American Health Organization (PAHO).

She echoed the observations of others regarding the dearth of data on these groups. Further complicating the quest for insight, she said, is the fact that an analysis of cost must consider not just the direct cost of treatment, but also other issues, such as lost productivity.

Constenla and her colleagues looked at different types of cost: the average cost for patients hospitalized with pneumonia or meningitis, and the impact of invasive pneumococcal diseases on GDP per capita. To estimate treatment costs, they looked at treatment guidelines at the country level and supplemented this information with physician surveys.

Looking at five countries—Argentina, Brazil, Chile, Colombia, and Uruguay—they estimated that the cost of treating a case of invasive pneumococcal disease ranged from US$993 to US$3,132 in older children (5-17 years), from US$1,274 to US$3,247 in

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“Invasive pneumococcal disease, namely bacterial pneumonia and meningitis, generate considerable healthcare costs (in older age groups) in the countries we studied.”

~ Dagna Constenla, Johns Hopkins University
adults (18-64 years) and from US$1,746 to US$3,535 in elderly (65+ years), respectively, with higher costs incurred in the elderly due to higher level of resources used for treating pneumonia. Across countries, treating IPD was more expensive in Chile than in Colombia, Argentina, Brazil and Uruguay, due to higher hospital care costs incurred in that country. Overall, the costs of hospital stay accounted for 45% of the total treatment costs in these countries. They also gathered evidence from a variety of sources to generate a regional estimate for overall health expenditures for IPDs. Across the region, the health care costs of IPD ranged from US$8.2 million to US$14.1 million, with higher costs incurred by the elderly due to higher level of resources used for treating the elderly.

“Invasive pneumococcal disease, namely bacterial pneumonia and meningitis, generate considerable healthcare costs (in older age groups) in the countries we studied,” Constenla said.

### Healthcare Costs* Of IPD In Selected Countries

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Argentina</th>
<th>Brazil</th>
<th>Chile</th>
<th>Colombia</th>
<th>Uruguay</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-17 years</td>
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*Cost per case US$, 2012

As for the impact on GDP, the analysis found that total health expenditures for IPDs for patients above the age of five amounted to 0.1% percent of GDP, compared to the reported 8-10% of GDP spent on healthcare overall in the region. An estimated 28.9% of the health expenditures for IPD in this age group were attributed to health service costs related to hospitalized IPD, while 3.7% was due to health services for pneumonia treated in an ambulatory setting. The remaining 70.5% of these expenditures were due to costs borne by families. The long term lost productivity over the course of their lifetimes of children with IPD was not calculated.

Overall, Constenla said, the analysis revealed that IPDs “incur considerable cost to healthcare systems in the countries studied.” She noted that the estimates did not consider costs borne by families or by the private sector. Also the estimates focused only on costs related to infections with bacterial pneumonia and meningitis.
Vaccinating the Elderly in Colombia

Nelson Alvis-Guzmán, of the University of Cartagena, discussed a recent study he co-authored that considered the cost-effectiveness of introducing the PPSV23 in an elderly population in Colombia. He said it was the first to assess the introduction of PPSV23 in a developing country.

Essentially, the study calculated the cost of pneumococcal diseases in older adults in Colombia and compared that to the cost and efficacy of vaccination. Spanning a five-year period, the analysis compared the cost of disease in Colombians over the age of 60 to the cost of vaccination, and found that vaccination would net close to US $8 million in savings.

“There’s a great reduction on the cost of the disease following vaccination,” he said.

The analysis also looked at the annual per capita income in Colombia to consider the benefits to be derived from saving a year of life. Alvis-Guzmán said he followed the WHO recommendation for assessing cost-effectiveness, which asserts that “if winning an extra year of life costs close to the per capita” income, then the intervention will be cost effective. Per capita income in Colombia in 2008 was about US $4,800, while the costs of saving a year of life via immunization with PPSV23 would be between US $1,285 and $1,500, he said.

Alvis-Guzmán said that, overall, considering both savings to the health care system and the cost-benefit of saving lives, vaccinating Colombians over 60 years old with PPSV23 appears to “to be highly cost-effective when compared to the non-vaccination scenario.”

In deciding whether to introduce the vaccine widely, it will be important to also consider as well that demographic growth in Colombia “is heavy at the 60 and over segment,” he said.

The study was originally published in the October 13, 2011 edition of the journal Vaccine.

ProVac: Informing Decisions on Pneumo Vaccines

Cara Janusz discussed the work of the ProVac initiative, which was created by PAHO’s Immunization Project to strengthen national capacity to make evidence-based decisions on new vaccine introduction.

She noted that ProVac has developed a tool called TriVac, which, among other things, has provided insights regarding the cost-effectiveness of immunizing children with either PCV10 or PCV13. She said there are discussions about expanding the focus to include information on the cost-effectiveness of pneumococcal vaccination in adults.

