GAVI’s PneumoADIP

Surveillance and Research Report

About This Report:
This report contains information about GAVI’s PneumoADIP, its pneumococcal surveillance and research activities, and WHO country health indicators. This report also contains surveillance data from PneumoADIP sponsored pneumococcal surveillance projects.
Acknowledgements

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Introduction

The following report outlines the extensive work the PneumoADIP surveillance and research network is undertaking around the world. This document is a useful tool describing the research and surveillance being undertaken in your region and includes surveillance data from PneumoADIP. The appendices provide a detailed breakdown of activities and research projects from each region including objectives, current status and results (where available) and also lists relevant non-PneumoADIP supported projects.

Key components of the document are:

- About PneumoADIP
- The Rationale for Surveillance
- Overview of PneumoADIP Surveillance Networks
- PneumoADIP Summary Data and Trends
- Other PneumoADIP Research Activities

We hope you find this document useful and informative. For further information on PneumoADIP and our activities, please visit www.preventpenumo.org
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1. Background Information

1.1 GAVI’s PneumoADIP

GAVI’s PneumoADIP is a small, dedicated team based in the Department of International Health at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. PneumoADIP is supported by a $40 million grant from the GAVI Alliance. PneumoADIP’s mission is to improve child health and survival by accelerating the evaluation of and access to new, life-saving pneumococcal vaccines for the world’s children.

PneumoADIP aims to achieve its goals through partnership with countries, donors, academia, international organizations and industry, while coordinating its activities through a strategic alliance with the World Health Organization (WHO). PneumoADIP is organized around three main areas of activities: establishing; communicating; and delivering the value of vaccination.

1) Establish Value: Establishing the value of vaccination by demonstrating the burden of meningitis and pneumonia caused by pneumococcal bacteria and the value of protection through vaccination.

2) Communicate Value: Maximizing communication of information about disease burden and the value of vaccination by ensuring that research data are made available to decision-makers in an appropriate form and through optimal channels.

3) Deliver Value: Delivering the value of the vaccine by ensuring that there is a predictable supply of quality vaccine at an affordable price, an adequate system to deliver it to the children who need it, and financing systems in place to sustain its use.

1.2 Pneumococcal Disease

Invasive pneumococcal disease is caused by the bacterium Streptococcus pneumoniae (S. pneumoniae). S. pneumoniae is a major cause of childhood and adult disease throughout the world. Clinical manifestations of S. pneumoniae infections in young children are serious and include pneumonia, meningitis, sepsis, bacteremia, otitis media, abscesses, and bone and joint infections. Worldwide, it is the most common cause of bacterial pneumonia mortality and the most severe cause of bacterial meningitis in children under five years of age.

Pneumococcal disease kills up to one percent of all children born in high mortality areas, and pneumococcal meningitis leaves approximately 50 percent of surviving children with life-long neurologic disabilities including deafness and seizures. According to the Centers for Disease Control (CDC), Epidemiology and Prevention of Vaccine-Preventable Diseases, HIV infection increases the risk of pneumococcal disease by 20 to 40 times. Other co-morbidities such as malnutrition and sickle cell anemia are also important risk factors for pneumococcal disease.

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The WHO estimates that more than 1.6 million people die of pneumococcal disease annually and that about half of these deaths are in children under five years of age (see Figure 1.2.1). The vast majority of these deaths occur in the developing world where there is currently limited access to potentially life-saving pneumococcal vaccines (see Figure 1.2.2).

Figure 1.2.1: Global distribution of causes of mortality

![Figure 1.2.1](image1)

**S. pneumoniae:**

1.6 million pneumonia deaths - 800,000 among children less than 5 years of age

Figure 1.2.2: ARI deaths in children less than 5 years old (2005)

![Figure 1.2.2](image2)

Based on WHO estimates in Williams BG et al. Lancet ID 2002
Map source: www.preventpneumo.org June, 2006

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1.3 Description of Pneumococcal Conjugate Vaccines

1.3.1 Safety and Efficacy of Pneumococcal Vaccines

Although common and often serious, pneumococcal disease is largely preventable by vaccination. While over 90 serotypes of \textit{S. pneumoniae} have been identified and most can cause human disease, seven to eleven serotypes cause the large majority of invasive infections globally. The first pneumococcal conjugate vaccine was licensed in the United States in 2000. The vaccine includes purified capsular polysaccharide of seven important serotypes of \textit{S. pneumoniae}. Studies have shown the conjugate vaccine to be safe and effective. Introduction of the vaccine has significantly decreased both infant and childhood pneumococcal disease caused by pneumococcal serotypes contained in the vaccine.\(^4\)\(^5\) Perhaps equally important, the vaccination of infants has resulted in ‘herd immunity’ and has reduced transmission of the bacterium to adults. As a result, an indirect effect of pneumococcal vaccination of infants is decreased pneumococcal morbidity and mortality among the elderly.\(^6\)

The vaccine has also been shown to be effective in developing world settings. A recent clinical trial using the 9-valent pneumococcal conjugate vaccine (PCV-9) in The Gambia demonstrated a substantial decline in radiologic pneumonia, meningitis and mortality.\(^7\) Another clinical trial conducted in Soweto, South Africa demonstrated efficacy of PCV-9 in both HIV infected and uninfected children.\(^8\)

1.3.2 Pneumococcal Vaccine Development Strategies and Pipeline

Currently, the 7-valent pneumococcal conjugate vaccine (PCV-7), Prevnar, is the only pneumococcal conjugate vaccine licensed for routine use in infants. This vaccine includes seven serotypes that are important causes of childhood pneumococcal disease. PCV-7 is currently included in the infant immunization schedule in several industrialized countries including Australia, Canada, the United Kingdom and the United States. This vaccine, however, does not include two prevalent disease-causing serotypes, 1 and 5, which contribute to severe pneumococcal disease in many developing countries. Newer formulations containing 10 or 13 serotypes that include the important serotypes in the 7-valent vaccine, plus serotypes 1 and 5 are in advanced stages of development and testing. These vaccines are expected to be licensed between 2008 and 2009.

<table>
<thead>
<tr>
<th>Vaccine characteristic</th>
<th>Polysaccharide vaccines (unconjugated)</th>
<th>Conjugate vaccines (protein + saccharide)</th>
<th>Common protein candidate vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven efficacy for prevention of <strong>invasive disease</strong> in children &lt; 2 years old</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Proven efficacy for prevention of <strong>pneumonia</strong> in children &lt; 2 years old</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Licensed for use in children &lt; 2 years old</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prevents invasive disease in adults and children &gt; 2 years old</td>
<td>Yes</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Recommended for older children and high-risk adults</td>
<td>Yes</td>
<td>Yes</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Generates T cell memory</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Prevents colonization with vaccine serotypes</td>
<td>No</td>
<td>Yes</td>
<td>No data</td>
</tr>
<tr>
<td>Number of pneumococcal serotypes targeted</td>
<td>23</td>
<td>7–13</td>
<td>Theoretically all</td>
</tr>
</tbody>
</table>
Figure 1.3.1: Pneumococcal vaccine pipeline status

<table>
<thead>
<tr>
<th>Vaccine manufacturers</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-valent (Wyeth)</td>
<td></td>
</tr>
<tr>
<td>10-valent (GSK)</td>
<td></td>
</tr>
<tr>
<td>Multi-valent (emerging suppliers)</td>
<td></td>
</tr>
<tr>
<td>New technology vaccines</td>
<td></td>
</tr>
</tbody>
</table>

Vaccine serotypes:
- **7-valent**: 4, 6B, 9V, 14, 18C, 19F, 23F
- **10-valent**: 7-valent + 1, 5, 7F
- **13-valent**: 10-valent + 3, 6A, 19A

- **Licensure (FDA, EMEA)**
- **Available for emerging markets (developing countries)**
- **replaces 7-valent**
1.4 Vaccine Policy Status

1.4.1 Recommendation of Pneumococcal Conjugate Vaccines

In March 2007, following deliberations of its Strategic Advisory Group of Experts (SAGE), the WHO released its position statement on the use of pneumococcal conjugate vaccines for the world’s children. The WHO recognized that pneumococcal disease is a cause of serious illness and death among children under five, as well as among adults, especially those infected with HIV. The WHO further recognized that the 7-valent conjugate vaccine is safe and effective for use in both industrialized and developing countries. As a result, the position statement recommends that PCV-7 become a priority for national immunization programs. In particular, countries with more than 50,000 annual deaths among children less than five years of age should prioritize the introduction of PCV-7 into the national Expanded Program on Immunization (EPI).

1.4.2 Financing of Vaccines

Long-term, sustainable financing for GAVI-eligible countries to procure pneumococcal vaccines is now available. In November 2006, GAVI approved an investment case for pneumococcal vaccines that will ensure financing for use of the existing 7-valent vaccine from 2008 to 2010. In addition, $1.5 billion US dollars was recently committed for use in an Advance Market Commitment (AMC) for pneumococcal vaccines. The AMC is a commitment to subsidize the purchase of pneumococcal vaccines for GAVI countries beginning in 2010. The AMC will also help accelerate affordable pricing by requiring manufacturers to provide the vaccines beyond the AMC period at lower prices.

In February 2007, GAVI announced its new Phase II financing that will require countries to make a co-payment for procurement of new vaccines. Countries, depending on where they fall within the GAVI guidelines, will pay 10 to 30 cents per dose for the pneumococcal conjugate vaccine or any other new vaccines.

GAVI countries began submitting applications for the 7-valent pneumococcal conjugate vaccine in September 2007. Countries with approved applications can expect delivery of pneumococcal vaccines as early as the second half of 2008.

1.4.3 Vaccine Supply and Cold-Chain

Currently, PCV-7 is included in the infant immunization schedule in more than fifteen countries. Countries with an existing or announced National Immunization Program include Australia, Belgium, Canada, Costa Rica, Cyprus, Denmark, France, Germany, Greece, Ireland, Italy, Kuwait, Luxembourg, Mexico, Netherlands, Norway, Qatar, Sweden, Switzerland, the United Kingdom, the United States, and the United Arab Emirates. In addition, Korea, Portugal and Spain have high private-market use of PCV-7. There is sufficient supply of PCV-7 to meet projected GAVI demand between 2007 and 2010. WHO pre-qualification of the PCV-7 is expected in the first half of 2008.

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Introduction of pneumococcal vaccines will require substantial attention to cold chain, logistics, and vaccine management issues. The current presentation of the PCV-7 (pre-filled single dose syringe) has a packed volume of 59.7 cm³/dose, which is relatively large compared to vaccines prepared in multi-dose vials. The introduction of this vaccine would likely require expansion of cold storage and careful planning for vaccine management, although relatively little expansion of dry storage would be necessary. The 7-valent conjugate vaccine is expected to be available in smaller single dose vials as early as 2009. The relative impact on cold storage is likely to be less substantial in countries that have already introduced rotavirus vaccines.

2. PneumoADIP Surveillance and Research: Scope of Work

2.1 Rationale for Surveillance

Decision-makers in developing countries need accurate data at a local and regional level in order to justify dedicating resources to combating pneumococcal disease. Supporting research and surveillance in these countries to provide such data is one of PneumoADIP’s strategic goals. An increased understanding of the potential impact of vaccination against pneumococcal disease will enable decision makers to weigh various options for making the best use of limited resources.

