PROCEEDINGS OF THE

Third Regional Pneumococcal Symposium

February 13–14, 2008
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Pneumococcal
Symposium

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Pneumococcal disease is a major cause of sickness and death among children worldwide. This bacterial infection causes serious diseases including meningitis, pneumonia and sepsis as well as less serious conditions such as otitis media and sinusitis. According to the World Health Organization, acute respiratory infections, many caused by pneumococcus bacteria, kill an estimated 2.6 million children under 5-years of age annually. Most of these deaths occur in developing countries. Recently, pneumococcus has threatened to become even more deadly by developing resistance to the most commonly used antibiotics, making prevention ever more urgent.

The goal of this meeting was to review what we know about the burden of pneumococcal disease in the region and what we know about the ability of recently developed pneumococcal conjugate vaccines to dramatically reduce sickness. There is one conjugate vaccine already on the market and two new conjugate vaccines could be available in the next year. Many more are in the pipeline.

The quest for better insights into the burden of pneumococcal diseases and the efficacy of vaccines will continue in the coming years. But the wealth of information presented at the symposium, and contained in these proceedings, shows that we know enough to act now and save lives.
Executive Summary

The Third Regional Pneumococcal Symposium held in Istanbul revealed that, despite the need for more data on the burden of disease, the knowledge available today in Turkey and surrounding countries is sufficient to conclude that widespread adoption of a conjugate pneumococcal vaccine is likely to save scores of children from dying of pneumonia, meningitis and other invasive pneumococcal diseases.

Officials from the World Health Organization provided new data showing that the deaths caused by pneumococcal disease in countries in the region are at least as high as they were in North America and Europe prior to their introduction of a 7-valent pneumococcal conjugate vaccine in 2000. Data at the conference presented by United States health officials showed that since adding the vaccine to the country’s national immunization program, incidence of invasive pneumococcal disease has dropped by about 75 percent and prevented some 10,000 premature deaths in children from the disease.

Experts from countries represented at the conference noted that due to variations in the particular pneumococcal strains causing the majority of culture proven illness in the region, the 7-valent vaccine might not be as effective there as it has been in the U.S. However, they presented evidence that the vaccine, even by conservative estimates, could reduce invasive pneumococcal infections in the region by 50% or more, thus saving a substantial number of lives. Furthermore, industry representatives at the conference claimed pneumococcal vaccines that could soon be on the market will offer even higher degrees of effectiveness.

There was also an abundance of evidence that as the region evaluates the vaccine, health authorities are fighting a rear-guard action against invasive pneumococcal disease. All countries reported a rise in virulent strains that are showing at least some level of resistance to antibiotics. They discussed research showing that immunization, in addition to preventing disease, can be effective at subduing these dangerous antibiotic resistant strains.

There has been concern globally that the success of pneumococcal immunizations may be short-lived and the pneumococcal serotypes targeted by a vaccine will simply give way to non-vaccine “replacement” serotypes. During the symposium, an expert on the phenomenon asserted that while, indeed, non-vaccine serotypes are becoming more evident in areas that have adopted immunization, so far that has not translated into a serious increase in “replacement disease.” The evidence, he said, is that invasive pneumococcal diseases are continuing to drop in the face of immunization.

Much of the conference focused on how to inform decision makers in the region that conjugate pneumococcal vaccines — which are considerably more expensive than previous immunizations — are a prudent investment. Numerous participants talked about how difficult it can be to get precise data on how many people in a particular country are suffering or dying from a disease caused by pneumococcus bacteria.

A WHO expert talked about the organization’s efforts to address this challenge by drawing on evidence from a variety of sources. For example, a WHO team is conducting comprehensive surveys of the scientific literature and weighing evidence of disease reduction following vaccine introduction to develop methods that can provide country-by-country estimates of disease burden. Country representatives spoke of developing new surveillance or research projects that can provide a window on pneumococcal disease and also document which serotypes are the main causes of invasive disease at the national level.

It was clear that data collection is a challenge. One presenter noted that the countries that could benefit the most from vaccination are also the ones least likely to have the capacity to conduct comprehensive disease surveillance. Other experts noted that even with the proper tools, pneumococcal diseases often elude detection. For example, antibiotics can mask their presence in pneumonia, samples collected for laboratory confirmation are easily contaminated, and methods of detecting and defining diseases caused by pneumococcus vary widely.

Despite the challenges in data collection, the overall sense at the conference was that progress is being made. Several participants observed that it is important for researchers to not allow their justifiable desire for better data to be used by decision makers as an excuse to delay adopting what has proven to be a very effective vaccine. They also suggested that in addition to pursing better science, it was important for the participants to become more aggressive public advocates for pneumococcal disease prevention.

Ultimately, the conference made it clear that these are exciting times for pneumococcal prevention.

For example, a scientist from the PATH Pneumococcal Vaccine Project talked about how PATH is aggressively pursuing new approaches and technologies that could simultaneously boost the effectiveness and reduce the costs of pneumococcal immunization. A representative from the GAVI Alliance reported that a new effort to spur pneumococcal vaccine development through what are known as Advanced Market Commitments (AMCs) is close to roll-out. The initiative seeks to attract more industry interest in pursuing a range of vaccines for developing countries by promising them a quick financial return on their investment. Pneumococcal vaccines have been selected as a first, “pilot project” for the AMC concept.

After exploring all of the many details regarding the biology and epidemiology of pneumococcal diseases, Ciro de Quadros of the Sabin Vaccine Institute said that it is important to return to the central reason for the meeting: the disease is killing millions of children, there is a vaccine already on the market that could prevent many if not most of those deaths, and new vaccines are on the way.

To drive the point home, he pointed out that during the two days of the symposium, “700 children died from this disease.” “Imagine if we have a crash of a jumbo jet every day, would we see it still and not do anything?” he asked. “And I think that is what is happening with this disease is that these children are dying, an average of 15-16 children per hour, and the world is doing nothing.”
Introduction

On February 13 and 14, 2008, health experts gathered in Istanbul, Turkey for the 3rd Regional Pneumococcal Symposium to build consensus on how to intensify the fight against the disease in Central Asia, Eastern Europe and the Middle East.

The meeting covered the status of pneumococcal vaccine development and implementation, reviewed existing knowledge about pneumococcal disease and what needs to be further understood about the health and economic burden caused by the disease. The meeting also identified key actions for advancing pneumococcal disease prevention.

Pneumococcal disease actually involves a host of afflictions—chief among them are severe forms of pneumonia and meningitis—caused by the bacterial pathogen Streptococcus pneumoniae. According to the World Health Organization (WHO), each year some 2.6 million children under 5-years old die of acute respiratory infections and about 1 million of those deaths are caused by pneumococcal disease.

Most of the burden of pneumococcal disease is born by developing countries, where pneumococcus is potentially the most dangerous pathogen threatening children under 2-years old. Over the past few decades, treatment for the disease, where it is available, has gotten weaker and weaker due to the fact that a growing number of pneumococcus strains or “serotypes” are becoming resistant to commonly used antibiotics.

Today, disease experts believe that a new generation of pneumococcal vaccines, known as conjugate vaccines, has the potential to dramatically reduce illness and deaths caused by pneumococcus worldwide. The technology behind the conjugate vaccine is technically complex, but the end result is relatively simple: it is an immunization that, unlike the older pneumococcal polysaccharide vaccine (which has been available since the late 1970s), prevents diseases in the group most vulnerable to invasive pneumococcal infections: children under 2-years old.

There is now a conjugate vaccine on the market that targets 7 pneumococcus serotypes (the heptavalent or 7-valent pneumococcal vaccine). In the U.S., where the vaccine was introduced in 2000, the serotypes covered are responsible for the majority of pneumococcal disease. However, the dominant disease serotypes can vary from region to region.

There are currently 10-valent and 13-valent conjugate vaccines in the late stages of development that, based on evidence from clinical trials, would expand the biological reach of pneumococcal immunization. Meanwhile, there are believed to be about 20 other pneumococcal vaccines in the early stages of development.

The challenge for countries represented at the symposium is two-fold. Scientifically, there is a need for better data on the burden of pneumococcal disease and the dominant serotypes in the region in order to predict the potential impact of a vaccine. Politically, policymakers need to be convinced that the threat is sufficient and the vaccine effective enough at reducing burden of disease to justify the relatively high costs of a pneumococcal immunization.

Setting the Stage for Discussion

For Najwa Khuri-Bulos, head of Pediatrics and Infectious Disease at Jordan University Hospital in Amman, the core issue confronting those attending the conference did not necessarily concern the effectiveness of the existing 7-valent vaccine. “Everyone knows it is a very good vaccine,” she said. Rather, the “major challenge,” she said, is to convince people to “give this vaccine so that we can move forward with prevention of this disease.”

In her opening keynote address, Khuri-Bulos expressed impatience with the pace of pneumococcal conjugate vaccine introduction in his region, where only Qatar had added the vaccine to its national immunization program at the time of the symposium. (Saudi Arabia was providing the vaccine for high-risk groups). She sees the slow pace of pneumococcal vaccine adoption as illustrative of a rapidly widening “immunization gap” between the developed and developing world. She noted that the gap already has widened to the point that the immunization schedule in many developing countries provides children with “only seven” vaccines against various infectious diseases while the immunization package in wealthy countries may provide twice that amount.

The gap can be considerable even between neighboring countries, which is the case in the Arab region, she said. “We have people who are terribly rich—they don’t know what to do with their money—and there are people dying of hunger.”

For example, she said about one third of Arab countries have yet to adopt the vaccine against haemophilus influenzae B or Hib, which is another major killer of children. “I can’t forget that we have about 80 million people (in Egypt) who do not have the haemophilus influenzae vaccine.”

Khuri-Bulos said that today pneumococcal immunization is high on what her students call the “wish list” for new vaccines, a list that also includes chicken pox, rotavirus, influenza, and human papillomavirus (HPV) vaccines. She said she understands that there are other, older vaccines
available that also need to be added to immunization programs, but she doesn’t want that problem to become an excuse to delay consideration of the newer vaccines.

“I would hesitate to say that you have to wait until the job is done for the old vaccines,” she said, noting that “maybe introducing the new vaccines will make you do a better job” for the old vaccines.

Khuri-Bulos is particularly concerned that adoption of the existing 7-valent pneumococcal vaccine will be delayed in many countries by a perceived need for more data documenting burden of disease. The irony, she said, is the poor countries likely to gain the most benefit from the vaccine are also those countries with the fewest resources to pay for such a data gathering exercise.

“We are talking about countries that have very few funds to start out with to provide vaccines, let alone pay for this relatively expensive process,” she said.

Debates about the vaccine’s varying degrees of effectiveness could also lead to inaction, Khuri-Bulos said. She was referring to the fact that the vaccine might not target all of the serotypes that play an important role in pneumococcal disease in the region, thus making it less effective than it is in the U.S. and northern Europe.