Janusz said ProVac also needs to be thinking “beyond cost-effectiveness” to explore other issues such as the “programmatic and financial implications” of vaccine introduction.

“The cost of vaccination or rather the feasibility, financially, of introducing a vaccine can have a very different meaning for a country than just purely the cost-effectiveness,” she said.
Experiences with Adult Immunization

Several presentations explored the experience of a number of countries with adult immunizations in general and with pneumococcal vaccines in particular.

The CDC’s Carolyn Bridges said that despite the progress made with pneumococcal vaccination, the US has a "substantial burden of pneumococcal disease.”

Her colleague, Shannon Stokley, noted that, while the 23-valent vaccine is recommended for all people over 65, as of 2011, only about 62 percent of seniors had been immunized. The goal is 90 percent by 2020. The vaccine is also recommended for high-risk individuals 19 to 64. The goal is to reach at least 60 percent of this group by 2020, but coverage remains at about 20 percent.

She said the US also sees a racial divide in provision of adult vaccines, with higher coverage in white non-Hispanics when compared with other racial and ethnic groups.

One trend suggests that more and more adults are being immunized outside of the doctor’s office. For example, in 2012, 20 percent of adults got their flu vaccine in a pharmacy or store, and 14 percent were immunized in their workplace. Stokley said these venues are increasingly offering other vaccines, including pneumococcal and zoster vaccines.

“This definitely creates many opportunities, but also some challenges in being able to make sure that the primary care medical provider and others have a good record of checking what the patient has received,” she said.

Costs also can be a factor influencing adult vaccination rates, Stokley said. While some vaccines are covered by insurance, others require co-pays that may seem steep for some adults, “especially for the zoster vaccine,” she said.

There are additional challenges, she said. These include a general inattention to immunization in adult care practices; fewer public health resources available for adult immunization, and there is a general lack of awareness of what vaccines are available for older adults. For example, while surveys show the vast majority of adults are aware of the influenza vaccine, many do not know that they should get vaccinated for pneumococcal diseases, or they say their doctor did not recommend it.

Pneumococcal Vaccination in Older Age Groups in Argentina

Alejandra Gaiano with Argentina’s Ministry of Health discussed efforts in her country to offer pneumococcal vaccines to older age groups.

Argentina provides PPSV23 to people 65 and over and to anyone between the ages of two and 65 years old who might be considered at a higher risk if exposed to pneumococcal pathogens.

In 2012, Argentina introduced the PCV13 for children starting at two months of age and as a catch-up vaccine for children 12 to 24 months old. In addition, at-risk children between 24 and 59 months receive the PCV13 first followed by the PPSV23. At-risk patients between the ages of five and 64 get only the polysaccharide vaccine.

Gaiano noted that surveillance done prior to introduction of the PCV13 showed that 23 percent of IPDs occurred in children over five years old, with the most prevalent serotypes being 5, 14, 1, and 19A. He said studies were ongoing to assess the impact of PCV13 across the population.

He said the challenge at the moment is to improve coverage for children under the age of two and for children older than two who have a co-morbidity.
**Adult Immunization in Brazil**

Carla Domingues said Brazil’s “big work” to vaccinate older groups began in 1992 with a campaign to eliminate measles, focusing on children up to the age of 15. Other immunization efforts involving older cohorts include an initiative launched in 2008 to eliminate rubella and congenital rubella by vaccinating women and men between the ages of 12 and 39. Also, in 2011, Brazil began offering hepatitis B to young adults aged 20 to 29.

Overall, Brazil has available 12 vaccines for children, four for adolescents and adults, and one for the elderly. In addition, the public health system offers several other vaccines, including PPSV23 and hepatitis A, to older, high-risk populations.

“We still have a huge path ahead of us in terms of adult vaccination, because we have to make sure women of childbearing age are properly vaccinated, (and) we have a country in which yellow fever is endemic,” Domingues said. “There are three thousand municipalities in which the virus is wild--and we have to make sure the population is duly vaccinated. So in considering whether to introduce a new vaccine, we should do so…only if we can ensure coverage with the other vaccines.”

**In Colombia, Looking for New Ways to Reach Adults**

Cristina Pedreira, PAHO advisor in Colombia, discussed Colombia’s attempts to move vaccines beyond young, pediatric populations, as well as the challenges the country faces in reaching older children and adults. For example, Colombia’s Health Ministry is seeking stronger alliances with labor unions to reach working populations, while also looking for opportunities to engage with informal sectors.

Colombia’s first major adult vaccination effort was a campaign to eradicate measles and rubella, which was launched in 2005. And during the recent flu pandemic, Colombia focused on vaccinating at-risk adults. Colombia also is providing hepatitis B vaccine to adults aged 20 to 30 in the Amazon region.