Although pneumonia is consistently ranked among the top killers of infants and children in the developing world, most regions have limited capacity to isolate *S. pneumoniae* and to diagnose pneumococcal disease. High quality surveillance is an important tool for monitoring changes in pneumococcal serotype distribution and antibiotic resistance patterns, and for evaluating the impact of vaccination on invasive pneumococcal disease after vaccine introduction. Systematic evaluation of suspected cases and use of appropriate specimens and laboratory diagnostic tests are key elements of good quality surveillance. Moreover, surveillance must cover a sufficient time period to be representative of local disease epidemiology and capture seasonal variations. Given the challenges inherent to detecting pneumococcal disease, even high quality surveillance cannot accurately measure the burden of disease due to pneumococcus. Using surveillance data alone will lead to an under-appreciation of the morbidity and mortality attributable to pneumococcal disease. Accurate disease burden estimates can only be derived through modeling, using the results of clinical trials with pneumococcal vaccines.

<table>
<thead>
<tr>
<th>Why perform surveillance for pneumonia and meningitis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Surveillance provides important data on pneumococcal serotype distribution and antibiotic resistance trends</td>
</tr>
<tr>
<td>• Surveillance allows monitoring of the impact of vaccination on pneumococcal disease caused by serotypes included in the vaccine</td>
</tr>
<tr>
<td><strong>BUT</strong></td>
</tr>
<tr>
<td>• Surveillance does not accurately measure the burden of pneumococcal and Hib disease. Good estimates of disease burden for these pathogens can only be obtained through vaccine probe trials and statistical models</td>
</tr>
<tr>
<td>• Poor quality surveillance should not be used for evidence-based decision-making</td>
</tr>
</tbody>
</table>

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2.2 Serotype Distribution

Pneumococcal serotype distribution is a key parameter for vaccine development and for helping country decision-makers choose the most appropriate vaccine. Knowledge of serotype distribution is required to estimate the potential benefits of various pneumococcal conjugate vaccine formulations. Serotype distribution may vary by geographic location, patient age, disease syndrome (e.g. meningitis vs. pneumonia), isolate type (e.g. blood vs. cerebrospinal fluid), HIV status or time period. Until now, there have been two major reviews of available data on pneumococcal serotype distribution. The first included a limited number of studies, primarily from North America and Europe, and was used in the formulation and development of early conjugate vaccines. The second review incorporated studies performed between 1980 and 1999 across the globe. Data from Africa and Asia were fairly limited at the time, yet provided the basis of our current knowledge of global and regional serotype distribution.

Recently, the WHO asked PneumoADIP to undertake a global pneumococcal serotype project (GSP) and analysis as part of the Advanced Market Commitment (AMC) process to establish the Target Product Profile (TPP). The TPP describes the minimum characteristics required for a pneumococcal vaccine to be eligible for AMC funding. The objective of the GSP was to provide the TPP Expert Committee with a meta-analysis and summary of the serotype burden among young children with invasive pneumococcal disease globally and by region (according to World Bank regions). The summary GSP Report for Version 1.0 analyses presented to the TPP Expert Committee is available at: http://www.preventpneumo.org/pdf/GSP%20Summary%20for%20SAGE%20Nov6-8%202007_Oct%2019-07.pdf

Data from GSP Version 1.0 analyses indicates that in each region, three serotypes (1, 5, and 14) account for between one-third and one-half of invasive pneumococcal disease in children less than five years old. Serotype 1 is ranked in the top four serotypes in every region, except North America and Oceania. In each region, three to five serotypes account for greater than 50 percent of isolates, five to seven serotypes account for more than 65 percent of isolates, and seven to eleven serotypes account for greater than 80 percent of isolates among children less than five years old with invasive pneumococcal disease. Africa and Asia shared the same top eight serotypes (1, 5, 6A, 6B, 14, 19A, 19F, 23F) in the Version 1.0 analysis. The cumulative proportion of these eight is somewhat higher in Africa than in Asia, with a range of approximately 70 to 80 percent.

The GSP Version 1.0 analyses also estimated coverage with serotypes included in existing or developed vaccine formulations and assumed that all vaccine formulations with 6B would also provide cross protection against serotype 6A. In every region, the serotypes included in the existing 7-valent conjugate vaccine (Prevnar) are estimated to account for 54 to 75 percent of invasive pneumococcal disease among children less than five years old, with substantial regional variability. The lowest estimated coverage is in Africa and Asia. The serotypes included in the 10-valent formulation produced by GSK are estimated to account for 75 to 90 percent of serotypes causing invasive pneumococcal disease in children less than five years old, with

considerable increases over the 7-valent serotype coverage for the Africa, Asia, and Latin America and Caribbean regions. The serotypes included in the 13-valent formulation produced by Wyeth account for 80 to 92 percent of serotypes causing disease in children less than five years old in every region. Regional variations are minor.

The GSP will be finalized (GSP Version 2.0 analyses) in first quarter 2008 and will include additional serotype data from PneumoADIP and non-PneumoADIP surveillance sites and analyses of serotype distribution by age, disease syndrome, specimen type, and HIV status.

2.3 Serotype Replacement

Serotype replacement involves a natural process where the prevalence of pneumococcal serotypes change over time. Vaccine developers and epidemiologists anticipated the potential for serotype replacement to occur following introduction of PCV-7. In the United States, PCV-7 was introduced into the general population in 2000. While serotype replacement has been observed among Alaskan Natives who received PCV-7, this trend has not been seen to a similar degree across the remainder of the U.S. population. Serotype replacement could occur in both developed and developing countries, which necessitates the need for post-introduction surveillance to monitor vaccine impact and any shifts in the serotype distribution. Pneumococcal disease caused by emerging serotypes represents only a small fraction of the total pneumococcal disease burden. In spite of serotype replacement, the pneumococcal vaccine prevents a substantial proportion of pneumococcal disease. Because serotype replacement occurs over a relatively long period of time, vaccine developers have sufficient time to complete development and licensure of the 10- and 13-valent vaccines that contain additional serotypes that could become more important in the future.

2.4 Antibiotic Sensitivity

Surveillance can also be used to measure trends in antibiotic sensitivity patterns over time. In general, inappropriate prescription practices, overuse, and unregulated sales have contributed to a growing problem of bacterial resistance to antibiotics. Even with completely appropriate use of antibiotics, selective pressures induce evolution of disease-causing bacteria to resist drug therapy. Resistance to first-line drugs necessitates the use of higher priced second- and third-line medications. When these second- and third-line antibiotics are not available, resistance may lead to more severe disease, increased case fatality ratios, and higher rates of clinical sequelae among survivors.

Substantial anecdotal documentation of antibiotic resistance patterns from the developing world is available. Resistance patterns depend on many factors including local medical practices, access to antibiotics, patient compliance, geography, population make-up, and population movement. PneumoADIP’s surveillance networks are ideally suited to collect antibiotic resistance data on a population level across participating countries and regions. The networks can monitor changes in antibiotic resistance and provide local, up-to-date information. This information can lead to improved clinical management practices by guiding physicians’ prescription choices for ill children.

2.5 PneumoADIP-Supported Surveillance Networks

PneumoADIP-funded research and surveillance activities include surveillance networks, small grant projects, and other research projects. Currently, seven networks in Africa (AFRO), South Asia (SEARO), Latin America (PAHO), the Eastern Mediterranean (EMRO) and the Western Pacific (WPRO) regions have collected surveillance data on meningitis, pneumonia, and sepsis in children and adults (see Table 2.5.1). Through these networks, investigators are conducting pneumococcal disease surveillance in both rural and urban areas while working to promote information sharing on disease serotypes and antimicrobial-resistance patterns among local clinicians and policy-makers.

In 2007, GAVI’s PneumoADIP was supporting projects in over 56 countries in Africa, Asia, the Western Pacific region, the Eastern Mediterranean region and Latin America (Figure 2.5.1).

Figure 2.5.1: PneumoADIP supports activities in 56 countries

Map source: www.preventpneumo.org June, 2006
<table>
<thead>
<tr>
<th>WHO region</th>
<th>PneumoADIP-funded Surveillance Networks</th>
</tr>
</thead>
</table>
| AFR (Appendix I) | netSPEAR: The Network for Surveillance of Pneumococcal Disease in the East Africa Region  
- Burundi, Eritrea, Ethiopia, Kenya, Rwanda, Tanzania and Uganda  
- A pneumococcal and Hib disease surveillance network currently operating in four countries in East Africa (Ethiopia, Kenya, Tanzania, Uganda). The network functions in conjunction with the WHO/AFRO Pediatric Bacterial Meningitis Network within many of the surveillance sites. |
| EMR (Appendix II) | EMR: Eastern Mediterranean Region Bacterial Meningitis and Pneumonia Surveillance Network  
- Iran, Libya, Morocco, Pakistan, Sudan, Syria and Yemen  
- In 2004, the Bacterial Meningitis Network began data collection on meningitis disease and trends. In 2006, surveillance was enhanced to include pneumonia. The bacterial meningitis and pneumonia surveillance hospital network spans six countries including Libya, Morocco, Yemen, Pakistan, Syria and Sudan. Iran is conducting population-based surveillance in a catchment area located in the capital city of Tehran. The surveillance network is slated to begin data collection in late Q3 of 2007. |
| PAHO (Appendix III) | SIREVA II, SIREVA II+: Pan American Health Organization (PAHO)  
- SIREVA II+: Brazil, Columbia, Dominican Republic, Guatemala, Nicaragua and Uruguay  
- SIREVA I was a surveillance network consisting of 21 countries. SIREVA II builds upon SIREVA I activities, to include epidemiological and clinical components. Six SIREVA II+ countries will conduct enhanced surveillance and collect population-based incidence data in children less than 5 years of age. Two SIREVA II+ countries – Brazil and Uruguay – will conduct surveillance activities in both children and adults. SIREVA II countries that have initiated surveillance include: Brazil, El Salvador, Ecuador, Guatemala, Honduras and Paraguay. Other SIREVA II sites are scheduled to begin surveillance before the end of 2007. Brazil has initiated SIREVA II+ surveillance activities, while the remaining sites plan to start data collection by the end of 2007. |
| SEAR (Appendix V) | ICDDR, B: The International Centre for Diarrheal Disease Research  
- Bangladesh  
- A surveillance network that consists of two population-based surveillance sites and a seven hospital surveillance network. The sites aim to establish the value of pneumococcal vaccine and Hib disease by determining the local burden of childhood meningitis and pneumonia in Bangladesh and the distribution of serotypes causing severe pneumococcal infections.  
IBIS/SAPNA: The Invasive Bacterial Infections Surveillance/South Asian Pneumococcal Alliance  
- India, Nepal and Sri Lanka  
- A consortium of Nepalese and Sri Lankan hospitals combined with an existing Indian surveillance network to collaborate in an ambitious project to better define the regional burden of pneumococcal and Hib disease. The investigating team has made close links with national health policy makers to ensure that the data gathered will help to influence health policy in these countries.  
IEIP: The International Emerging Infections Program  
- Thailand  
- IEIP’s existing population-based pneumonia surveillance program was enhanced to include microbiologic surveillance. This addition has allowed investigators to collect blood cultures from hospitalized patients of all ages with pneumonia and sepsis in Thailand to describe serotype distribution and antimicrobial use and resistance patterns. |
| WPR (Appendix VI) | IVI: The International Vaccine Institute  
- Vietnam  
- IVI conducted a pilot study of hospital-based pneumococcal disease surveillance in Khanh Hoa Province.  
Mongolian Surveillance Network  
- With the support of WHO, bacterial meningitis surveillance was initiated in the capital city of Ulaanbaatar in 2002. In 2007, PneumoADIP added pneumonia surveillance activities to the existing surveillance system. Mongolia is in the process of acquiring the necessary tools and receiving the |
2.5.1 netSPEAR (East Africa – Ethiopia, Kenya, Tanzania and Uganda, plus Burundi, Eritrea, Rwanda)

The Network for Surveillance of Pneumococcal Disease in the East African Region (netSPEAR) consists of seven countries: four that are actively participating in surveillance (including Ethiopia, Kenya, Tanzania and Uganda) and Burundi, Eritrea, and Rwanda that are preparing to begin surveillance activities in the future. netSPEAR is hosted by the KEMRI/Wellcome Trust Collaborative Research Programme in Kenya and currently operates in twelve hospitals in Kenya, Tanzania, Uganda, and Ethiopia. The network operates closely in coordination with the WHO African Regional Office and its pre-existing Pediatric Bacterial Meningitis network. Eventually, netSPEAR aims to expand to include hospitals in Burundi, Rwanda, and Eritrea to grow to a total of seven participating countries. netSPEAR’s primary goal is to provide a focal point in East Africa for compiling and sharing data on *S. pneumoniae* and *H. influenzae* type b (Hib). It will also expand the region’s capacity for effective, routine surveillance. Once collected, the network will disseminate the surveillance results to regional network partners, including surveillance sites, ministries of health, multilateral organizations, and donors supporting vaccination programs. For additional information, see Appendix I: Africa Region (AFRO) on page 42.