“Maybe someone will tell me it is only 60% efficacious (against invasive pneumococcal disease) because our serotypes are different,” she said. “I think whenever a vaccine is very good, even if the output may only be 60% or 70%, if it is safe, if it is efficacious, if it prevents mortality, we should do more to push for introducing that vaccine.”

Khuri-Bulos said that despite the challenges that are impeding regional introduction of a pneumococcal vaccine, there is reason to hope that progress is on the near horizon.

Globally, she said she is heartened by what she sees as a much broader recognition that infectious diseases are a “major threat” to global security and economic viability. She credits this awareness with playing a role in the emergence of new financial mechanisms that are spurring industry interest in producing vaccines for developing countries.

She also sees opportunities to address the barriers of vaccine adoption, like the high cost of some vaccines, through stronger

FIGURE 0.2 Classification of the economic status of Arab countries

<table>
<thead>
<tr>
<th>LOW INCOME</th>
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<td>Mauritania</td>
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From Najwa Khuri-Bulos, Jordan University
Source: Global Alliance for Vaccines and Immunization, 2000
Khuri-Bulos is particularly impressed by the regional approach to immunization efforts undertaken in Latin America and the Caribbean where Pan American Health Organization (PAHO) has created, among other things, a regional purchasing program that lowers immunization costs by buying in bulk.

Khuri-Bulos also believes that, while it might “raise some eyebrows,” the time may be ripe to tap into swelling national defense budgets to pay for immunizations. She said that since infectious diseases are now being portrayed as a threat to national security, it could be “argued that vaccines are, in fact, necessary for national defense.”

Borrowing rhetoric from the U.S. presidential campaign, Khuri-Bulos called for a “new paradigm” in the region’s approach to adopting new vaccines, from one that starts with the question “can we do it?” to one that begins with answer “yes, we can.”

“I think whenever a vaccine is very good, even if the output may only be 60% or 70%, if it is safe, if it is efficacious, if it prevents mortality, we should do more to push for introducing that vaccine.”

—NAJWA KHURI-BULOS, JORDAN UNIVERSITY, JORDAN

**FIGURE 0.3**

**Arab Countries and new vaccines**

- **HepB vaccine:** Introduced in all except Somalia & South Sudan
- **Hib Vaccine:** All except
  - Egypt, Tunisia (competing priorities) & Iraq
  - Somalia & Mauritania: eligible for GAVI but not for NVI window
- **Pneumococcal Vaccine:**
  - Introduced in Qatar (routine) and Bahrain & Saudi Arabia (high risk groups)
  - Yemen: GAVI support approval with clarifications
- **Rotavirus vaccine:** Not yet

From Najwa Khuri-Bulos, Jordan University
Global Pneumococcal Disease Burden

Thomas Cherian, Coordinator of WHO’s Expanded Program on Immunization (EPI), discussed his work to develop a better understanding of the burden of pneumococcal disease. It is being done in collaboration with GAVI’s PneumoADIP, based at Johns Hopkins.

Assessing data on burden of disease is crucial, he said, because health interventions must be chosen and prioritized based on a solid understanding of the severity of the problem they are intended to address.

In studying the burden of disease caused by pneumococcal pathogens, Cherian said he and his colleagues focused on the “severe end of the spectrum” since that is where the vaccine has the potential to make the greatest impact. Therefore, they were primarily interested in uncovering the burden of pneumococcal meningitis and pneumococcal pneumonia.

Part of the assessment involved scouring the scientific literature for relevant studies. The process initially found 14,000 articles, which were eventually whittled down to 426 studies. Cherian said those articles did not provide data for every country. So researchers used what Cherian called the “nearest neighbor” method. They stratified country data based on the region, subregion and child mortality rates. In countries that did not have local data, they used data from nearby countries that fall into a similar child mortality strata to estimate the burden. The goal was to get a broad, country-by-country estimate of severe illness and death caused by pneumococcus as of 2000, the year the 7-valent vaccine was introduced in the U.S.

Figuring Out When Pneumonia is Pneumococcal Pneumonia

There is a fair amount of information available estimating the overall burden of pneumonia. But, Cherian said that because pneumonia has such a variety of causes, it is a challenge to make a definitive statement about how many people get sick or die specifically from pneumococcal pneumonia.

Cherian said researchers decided one way to estimate the proportion of pneumonias caused by pneumococcus is to look at clinical trials that have tested the effectiveness of pneumococcal vaccines against pneumonia. Simply, pneumonia prevented by the vaccine is likely pneumococcal pneumonia, he said.

With the insights gained from these trials, and other data on pneumonia, Cherian and his colleagues were able to come up with a formula they believe produces a credible estimation of the proportion of pneumonia cases and pneumonia deaths that are likely to have been caused by pneumococcal disease. Their analysis concluded that while pneumococcus was linked to only 8% of pneumonia illness, it is responsible for 36% of deaths from the disease.
Doing the Best with What They Have

Cherian acknowledged that the data on burden of disease is not perfect. For example, in trying to estimate the burden of pneumococcal meningitis, he and his colleagues found 90 studies, almost half of which were considered low quality. Furthermore, there were no studies that documented incidence of pneumococcal meningitis in the Southeast Asia region. He said the data was sufficient, however, to conclude that most deaths from pneumococcal disease are due to pneumonia, not meningitis.

Cherian showed brief results—he was still lacking exact figures—that put the number of pneumococcal cases and deaths in each country in one of four categories. For cases of disease, they ranged from less than 1,500 per 100,000 children under 5-years old to more than 4,000. For deaths, they ranged from less than 100 to more than 500 per 100,000. (See Graphic).

The work of Cherian’s team shows that having a high incidence of pneumococcal disease does not always translate into a high number of deaths. For example, South Africa (due to its high rate of immune comprised HIV patients) has a particularly high number of pneumococcal cases. But South Africa’s death rate from the disease is lower than in other areas of Africa.

Cherian said the difference is attributable to “access to care.” Even though many countries in sub-Saharan Africa have a lower rate of pneumococcal disease than South Africa, the death rate is higher because it is harder to get treatment.

He also said that while the death rates in Europe and North America are relatively low compared to sub-Saharan Africa or South Asia, the disease, prior to immunization was still killing 100 out of every 100,000 children and sickening 1,000 out of every 100,000.

“I don’t want anyone going away with the feeling that this disease is not important in certain regions,” Cherian said.

While he acknowledged that his team was working with a “paucity of data,” Cherian said the estimates are nonetheless insightful and that it is important not to “make the perfect the enemy of the good.”

“We don’t see this as an end in itself but as the beginning of a process that will allow us to continually refine and revise our burden estimates,” he said.

Identifying Important Strains of Pneumococcus

Around the world there are several different strains or “serotypes” of pneumococcus that pose a threat. A major consideration for the global effort to combat pneumococcal disease through immunization is the extent to which vaccines contain proteins or “antigens” that will elicit an immune response against the strains that are predominant in a given region.

Hope Johnson from GAVI’s PneumoADIP at Johns Hopkins Bloomberg School of Public Health presented preliminary results from the Pneumococcal Global Serotype Project (Version 1), which aimed “to identify and collect all existing data on serotypes causing invasive pneumococcal disease among children worldwide,” estimate regional distribution, and identify what determines variance around the globe.

What they have found thus far, she said, is that, serotype 14 was the most commonly isolated serotype in children under...
five years of age in all regions except Asia, where serotype 1 co-ranks as the most common serotype. Between 7 and 11 serotypes account for >80% of all isolates in each region, although the specific set of serotypes may differ. Africa and Asia share the same top eight serotypes, but the percent covered by these eight is lower in Asia than in Africa.

Despite regional differences in the number of serotypes causing disease, Johnson said it appears that there is more overlap than divergence in terms of the particular pneumococcal strains that are causing disease. When researchers look across the various regions, one thing that stands out, Johnson said, is that there is a “limited set of seven serotypes” accounting for greater than 60 percent of invasive pneumococcal disease. She said that, contrary to previous analyses “the serotypes in the existing 7-valent” vaccine—that is, a vaccine that prompts an immune response to those seven common serotypes—will represent approximately 50-75 percent (assuming 6A/6B cross-protection) of invasive pneumococcal disease in every region. She said coverage with the 7-valent vaccine for children under five varies from region to region (though the variability lessens when looking only at children under two). However, Johnson said there is less regional variation in projected coverage with the 10 and 13-valent vaccines now in development, which, she noted, include serotypes that could account for at least 70 percent of invasive disease. Johnson cautioned that a key limitation of the serotype study is that there was limited data available from “some countries with very large under 5 populations,” including China, India, Nigeria and Indonesia.

DISCLAIMER: The Pneumococcal Global Serotype Project analyses presented in these proceedings (Version 1) were preliminary and have since been finalized (Version 2) and are available at: http://www.vaccineamc.org/files/TTP_Codebook.pdf .

“I don’t want anyone going away with the feeling that this disease is not important in certain regions.”

—THOMAS CHERIAN, WORLD HEALTH ORGANIZATION
As health officials in the region seek greater insight into the burden of pneumococcal disease in their particular countries, it is important to step back and consider some of the issues involved in pneumococcal surveillance, said Orin Levine, Executive Director of GAVI’s PneumoADIP. He said that for him, “finding pneumo” is a bit like trying to “find Nemo.” Scientists know it’s there, he said, but they must search through a vast ocean of data to find it.

One issue most agree on, he said, is that surveillance almost always underestimates the true burden of disease because reporting systems are limited and diagnostics only capture a fraction of actual cases.

As was noted earlier, the problem with surveillance is that epidemiologists are trying to come up with systems that accurately track and identify cases of pneumonia, meningitis, ear infections and sepsis that are caused by pneumococcal infections rather than one of several other potential conditions. But Levine said doctors and hospitals do not routinely collect the culture (such as spinal fluid or blood) required to identify the underlying cause of a disease.

So the cases of pneumococcal disease that actually are reported reflect only “the tip of the iceberg” Levine said. And like an iceberg, he said, what one sees “above the water,” so to speak, is “only a fraction of the problem.” The majority of cases remain hidden, he said, “underneath the water.”

For example, he pointed out that surveillance data indicated that after introducing the 7-valent vaccine, the U.S. saw 129 fewer cases of pneumococcal disease per 100,000 people. But was that the true impact of the vaccine? CDC officials, he said, have reported that after the vaccine was introduced, hospital admissions for pneumonia fell by 500 per 100,000. While there was no data on how many of those pneumonias involved pneumococcus, Levine said there would appear to be a vaccine-related impact.

“It was four times greater than the reduction” in confirmed pneumococcal cases, Levine said.

Nonetheless, despite its limitations, Levine said surveillance that tracks confirmed cases remains important for a variety of reasons. He pointed out that while it may not paint the complete picture, it still contributes to our understanding of burden of disease and impact of immunization programs. It also can reveal whether pneumococcal serotypes not contained in a vaccine are becoming more common in the wake of immunization.