Pedreira said achieving adequate coverage in adult populations targeted for immunization has required Colombian health officials to consider new ways of using conventional and social media to raise awareness.
Session V: Roundtable — Pneumococcal Vaccination in Adults, Country Spotlights

“The concept of adult vaccination is not yet internalized as an essential element for a healthy male or female. Vaccination is still imprisoned inside a pediatric framework.”
~ Gabriela Moreno, Chile Ministry of Health

Experts from several countries in the region briefly shared their experience with moving pneumococcal vaccinations into adult populations.

Perspectives from Chile, Costa Rica, Panama and Uruguay

Chile

Gabriela Moreno with Chile’s Ministry of Health said pneumococcal vaccination is a key part of Chile’s 2020 strategic plan to meet a variety of public health goals. Chile introduced the PPSV23 vaccine in 2007 for adults over 75 years old; by 2010 it was offering the vaccine to anyone over 65.

There have been challenges with achieving consistently high coverage rates in Chile with PPSV23 in seniors, however. The overall average is around 52 percent, she said, though it can range from 26 to 74 percent, depending on the region.

“We are pushing with communications campaigns to get this age group vaccinated against both influenza and pneumococcal (disease),” she said.

The Ministry of Health recently launched an effort to measure the efficacy of the 23-valent vaccine on pneumococcal infections in older adults, in addition to gauging its cost-effectiveness and years of life saved.

Costa Rica

Roberto Arroba, with Costa Rica’s Health Ministry, discussed his country’s experience with PPSV23. The vaccine was first offered in 2011 to people over 65 years old. Coverage had reached 63 percent by 2012, he said, and is expected to climb to 67 percent in 2013. The country has had little success with offering the vaccination to at-risk populations. It also experimented with offering the vaccine to the older adult groups together with influenza vaccination, but there was resistance to getting both at once.

Uruguay

Mariana Casas, with Uruguay’s Department of Health Surveillance, said the PPSV23 vaccine is offered to individuals over 65 in addition to anyone over the age of two who is in a high-risk group. The vaccine is free if received during special vaccination campaign periods. Coverage thus far has been relatively low for both of the targeted populations.

Panama

Yadira Moltó of Panama’s Ministry of Health said her country offers the PPSV23 vaccine to anyone 60 or older. Panama has recently started including the vaccine in influenza immunization campaigns, which has helped raise coverage rates. PCV is offered to young children and recently became available to children five to 19 who have certain risk factors.
Summary

Rosanna Lagos of the Roberto del Rio Children’s Hospital in Santiago, Chile, and moderator of this session summarized that all countries seem to have difficulty achieving high coverage rates for adults targeted with pneumococcal vaccination. She also noted that countries pursuing pneumococcal vaccination in older age groups need data on “the impact of investing all those human resources and capital investments.”

“We need intense, exhaustive, clinical and laboratory monitoring, with clear follow up of the vaccine lots and also of the vaccinated people for reports of invasive infections,” she said.

Chile’s Moreno said any effort to vaccinate adults faces a fundamental challenge.

“The concept of adult vaccination is not yet internalized as an essential element for a healthy male or female,” she said. “Vaccination is still imprisoned inside a pediatric framework.”

De Oliveira said a key to improving immunization rates among adults hinges on obtaining support and advocacy from health professionals. She said that the endorsement of health professionals has made a big difference with overcoming resistance to HPV vaccines, for example.

Conclusion

“I feel the same vibes I felt almost eight years ago…This gives me the certainty that the nations represented take with them an important challenge. And it is to determine exactly what goes on with adult populations with this disease.”

~ Ciro de Quadros, Sabin Vaccine Institute

PAHO’s Cuauhtémoc Ruiz-Matus acknowledged that moving from the now familiar world of pediatric immunization to embrace adolescents and adults “presents all of us with great challenges.”

“To get an adolescent to do anything, including vaccination, is quite a challenge, and getting an adult to do so poses an even greater challenge,” he said.

“And the male adult poses an even bigger challenge. So, operationally, we face a great challenge.”

But he drew inspiration from how quickly countries in the Americas have added PCVs to their childhood immunizations schedules.

“Eighty-one percent of children born in the Americas, from Canada to Argentina and Chile, are born in countries with the PCV vaccine already in their vaccination schedules,” she said.

Similarly high adoption rates have been achieved for vaccines against rotavirus. And efforts to introduce those vaccines, he said, were fuelled by “conversations like ours, at this symposium, which provide data that inform policy and decision making.”

De Quadros said that at this most recent symposium, “I felt the same vibes I felt almost eight years ago, when we met to present findings on morbidity, mortality and all the costs” of the burden of pneumococcal disease in children.

“I feel the same energy in the air and this gives me the certainty that the nations represented here will take with them an important challenge,” de Quadros said. “And it is to determine exactly what goes on with adult populations with this disease, and to come up with all the data needed by governments in order to introduce the vaccine to cover other age groups.”

He reiterated that rough estimates gleaned from the various presentations “suggest that we have a great problem that not only costs many lives, it also poses grave difficulties for the economies of these countries.”
### Speakers

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Ecuador
# Delegates

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