2.5.2 EMRO: Eastern Mediterranean Region Bacterial Meningitis and Pneumonia Surveillance Network (Iran, Libya, Morocco, Pakistan, Sudan, Syria, Yemen)

Surveillance for vaccine preventable diseases is a key activity supported by the Eastern Mediterranean Regional Office (EMRO) in this region. The data collected through surveillance can support evidence-based decision making related to the introduction of new vaccines and evaluating the impact of vaccines once they are introduced. The objective of the bacterial meningitis and pneumonia network is to build on the existing bacterial meningitis surveillance network by expanding current knowledge on Hib and pneumococcal invasive disease epidemiology in the region and to establish a mechanism to evaluate post-introduction vaccine impact. Data collected includes serotype distribution and antimicrobial resistance. For additional information see Appendix II: Eastern Mediterranean Region on page 62.

2.5.3 SIREVA II, SIREVA II+ (PAHO - Brazil, Colombia, Dominican Republic, Guatemala, Nicaragua, Uruguay)

Surveillance of Pneumococcal disease in the Americas dates back to the establishment in 1993 of the *Sistema Regional de Vacunas* (SIREVA I) project for laboratory surveillance of bacterial meningitis and pneumonia, including pneumococcal disease. The objective of the SIREVA I network was to determine the distribution of pneumococcal serotypes causing severe disease and the prevalence and epidemiology of antimicrobial resistant pneumococci. The major limiting factor of the data produced by SIREVA I was the inability to link clinical and epidemiological data to isolates obtained through the lab-based network. The aim of SIREVA II is to continue collecting facility-based data with both clinical and epidemiological components from all existing sites (SIREVA II) along with population-based data in selected sites (SIREVA II+). For additional information see Appendix III: Region of the Americas (PAHO) on page 69.
2.5.4 ICDDR,B (Bangladesh)

A project consisting of a consortium of Bangladeshi hospitals and community-based population surveillance and led by the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) Center for Health and Population Research has embarked on an ambitious disease surveillance project to better define the regional burden of pneumococcal disease. Bangladesh is a low-income country with many health problems that compete for limited resources. Though Bangladesh is primarily known for its diarrheal disease burden, pneumonia is currently the leading cause of death for children under five years of age. To date, more than 33,000 blood cultures and CSF specimens have been collected in Bangladesh. The surveillance project has three components: a hospital-based surveillance network (comprised of four hospitals in Dhaka, two in Chittagong and one hospital in Mirzapur); and two population-based surveillance sites (one in a rural and the other in an urban setting). For additional information, see Appendix V.1: ICDDR,B Surveillance Network (Bangladesh) on page 77.

2.5.5 IBIS/SAPNA (South Asia – India, Nepal, Sri Lanka)

PneumoADIP’s collaboration in South Asia is providing support and helping local investigators to link an existing Invasive Bacterial Infections Surveillance (IBIS) network in India to new surveillance sites in neighboring countries Nepal and Sri Lanka. PneumoADIP provides support to five IBIS hospitals in India as well as two hospitals in Nepal and one in Sri Lanka. This expanded surveillance network is known as the South Asian Pneumococcal Alliance or SAPNA—the Sanskrit word for ‘dream’. PneumoADIP support allows IBIS and SAPNA to coordinate their activities closely with one another, thereby improving the comparability of the data from all of the South Asian sites. This network includes one of the largest children’s hospitals in the world (Lady Ridgeway Hospital in Colombo, Sri Lanka). It is helping to improve our understanding of invasive bacterial disease epidemiology in the region, one of the world’s most populated areas, and it is providing new information on the pneumococcal serotypes causing disease and on antimicrobial resistance patterns. This network has enrolled over 7,800 children and is serving a crucial role in accelerating introduction of the pneumococcal conjugate vaccine in South Asia. For additional information, see Appendix V.2: South Asian Pneumococcal Network Alliance (SAPNA) on page 82.

2.5.6 IEIP (Thailand)

PneumoADIP is supporting the addition of microbiologic surveillance into an existing pneumonia surveillance system organized by the Thailand International Emerging Infections Program (IEIP), a joint collaboration of the Thailand Ministry of Public Health and the Centers for Disease Control in the United States. Since August 2002, the IEIP has supported active, population-based surveillance for hospitalized cases of pneumonia in Sakaeo Province. The partners have worked to design a network that ensures a high degree of standardization from site-to-site and encourages data sharing between sites. This system was expanded in 2003 to include Nakhon Phanom Province. All hospitals in this surveillance system were equipped with basic laboratory facilities and staffed by university-trained laboratory technologists. However, equipment and materials to conduct bacteriological testing were generally absent prior to PneumoADIP funding, except at the central provincial hospital.

With PneumoADIP funding, IEIP has introduced automated blood culture systems to estimate the burden of culture-confirmed pneumococcal pneumonia and sepsis in patients of all ages. Data
through December 2006 show that the project has collected over 15,000 blood specimens in 20 hospitals. IEIP also collects antibiotic use information to assess the impact of pre-culture antibiotics on culture yield. Ultimately, this population-based surveillance for pneumonia syndromes and culture-confirmed disease in patients of all ages should provide useful information on the serotype distribution and antimicrobial resistance patterns for invasive pneumococcal isolates and will contribute to our understanding of the burden of vaccine-preventable pneumococcal disease in Thailand. For additional information, see Appendix V.3: International Emerging Infections Program (IEIP), Thailand on page 86.

2.5.7 IVI (Viet Nam)

Viet Nam is a country of more than 80 million people with a strong history of proactive public health programs. Although data from Asian countries suggest that *S. pneumoniae* is a common cause of pneumonia and meningitis in the region, there has historically been minimal experience with active pneumococcal disease surveillance. PneumoADIP is supporting the International Vaccine Institute (IVI) to conduct a pilot study of hospital-based pneumococcal disease surveillance at Khanh Hoa General Hospital in Khanh Hoa Province. Researchers are attempting to isolate *S. pneumoniae* from severely ill children and evaluate antibiotic resistance and serotype distribution of isolates. For additional information, see Appendix VI.1: Overview of International Vaccine Institute – Viet Nam on page 93.

2.5.8 Mongolian Surveillance Network

Surveillance for bacterial meningitis started in six hospitals located in the capital city of Ulaanbaatar with support from WHO between 2002 to 2005. The surveillance activities were very successful in identifying cases of confirmed bacterial meningitis, leading to the government’s decision to introduce the Hib vaccine into the national immunization schedule. Surveillance activities documented a dramatic decrease in the number of Hib meningitis cases and prompted the participating hospitals to continue conducting surveillance after the end of WHO funding in 2005. In September 2007, with support from both PneumoADIP and the Hib Initiative, pneumonia surveillance was added to the existing meningitis surveillance system. For additional information, see Appendix VI.2: Mongolia Surveillance Network on page 96.
<table>
<thead>
<tr>
<th></th>
<th>PneumoADIP Surveillance Network achievements</th>
</tr>
</thead>
</table>
| 1 | Improved country and regional representation and generalizability of data related to pneumococcal disease.  
   - Improved generalizability of data throughout a region by standardizing methods across countries and networking countries together (netSPEAR, SAPNA).  
   - Expanded from surveillance in one country to several countries in the region (netSPEAR, SAPNA).  
   - Expanded surveillance from generally only one hospital or one city to many hospitals and throughout the country (ICDDR,B, netSPEAR, SAPNA).  
   - Added rural surveillance where only urban surveillance had existed (netSPEAR, ICDDR,B). |
| 2 | Estimated invasive pneumococcal disease incidence among children.  
   - Estimates available for the first time in Bangladesh (ICDDR,B).  
   - First invasive disease incidence rates in Thailand (IEIP).  
   - Incorporated population-based, active surveillance into regular activities (EMRO, PAHO). |
| 3 | Expanded data on pneumococcal serotype distribution and vaccine serotype coverage.  
   - All sites.  
   - First reported data from Nepal and Uganda (netSPEAR, SAPNA).  
   - First systematically collected isolates in Thailand (IEIP). |
| 4 | Informed physician prescribing practices related to antimicrobial resistance.  
   - The evaluation of antimicrobial resistance uncovered resistance of pneumococcal strains to cotrimoxazole and penicillin in hospital patients, resulting in changing the medical practice in Sri Lanka (SAPNA). |
| 5 | Demonstrated the benefits of using other diagnostic techniques in addition to culture.  
   - Use latex agglutination, Binax and PCR on CSF specimens significantly improved detection of *S. pneumoniae* above culture alone (Pakistan, Burkina Faso, Togo, IVI, SAPNA). |
| 6 | Laid the groundwork to enable estimation of the potential indirect effects of vaccination with PCV-7 in preventing disease in unimmunized children and adults.  
   - Activities were expanded beyond vaccine-eligible children to include surveillance of pneumonia, meningitis and sepsis in older children and adults (IEIP, netSPEAR, PAHO, SAPNA). |
| 7 | Identified ‘other’ pathogens not previously recognized as important causes of pneumonia, meningitis and sepsis.  
   - Isolated pathogens such as *Burkholderia pseudomallei* and non-typhoidal *Salmonella* not found in Western countries (IEIP, SAPNA - Nepal).  
   - Detected higher rates of invasive disease than previously thought (ICDDR,B, SAPNA). |
3. PneumoADIP Surveillance Methods

3.1 Representativeness of Surveillance and Standardization of Surveillance Methods

Pneumococcal data from the developing world, particularly Africa and Asia, has historically been very limited. Prior to 2003 and support from PneumoADIP, there were few surveillance sites located in GAVI-eligible countries. Importantly, the data that was available was rarely representative of an entire country or region. For example, surveillance data from a tertiary care hospital in an East African capital city, (a facility that sees only the sickest children who can also afford hospital care) may not be extrapolated to the entire East African region. Collaboration and linkage between early surveillance sites was minimal and data generated from these sites was often not transmitted effectively to relevant domestic and international policy makers. Finally, data collected at one site could usually not be either compared or aggregated to data from another site because different definitions were used for classification of pneumonia, meningitis and sepsis.