“But it is important that we point out that surveillance itself...always underestimates the true disease burden and should not be used as a summary of disease burden in and of itself,” he said. “And we know this because vaccine impact studies show a much higher burden of preventable disease by uncovering the cases missed by laboratory confirmation.”
"It is important that we point out that surveillance itself... always underestimates the true disease burden and should not be used as a summary of disease burden in and of itself."

— ORIN LEVINE, GAVI'S PNEUMOADIP, US

**SIDEBAR 2.1**

**In the Laboratory, the Inexact Science of Pneumococcal Surveillance**

A key technical challenge of disease surveillance is that laboratory diagnosis of pneumococcal disease has long depended on "culture based methods"—taking a sample from a patient and observing it to see if pneumococcal colonies grow on laboratory culture media such as sheep blood agar. But cultures are particularly vulnerable to producing false negatives, said David Murdoch, Head of Pathology at New Zealand’s University of Otago, Christchurch.

“We are happy with the ones we diagnose,” he said, “but we are afraid of missing the ones that (falsely) test negative.”

There are many steps involved in culture based testing and each one presents an opportunity for errors, Murdoch said. Samples may not be collected properly. There can be delays in getting them to the laboratory or in processing them once they arrive. Technicians may put them on the wrong growth media, he said, or they may become inadvertently contaminated.

He said culture-based tests are more reliable for revealing cases of pneumococcal meningitis than pneumococcal pneumonia, largely because it is easier to get a high-quality sterile sample from the site of infection (i.e. spinal fluid—which is used for meningitis diagnosis) than it is to get an “appropriate” sample from the lung in the case of suspected pneumococcal pneumonia.

For example, the upper airways (nose and throat) can be “colonized” with pneumococcus that is not actually causing disease, making it difficult to determine whether pneumococcus isolated from fluid taken from the lungs is a “true pathogen,” said Murdoch, or merely an “innocent bystander.” Also, he said it is particularly difficult to get fluid or “sputum” from the lungs of children.

Given the issues with lung samples, Murdoch said surveillance of pneumococcal pneumonia tends to rely on data derived from blood cultures from pneumonia patients. But he said cases identified through blood cultures are a fraction of the actual number of pneumococcal pneumonias.

Another problem with conducting surveillance via laboratory tests, Murdoch said, is that widespread use of antibiotics may be masking the presence of pneumococcus in pneumonia patients. He pointed to a study showing that in the “pre-antibiotic” era, blood and sputum cultures indicated that 80 percent of pneumonias, at least in adults, were pneumococcal pneumonias. Now the percentage of pneumococcal pneumonias revealed by laboratory testing is in the single digits, Murdoch said, though researchers “of course believe” that the proportion is far higher.

There are new tests for pneumococcal pneumonia under consideration. Studies exploring a new way of detecting pneumococcal antigens in urine show that the test, which can produce results in 15 minutes, can identify a high proportion of pneumonias caused by pneumococcus, Murdoch said. The test appears to be less susceptible to interference from antibiotics than culture-based methods, with studies showing pneumococcus antigens still detectable in half of adults with pneumonia six weeks after starting medication. But the test, unfortunately, does not perform as well with samples taken from children, he said. In addition, the high costs of the test remain a barrier to broader use.

Today, there is increasing use of the polymerase chain reaction (PCR) methodology to detect specific microbial DNA associated with particular infections. Murdoch said there has been considerable work exploring PCR tests that could detect pneumococcus, but the results thus far have been “quite mixed and disappointing.”

He said researchers are in the “early stages” of exploring other testing techniques, including one that seeks to detect pneumococcus in breath samples.
Burden of Disease in Turkey: Seeking Understanding Amidst a Dearth of Data

Mehmet Ceyhan of Hacettepe University in Ankara said the main problem with discussing the burden of pneumococcal disease in Turkey is that there is “no surveillance.” However, he said there is research that can offer some insights into Turkey’s situation.

Ceyhan and his colleagues are working on one study that, since 2005, has collected 408 cerebrospinal fluid (CSF) samples. In the first year that samples were gathered, there was an outbreak of meningitis caused by meningococcus bacterium. Pneumococcus was found in only 22.5 percent of samples. But, as the epidemic subsided in the subsequent two years a greater proportion of meningitis samples (37%) contained pneumococcus.

Ceyhan said researchers are also using data gathered in other countries to calculate an estimate of pneumococcal disease incidence in Turkey. He said such analyses currently suggest that each year in Turkey pneumococcus causes:

- 250 cases of meningitis,
- 2,500 cases of bacteremia (bacterial infection of the blood),
- 250,000 cases of pneumonia, and
- 2.5 million ear infections or “otitis media”

He said there have been studies in Turkey that have attempted to assess the potential effectiveness of the existing 7-valent pneumococcal vaccine. One found it would cover only 40% of locally documented serotypes. But, in that study,
Ceyhan said, the age group of the subjects—6 to 16 years old—was higher than the target group, which is children from under two to under five. Three other pediatric studies involving a range of age groups, including the target and other age groups, reported serotype coverage ranging from 76% to 83%.

Ceyhan reported on a study from 1998 that looked at the potential impact of a 9-valent vaccine. It found the vaccine would have 90% serotype coverage in children under 2-years old. Another study is underway, he said, and with only 21 samples analyzed so far, only about 40 percent contain serotypes that are in the “vaccine spectrum.” But Ceyhan cautioned that those are “very preliminary results.”

“I can say that there is a need for disease burden studies, a surveillance system for pneumococcal diseases and serotype distribution, and cost effectiveness studies not only for deciding the need for routine pneumococcal vaccination but also to follow the serotype change and the change in the disease burden,” Ceyhan said. “And I expect that (in Turkey) we will find the conjugate pneumococcal vaccine is cost effective.”

“...”

—MEHMET CEYHAN, HACETTEPE UNIVERSITY, TURKEY
The burden imposed on people and populations by pneumococcal diseases is not confined to the immediate effects of illness but to long-term problems as well. Samir Saha discussed the work of the Meningitis Collaborative Study Group in Bangladesh to monitor two groups of 50 children after they were discharged from treatment for pneumococcal meningitis. One group was monitored for the short-term (30-40 days post-hospital discharge) and the other for a longer period of time (six to 24 months).

For the subjects in the short-term group, 65% suffered at least one impairment. Hearing impairment was observed in 33% of cases, visual impairment in 8%, and there were mental impairments and psychomotor impairments (movement problems associated with brain functioning) in 41% and 49% of cases respectively. But Saha observed that with timely intervention, “these children can turn out to be normal.”

However, lack of attention can lead to long-term problems. Saha said in the group of meningitis patients followed for a longer period of time, 50% still were having problems six months to a year following initial treatment. There were hearing problems in 18% of the children, 41% had mental impairments and 35% experienced psychomotor delays.

Saha’s group also observed that in many instances the costs of care imposed a crushing economic burden on the families involved. Parents frequently took out extremely high-interest loans to pay for hospital stays or sold land to raise cash. Saha said it was not uncommon for a father to abandon the mother of a child disabled by meningitis. Further complicating their long-term outlook, Saha said, is the fact that in Bangladesh and other developing countries, there are not the services and accommodations for the disabled that are now ubiquitous in the developed world.

Efforts to ameliorate this substantial burden, he said, could start with better treatment of meningitis. Saha noted that early intervention is fairly effective against the disease since pneumococcal strains that cause meningitis in Bangladesh, India, Pakistan and other Asian countries are “very sensitive to penicillin.” The problem, he said, is that in many areas less than 50% of potential patients are getting treatment. Even with good initial treatment, Saha said better strategies for preventing long-term disabilities also are needed.

Ultimately, he believes “prevention by immunization could be the main strategy.”

“The developing countries have very few things to be proud of, but we have one thing and that is very successful immunization programs,” Saha said.

Saha added that despite the clear benefits that would be gained from adopting a pneumococcal vaccine, policymakers struggle with limited resources and competing priorities. He said the hope at the moment is that innovative international efforts to make pneumococcal vaccines more affordable, such as the pilot Advance Market Commitment (AMC) program that could offer companies a financial incentive to produce pneumococcal vaccines for poor countries, will accelerate immunizations “and prevent these disabilities.”

SIDEBAR 2.2
The Human Toll of Pneumococcal Diseases

Bangladesh Study Offers Perspective on the Burden of Meningitis

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Antibiotic Resistance in the Region
Worldwide, a key reason health officials are keen to prevent pneumococcal diseases via immunizations is that there are a growing number of strains resistant to treatment with antibiotics. Cigdem Kayacan of the Istanbul University, Istanbul Faculty of Medicine observed that drug-resistant pneumococcal bacteria are on the rise “in many countries, including Europe.” Particularly alarming, he said, is the rapid rise in strains that are resistant to both penicillin and a category of antibiotics known as macrolides, which includes erythromycin.

Kayacan explored data from a variety of studies looking at antibiotic resistance in the region that collectively confirm that antibiotics are under assault. For example, in Turkey, about 40% of pneumococcal strains examined exhibited at least an “intermediate” level of resistance to penicillin while 5-10% were “fully resistant.” Resistance to erythromycin was lower at less than 20%.

Regionally, she said, there are high rates of penicillin-resistant pneumococcus in Cyprus, Israel, Romania and Lebanon, with Lebanon having the highest rate at over 65%. By contrast, Egypt, Jordan, Morocco, Malta, Tunisia and Algeria have low rates-around 5 to 15%-of penicillin-resistant strains. As for rates of resistance to erythromycin and other macrolides, Greece, Bulgaria and Israel are about the same as Turkey (below 20%). Cyprus and Lebanon stand out, Kayacan said, with macrolide-resistance rates of over 30%. Regionally, the rate of “dual resistance”—resistance to both kinds of antibiotics—is between 10 and 25%, she said.

Kayacan also noted evidence of pneumococcal strains becoming resistant to drugs in another class of antibiotics known as fluoroquinolones, which includes ciprofloxacin. One study in Greece reported a 23% rate of ciprofloxacin resistance in adult infections, she said. However, overall, fluoroquinolones appear to be still quite effective. Kayacan said that in Turkey, a review of research studies indicated that resistance to fluoroquinolones was around 2% to 3%.

—CIGDEM KAYACAN, ISTANBUL UNIVERSITY, TURKEY
SESSION III
Impact of Conjugate Pneumococcal Vaccines: Direct and Indirect Effects

The Complicated Math of Vaccine Impact
Researchers are eager to understand as much as possible about what happens to a targeted disease or diseases following the introduction of a vaccine to prevent them. Hanna Nohynek discussed findings from studies conducted in the United States on the impact of the 7-valent pneumococcal vaccine and the impact of an experimental 9-valent vaccine in Africa (in The Gambia and South Africa), which protects against two additional serotypes not found in the 7-valent formulation.

A key difference in the various trials was the amount of disease in the targeted population—children under 2 years old—prior to vaccination. For the two U.S. trials analyzed, one was conducted in California where 167 of every 100,000 children were suffering from invasive pneumococcal disease. The other trial was carried out among Navajo and Apache Indian children, where the rate of disease ranged from 537 to 1,820 per 100,000 children. In the Africa populations, the rate of disease was 380 per 100,000 children in The Gambia and 112 per 100,000 in South Africa.