Through its surveillance activities, PneumoADIP has attempted to increase the number of countries with pneumococcal data and ensure that the data generated is of a high quality. Data is collected in a standardized manner with common clinical diagnostic algorithms and laboratory protocols (see Appendix VII for case definitions flow chart). Through the use of networks spanning countries and regions and including both hospital- and community-based surveillance, PneumoADIP strives to generate data that expands representativeness and improves the comparability of pneumococcal surveillance across a country or region and between regions. Ensuring data comparability between countries and regions enables the estimation of disease burden in areas without ongoing surveillance activities by creating models and extrapolating results. Additional benefits of networking surveillance projects include intra- and cross-network peer pressure to improve quality, ease of communication of findings across borders, promotion of best practice sharing, and south-south collaborations.
3.3 Location and Types of Hospitals, Specimens, and Diagnostic Methods

3.3.1 Location and types of hospitals performing surveillance

PneumoADIP-sponsored surveillance is conducted in a variety of geographic locations and hospital settings (Table 3.3.1). Different locations and types of facilities see different patient populations, leading to variations in pneumococcal yields and serotype distribution. More specifically, outpatient facilities typically encounter patients with less severe forms of disease, which should lead to lower isolation rates compared to referral facilities. On the other hand, patients presenting to outpatient facilities are less likely to have received antibiotics prior to specimen collection than those seen at referral hospitals. Since antimicrobial treatment decreases the likelihood of identifying viable organisms in the blood or CSF by culture, yields from outpatient facilities may actually be comparable to those from inpatient referral facilities. For pneumococcus in particular, non-severe occult bacteremia has been extensively documented in industrialized countries; outpatient surveillance in developing countries may uncover a similar epidemiological picture. Another advantage of outpatient surveillance is that it may improve our understanding of the serotype distribution of mild pneumococcal disease, which probably differs from that of severe disease. In addition, the pneumococcal strains obtained may be more representative of disease-causing types, given that serotypes susceptible to antibiotics are not found once children have been treated, which is frequently the case of hospitalized patients.

The use of standard case definitions and laboratory methods across networks enables the comparison of surveillance results from sites with varying characteristics and provides an in-depth understanding of how these characteristics affect bacterial yields and pneumococcal serotype distribution.

<table>
<thead>
<tr>
<th>Table 3.3.1: Locations and types of hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
</tr>
<tr>
<td>Rural</td>
</tr>
<tr>
<td>Bangladesh, rural community (1)*</td>
</tr>
<tr>
<td>Urban</td>
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<td>Both</td>
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</tbody>
</table>

*Population-based surveillance; all other locations are hospital-based surveillance.
**PAHO – Ecuador, Bolivia, El Salvador, Guyana, Honduras, Nicaragua, Uruguay, Brazil, Colombia, Dominican Republic, Guatemala.
***EMRO – Iran, Libya, Morocco, Pakistan, Sudan, Syria, Yemen.
3.3.2 Specimen types and diagnostic methods

Currently, seven countries have sites collecting both blood and CSF specimens, five collect only CSF samples, and two collect only blood (Table 3.3.2). The clinical condition dictates the body fluids to be sampled, within the limits of diagnostic tests available at the site of presentation. A patient meeting the standardized clinical case definition for meningitis will have both blood and CSF sampled for identification of the pathogenic organism, whereas a patient who meets the clinical definition for pneumonia or sepsis/very severe disease will have only blood drawn.

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children &lt; 5 years</td>
</tr>
<tr>
<td>CSF</td>
<td>Pakistan</td>
</tr>
<tr>
<td>Blood</td>
<td>Bangladesh (urban community)</td>
</tr>
<tr>
<td>CSF and blood</td>
<td>Bangladesh (hospitals &amp; rural community)&lt;br&gt;Vietnam&lt;br&gt;Mongolia&lt;br&gt;Ecuador&lt;br&gt;El Salvador&lt;br&gt;Honduras</td>
</tr>
</tbody>
</table>

There are multiple methods available for the identification of pathogenic bacteria in blood or CSF specimens. **Bacterial culture**, used for well over a century, is considered to be the gold standard of direct microbiologic identification and consists of growing organisms on a favorable media in a laboratory environment. Culture lacks sensitivity, but allows a thorough characterization of the disease-causing organism, such as serotype and antimicrobial resistance. It is the only validated method for identifying bacteria in blood specimens, whereas additional, more sensitive, methods are available for testing CSF specimens.
Other diagnostic techniques used by PneumoADIP-supported projects for bacterial identification from cerebrospinal fluid include polymerase chain reaction (PCR), latex agglutination (LA), and the Binax NOW® *S. pneumoniae* immunochromatographic test (ICT) (see Table 3.3.3).

<table>
<thead>
<tr>
<th>Region</th>
<th>Culture only</th>
<th>PCR and/or LA and/or Binax</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td></td>
<td>Burkina Faso</td>
</tr>
<tr>
<td>Ethiopia</td>
<td></td>
<td>Togo</td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td></td>
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<tr>
<td>Uganda</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td></td>
<td>Pakistan</td>
</tr>
<tr>
<td>Thailand</td>
<td></td>
<td>Sri Lanka</td>
</tr>
<tr>
<td>India</td>
<td></td>
<td>Nepal</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td></td>
<td>Vietnam</td>
</tr>
<tr>
<td><strong>Eastern Mediterranean (EMRO)</strong></td>
<td></td>
<td>All sites</td>
</tr>
<tr>
<td><strong>Central and South America (PAHO)</strong></td>
<td></td>
<td>All sites</td>
</tr>
</tbody>
</table>

**PCR** is a molecular biologic technique that exponentially amplifies specific DNA sequences and is able to identify the causative infectious organism with a high degree of sensitivity and specificity. Both latex agglutination and immunochromatographic testing are indirect methods of identifying pathogens. **Latex agglutination** utilizes latex beads covered in organism-specific antibody that cross-reacts with antigen found in the CSF, if the pathogen of interest is present. Interaction between the antigen and antibody results in agglutination, or clumping together, of the latex beads into visible particles signifying a positive test. Many latex kits can identify all three of the main meningitis-causing organisms (*S. pneumoniae*, *N. meningitidis*, and *H. influenzae* type b). The **Binax ICT** is an antigen detection assay that may be used in the CSF of meningitis patients and in the urine of adult pneumonia patients to identify C-polysaccharide, a capsular antigen common to all pneumococcal strains. Of note, latex agglutination relies on visual interpretation by a skilled technician, and is thus subject to error, whereas the Binax ICT is easy to perform, but is more expensive than latex agglutination and can only identify pneumococcus. Prior antimicrobial treatment, extended transport time between specimen collection and laboratory testing, and improper storage may compromise a laboratory’s ability to grow pathogens from culture. Polymerase-chain reaction, latex agglutination, and the Binax ICT, when used in conjunction with bacterial culture, hold the potential to significantly increase the sensitivity of diagnosis of pneumococcal infection, since they enable the identification of antigens and genetic material that persist even in the absence of viable pathogens.
4. PneumoADIP Summary Data and Trends

Thirteen countries report data monthly to PneumoADIP using a standardized data reporting form. Of these, ten have at least one calendar year of data, while three do not (Burkina Faso and Togo: ten months; India: nine months) (Figure 4.1). The data presented below were obtained from these reports.
**Specimens collected:** As of April 2007, over 100,000 blood and cerebrospinal fluid (CSF) specimens (75,000 blood and 25,000 CSF specimens) had been collected for microbiologic analysis. As new countries have initiated surveillance activities, the total number of samples collected each month has increased steadily (Figure 4.2).

![Figure 4.2: Cumulative blood and CSF specimens collected](image)
**S. pneumoniae, H. influenzae, and N. meningitidis isolates:** In a majority of sites, *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* are the leading causes of bacterial illness. Of these three organisms, pneumococcus was the most frequently isolated from blood culture of the three, followed by *H. influenzae* and *N. meningitidis* (Figure 4.3). *N. meningitidis* was seen rarely in blood culture. In some sites surveillance uncovered previously unrecognized endemic bacterial illness caused by organisms other than Sp, Hi andNm. For example, Patan Hospital in Nepal had a blood culture isolation rate for *Salmonella typhi/paratyphi* in children less than five years of age that was greater than pneumococcus. *Salmonella* outpatient yields were higher than inpatient yields. Surveillance has provided information on all bacteria causing pneumonia and meningitis, and is particularly useful for local decision-making.

![Figure 4.3: Proportion of blood specimens' culture positive for S. pneumoniae, H. influenzae and N. meningitidis in children < 5 years old, by site](image)

*OP, outpatient
These specimens were isolated from culture only*
Significant heterogeneity in the proportion of CSF samples culture-positive for *S. pneumoniae*, *H. influenzae* and *N. meningitidis* is present across sites (Sp range: 0 - 4%, Hi range: 0 - 23%, Nm range: 0 - 2%) (see Figure 4.4). Factors contributing to these observed differences between sites include geographic location and variations in patient populations, disease severity, Hib vaccine use, and prevalence of other meningitis-like illnesses.

Figure 4.4 highlights the importance of *N. meningitidis* as a cause of meningitis in both Burkina Faso and Togo. Both countries are located in the African meningitis belt that extends from Western Africa to Ethiopia and often experiences epidemics of meningitis caused by *N. meningitidis*. Because surveillance was conducted during the meningitis season in Burkina Faso and Togo, the high isolation rate of meningococcus from CSF is expected. However, high isolation rates of pneumococcus were unexpectedly observed in these countries. These data, as well as published data from Burkina Faso\textsuperscript{14} and Ghana\textsuperscript{15}, suggest that a higher proportion of meningitis cases in this region may be caused by *S. pneumoniae* than was previously thought.

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**Additional value of non-culture based diagnostic tests:** Surveillance has also made clear the advantages of using highly sensitive diagnostic tests such as antigen testing and PCR to increase the identification of pathogens from CSF. Because the use of diagnostic tools differs across surveillance sites, a comparison of the proportion of pneumococcus positive specimens by diagnostic method demonstrates the benefit of using supplemental diagnostic tools to identify pathogens from CSF. In general, sites using antigen testing and/or PCR in addition to culture had higher pneumococcal yields than sites using culture alone (Figure 4.5), though there were some variations within each group. Importantly, all sites employing methods in addition to culture saw gains in diagnostic sensitivity.

![Figure 4.5: Proportion of CSF specimens positive for S. pneumoniae, sites using culture only vs. culture plus LA, Binax or PCR](image)

**Serotype distribution:** Following similar trends to those observed in the Version 1.0 analysis of the Global Serotype Project (section 2.2), a majority of invasive pneumococcal disease is caused by a similar collection of serotypes across surveillance sites. Evidence of this is seen in the summary data presented in Table 4.1 that summarizes the serotypes most often identified from children less than five years at PneumoADIP-supported surveillance sites. The data show that serotype 1 (which is not commonly found in industrialized countries) was isolated frequently at three of the six sites; low isolation of this serotype in Uganda was unusual considering the high isolation rate of serotype 1 from neighboring country, Kenya. Other serotypes commonly identified from multiple sites included serotypes 2, 5, 6A, 6B, 12A, 14, 19A, 19F and 23F.
The percent of invasive pneumococcal disease in children that could be prevented through use of the 7-, 10- and 13-valent conjugate vaccines (PCV-7, PCV-10 and PCV-13) was estimated. Coverage with PCV-7 varied across sites: it was relatively high in Kenya, Uganda, Sri Lanka and Thailand (but few isolates were available from Sri Lanka and Thailand and inferences should be interpreted with caution for these sites); moderate in Bangladesh; and low in Nepal. PCV-10, which adds serotypes 1, 5 and 7F to the PCV-7 types, markedly improved coverage in countries where serotypes 1 and 5 were highly prevalent (Kenya, Bangladesh, and Nepal), and may provide significant additional protection over PCV-7 at these sites. PCV-13 contains three additional serotypes (3, 6A and 19A) and further increases the vaccine serotype coverage at some sites. Despite serotype coverage at some sites that appears “low” relative to the 80 percent or greater coverage observed in industrialized countries, pneumococcal conjugate vaccines could prevent large numbers of cases and deaths because the incidence and severity of pneumococcal disease in these countries is so high.

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Country</th>
<th># of Sp. isolates serotyped</th>
<th>Top-ranked serotypes</th>
<th>Percent PCV-7 coverage</th>
<th>Percent PCV-10 coverage</th>
<th>Percent PCV-13 coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>Kenya</td>
<td>246</td>
<td>1, 14, 6B, 5, 23F, 6A, 19F, 4</td>
<td>50</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Uganda</td>
<td>42</td>
<td>14, 23F, 6B, 6A, 19A, 19F, 22A</td>
<td>67</td>
<td>70</td>
<td>79</td>
</tr>
<tr>
<td>SEAR</td>
<td>Bangladesh</td>
<td>165</td>
<td>1, 2, 45, 14, 5, 12A</td>
<td>26</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Nepal</td>
<td>39</td>
<td>1, 12A, 2, 16, 7F, 19B</td>
<td>8</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Sri Lanka</td>
<td>12*</td>
<td>19F, 14, 6B</td>
<td>64</td>
<td>64</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Thailand</td>
<td>14*</td>
<td>19F, 19A, 6A, 6B, 14</td>
<td>71</td>
<td>71</td>
<td>93</td>
</tr>
</tbody>
</table>

* Inferences on pneumococcal conjugate vaccine coverage must be made with caution due to small numbers of cultured isolates available.
**Antimicrobial resistance:** Antimicrobial resistance data was available from pneumococcal isolates cultured at eight sites in six countries (see Figure 4.6). Resistance to cotrimoxazole was prevalent across all eight sites, suggesting that this antimicrobial may not be appropriate for treatment of suspected pneumococcal infections. In Kenya and Uganda, cotrimoxazole resistance has increased from 25 percent in 2003 to 85 percent in 2006. While penicillin resistance is of concern in Sri Lanka and Thailand, very little to no resistance was found in isolates from Bangladesh, Nepal, Kenya and Uganda. Gentamicin resistance is very high across all sites in Bangladesh, but this trend is not observed among additional sites. Cotrimoxazole and penicillin resistance of pneumococcal strains was previously unknown in Sri Lanka, and resulted in changing the medical practice in all Sri Lankan hospitals from prescribing these antibiotics for treatment of suspected pneumococcal disease.

**Key Findings**

- Pneumonia is a common and serious problem faced by children at all sites.
- Isolates from these sites are representative of the broad spectrum of pneumococcal disease, including pneumonia, meningitis and sepsis.
- As is typically observed, pathogens were isolated at higher rates from CSF than from blood. This is probably partly the result of prior treatment with antimicrobials, which prevents the growth of organisms in blood cultures but to a much lesser degree in CSF. Antigen detection tests that are more sensitive than culture alone are also available only for CSF and enable identification of pathogens that did not grow in culture.
- Inferences on the pneumococcal disease burden that are based on invasive disease
detection alone underestimate the true burden of pneumococcal disease, which can only be estimated using vaccine probe trials and statistical modeling.

- The prevalence of confirmed pneumococcal and Hi cases among patients with suspected meningitis decreased with age: infants were the most likely to have a pathogen identified from CSF.
- *S. pneumoniae* was more commonly identified than either *H. influenzae* or *N. meningitidis* as the cause of bacterial meningitis in Nepal and India, but more sensitive tests were used for *S. pneumoniae*. In contrast, Hi was more frequently identified in meningitis cases in Sri Lanka. The low isolation rate of *H. influenzae* from both CSF and blood in Kenya and Uganda illustrates the impact of Hib vaccine introduction in reducing this disease.
- Although there are 90 pneumococcal serotypes, only a limited number were responsible for the disease observed at these sites.
- All pneumococcal conjugate vaccines (7-, 10- and 13-valent) provided good coverage of serotypes found in Kenya, Uganda, Sri Lanka and Thailand (50 to 93 percent coverage) and vaccines containing serotypes 1 and 5 provided good coverage in Bangladesh and Nepal (~50 percent).
- The percent of invasive pneumococcal disease in children that could be prevented through use of the 7-, 10- and 13-valent pneumococcal conjugate vaccines was similar between some Asian sites and the African sites. There was diversity in coverage across the Asian sites.
- PCV-10 substantially improved coverage above PCV-7 in countries where serotypes 1 and 5 were highly prevalent (Bangladesh, Kenya and Nepal).
- Despite serotype coverage at some sites that appears “low” relative to the coverage observed in industrialized countries, pneumococcal conjugate vaccines that are available now (PCV-7) could prevent large numbers of cases and deaths because the incidence and severity of pneumococcal disease in these countries is so high. For example, with 51.4 percent coverage in Kenya and 41.2 percent coverage in urban Bangladesh, PCV-7 could lead to reductions in the incidence of invasive pneumococcal disease of 224/100,000 and 180/100,000 children in these countries, respectively, compared to reductions of 73/100,000 in the US following vaccine introduction.  

- Resistance to cotrimoxazole was prevalent across all sites, suggesting that this antimicrobial may not be appropriate for treatment of suspected pneumococcal infections.
- Very high resistance to gentamicin and penicillin was also observed at some sites.

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5. PneumoADIP Small Grants Program

PneumoADIP’s Small Grants Program supports small projects across the globe. These projects are diverse and include pneumococcal surveillance activities, projects focused on assessing the short- and long-term disability and developmental consequences of pneumococcal disease, and research to estimate the costs to families and health systems of treating pneumococcal disease. The studies aim to establish evidence-based messages about pneumococcal vaccines for informing health professionals and assess risk factors for pneumococcal disease. The Small Grants Program enables broader geographic involvement and a greater variety of projects than is possible by other means. Small grants can represent a significant investment in developing countries - achieving significant results in a short time and sowing the seeds for larger projects. In many cases, data from different projects may be complementary, acting as pieces of a puzzle that develop into a bigger picture. All of these activities work to further PneumoADIP’s mission to accelerate the evaluation of and access to pneumococcal vaccines for those who are most in need.

The successes of PneumoADIP’s five large surveillance networks have generated interest in scaling up surveillance activities amongst some small grant recipients. Some small grant projects involved in surveillance activities, including sites in Togo, Burkina Faso, Nigeria, Dominican Republic and Pakistan, have agreed to standardize surveillance data collection and submit reports on a monthly basis to PneumoADIP. As a result of standardization, these data now contribute to the larger PneumoADIP surveillance activities.

The accomplishments of the surveillance networks have also stimulated interest amongst small grant recipients in the formation of new networks. In May 2006, a meeting was held with stakeholders in Ouagadougou, Burkina Faso, to discuss the formation of a West African sub-regional surveillance network. Items discussed at this meeting included identifying the structure and participants of the potential network, deadlines for developing the network, the location of a regional reference microbiology laboratory, and review of a draft proposal to PneumoADIP.
<table>
<thead>
<tr>
<th>WHO region (Appendix #)</th>
<th>Country</th>
<th>Type of project</th>
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<td></td>
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<td>AFR (Appendix I)</td>
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<td>Togo</td>
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<tr>
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<td>Tanzania</td>
<td>Invasive bacterial disease and nasopharyngeal colonization</td>
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<td>India</td>
<td>Risk factors for Sp colonization in infants</td>
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<td>SEAR (Appendix V)</td>
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<td>Mongolia</td>
<td>Pneumonia and meningitis</td>
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<td></td>
<td>Vietnam</td>
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</table>
6. Other PneumoADIP Research Activities

- **Binax Study** - This multi-site study aims to evaluate the utility of Binax Now® *S. pneumoniae* antigen test as an adjunct to CSF culture for the diagnosis of pneumococcal meningitis in a variety of settings. The study was built onto existing PneumoADIP-funded meningitis surveillance in five sites in Africa and Asia. A rapid and sensitive test like the Binax Now® *S. pneumoniae* may improve the diagnosis and treatment of children with pneumococcal meningitis. Particularly in rural areas with inadequate laboratory infrastructure and in regions with high levels of antibiotic use. In some of our study sites, the use of this test on culture-negative CSF has already significantly increased the number of confirmed pneumococcal meningitis cases. The new method will enable us to provide more accurate estimates of pneumococcal invasive disease.

- **Cost-Effectiveness Study** - Vaccinating children in developing countries against pneumococcal infection has great potential to save lives and reduce disability, but will also require substantial new financing. A cost-effectiveness analysis of pneumococcal vaccination in GAVI-eligible countries, led by A. Sinha and T. Lieu was published in *The Lancet* in February 2007.\(^{20}\) The analysis indicates that pneumococcal vaccination in GAVI-eligible countries is highly cost effective in saving lives. At a vaccine cost of $5 per dose, vaccination would cost $100 per DALY averted. This estimate is conservative because it does not account for savings in morbidity, protection beyond the age of 29 months, or for herd immunity. These types of comparable units of cost and benefits will facilitate decision makers to prioritize interventions.

- **Global Disease Burden Estimate** – The WHO, with support from PneumoADIP and Hib Initiative, is working to develop official estimates of global pneumococcal and Hib disease burden, including deaths in children. These figures will assist countries when prioritizing among the many health needs of children and help with efforts to increase financing by illustrating the potential health benefits of vaccination. Over 1,000 articles were systematically reviewed and abstracted, and the models have been evaluated and approved by an external technical advisory group. The estimates generated will be at a global, regional and country level, and will include estimates of pneumococcal and Hib pneumonia, meningitis, and non-pneumonia, non-meningitis disease. The country level estimates have been sent to each country for verification and all estimates are expected to be publicly available by early 2008.

- **Global serotype distribution modeling** - The serotype distribution of pneumococcal disease is a key parameter for polysaccharide-based vaccine development. Previous analyses of the global and regional serotype distribution have been published, which were valid and adequate for their purpose. Since these publications, substantially more data that is more representative has become available, making refined analyses possible, which are needed for second-generation vaccine development and country-level decision-making regarding pneumococcal conjugate vaccine introduction. The PneumoADIP, together with WHO, has undertaken a project to update existing analyses and provide evidence-based information about the potential for pneumococcal conjugate vaccine to reduce mortality and morbidity from pneumococcal disease in GAVI-eligible countries. The outputs from this analysis were

used by WHO to formulate a target product profile for the Advanced Market Commitment (AMC) guidelines, which describes minimal vaccine characteristics necessary for eligibility.