In the California trial, the 7-valent vaccine showed 97% efficacy against invasive pneumococcal disease compared to 77% in the Navajo study. In the Gambian study, the 9-valent vaccine achieved 77% efficacy. In South Africa, where researchers distinguished between HIV-positive and the more disease-vulnerable HIV-negative populations, the efficacy was 58% for those who were HIV-positive and 85% for HIV-negative subjects.

Recently, there has been an effort to take data from all of these trials and examine the effect of the vaccines on the individual pneumococcal serotypes they are formulated to fight. Looking at the seven serotypes that are targeted by both vaccines, Nohynek referred to the meta-analysis of Klugman et al and noted that the overall efficacy against the 7 vaccine serotypes was 85%, with 95% confidence interval ranging from 75% to 91%. Vaccine efficacy was highest against serotype 14 at 81%. An analysis of the two additional serotypes contained in the 9-valent vaccine—known as types 1 and 5—reported that efficacy was 83% against serotype 5, but appeared to be only 27% against serotype 1. However, Nohynek cautioned that due to the small number of observations (12 cases in total), researchers cannot draw far reaching conclusions from this particular result.

A difficulty arises, she said, in trying to understand how the success of the vaccines against invasive pneumococcal disease—which, strictly speaking, is defined as the presence of pneumococcus in what should otherwise be a sterile site, such as the blood—translates into an impact on pneumonia. This type of analysis can become convoluted, she said, as one needs to understand “the complicated relationship of the observed versus the true vaccine efficacy.”

To illustrate this, she showed how vaccine efficacy depends on what definition of pneumonia is being used:
- “clinical pneumonia” (which Nohynek noted is in some 7% of cases caused by pneumococcus);
- a category of pneumonia the WHO classifies as “severe pneumonia;”
- pneumonia that is diagnosed with an x-ray, or “x-ray-confirmed pneumonia;” or
- pneumonia that is associated with a specific pneumococcal serotype targeted by a vaccine.

Wading into these different categories of pneumonia, Nohynek said, can lead one into a tangled statistical thicket, particularly if the goal is to make an exact connection between a pneumococcal vaccine and a prevented fraction of pneumonia.

For example, in looking just at cases of x-ray confirmed pneumonia, Nohynek said one must first focus only on the percentage of x-ray confirmed cases that are caused by pneumococcus bacteria, which, she said, “we presume” to be 50 to 70%. That particular subset of cases, she said, must then be further narrowed by considering that only 50 to 70% of these “pneumococcal pneumonias” are caused by serotypes specifically targeted by the vaccines. Finally, the analysis has to be further refined by calculating the expected success of the vaccine against the serotypes, which depending on the serotype can be anywhere from 30 to close to 100%.

“We have a good vaccine on our hands, and yet when we look into the proportion (of pneumonia) that you prevent out of all x-ray-confirmed pneumonias, it is not that high,” she said, noting that out of 100 cases, the data would lead one to conclude that “we can only expect to prevent 10 to 30 such cases” with the vaccine.

Even though that is actually a good success rate and when converted into absolute number of cases averted, the vaccine will have a significant public health impact as pneumonia is such a common disease in developing countries, Nohynek said the analysis is so complex the results are hard to explain even to fellow disease experts, much less to “the Ministers of Health and to people in general.”

Given the difficulty in isolating its effect on pneumonia—one that is further complicated by the fact that, as other speakers pointed out, many cases of pneumonia go undetected—Nohynek said it is important to stay focused on
“How much (a pneumococcal vaccine) will prevent pneumonia depends on where you are, how you define your pneumonia, and the causative agents in that areas, which vary — viruses, bacteria, viral-bacterial interaction, and then maybe malnutrition and maybe seasonal and other effects.

So I’m sorry. I don’t have a clear-cut answer.”

— HANNA NOHYNEK, NATIONAL PUBLIC HEALTH INSTITUTE, FINLAND

the fact the vaccine clearly has a high efficacy against invasive pneumococcal disease, and a good efficacy against X-ray confirmed pneumonia. Moreover, she said, in the Gambia “the vaccine was found to reduce all causes of child mortality by 16%.”

In other words, the vaccine is a proven life-saver even from the point of view of pneumonias.

“How much the pneumococcal vaccine will prevent pneumonia depends on where you are, how you define pneumonia, and the causative agents in that area, which vary — viruses, bacteria, viral-bacterial interaction, and then maybe malnutrition and maybe seasonal and other effects,” she said.

The Elusive Effect on Otitis

The difficulties in nailing down the impact on pneumonia can also be seen in efforts to understand the effect on another problem associated with pneumococcal infections: acute otitis media, which is more commonly known as an infection of the inner ear.

Terhi Kilpi of the Department of Vaccines at Finland’s National Public Health Institute explored the issue by reviewing research that has probed the impact of three different pneumococcal vaccines on ear infections. The studies focused on the effect of two 7-valent vaccines and one 11-valent vaccine, all of which employed different types of “carrier proteins” to boost immune response.

FIGURE 3.1 PCV efficacy is higher with a more specific diagnosis of pneumococcal pneumonia

From Hanna Nohynek, National Public Health Institute, Finland
While some studies have evaluated effectiveness against particular causes of ear infections, Kilpi believes “the thing that ultimately matters” is the effect of the vaccine against overall “burden” of otitis media.

There have been studies showing that a 7-valent vaccine formulated with a diphtheria protein reduces acute ear infections, regardless of cause, by 6 to 7% while a 7-valent vaccine formulated with a different carrier protein had no impact, she said. Meanwhile, there is evidence that an experimental 11-valent vaccine that uses a carrier protein derived from *haemophilus influenzae* could achieve a 34% reduction in ear infections.

Kilpi said that one possible explanation is the *haemophilus* protein is somehow boosting overall effectiveness against ear infections. But, she said it is “difficult” to determine whether the carrier proteins explain the difference.

The uneven and unexpected effects revealed by the various studies points to the challenge of trying to understand “what kind of impact these vaccines could and would have on otitis media in real life,” Kilpi said. She cautioned against trying to avoid these difficulties by moving too quickly to see clear cause-and-effect in data that is actually quite murky.

For example, she cited a study in the U.S. that tried to assess vaccine impact by considering how many times between 1994 and 2003 children under 2-years old received medical attention for ear infections. Kilpi said the study concluded that “otitis media visits were reduced by 20% after introduction” of the 7-valent pneumococccus vaccine in 2000. However, she noted that data actually show visits were steadily declining several years before immunizations began. In fact, the drop was steeper in the years prior to 2000.

“For me it is very difficult to come to the same conclusion,” Kilpi said. “When I look at this I see a decreasing trend of otitis media that is a little less decreasing after introduction of pneumococcal conjugate vaccines.”

Kilpi said she is very careful when it comes to stating whether or not the vaccine has an impact against ear infections. She said there is evidence that the vaccines have “the potential” to reduce the disease burden caused by ear infections, but “it is extremely difficult to estimate the ultimate vaccine effect.”

Ron Dagan, of the Pediatric Infectious Disease Unit at Israel’s Soroka University Medical Center, noted that there is a more recent study—from the February 2008 issue of Pediatrics (Zhou et al)—that documented not just a post-vaccine drop in doctors visits for ear infections but also a drop in antibiotic prescriptions. He acknowledged that while there was a reduction a few years prior to vaccine introduction, the new study indicates that after the vaccine was introduced, the trend in the U.S. became “much, much stronger.”

(According to the study, “In a comparison of 2004 with 1997-1999 (baseline period), rates of ambulatory visits and antibiotic prescriptions attributable to acute otitis media decreased from 2173 to 1244 visits per 1000 person-years (42.7% reduction) and from 1244 to 722 prescriptions per 1000 person-years (41.9% reduction), respectively.”)

The acceleration in the reduction, particularly of antibiotic prescriptions, Dagan said, “could be for many reasons, but it is so much of a coincidence (that it occurred) with the time of the vaccine.”
Pneumococcal Conjugate Vaccines: A Clear Success in the U.S.

If the experience in the U.S. is a guide, pneumococcal conjugate vaccines appear capable of accomplishing dramatic reductions in disease. Data from 2006 show the incidence of invasive pneumococcal disease in children under 5-years old caused by any of the 7 serotypes targeted by the vaccine Prevnar has declined from 80 per 100,000 pre-immunization to one per 100,000, according to Rosalyn O’Loughlin of the U.S. CDC. The seven vaccine serotypes are believed to be responsible for 80% of pneumococcal disease in the U.S. A decline in non-vaccine serotypes since vaccine introduction has also been seen, O’Loughlin said. Invasive pneumococcal disease in the U.S. caused by non-vaccine serotypes has dropped from about 100 cases per 100,000 children to 22 to 25 cases.

O’Loughlin said that in terms of total numbers, in the U.S., each year from 2001 to 2006, pneumococcal immunization is estimated to have prevented 11,000 to 15,000 cases of invasive pneumococcal disease in children under 5-years old and 9,000 to 18,000 cases in children older than 5-years old. Overall, the 7-valent vaccine is credited with preventing an estimated 170,000 cases of pneumococcal disease and 9,800 deaths, since its introduction.

In addition to reducing the overall burden of invasive disease, O’Loughlin noted that post-vaccine introduction, there was a 39% drop in all cause pneumonia hospitalizations and a 65% reduction in hospitalizations for pneumococcal pneumonia in children less than 2 years of age.

She also said the positive effects of the vaccine have extended beyond the immunized group by reducing the spread of pneumococcal pathogens in the general population. The so-called “herd immunity” effect is credited with a drop in disease among children and youth either too young or too old to be vaccinated, and among adults—especially seniors—O’Loughlin said. For example, widespread childhood pneumococcal immunization has been associated with a 32% drop in invasive pneumococcal disease (irrespective of serotypes) in adults 65-79 years old and an 88% drop in disease caused by vaccine serotypes.

FIGURE 3.3 Estimating the impact of PCV7 in the U.S.

During 2001–2006…

\[
\begin{align*}
<5 \text{ year-olds: } & \quad 11,000-15,000 \text{ cases prevented per year} \\
\geq5 \text{ year-olds: } & \quad 9,000-18,000 \text{ cases prevented per year} \\
\end{align*}
\]

\[
= 170,000 \text{ cases and } 9,800 \text{ deaths prevented}
\]
The U.S. experience also sheds light on dosing schedules. O’Loughlin said one study found that the vaccine was 73% effective against vaccine serotypes in children who got just one dose by seven months of age, and 95% effective for children who got two or three doses by that age. However, this study had a relatively short follow-up period so longer term protection is unknown.

There are some concerns however, O’Loughlin said. Since the vaccines were introduced, there has been a modest rise in pneumococcal serotype 19A, which is not targeted by the vaccine and which can cause severe disease and is often resistant to antibiotics. In addition, she cited a widely discussed study of Alaskan natives that found an especially large rise in non-vaccine pneumococcal serotypes following adoption of the pneumococcal immunizations.