- Tracheal Aspirate Study - In China, local researchers conducted a study to evaluate the usefulness of the orotracheal aspiration (OTA) method, a clinical technique for diagnosing bacterial pneumonia, among children less than three years of age. Alternative diagnostic techniques are needed to provide researchers and clinicians with better ways to diagnose, document and treat pneumococcal disease, but the specificity and sensitivity of these tests need to be validated. Use of inappropriate tests may lead to misleading results. Interim data from the project was evaluated by a technical advisory group and the results will be published soon.

- Vaccine Trial Ancillary Studies - PneumoADIP and the WHO support ancillary studies from pneumococcal vaccine clinical trials in South Africa, The Gambia, and the Philippines. Funding for these ancillary studies allows researchers to conduct various in-depth analyses on their existing vaccine trial data. The majority of the ancillary studies evaluate the usefulness of various diagnostic techniques in confirming pneumococcal disease cases at diverse geographic settings in order to better estimate the potential health and economic impact of pneumococcal vaccination. A more comprehensive description of these studies can be found in the region specific sections for Africa and the West Pacific.

- Alternative regimen project - PneumoADIP and the WHO are supporting a trial in The Gambia to evaluate alternative dose schedules for the delivery of pneumococcal vaccine. The trial is expected to end in 2007 and results should be available by early 2008.

- Asian field site identification - In 2004, PneumoADIP evaluated sites in Asia to identify field sites that could be developed for vaccine impact studies. A request for letters of interest was sent out to all GAVI-eligible countries and 22 letters of interest were received. The rigorous evaluation process included site visits by members of a technical advisory group. Due to funding constraints, only a limited number of project sites could be supported by PneumoADIP. One project (Mongolia) is still ongoing with PneumoADIP’s support for the surveillance component.

- WHO Reference Laboratory - PneumoADIP contributes towards supporting two reference laboratories for pneumococcal serological assays. One is located at the Institute of Child Health in London and the other at the University of Alabama, Birmingham, Alabama (http://www.vaccine.uab.edu/). These laboratories provide technical support for establishing standardized testing procedures for measuring pneumococcal anti-capsular antibody, including provision of assay protocols, standard reagents and reference sera, training of laboratory personnel, and quality assurance. The laboratories are currently in the process of standardizing an opsonophagocytic assay for pneumococcus by establishing a reference protocol, reference sera and standards, and undertaking a multi-laboratory standardization process. For more information, please visit the University of Alabama website (http://www.vaccine.uab.edu/) or contact the lab directors, David Goldblatt and Moon Nahm.
Gambia and Kenya Vaccine Impact Studies - Accelerated and sustained introduction of pneumococcal vaccines is a GAVI Alliance priority. Widespread use of pneumococcal vaccines will contribute to meeting GAVI and GIVS goals, and to achieving Millennium Development Goal Four. The efficacy of 9- and 11-valent pneumococcal conjugate vaccine (PCV) has been evaluated in clinical trials in Africa and Asia. These trials, however, do not provide information on the herd immunity effect and are typically not able to assess serotype replacement if it occurs. In order to accelerate the use of pneumococcal vaccines in a limited number of developing countries and to provide an evidence-base for policies to expand the use of the vaccines, GAVI’s PneumoADIP identified two sites with the potential to demonstrate a substantial impact on disease from the use of the 7-valent pneumococcal conjugate vaccine (The Gambia and Kenya). The goals of the vaccine impact studies in The Gambia and Kenya are to:

1. Evaluate the health impact of pneumococcal vaccination in two early-adopter countries.
2. Determine whether catch-up programs can “front load” the prevention of pneumococcal disease and prevent illness among unvaccinated populations through herd immunity.
3. Assess changes in the incidence of serotypes not included in the 7-valent vaccine (i.e., serotype replacement) and its impact on overall invasive pneumococcal disease rates.
## 7. Non-PneumoADIP Research Activities by WHO Region

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Country</th>
<th>Participating investigator or organization</th>
<th>Project activity</th>
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</thead>
<tbody>
<tr>
<td>AFRO</td>
<td>Benin</td>
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<td>Botswana</td>
<td>WHO/AFRO</td>
<td>Pediatric Bacteria Meningitis Network</td>
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<td>Cameroon</td>
<td>WHO/AFRO</td>
<td>Pediatric Bacteria Meningitis Network</td>
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<td>WHO/AFRO</td>
<td>Pediatric Bacteria Meningitis Network</td>
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<td></td>
<td>Kenya</td>
<td>KEMRI/Wellcome Trust</td>
<td>Invasive Bacterial Disease among ages fifteen years and younger</td>
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<td></td>
<td>Mali</td>
<td>University of Maryland – Center for Vaccine Development</td>
<td>Invasive bacterial disease surveillance</td>
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<td>Rwanda</td>
<td>WHO/AFRO</td>
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<td>WHO/AFRO</td>
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<td>WHO/AFRO</td>
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</tr>
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<td>EMRO</td>
<td>Egypt</td>
<td>WHO/EMRO</td>
<td>Bacterial Meningitis Surveillance Network Identify and control emerging infections via surveillance, research, training and outbreak support</td>
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<td>Bacterial Meningitis Surveillance Network</td>
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<td>Research activities include: vaccine development and candidate evaluation, diagnostics, treatment, prevention</td>
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<td>Chile</td>
<td>University of Maryland –</td>
<td>Clinical evaluation of</td>
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<td>Country</td>
<td>Location</td>
<td>Institution</td>
<td>Activities</td>
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<tr>
<td>USA</td>
<td></td>
<td>Meningitis Research Foundation</td>
<td>Research activities include: vaccine development and candidate evaluation, diagnostics, treatment, prevention</td>
</tr>
</tbody>
</table>
| SEARO   | Bangladesh | Samir K Saha, Dhaka Shishu Hospital | • Observational study to assess the safety of outpatient treatment of severe pneumonia with oral amoxicillin in children aged 3 to 59 months  
• Comparison of 5 vs 10 days of ceftriaxone therapy for bacterial meningitis in children  
• Surveillance for influenza and viral etiologies of respiratory illnesses  
• Hospital-based influenza surveillance  
• Hospital mortality surveillance of pneumonia and meningitis  
• Meningo-encephalitis project  
• Zinc in outpatient pneumonia as adjunct therapy |
| Thailand |          | International Centre for Diarrhoeal Disease Research, Bangladesh | Identify and control emerging infections via surveillance, research, training and outbreak support |
| WPRO    | China    | Centers for Disease Control – International Emerging Infections Program | Identify and control emerging infections via surveillance, research, training and outbreak support (not yet started)  
Determine the proportion of hospitalized pneumonia cases in children associated with 7-valent type pneumococcal disease |

*Please contact PneumoADIP at pneuadip@jhsph.edu to submit any additional research activities in your country or region.*
8. Appendices – PneumoADIP Surveillance Networks, Small Grants and Other Research Projects

Appendix I: African Region (AFRO)

Appendix I lists all PneumoADIP-supported projects in the African Region and provides additional detail on data from the netSPEAR network. The section also includes a brief list of non-PneumoADIP activities in the region.

### PneumoADIP-funded projects in the African region

<table>
<thead>
<tr>
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<th>Project type</th>
<th>Section</th>
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<td>Surveillance</td>
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<td>Surveillance</td>
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<td>PCV-7 impact evaluation</td>
<td>I.3.4</td>
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<td>The Gambia</td>
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### Non-PneumoADIP projects in the African region

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<th>Project activity</th>
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*Please contact PneumoADIP at pneudip@jhsph.edu to submit any additional research activities in your country or region.*
I.1 Overview of Activities for the Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR)

Title: Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR)

Date Started: August 2003

Project Leaders:
Dr. Maranga Wamae - netSPEAR Manager, KEMRI/Wellcome Trust, Nairobi Kenya
Dr. Mike English - Senior Research Fellow, KEMRI/Wellcome Trust, Nairobi, Kenya
Dr. Anthony Scott - Senior Research Fellow, KEMRI/Wellcome Trust, Kilifi, Kenya

Coordinating Center: Kenya Medical Research Institution / Wellcome Trust Collaborative Programme

Countries: Burundi, Eritrea, Ethiopia, Kenya, Rwanda, Tanzania, Uganda

Project Description: The Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR) is overseen by the KEMRI/Wellcome Trust Collaborative Research Programme in Kenya. The KEMRI/Wellcome Trust Research Programme has a longstanding presence in both Nairobi and Kilifi, Kenya, before PneumoADIP-related activities. Research conducted by KEMRI/Wellcome Trust focuses on infectious diseases of particular importance to Kenya, including invasive bacterial disease. Kilifi District Hospital, in particular, conducts surveillance of invasive bacterial disease in all children aged 15 years and younger. The Pediatric Bacterial Meningitis (PBM) network, overseen by the WHO African Regional Office (AFRO), has coordinated bacterial meningitis surveillance targeting H. influenzae type b, S. pneumoniae and N. meningitidis in children under five years of age in 26 African countries beginning in 2001; all of the netSPEAR countries participate in the PBM network. The pre-existing research program and PBM network has created a solid infrastructure for implementing PneumoADIP-related surveillance activities.

netSPEAR conducts surveillance in 12 participating hospitals in Ethiopia, Kenya, Tanzania and Uganda and continues to work closely with the Pediatric Bacterial Meningitis network. Eventually, it aims to expand to include hospitals in Burundi, Rwanda, and Eritrea to grow to a total of seven participating countries. netSPEAR aims to create conditions in which a network of regional identity can evolve over a period of two to five years. netSPEAR coordinates and conducts surveillance of invasive bacterial disease caused by S. pneumoniae and H. influenzae type b in both children and adults. The East African region is projected to benefit tremendously in reduction of morbidity and mortality from the introduction of the pneumococcal conjugate vaccine. The surveillance results will be disseminated to regional network partners, including surveillance sites, ministries of health, multilateral organizations, and donors supporting vaccination programs as a source of evidence for including pneumococcal conjugate vaccines into the routine immunization schedule.

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netSPEAR Objectives:

- To provide a focal point within the East African Region for collating and sharing data on *S. pneumoniae* and *H. influenzae* that is already currently being collected at research units, private hospitals and major clinical institutions with routine microbiological services.

- To expand the capacity for effective, routine surveillance by developing clinical case definitions that triggers sample collection and laboratory procedures that result in bacterial isolation within government funded hospitals.

- To establish a minimal administrative and IT capacity to update available data and to disseminate findings to regional network partners including Ministries of Health, multilateral organizations and donors who support EPI vaccines.

- To apply clinical, epidemiological and microbiological research findings from academic centers in the region to extrapolate surveillance findings to regional incidence estimates of pneumococcal disease burden.

Participating Countries and Institutions:

The seven countries of Burundi, Eritrea, Ethiopia, Kenya, Rwanda, Tanzania and Uganda comprise the Eastern block of the WHO Regional office for Africa (AFRO). They are united by political and economic ties, by common historical links with former colonial administrations and by language; English and/or Kiswahili are widely spoken in the region. The East African region is one of the poorest in the world and has high infant and child mortality rates. Each of the seven is eligible for Vaccine Fund support.

East Africa is a wide area for establishing a surveillance network. It is also an area with a long history of limited resources available to the health sector, leaving it with limited logistical framework for surveillance. In particular, access to diagnostic microbiological services in cases of suspected severe infection is very rare in the government health sector even in secondary and tertiary hospitals.

PneumoADIP has been involved in strengthening surveillance activities in the East Africa region since 2003. The Network for Surveillance of Pneumococcal Disease in the East Africa Region (netSPEAR) currently operates in four countries with plans to expand to up to three more.

Currently Active Sites (approximate number of pediatric admissions per month):

Kenya
- Kenyatta National Hospital, Nairobi (1,200)
- Moi Teaching and Referral Hospital, Eldoret (200–250)
- Eastern Provincial General Hospital, Embu (250)
- Kilifi District Hospital, Kilifi (420)
- Nyeri Provincial General Hospital, Nyeri (500)
Uganda
• Mulago National Referral Hospital, Kampala (1,200)
• Mbarara University of Science and Technology, Mbarara Hospital, Mbarara (550)
• St Mary’s Lacor Hospital, Gulu District Gulu (1,200–1,600)
• Mbale Regional Referral, Hospital, Mbale (1,100)

Tanzania
• Muhimbili Centre for Health Sciences, Muhimbili Hospital, Dar es Salaam (1,250)
• Muheza D. District Hospital, Muheza, Tanga Region (440)

Ethiopia
• Tikur Anbessa Hospital, University of Addis Ababa, Addis Ababa (400)

Status of Remaining Sites:

Rwanda
• No sites at present

Burundi
• No sites at present

Eritrea
• No sites at present
<table>
<thead>
<tr>
<th>netSPEAR – Summary of Main Findings:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specimens and Isolates:</strong></td>
</tr>
<tr>
<td>▪ &gt;21,000 CSF specimens collected from twelve sites</td>
</tr>
<tr>
<td>▪ &gt;25,000 blood specimens collected from four sites</td>
</tr>
<tr>
<td>▪ &gt;1,100 pathogens isolated of which 750 were <em>S. pneumoniae</em></td>
</tr>
<tr>
<td><strong>Data Collection Period:</strong></td>
</tr>
<tr>
<td>Kenya</td>
</tr>
<tr>
<td>▪ August 2003 – April 2007</td>
</tr>
<tr>
<td>Uganda</td>
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<tr>
<td>▪ January 2004 – April 2007</td>
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<tr>
<td>Tanzania</td>
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<tr>
<td>▪ August 2004 – April 2007</td>
</tr>
<tr>
<td>Ethiopia</td>
</tr>
<tr>
<td>▪ January 2005 – February 2007</td>
</tr>
<tr>
<td><em><em>Yields</em>:</em>*</td>
</tr>
<tr>
<td>Kenya</td>
</tr>
<tr>
<td>▪ Pneumococcal yield: 1.8% from CSF, 1.4% from blood</td>
</tr>
<tr>
<td>▪ <em>N. meningitidis</em> yield: 0.1% from CSF, 0% from blood</td>
</tr>
<tr>
<td>▪ <em>H. influenzae</em> yield: 0.6% from CSF, 0.2% from blood</td>
</tr>
<tr>
<td>▪ Pneumococcal yield: 2% from CSF, 0.8% from blood</td>
</tr>
<tr>
<td>Uganda</td>
</tr>
<tr>
<td>▪ <em>N. meningitidis</em> yield: 0.2% from CSF, 1.8% from blood</td>
</tr>
<tr>
<td>▪ <em>H. influenzae</em> yield: 0.8% from CSF, 0.2% from blood</td>
</tr>
<tr>
<td>▪ Pneumococcal yield: 1.4% from CSF</td>
</tr>
<tr>
<td>Tanzania</td>
</tr>
<tr>
<td>▪ <em>N. meningitidis</em> yield: 0% from CSF</td>
</tr>
<tr>
<td>▪ <em>H. influenzae</em> yield: 3.3% from CSF</td>
</tr>
<tr>
<td>▪ Pneumococcal yield: 4.9% from CSF</td>
</tr>
<tr>
<td>Ethiopia</td>
</tr>
<tr>
<td>▪ <em>N. meningitidis</em> yield:0.6% from CSF</td>
</tr>
<tr>
<td>▪ <em>H. influenzae</em> yield: 8.5% from CSF</td>
</tr>
<tr>
<td><strong>Vaccine Serotypes:</strong></td>
</tr>
<tr>
<td>Kenya</td>
</tr>
<tr>
<td>▪ PCV7 and PCV10 provide protection against 50% and 79% of pneumococcal serotypes among children under five, respectively</td>
</tr>
<tr>
<td>▪ Most common serotypes: 1, 14, 6B</td>
</tr>
<tr>
<td>Uganda</td>
</tr>
<tr>
<td>▪ PCV7 and PCV10 provide protection against 67% and 70% of pneumococcal serotypes among children under five, respectively</td>
</tr>
<tr>
<td>▪ Most common serotypes: 14, 23F, 6B, 6A</td>
</tr>
<tr>
<td>Tanzania</td>
</tr>
<tr>
<td>No serotype data available</td>
</tr>
<tr>
<td>Ethiopia</td>
</tr>
<tr>
<td>No serotype data available</td>
</tr>
<tr>
<td><strong>Antibiotic Resistance:</strong></td>
</tr>
<tr>
<td>▪ Little or no resistance observed for Chloramphenicol, Cefotaxime, Benzylpenicillin, Amoxicillin, Erythromycin, Penicillin and Ampicillin (range 0% – 4%)</td>
</tr>
<tr>
<td>▪ Cotrimoxazole antibiotic resistance has increased from 25% in 2003 to 85% in 2006</td>
</tr>
</tbody>
</table>

*The yields shown here are from culture only.*
I.2 Small Grant Projects: African Region Office (AFRO)

I.2.1 Burkina Faso and Togo – Capacity building and operational research on bacterial meningitis due to *S. pneumoniae* in the Bobo-Dioulasso region and the proportion of bacteremic pneumococcal disease among people hospitalized with pneumonia (Association pour l’aide à la Médecine Préventive)

**Principal Investigator:**
Dr. Bradford D. Gessner  
Agence de Médecine Préventive  
Paris, France

**Summary:**
Study sites were established in the Bobo-Dioulasso region of Burkina Faso and in two adjacent districts of Togo to systematically isolate *S. pneumoniae* and other causes of bacterial meningitis from severely ill children. The outputs of the project include information on number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distributions among pneumococcal isolates associated with meningitis and pneumonia by surveillance site. In addition, the Binax NOW® *S. pneumoniae* antigen test was evaluated prospectively in Burkina Faso to see if it could improve the identification of pneumococcal meningitis cases in Burkina Faso.

**Goals and Objectives:**
- Establish sentinel sites for monitoring the importance of *S. pneumoniae* as a causative agent of bacterial meningitis in sub-Saharan Africa.
- Maintain the quality of data collection in the region of Bobo-Dioulasso in anticipation of future comprehensive population-based *S. pneumoniae* vaccine introduction evaluations.
- Determine various characteristics of pneumococcal pneumonia in Burkina Faso.

**Primary objectives:**
1. To obtain information on number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distributions among pneumococcal isolates associated with meningitis in Burkina Faso and Togo from November 2004 through October 2005.
2. To collect blood cultures from all pneumonia cases presenting to the Centre Hospitalier National Sourou Sanou (CHNSS) in Bobo Dioulasso from April 2005 through October 2006.
3. To determine the utility of the Binax test in identifying pneumococcal meningitis in subjects of all ages with CSF specimens of varying characteristics.

**Secondary objectives:**
1. To estimate the case fatality rate of meningitis due to SP.
2. To estimate the burden of sequelae due to SP meningitis.
3. To estimate the proportion of clinical and purulent meningitis that is due to SP.
4. To describe the serotype distribution of pneumococcal pneumonia isolates.
5. To describe antibiotic susceptibility patterns of pneumococcal pneumonia isolates.
6. To determine genetic characteristics of pneumococcal pneumonia isolates.
7. To evaluate temporal trends in pneumococcal pneumonia.
8. To compare the characteristics of pneumococcal pneumonia to meningitis isolates.
9. To initiate pneumonia surveillance in anticipation of eventually implementing pneumococcal vaccine with monitoring of vaccine impact.
10. Given funding and political limitations, expand surveillance during the study period to at least one district each in Benin, Mali, and Northern Burkina Faso.
11. Given funding and logistic limitations, to evaluate the feasibility of routinely collecting blood cultures for presumed pediatric sepsis (i.e. sepsis among children less than five years of age).

Status and Results:
Between November 2004 and October 2005, 2,843 patients were admitted with suspected meningitis, of which sixteen percent had confirmed pneumococcal meningitis (case fatality ratio of 47 percent). Pneumococcal meningitis occurred in an epidemic pattern similar to meningococcal meningitis. These results will be published in the upcoming PneumoADIP sponsored CID journal supplement. Because both Burkina Faso and Togo are considering the addition of PCV into their EPI programs, meningitis surveillance restarted in the fall of 2007 and will continue to December 31st 2008.

1.2.2 Democratic Republic of Congo – invasive CSF disease burden attributable to *S. pneumoniae* in Dem. Rep. Congo (Kinshasa School of Public Health, Kinshasa)

Principal Investigators:
Dr. Antoinette Tshefu Kitoto (Co-principal investigator)
University of Kinshasa School of Public Health
Kinshasa, DRC

Dr. Anne W. Rimoin (Co-principal investigator)
UCLA School of Public Health
Los Angeles, California, USA

Summary:
This is a pilot study supporting a larger prospective cohort study to establish study sites at four large hospitals in Kinshasa, DRC, to systematically isolate *S. pneumoniae* and other causes of bacterial meningitis from severely ill children. Outputs of the project will include information on number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distributions among pneumococcal isolates associated with pediatric meningitis.

Goals and Objectives:
1. To establish the presence of pneumococcal meningitis among children in the Democratic Republic of Congo and measure local disease characteristics such as serotype distribution and antimicrobial resistance levels.

2. To measure local disease characteristics such as serotype distribution and antimicrobial resistance levels of *S. pneumoniae* and *H. influenzae* strains.

Primary Objective:
To measure the prevalence of pneumococcal CNS infection among children with community-acquired meningitis in hospitals in Kinshasa, Democratic Republic of the Congo.

Secondary Objectives:
1. To quantify levels of resistance to commonly prescribed antibiotics in *S. pneumoniae* isolates from cases of pediatric community-acquired meningitis in Kinshasa, DRC.
2. To identify the distribution of pneumococcal serotypes in pediatric community-acquired meningitis in Kinshasa, DRC.
3. To improve local laboratory infrastructures for epidemiologic monitoring of pneumococcal disease, in the resource-limited setting of Kinshasa and surroundings, DRC.
4. To provide preliminary serotype distribution information for estimation of the likely effect of current pneumococcal vaccines in DRC.
5. To collect data to develop guidelines for rational use of empiric antimicrobials among infants and children with clinically suspected meningitis in Kinshasa, DRC.

Status and Results:
This project was delayed due to political upheaval in the DRC, but should now begin shortly.

**I.2.3 Ghana – Invasive infections of *S. pneumoniae* in Ghanaian children: the burden and control with conjugate vaccines (University of Ghana Medical School, Accra, Ghana)**

Principal Investigator:
Eric Sampane-Donkor
University of Ghana Medical School
Legon, Accra, Ghana

Summary:
The University of Ghana Medical School established study sites in three hospitals geographically distributed over Ghana to systematically isolate *S. pneumoniae* from severely ill patients of all ages. These hospitals include Korle-Bu Teaching Hospital (KBTH), Komfo Anokye Teaching Hospital (KATH) and War Memorial Hospital (WMH). Outputs of the project include information on the number of specimens and pneumococcal isolates collected, as well as serotype distribution and antibiotic resistance patterns of pneumococci isolated from normally sterile sites, in patients with invasive bacterial illnesses.