O’Loughlin cautioned that the sharp increase in non-vaccine serotypes should not be read as evidence that the vaccine doesn’t work. She said other groups, like Alaskan natives, with high rates of pneumococcal disease prior to initiating immunizations, have not had the same experience.

For example, among the Native America population and Australian aboriginal groups, the increase in non-vaccine serotypes “has not been as dramatic.” Continued Surveillance is essential to continue to monitor trends in serotypes and new vaccines currently in development will include a larger number of serotypes.
The Rise of the Non-Vaccine Serotype: Assessing the Threat

Ron Dagan offered an in-depth exploration of one of the most controversial issues in the world of pneumococcal vaccines: whether the effectiveness of the vaccines against the serotypes they target provides an opening for new—and possibly equally virulent serotypes—to emerge.

Dagan said that to understand the phenomenon of “replacement serotypes,” one must first remember that pneumococcus is a naturally occurring bacteria in the “flora” of the human nose. So, when a vaccine is introduced that targets a specific group of pneumococcus serotypes, one of its effects is to provide an opening for the human “carriage” of “non-vaccine serotypes” to dramatically increase. Dagan believes there is no doubt that this routinely happens. He said there is abundant evidence of the emergence of “replacement serotypes” in countries where children have been vaccinated.

“The question is not whether there is a replacement,” he said. “The question is whether those bugs replacing the vaccine serotypes are as bad, as mean, as virulent, causing as much disease and antibiotic resistance, as those who were there before; because if they are, then the vaccine is not worth anything.”

Dagan believes the answer is no, they are not as bad. He said evidence thus far indicates that replacement serotypes are causing “replacement disease” mainly in people who would be considered “compromised hosts”—such as people with HIV or the elderly. Overall, he said, there is scant evidence of replacement serotypes threatening the vaccine’s considerable achievements.

For example, Dagan said, despite the difficulty in discerning the exact effect of immunizations on pneumonia, in the U.S. the fact remains that pneumonia hospital admissions are “going down, not up,” having dropped 39% since introduction of the 7-valent vaccine. He also cited a 2006 study that documented a 52% drop in pneumonia hospitalizations of children 2-years and younger. In addition, he discussed research indicating that similar reductions are occurring in meningitis hospitalizations. These trends, he said, “do not suggest, so far, that replacement is so important.”

“Replacement is not really causing something beyond what we expected,” he said. “In fact, it is causing maybe less.”

Another way to detect problems arising from replacement serotypes is to look at what is happening in the elderly. As Dagan pointed out, in the U.S., children who have received a pneumococcal vaccine will now be carrying and “transmitting to others mainly non-vaccine serotypes.” Indeed, Dagan noted that there has been significant rise in non-vaccine serotypes in people over 65 in the U.S. But, the issue is whether these replacements are causing disease. Dagan noted one study looked at meningitis hospitalizations in the elderly and found that despite the rise in non-vaccine serotypes, hospitalizations are “not starting to climb.”

Dagan said research probing HIV-positive young adults has documented an increase in pneumococcal disease caused by non-vaccine serotypes. But, he said that other than the effect on this “compromised” population, there is almost “no replacement (disease) whatsoever.”

He said the main focus at the moment is the rise of a virulent non-vaccine serotype known as 19A. While Dagan acknowledged that 19A is a “bad bug” that has become more prominent in areas where the vaccine has been introduced, he questioned whether the vaccine is really the main culprit in the area of most immediate concern: the rise of antibiotic resistant 19A.

Dagan asserted that drug resistance in 19A is “not a pattern that is influenced by the vaccine.” Rather, he viewed the problem as part of a broader trend of serotypes acquiring drug-resistance due to overuse of antibiotics. In fact, Dagan said 19A became the “king of invasive infections” in South Korea before

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— RON DAGAN, BEN-GURION UNIVERSITY, ISRAEL
they adopted the pneumococcal vaccine and has been displaying increased drug resistance in areas of Israel, which does not yet vaccinate against pneumococcus.

“The dramatic increase in serotype 19A (drug resistance) is universally related to antibiotic use and resistance and it is seen also in non-vaccine countries,” Dagan said.

Nonetheless, he acknowledged that, while the contribution of the vaccine to the general expansion of 19A is unclear, “we have to take into account that there is an effect of the pneumococcus vaccine that reduces some of the competition for 19A and permits 19A to go up.”

He said researchers should not rule out “the role of the vaccine in the expansion of this bad bug or other bad bugs that will be coming, but again, we have to put things in perspective.”

The Future of Pneumococcal Vaccines

Pneumococcal Vaccine Development at Wyeth

Peter Paradiso from Wyeth Vaccines—which makes the 7-valent pneumococcal conjugate vaccine Prevnar—said the company is building capacity to meet an anticipated increase in global demand for pneumococcal immunization. Wyeth has tested a 9-valent vaccine in trials in Africa and is currently focused on developing a 13-valent vaccine.

Acknowledging the growing role of serotype 19A in causing disease, Paradiso said Wyeth had hoped that targeting serotype 19F in the 7-valent formulation would have provided cross protection for 19A. But it appears to offer none, he said.

Paradiso said Wyeth has pursued a “second generation” of pneumococcal vaccines with the goal of expanding “serotype coverage for invasive pneumococcal disease.”

“The important point here is that as we have added more serotypes, we have been able to do that without negatively impacting the response to the serotypes that were already present,” he said.

Paradiso reported on a recent efficacy trial that compared Wyeth’s 13-valent vaccine to the 7-valent vaccine. The vaccines were randomized among 250 infants, with doses administered at two, four, and six-months of age. He said the results show that response to the original 7-valents was the same for both vaccines.

“This was obviously important for us to see and something of a relief to see since we are almost doubling the number of serotypes,” he said.

Also, for infants who received the 13-valent vaccine, there was evidence, he said, of a protective immune response to the 19A serotype.

Assessing the effectiveness of new vaccines against pneumococcus is more difficult today, Paradiso said, because there is already a licensed vaccine on the market. He said “placebo control trials” in which some subjects would get a pneumococcal vaccine and others a placebo, are “no longer ethical.”

He said pneumococcal vaccines are now measured by a WHO standard, which has established the level of serotype-specific antibodies that must be present in vaccine recipients after three doses in order to be considered efficacious.
At the time of the conference, Paradiso said Wyeth was preparing to test the 13-valent vaccine in a large Phase 3 trial of 3000 to 4000 infants. The trial is to be completed by the end of 2008.

He said Wyeth believes that globally its 13-valent vaccine has the potential to cover “the vast majority of causes of invasive disease and other mucosal infections.”

**Pneumococcal Vaccine Development at GSK**

Bernard Hoet with GlaxoSmithKline Biologicals focused on potential concerns related to the role of so-called “passive carrier proteins” used in conjugate vaccines, which are crucial to eliciting the desired immune response. Hoet said there has been “some demonstration” that the carrier protein can cause different vaccines to interfere with one another, “especially when diphtheria proteins or tetanus proteins are used.”

He said GSK is seeking to avoid potential problems by using a new carrier protein from *haemophilus (h.) influenzae* in its new 10-valent conjugate pneumococcal vaccine. The vaccine, likely to be called Synflorix, targets the same serotypes found in the 7-valent vaccine and adds three more, types 1, 5 and 7F. Hoet said adding protection against these three serotypes should allow the vaccine to cover more than 80% of the pneumococcal serotypes responsible for invasive diseases in all areas of the world except Asian countries outside of the Pacific Rim.

He said while the vaccine’s serotype coverage is estimated to be 71% in Bangladesh, India, Israel, Malaysia, Pakistan, the Philippines, Saudi Arabia and Thailand, it is still considerably greater than the 49% coverage they would achieve with the 7-valent vaccine.

Hoet pointed to research indicating that, in particular, serotypes 1 and 5 are “highly invasive” and are “important causes of epidemic meningitis.”

As for the GSK vaccine’s formulation endowing it with any capacity to fight *haemophilus influenzae*, Hoet pointed to a study involving an earlier, 11-valent formulation that demonstrated 35% efficacy against ear infections caused by “non-typable” *h. influenzae*. Hoet said the *h. influenzae* impact was “statistically significant,” and that the efficacy was “sustained over time.” (Since that study, GSK has decided to drop one serotype, serotype 3, from its conjugate vaccine because the vaccine showed no efficacy against it.)

Hoet said its 10-valent Synflorix vaccine is now being tested in clinical trials to assess its potential efficacy against pneumonia and that GSK hoped to begin distributing the vaccine in 2009.

**FIGURE 4.2 Ten Pneumococcal serogroups are responsible for most IPD in young children**

![Diagram showing serogroup coverage](Image)

*From Bernard Hoet, GlaxoSmithKline Biologicals*  
Sources for all regions except Asia: adapted from Hausdorff et al CID 2000  
Sources for Asia: Hausdorff (2006 unpublished literature analysis)
The PATH Pneumococcal Vaccine Project

The Pneumococcal Vaccine Project (PVP), underway at PATH and which is funded by the Bill and Melinda Gates Foundation, is investing in efforts to accelerate the development of safe and effective pneumococcal vaccines that would be a good match for the economics and infrastructures of low-income countries.

Mark Alderson, PATH’s Director for pneumococcal vaccines, said PATH has several key objectives. First, it wants to see more low cost conjugate vaccines on the market. Therefore, it is interested, among other things, in technologies that can bring greater efficiencies to vaccine manufacturing, particularly in developing countries. PATH also supports researchers who are using genome analysis to find better vaccine targets and has invested in cutting edge approaches to pneumococcal vaccines.

One partner, Alderson said, is attempting to develop what is known as a “protein vaccine.” He described how researchers at Intercell in Vienna, Austria are isolating proteins using serum taken from individuals who have suffered pneumococcal infections. The idea is that if these proteins or “antigens” are formulated with the proper vaccine delivery system or “adjuvant,” they may have the potential to stimulate an immune response in humans that could provide broad protection against pneumococcal bacteria irrespective of serotype.

In a separate endeavor, PVP is working with Children’s Hospital in Boston to explore the potential of a vaccine that, instead of eliciting protective antibodies, focuses on the role of CD4 positive T-cells in providing natural immunity to pneumococcal diseases. The goal, Alderson said, is to develop what is known as a “whole-cell vaccine.” A whole-cell vaccine uses inactivated or “killed” pneumococcus bacteria to stimulate CD4 T-cells in a way that prompts them to recognize basic components of pneumococcus common to all serotypes and, like the protein vaccine, provide broad protection.

Alderson said that in addition to being cheap to produce, a whole-cell vaccine could be ideal for developing countries because it “may not require refrigeration” and might be possible to administer via a nose spray instead of an injection. He noted that Children’s Hospital has established a partnership with Brazil’s Butantan Institute to manufacture a whole-cell vaccine.

Along with its vaccine development work, Alderson said PVP is working to provide vaccine scientists with data and research tools. For example, he said PVP was considering a partnership to establish a collection of pneumococcal strains that would be geographically diverse and include “recent human isolates from developing countries.”

Another partnership under discussion, he said, would establish “reference labs for standardized animal models” that could be particularly useful for screening antigens for a protein vaccine. PVP also is interested in developing better estimates of burden of disease and new diagnostics, particularly for use in diagnosing pneumococcal pneumonia.

Finally, PVP is funding an effort to find “novel” vaccine adjuvants that would enhance the “protective capacity” of pneumococcal immunization.

Emerging Market Vaccine Manufacturers

Akira Homma of the Brazilian vaccine producer Bio-Manguinhos talked about the rapid rise of vaccine manufacturing capacity in the developing world. His company has played a key role in organizing the Developing Country Vaccine Manufacturing Network (DCVMN) that now has 19 members. He said DCVMN members are collectively producing two-thirds of the world’s vaccines.

Homma believes developing country producers will be critical to making pneumococcal vaccines affordable to middle income countries. He said the vaccine is essentially affordable for high-income countries and in low-income countries, where the GAVI Alliance will facilitate purchases. But, Homma said it is still not clear how to make conjugate pneumococcal vaccines affordable for middle income countries, a category that includes many nations in Latin America and the Middle East.

Governments are convinced of the vaccines’ effectiveness, he said, but the high price “is a big obstacle for introduction in middle income countries.”

He said one way to address this challenge is to “accelerate” the availability of pneumococcal vaccine technology to members of the DCVMN.

“I think the issue is to have more (companies) involved faster in production in order to increase the availability and make its price affordable to middle-income countries,” Homma said.

He said the situation calls for better vaccine development efforts with the DCVMN, stronger public-private collaborations focused on technology, and efforts to negotiate technology transfer agreements.

DISCUSSION

The CDC’s Rosalyn O’Loughlin said she wanted to make it clear that while the GSK vaccine might be effective against non-typable h. influenzae, the vaccine does not specifically target the most important type, which is h. influenzae type B or Hib. Like pneumococcus, Hib is a significant cause of severe pneumonia and bacterial meningitis. Therefore, she said that while countries already using Hib vaccine might see some additional benefit from the GSK pneumococcal vaccine, it is not intended as a substitute for Hib immunization.

Hoet said the potential of the vaccine to provide protection against Hib has not been studied, but is an “interesting hypothesis.”

Thomas Cherian wondered what vaccine manufacturers were doing to learn more about the possibility that carrier proteins in a pneumococcal vaccine might interfere with other vaccines.

Hoet said so far, GSK’s studies in animals prompted it to dispense with carrier proteins derived from diphtheria. He said thus far it has not observed any interference related to the use of the h. influenzae protein.

Paradiso observed that even with exhaustive testing, interference “has never been predictable in my experience.”

“Certain combinations and certain antigens put together seem to interfere for reasons that you would not expect,” he said.
### FIGURE 4.3 Pneumococcal vaccine portfolio

<table>
<thead>
<tr>
<th></th>
<th>RESEARCH</th>
<th>PRE-CLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
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<tr>
<td>1. Protein vaccine</td>
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<td>2. Protein vaccine</td>
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<td>3. Intercell</td>
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<td>4. Children’s Hospital</td>
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<td>5. Protein vaccine</td>
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<td>6. Protein vaccine</td>
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<td>7. Conjugate vaccine</td>
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<tr>
<td>8. Conjugate vaccine</td>
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<tr>
<td>9. Protein antigen discovery</td>
<td></td>
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</tbody>
</table>

From Mark Alderson, PATH

“I think the issue is to have more (companies) involved faster in production (conjugate pneumococcal vaccines) in order to increase the availability and make its price affordable to middle-income countries.”

—AKIRA HOMMA, BIO-MANGUINHOS, BRAZIL
SESSION V
Country Spotlights

There were brief presentations from health officials in the region that offered insights into the process underway in various countries to develop the knowledge they need to evaluate the potential of adding pneumococcal vaccines to national immunization programs.

Turkey

Turkey currently lacks data on both the national burden of pneumococcal disease and serotype distribution, though it hopes ongoing studies will provide more information in the next couple of years, according to Mehmet Ceyhan.

Ceyhan noted that pneumococcal vaccines are not the only new vaccines that could be useful in Turkey. He said new vaccines that target rotavirus, human papillomavirus, and hepatitis A also demand attention. But, he believes that once Turkey completes its national evaluation of pneumococcal diseases, a pneumococcal vaccine will be “the first candidate” for addition to its immunization program.

He said adopting a pneumococcal vaccine will not just be a technical decision but a financial one as well. Ceyhan said Turkey is already spending $131 million annually on immunizations.

“That’s big money for Turkey,” he said.

Ceyhan said public health care workers and the Minister of Health understand “the necessity of pneumococcal vaccine.”

“The only problem for the Minister to factor in is the cost,” he said.

Lebanon

Lebanon has recently set up a pneumococcal surveillance system it hopes will identify the country’s dominant serotypes. Knowing the dominant serotypes would determine “the most appropriate vaccine for coverage and protection,” said Ghasson Dibaibo with the Department of Pediatrics at the American University in Beirut. He said based on the serotypes identified so far by the surveillance network, the 7-valent vaccine would cover about 47% of the pneumococcal infections studied. The 10-valent vaccine would cover 58% and the 13-valent 68%.

“So this is fairly similar to what is seen in other parts of the region and in parts of Europe as well,” he said.

Focusing only on the serotypes found in children under 5-years old, the 7-valent vaccine would cover “72% of those cases,” Dbaibo said, the 10-valent would prevent 76%, and the 13-valent would prevent “up to 84% by virtue of coverage of 19A.”

He said the 7-valent pneumococcal vaccine is now available in Lebanon, though only in the private sector, where it costs about U.S. $100 per dose. In a country where per capita income is U.S. $5,400—in many areas it is much lower—this price effectively puts the vaccine out of reach for most children. Dbaibo said, based on vaccine sales, it appears that only about 6 percent of Lebanese children under 5-years old are getting immunized.

Providing adequate treatment for pneumococcal diseases is also a problem, Dbaibo said, as there are only a few public hospitals in Lebanon and most of them “tend to be under-staffed and under-equipped.” In addition, about 25% of the pneumococcal samples collected in the surveillance system have shown resistance to the antibiotic erythromycin and 35% showed at least an “intermediate resistance” to penicillin—15% were “highly resistant.” The serotype that accounted for most of the resistance was 19F, he said, which is covered by Prevnar.

Dbaibo said adding a pneumococcal vaccine to the country’s immunization program will depend largely on convincing government decision makers that the benefits justify the costs, particularly in light of the fact that Lebanon is currently weighed down by a U.S. $42 billion budget deficit.

“So to come to the government now to pay for it, we really need to have a lot of data to tell them that it is useful,” he said.

“So to come to the government (of Lebanon) now to pay for (a pneumococcal vaccine), we really need to have a lot of data to tell them that it is useful.”

— GHASSAN DBAIBO, AMERICAN UNIVERSITY IN BEIRUT, LEBANON
Saudi Arabia

According to a 5-year study of the patient populations at two hospitals in Jeddah and Riyadh, said Ziad Memish of the King Fahad National Guard Hospital, Saudi Arabia has a “very high prevalence” of invasive pneumococcal disease (IPD). Memish also sits on the national immunization committee. He said the IPD rate observed in children under 5-years old was 76 per 100,000. The meningitis rate was 20 per 100,000, and septicemia and bacteremia rate was 57 per 100,000.

He said that overall, various data on disease serotypes—while not “perfect”—indicate that for Saudi children under 2-years old, the 7-valent vaccine would provide 63% coverage, the 9-valent 67% coverage, and the 10-valent 78% coverage. Memish said studies also show that, as in Lebanon, serotypes exhibiting resistance to antibiotics in Saudi Arabia are among the serotypes that would be targeted by immunizations.

Memish said that in 2007 the National Immunization Committee recommended adding a pneumococcal conjugate vaccine as part of Saudi Arabia’s Expanded Program on Immunizations (EPI). The Ministry of Health has subsequently added the 7-valent vaccine to Saudi Arabia’s EPI schedule.

Israel

Pneumococcus is a “major cause of invasive infection and disease in children in Israel,” according to David Greenberg of the Soroka University Medical Center. Also, like other countries in the region, Israel is seeing a rise in pneumococcal serotypes resistant to one or more antibiotics.

He said there is surveillance data on both Israeli Jewish children and children in the country’s Bedouin population, where the epidemiology of pneumococcal disease is different. Greenberg also said research indicates that for children under 3-years old, the 7-valent vaccine would cover 52% of disease in Jewish children and 41% of disease in Bedouin children. For the 10-valent vaccine, the coverage in Jewish and Bedouin children would be 63% and 70%, respectively.

Greenberg said that despite its relatively low coverage of Israel’s dominant pneumococcal serotypes, the 7-valent vaccine could make a “significant” difference because there is a high incidence of disease in the country.

He said Israel’s Ministry of Health was preparing to introduce the 7-valent vaccine in 2009.

**FIGURE 5.1 Incidence of Invasive Pneumococcal Disease in Israel**

Tunisia
Amel Kechrid said data on serotypes gathered at the Children’s Hospital in Tunis indicate that Tunisia would expect about 64% coverage from the 7-valent pneumococcal vaccine, which is below the 65 to 80% coverage achieved in Europe. The research also confirmed that, as in other countries, there is a high percentage of antibiotic-resistant pneumococcus in Tunisia.

Kechrid said the 7-valent vaccine became available in the private sector in early 2008, but because of its high cost, “we don’t know when this vaccine will be incorporated into routine childhood immunizations.”

In the meantime, he said researchers in Tunisia will continue to be on the lookout for any changes in disease epidemiology, serotype, antimicrobial resistance patterns, and age of infection.

Morocco
Naima Elmdaghri of the University Hospital in Casablanca said data gathered from children 5 years old admitted to the hospital documented an incidence rate for invasive pneumococcal disease of 33 per 100,000. But, this figure likely underestimates the true burden of disease in Morocco, she said.

A recent study in Morocco found that the 7-valent vaccine would cover about 50% of the country’s pneumococcal serotypes known to be causing invasive disease. For the subset of serotypes showing resistance to penicillin, vaccine coverage would be about 77%.

Elmdaghri said the mix of pneumococcal serotypes in Morocco has changed substantially in the last 10 to 15 years, and in a way that would make the 7-valent vaccine more effective. But that shift, she said, also means “continuous surveillance” is mandatory in order to understand which vaccine formula has the greatest potential to reduce the burden of pneumococcal disease in Morocco.

“[In a disease that seems to be a real killer should we make sure] that every single country waits for the next three or four years collecting data while children are dying?”

— NAJWA KHURI-BULOS, JORDAN UNIVERSITY, JORDAN

Sidebar 5.2
Data Collection and Dying Children: When is Enough, Enough?

There was a moment in the conference when Jordan’s Najwa Khuri-Bulos became frustrated with the persistent calls for more data on pneumococcal disease. While she believes surveillance is important, her concern is that when scientists say they need to know more about burden of disease, decision makers will use their statements as an excuse to delay vaccine introduction.

When, she said, do we say “enough is enough” in data collection?

She added, “in a disease that seems to be a real killer, should we make sure that every single country waits for the next three or four years collecting data while children are dying?”

Khuri-Bulos said that “scientists encourage this kind” of delay when we “sit here and accept that we should keep on getting more data.”

Noting that even where the existing 7-valent vaccine has relatively low serotype coverage, it still appears capable of preventing about 50% of invasive disease, she said. “We have a lot of nice data, acceptable data,” she said. “Fifty percent of a good thing is not bad.”

She said that perhaps what was needed were more forceful statements from the leadership of international organizations that would “guide governments” toward vaccine adoption even though precise data on disease burden and cost effectiveness are not available for all or even most countries.
The Irony of Pneumococcal Vaccine Economics: Biggest Savings Among Those Who Can Least Afford Them

Cost has emerged as perhaps the single biggest barrier to widespread adoption of pneumococcal vaccination. Tom Ray, a researcher with managed care provider Kaiser Permanente, pointed out that when it was introduced in the U.S., the high price of the 7-valent vaccine doubled the overall cost for infant immunizations.

“This generated a lot of interest in (analyzing) the cost-effectiveness of the vaccine to see what kind of value we are getting for the money we are spending,” he said.

There are 14 studies—all conducted in North America, Europe or Australia—that have considered the cost-effectiveness of the 7-valent pneumococcal vaccine. Ray said all of them assumed immunization would have impact on ear infections, pneumonia, invasive pneumococcal disease and on long-term consequences, such as deafness or other disabilities. All of the studies sought to predict what would happen in the long-term to a group or “cohort” of infants who were vaccinated compared to what would happen in the same cohort of infants if they were not vaccinated.

One part of the analysis, Ray said, compared the cost of the vaccine to the cost of treating pneumococcal diseases. For example, by reducing incidence of pneumonia, the cost of the vaccine would be offset by the treatment costs saved. Another part of the analysis, he said, took the cost of vaccinating, divided it by the years of life saved by immunization and came up with an estimate of the “cost per life year saved.”

“The lower that is, the better,” he said.

Most of the studies assumed the vaccine costs about U.S. $60 per dose and that proper immunization requires three or four doses, meaning that the cost for the vaccine alone was from U.S. $180 to $240 for a full course. In addition, when assessing the cost of immunization, the studies considered not just the price of vaccine but also the cost of administering it.

The studies varied widely in terms of how much the cost of immunization was offset by the cost savings associated with preventing disease. Ray noted the “net cost” of vaccinating an infant ranged from about $45 in the United States to over $200 in Switzerland. Behind the variation, he said, are “different estimates of disease burden and different estimates of the costs of treating (the vaccine-preventable) disease.”

On average, he said, the studies “estimated that for every child you vaccinate, you save $81 in medical costs and $71 in non-medical costs,” which include such things as the cost of a parent taking time off work to care for a sick child, for a total of $152 in savings from “averted disease” in each vaccinated child.

As for the vaccines’ “cost per life year saved,” Ray said on average, the studies estimated that the 7-valent vaccine would prevent 4 to 4.5 deaths each year—they ranged from 2 to 9 deaths—for every 100,000 children vaccinated. Those averted deaths, he said, translated into cost per-life year saved that ranged from U.S. $30,000 to U.S. $160,000.

That’s a steep price to pay, Ray acknowledged. But those costs come down, he said, when one considers how vaccinating children limits the spread of pneumococcal pathogens, providing “herd immunity” that saves lives across the population, particularly among the elderly.

Five of the 14 studies added the herd effect in their analysis, Ray said, and doing so considerably reduced the cost per life year saved. For example, in Norway, the cost went down from $152,000 to $71,000 while in the U.S. it decreased from $80,000 to $7,500.

Ray said the studies are widely viewed as “conservative measures” of the cost-effectiveness of pneumococcal immunization.

Ray said that as challenging as it is to estimate cost-effectiveness in wealthy countries, where there is, relatively speaking, “a lot of data,” the task becomes even more difficult when seeking evidence of cost-effectiveness for poor countries.

He pointed to one study that has considered the cost-effectiveness of adding a pneumococcal vaccination—if it could be obtained at $5 a dose—to immunization programs in the 72 countries eligible for financial support from the GAVI Alliance, which are among the poorest countries in the world. Ray said the study assumed that, given the high rate of pneumococcal diseases in poor countries, a pneumococcal vaccine would prevent 3.7 to 7.4 deaths for every 1,000 children vaccinated. (Recall that the studies of the impact in wealthy countries estimated that in many instances the vaccine may not save that many lives out of every 100,000 children.)

The study used a slightly different measure of cost-effectiveness, looking not just at lives saved but at what are known to health economists as “disability adjusted life years” or DALYs. The DALY analysis is a tool used to estimate the number of healthy years of life saved by immunization that would otherwise be lost not just to premature death but also to sickness or disability.

Ray said the study found that at $5 a dose, the vaccine would cost $100 or less for each DALY saved. He said that according to WHO standards, this estimate would make the vaccine “highly cost effective in nearly all of the countries included in the study.”
FIGURE 6.1 Base-Case PCV cost-effectiveness analysis:
Cost per life-year saved, societal perspective
(without quality-of-life adjustments or indirect effects)

FIGURE 6.2 Summary of cost effectiveness analysis including herd effects
(cost per life year saved ($), base case)
Implementation Issues:

Santiago Cornejo, whose work at the World Bank has focused on new vaccine introduction, observed that the days of “penny-per-dose vaccines” are over. He said in the current era, where introducing just one new vaccine can cost more than all other immunizations combined, governments are confronted with a host of confounding choices. For example, he said decision makers have to consider not just the financial burden of the latest vaccine to hit the market, but also how adopting it will affect their ability to take advantage of vaccines now in the pipeline.

Cornejo said the fact that Saudi Arabia, one of the region’s relatively affluent countries, is concerned that pneumococcal immunization would effectively double their overall spending on immunizations provides a stark example of the financial challenge involved.

“What we know is that the paradigm of the cost of vaccines is changing,” he said.

Cornejo said the fact that new vaccines are likely to be more expensive requires a fresh approach to what the World Bank and International Monetary Fund (IMF) have called creating more “fiscal space for immunizations.” What this concept can mean in practice, is finding more money for vaccines by:

- reallocating money from other parts of the national budget to immunizations;
- offsetting immunization costs through savings generated by improving efficiency and reducing waste in health programs;
- raising revenues with new taxes;
- securing more funding from “outside donors;”
- funding immunizations through health insurance (in countries that have health insurance); and
- working with the private sector to develop plans in which vaccine purchases by the more affluent are used to “cross subsidize” purchases by “poorer populations.”

Another way to address costs, said the WHO’s Cherian, is to follow the purchasing model established by the Pan American Health Organization’s Revolving Fund for Vaccine Procurement, which negotiates low-cost bulk purchases of immunizations for Latin American and Caribbean countries. He said WHO is advising countries in other regions about the potential of establishing similar “pool procurement mechanisms.”

But, he acknowledged that the rising cost of immunization is occurring in an environment in which “every single health program”—such as programs that would intensify efforts against chronic disease—is asking for more money.

Cornejo noted that whatever individual mechanisms countries pursue, there needs to be a greater focus on vaccine advocacy, on doing more than just providing decision makers with better scientific data on burden of disease and vaccine efficacy. For example, Cornejo said that, like pneumococcal immunization, costs also are high for AIDS and malaria interventions. But they have become a priority at the national level, he said, in part because AIDS and malaria advocacy messages “are much better than ours.”

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**FIGURE 6.3 GAVI-eligible analysis: Results**

(Most conservative analysis highlighted)

<table>
<thead>
<tr>
<th>SCENARIO</th>
<th>LIVES SAVED (100K)</th>
<th>HOSPITALIZATIONS AVERTED (100K)</th>
<th>DISEASE COSTS SAVED ($, MILL)</th>
<th>DALYS AVERTED (MILL)</th>
<th>INTERNATIONAL $ PER DALY AVERTED</th>
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<td>Deaths</td>
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<td></td>
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<td>3 to 29 months</td>
<td>262</td>
<td>262</td>
<td>44</td>
<td>8.3</td>
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<tr>
<td>+ Non-fatal disease</td>
<td>262</td>
<td>1,158</td>
<td>218</td>
<td>8.3*</td>
<td>80</td>
</tr>
<tr>
<td>3 to 29 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Extended protection to 59 months</td>
<td>369</td>
<td>2,458</td>
<td>453</td>
<td>11.7</td>
<td>37</td>
</tr>
</tbody>
</table>

From Tom Ray, Kaiser Permanente
“So what are they doing that we are not and what can we learn?” he asked.

Cornejo said advocacy is critical because ultimately the decision on a particular vaccine is a “political decision” not a scientific decision.

“The evidence and the data can only take you so far,” he said. “At the end of the day it is going to be a political decision.”

Decisions, Decisions: In Addition to Price, Process Also a Barrier

Price is indeed a problem, but another barrier to accelerating the adoption of new vaccines is the decision making process—the mechanisms used in various countries for planning and priority setting, said Liudmila Mosina, Technical Specialist, Communicable Diseases Control with the World Health Organization Regional Office for Europe.

For example, she said a “national advisory body on immunization” can be an effective vehicle for providing “clear recommendations to the Minister of Health” on immunizations. But, she said, “unfortunately, in many of our developing countries, such boards do not exist or do not work effectively.”

Mosina also advised that decision making on the introduction of new vaccines in developing countries could be accelerated by establishing surveillance for diseases which could be prevented by new vaccines. She said that even if surveillance “cannot provide perfect data for disease burden, at least some data, some local data, might help to sensitize the Ministry of Health and the government and can raise the aware of the disease among healthcare workers.”

O’Loughlin with the U.S. CDC agreed that an insistence on comprehensive national data on disease burden in each and every country can become an unnecessary impediment to decisions about vaccine introduction. She suggested that countries lacking national data should consider whether regional data is an adequate substitute to inform a decision to introduce the vaccine. For O’Loughlin, health officials should question whether the disease burden in their country is really “so different” from their neighbors that it justifies “spending all this money” seeking national data. All countries should have some minimum level of surveillance in place to monitor the impact of vaccine introduction, but producing good quality data is expensive and time consuming. She said the same is true for cost effectiveness analysis, that regional and even global data might provide an adequate insight for national purposes.

For example, she said WHO has a “generic cost database that can give a rough indication of cost-effectiveness.”

Najwa Khuri-Bulos said the decision-making process needs more regular input from economic experts. She noted in Jordan, the national immunization advisory committee recommended the MMR vaccine in 1985, but due to cost concerns it was not actually added to the country’s immunization program until 2001. Khuri-Bulos wondered if an economic analysis might have revealed that, given the potential saving in healthcare costs, it was more expensive to wait 16 years to adopt the vaccine.

“We know a lot about medicine but, frankly, for myself, I am zero in economics,” she said. “I know nothing. All I know is what I want.”

Improving Availability and Access Through Advanced Market Commitments

Encouraging the private sector to develop and produce new vaccines that are both effective and affordable is the goal of an innovative funding mechanism known as Advanced Market Commitments or AMCs. The first or “pilot” AMC is engaging a group of donors (Italy, the UK, Canada, Russia, Norway and the Bill and Melinda Gates Foundation) along with the GAVI Alliance to fund an effort that would accelerate the availability of affordable pneumococcal vaccines.

According to Tania Cernuschi, who is managing the AMC process at GAVI, the AMC provides the private sector with a financial incentive to develop innovative, affordable vaccines for developing countries.

“What the AMC does is establish prices for vaccines before companies go into the research and development phase, or before they scale up capacity,” Cernuschi said.

Cernuschi noted the AMC commits to provide an established subsidy on a set number of doses to help vaccine suppliers defray the costs of research and development or of scaling up capacity. After the subsidy ends, companies have recouped their investment and must provide the product over the long-term at an established, low price—often referred to as a “tail price.” She noted that, typically, the cost of a vaccine decreases slowly over time. But the AMC accelerates this price drop, she said, by “front loading the return,” so that it comes down in “just a few years” instead of 15 to 20 years.

Cernuschi said the AMC plays a dual role. For industry, it provides an incentive to invest in vaccines for the developing world. For countries, it provides “predictability” in both pricing and availability. In addition, Cernuschi stressed that the AMC only pays for results: the AMC funds are spent only if the right vaccines are developed and requested by GAVI eligible countries.

She said pneumococcal vaccine development and production was viewed as a good place to test the AMC concept because there are a number of vaccines in the late stages of development and also because they can have a “very high impact” on disease and death.

In early 2008, work on the pneumo-AMC was focused mainly on examining the structure of the AMC for pneumococcal vaccines and recommend key terms and features, including the initial and long-term price for a pneumococcal vaccine. That process, she said, involved consulting developing countries, industry and civil society organizations. As for the vaccine formulation, Cernuschi said a technical committee convened by the WHO has established a minimum product profile of a pneumococcal vaccine that would be eligible for funding.

The pilot project will be officially launched in 2008, meaning that “we would be open to receiving applications from industry,” Cernuschi said.
Increasing the PACE

The need to infuse the campaign for pneumococcal vaccines with a greater sense of urgency prompted the Sabin Vaccine Institute to establish in 2006 what is known as the Pneumococcal Awareness Council of Experts (PACE). According to Sabin’s Ciro de Quadros, the council is “comprised of 15 leading experts in infectious disease and vaccinology from all regions of the world.” It is also mobilizing participation from “all of the international scientific societies” involved with various aspects of pneumococcal diseases.

“The pneumococcal diseases do not have the lobby that other diseases have today so we need to change this situation,” de Quadros said. “We need to move the issue from the health establishment to the political establishment because that is where the decisions are made.”

De Quadros said PACE will fight for increasing financial support from foundations, industry, and, “of course, the council brings the skills, knowledge and commitment necessary to accomplish this mission.”

He believes the coalition fighting for pneumococcal vaccination needs to be both broad and deep. It needs participation from the public and private sector, he said. De Quadros also said it is important to go beyond the health community to engage Ministers of Finance and members of Parliaments in different countries to help them understand the importance of securing pneumococcal vaccines at an “affordable and sustainable price.”

“When I say affordable, I mean affordable to the buyers and affordable to the sellers,” he added. De Quadros views pricing as a delicate balance that involves agreement on a price that is affordable to countries while at the same time sufficient to keep industry interested in developing vaccines primarily intended for the developing world.

PACE member Lulu Bravo, vice chancellor of the University of the Philippines, discussed recent efforts to boost awareness of pneumococcal diseases in Asia, a region that accounts for a substantial number of fatal childhood pneumonias. She said the campaign has organized seminars and media education events in collaboration with partners in Indonesia, the Philippines, Thailand, Malaysia, and Taiwan.

Known as the Asian Strategic Alliance for Pneumococcal disease prevention or ASAP, the initiative, Bravo said, has recently launched the “Unite for Pneumococcal Prevention” program. The Unite program encourages scientific and professional societies to disseminate information on pneumococcal diseases, participate in surveillance, support adding pneumococcal vaccines to immunization programs, and encourage parents to vaccinate their children. Unite also is encouraging countries to make pneumococcal disease a “notifiable disease” so that documenting cases would become a routine part of national disease surveillance activities.

Countries represented in the program as of early 2008 were Brunei, Hong Kong, India, Indonesia, Korea, Malaysia, Macao, Pakistan, the Philippines, Singapore, Sri Lanka, Taiwan and Thailand.

Another PACE member, Zulfiqar Bhutta of Pakistan’s Aga Khan University, said a key challenge confronting PACE is making a clear link between pneumococcal disease and child survival. For example, he said there is a clear connection between pneumococcal prevention and fulfilling the United Nations Millennium Development Goal (MDG) that commits countries to achieving a significant reduction in childhood mortality by 2015.

He also sees a particular need for pneumococcal education campaigns that target health care professionals.

“There is a great amount of disbelief within health care professionals themselves, pediatricians in particular, as to the relative importance of pneumonia,” he said.

In addition, Bhutta believes there needs to be more consistency between “major technical agencies” at the global level, such as the UN and the WHO and their regional counterparts, with respect to priorities for controlling invasive pneumococcal diseases. For example, he said if there is a global action plan for fighting pneumonia, there must be agreement on how that plan articulates the relationship between prevention strategies and vaccines.

Finally, Bhutta wants to see more contact between disease experts and “technocrats and policymakers” at the country level, and an advocacy strategy that focuses on generating support at the family and community level.

“The AMC plays a dual role. For industry, it provides an incentive to invest in vaccines for the developing world. For countries, it provides predictability in both pricing and availability.”

—TANIA CERNUSCHI, GAVI ALLIANCE, SWITZERLAND
“The pneumococcal diseases do not have the lobby that other diseases have today so we need to change this situation. We need to move the issue from the health establishment to the political establishment because that is where the decisions are made.”

—CIRO DE QUADROS, SABIN VACCINE INSTITUTE, US

The Pros and Cons of Public Awareness

A representative of the Turkish Social Pediatrics Association cautioned against moving too fast with public education efforts at the country level before an affordable vaccine is widely available. She said in Turkey, media coverage about high childhood mortality rates from pneumococcal respiratory diseases has been accompanied by advertisements promoting the benefits of pneumococcal vaccinations, which she said caused panic among parents who cannot afford them.

“First, we believe health staff should be aware of (pneumococcal vaccines) and after it is available for everyone else, then public awareness can follow,” she said.

Dagan said the issue is part of a broader ethical quandary about “how much the public” has a right to know about certain health interventions even if they cannot afford them.

De Quadros said a key reason PACE initiatives focus on creating coalitions composed of national scientific societies is that these groups are the ones most capable of striking that balance, of informing the public in a way that clarifies rather than confuses.

Levine sees a clear tension between “holding back awareness” until policies are in place to ensure equitable access to pneumococcal vaccines versus heightening awareness as a way to “drive the change that makes vaccines equitable for everybody.”

De Quadros noted that sometimes it is important to spotlight the lack of access to certain vaccines as a way to push politicians into action, particularly given the way vaccines began to fade as a public priority several years ago. “This type of noise puts it back into the discussion of politicians,” he said.

Cherian agreed.

“A Call to Action on Pneumococcal Conjugate Vaccines

The need for advocacy appeared to strike a chord with those attending the conference. Orin Levine of PneumoADIP, in his “call to action” presentation, spoke of building a broad-based coalition involving pediatricians, infectious disease specialists, microbiologists and other experts who can collectively convince decision makers that pneumococcal immunization “is the right thing to do.”

He said lessons from the AIDS battle demonstrate that “the technical community can be an important instrument of change”, that when scientists and health care professionals manage to convince politicians of the need to act, the support can be impressive. He noted that in the U.S. there is now competition at the political level over who can provide the biggest budget for AIDS treatment and prevention.

“Now I don’t pretend that pneumococcal is HIV, but I do think there is a lesson there,” Levine said. “There was a community of people that convinced a political group that this was the right thing to do and the result has been the mobilization of a tremendous amount of resources.”

“I think we have to go home to our community and continue to fight to increase awareness and to bring this vaccine to the have-nots,” he said. “Because the majority of those deaths involve the have-nots.”
CONCLUSION
Lessons Learned

There was a consensus that the meeting provided, as Bhutta described it, “an excellent summary of the field.”

He said that despite the need for more data on disease burden and disease serotypes, and “despite all of the challenges you have with diagnostics and surveillance,” the presentations at the conference demonstrated there is still “a lot of information” available on the effectiveness of this vaccine in preventing deaths.

“Nothwithstanding all of the challenges of how you diagnose and how you really put your finger on invasive pneumococcal disease, the data on reduction of deaths and severe diseases from this vaccination strategy are incontrovertible,” he said. “We also have convincing information of herd immunity. There are not a lot of vaccines out there that impact the extremes of ages like pneumococcal vaccine.”

As for fears of replacement disease erasing the benefits of immunization, Bhutta said that based on the presentations at the conference, it is a concern that warrants investigation. But he said the evidence thus far is that replacement disease is not a threat sufficient to justify postponing vaccine introduction.

Bhutta warned against what he sees as a false notion that simply providing more convincing scientific analyses will be sufficient to influence policy. For example, Bhutta is skeptical that better data on cost-effectiveness is going to play a role in budget allocations for immunization.

“I don’t think people look at dollars per DALYs saved as the bottom line in terms of how they spend their money,” he said.

Bhutta believes the most convincing argument is simply that “we know” invasive pneumococcal disease cause a “fairly large proportion” of the millions of childhood deaths that occur each year and today, as we speak, we have a vaccine that works.

“It may not be ideal,” he said, noting that a vaccine that targets a bigger group of serotypes might work better. But he said the fact remains that the current 7-valent vaccine “works.”

“The challenge is making this available to the people who need it most,” he said.

Scientists can help make this happen, he said, by reaching “technical consensus” on the basic facts of the disease, such as its relative burden and the most effective strategies for reducing it.

De Quadros said his sense was that everyone attending the conference left “more united than when we came.” He repeated his observation that in the two days of the conference, it is likely that, given the death rate attributed to pneumococcus infections, 700 people died from pneumococcal diseases, “the equivalent of two airplanes crashing.”

“Notwithstanding all of the challenges of how you diagnose and how you really put your finger on invasive pneumococcal disease, the data on reduction of deaths and severe diseases from this vaccination strategy are incontrovertible.

We also have convincing information of herd immunity.

There are not a lot of vaccines out there that impact the extremes of ages like pneumococcal vaccine.”

—ZULFIQAR BHUTTA, AGA KHAN UNIVERSITY, PAKISTAN
## List of Speakers

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