Goals and Objectives:
The goal of the study is to quantify the burden of invasive pneumococcal disease in Ghana, and the extent to which it can be prevented by conjugate vaccines.

Primary Objectives:
1. Determine the prevalence of invasive *S. pneumoniae* infections among children less than five years with meningitis and pneumonia in Ghana.
2. Determine the serotypes distribution of pneumococci causing these infections.
3. Identify the clones of *S. pneumoniae* involved in the infections.
4. Determine the prevalence of resistance of *Streptococcus pneumoniae* to antimicrobial drugs commonly used in treatment.
Status and Results:
During the first eight months of surveillance, 824 blood and CSF specimens were collected and 26 isolates were obtained. Surveillance will continue through the end of November 2007. Serotype data and antibiotic resistance data are forthcoming.

I.2.4 Kenya – Long-term survival and disability in children who survived pneumococcal meningitis treated in a district hospital in Kenya (Kenya Medical Research Institute, Kilifi District Hospital)

Principal Investigators:
Charles RJC Newton, Penny Holding, William Machira
Kenya Medical Research Institute
Kilifi, Kenya

Summary:
This retrospective cohort study aimed to document the frequency and extent of the neurological impairment in children and estimate the risk of developing sequelae following *S. pneumoniae* infection.

Goals and Objectives:
1. To determine the survival outcome of a retrospective cohort of children admitted with culture-proven *S. pneumoniae* meningitis in a rural district hospital.
2. To describe the prevalence and nature of neurological sequelae among surviving treated meningitis patients.
3. To classify the impairment in terms of the International Classification of Functioning Disability and Health, so as to estimate the burden of disease in terms of disability-adjusted life years (DALYs).

Status and Results:
The study (now completed) identified 323 children with pneumococcal disease (14 of whom died) who were discharged from the hospital. Seventy-five of these 323 were pneumococcal meningitis cases. Fifteen of these 75 cases had hearing loss, ten had speech impairments, three had vision impairment, eight had motor impairments and 11 had epilepsy.

I.2.5 Mali – Outcome of invasive *S. pneumoniae* disease among 0- to 35-month-old children receiving outpatient health care at a pediatric referral hospital in Bamako, Mali (Centre pour le Développement des Vaccins-Mali)

Principal Investigators:
Dr. Samba O. Sow (Local Principal Investigator)
Centre pour le Développement des Vaccins-Mali (CVD-Mali)
Centre National d’Appui à la lutte contre la Maladie (CNAM)
Bamako, Mali
Dr. Milagritos Tapia (Principal Investigator)
Center for Vaccine Development (CVD)
University of Maryland School of Medicine
Baltimore, Maryland, USA

Summary:
The Center for Vaccine Development (CVD) is conducting a prospective case-control study of 320 children to estimate the case fatality ratio associated with outpatient invasive pneumococcal disease in Bamako, Mali.

Goals and Objectives:
To further describe the burden of mortality due to invasive pneumococcal disease among 0- to 35-month-old Bamako children.

Primary Objectives:
1. To measure case-fatality among 0- to 35-month old children in the 30-day period after receiving outpatient care at the HGT ED in Bamako, Mali for:
   a. an episode of febrile illness and/ or suspected invasive bacterial infection with culture positive for S. pneumoniae versus
   b. an episode of febrile illness and/ or suspected invasive bacterial infection but found to have a negative blood culture.
2. To identify risk factors associated with IPD and death from IPD among 0- to 35-month old children receiving outpatient care at the HGT ED in Bamako, Mali.

Status and Results:
Enrollment is ongoing. To date, the study has recruited 47 cases of outpatient IPD and 140 age-matched controls.

1.2.6 Mozambique – Surveillance of bacterial meningitis among children under 15 years of age hospitalized in the Manhiça Hospital, Mozambique (Manhiça District Hospital)

Principal Investigator:
Dr. Anna Roca
Barcelona Centre for International Health Research (CRESIB), Hospital Clinic / IDIBAPS
Universitat de Barcelona, Spain
Centro de Investigação em Saúde da Manhiça (CISM)
Maputo, Mozambique

Summary:
This project established surveillance for bacterial meningitis and other invasive bacterial illnesses among children less than fifteen years of age at Manhiça Hospital in Mozambique. Outputs include the number of specimens collected, number of pneumococci and other bacterial pathogens isolated, as well as serotype distribution and antibiotic resistance patterns of pneumococci isolated from these patients.
Goals and Objectives:
1. To improve the diagnosis of meningitis infections among children less 15 years of age admitted to the Manhiça District Hospital.
2. To perform surveillance of invasive pneumococcal disease among children less than 15 years of age admitted to the Manhiça District Hospital for a 12-month period.

Primary Objectives:
1. To establish accurate clinical criteria to perform lumbar puncture among children.
2. To monitor the collection of the cerebrospinal fluid (CSF) of children meeting the clinical criteria compatible with bacterial meningitis.
3. To measure and record additional parameters on the current processing of CSF such as appearance, white blood cell count, polymorphonucleocyte count, leukocyte count, glycemia, glucose and total protein concentration.
4. To extend the culture and gram stain activities currently ongoing until the end of this study and for children up to fifteen years of age.
5. To include latex agglutination as additional etiological tests on the CSF (for pneumococcus, H. influenzae and meningococcus).
6. To determine clinical predictors for bacterial meningitis among children.
7. To measure crude and age adjusted incidence rates of invasive bacterial meningitis, pneumococcal meningitis and invasive pneumococcal disease.
8. To calculate case-fatality-rate of invasive bacterial meningitis, pneumococcal meningitis and overall invasive pneumococcal disease.
10. To characterize pneumococcal serotypes.
11. To evaluate potential coverage of the pneumococcal conjugate vaccines (7-, 9-, 11- and 13-valent).

Status and Results:
During the 18 months of meningitis surveillance, 65 cases of bacterial meningitis were identified. Fifty of these cases (77 percent from a total of 65) were meningitis caused by pneumococcus, H. influenzae or meningococcus. Fourteen cases of pneumococcal meningitis cases were confirmed by culture, latex agglutination or gram stain. More detailed results from the meningitis surveillance will be published in the upcoming PneumoADIP Sponsored Clinical Infectious Disease Journal supplement. The surveillance of all invasive pneumococcal disease started seven months after the surveillance for meningitis only and results are not yet available.

I.2.7 Nigeria – Serotypes and antibiotic sensitivities of invasive S. pneumoniae in Ile-Ife, Osun State (Obafemi Awolowo University Teaching Hospital Complex)

Principal Investigator:
Dr. Anthony Onipede
Obafemi Awolowo University/ Teaching Hospital
Ile-Ife, Nigeria

Summary:
Obafemi Awolowo University Teaching Hospital established study sites in two major hospitals and three primary care clinics in Ife-Ife to systematically isolate S. pneumoniae from severely ill children. Outputs of the project include information on the number of pneumococcal isolates from blood and cerebrospinal fluid, antibiotic resistance and serotype distribution patterns.
Primary Objective:
1. Obtain information on the number of pneumococcal isolates identified.
2. Describe the antibiotic resistance and serotype distribution patterns of the pneumococcal isolates.

Status and Results:
Two-hundred and thirteen children were enrolled in the surveillance project. Forty-seven children were diagnosed with meningitis, 63 with septicemia, and 103 with pneumonia. Isolates were found in 14 of 69 cerebrospinal fluid specimens cultured, with three identified as positive for pneumococcus (4.5 percent). No pneumococci were isolated from blood. This study has been completed.

I.2.8 Nigeria – A study of invasive pneumococcal disease among children in Ibadan City, Nigeria (University of Ibadan/University College Hospital)

Principal Investigator:
Professor A.G. Falade
University College Hospital
Ibadan, Nigeria

Summary:
The University College Hospital microbiology laboratory was strengthened to systematically isolate S. pneumoniae and other causes of bacterial meningitis from severely ill children. Outputs of the project include information on number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distributions among pneumococcal isolates associated with meningitis and pneumonia.

Goals and Objectives:

Primary Objective:
- To improve the laboratory capability of the UCH microbiology laboratory to isolate and to identify pneumococcus and other fastidious bacterial pathogens from samples of blood and cerebrospinal fluid of children with pneumonia and meningitis presenting at the University College Hospital, a tertiary health institution, in Ibadan, Nigeria and two secondary health institutions in Ibadan.

Secondary Objective:
- To obtain information on number of specimens and pneumococcal isolates collected, antibiotic resistance and serotype distributions among pneumococcal isolates associated with pneumonia and meningitis.

Status and Results:
In the 24-month surveillance period, 1,210 children were enrolled of which 481 had meningitis, 399 had pneumonia and 330 had bacteremia. There were 24 cases of definite meningitis caused by S. pneumoniae (9), H. influenzae type b (11) and Klebsiella species (4). Among the pneumonia patients, nine children were diagnosed with pneumococcal pneumonia and two with Hib pneumonia. Among children with suspected bacteraemia, three of 95 isolates were pneumococci. Eleven of the 23 S. pneumoniae isolates were serotyped. Five were serotype 5,
three were serotype 19F and three were serotype 4. Results from this study will be published in the upcoming PneumoADIP Clinical Infectious Disease Journal Supplement.

I.2.9 South Africa – Differences in blood culturing practices in rural and urban areas of South Africa (National Institute for Communicable Diseases (NICO), branch of the National Laboratory Service (NHLS))

Principal investigator:
Dr. Anne von Gottberg

Project coordinators/team members:
Linda de Gouveia
Nelesh Govender, Kerrigan McCarthy, Vanessa Quan, Elizabeth Prentice, Susan Meiring, Cheryl Cohen, Mireille Cheyip from GERMS-SA (Group for Enteric, Respiratory and Meningeal Disease Surveillance)

Specific objectives:
- To describe clinician culturing practices and perceptions.
- To survey clinicians on culturing practices including clinical presentations that trigger ordering of cultures, frequency of ordering cultures, and types of cultures ordered.
- To qualitatively explore clinical staff perception of the utility of blood culture and CSF specimens; the role of the laboratory in assisting with the diagnosis of acutely ill patients; and the burden of pneumococcal disease and available strategies for prevention.
- To document laboratory size, capacity and routine practices To evaluate aspects of specimen processing that may influence culture results.
- To quantify specimen-taking practices to use as a correction factor for reported cases.
- To quantify annual proportion of inpatient blood cultures and cerebrospinal fluids (CSF) by age (pediatric less than thirteen years, adult patients older than twelve years) and syndrome (meningitis or respiratory tract infection as captured in casualty/admission ward) admitted to each hospital compared to the total number of pediatric and adult admissions within that hospital, for the years 2004 and 2005.
- To quantify the proportion of culture-positive blood cultures and CSF specimens submitted to a laboratory, compared to the total number submitted per year in 2004 and 2005.
- Categorize coagulase-negative staphylococci, Bacillus spp. and Propionibacterium spp. as “contaminants” – this will give a crude measure of the quality of specimens submitted to the laboratory. All other bacteria or yeast to be considered “significant” – this will give a crude measure of the possible number of significant pathogens isolated.

Current status:
This project was completed in 2007, and examined the correlation between blood culturing, CSF specimen collection within hospitals in 2005 and how this related to the estimated prevalence of invasive pneumococcal disease in South Africa. Questionnaires were sent to 22 hospitals (at least two from each province) and were classified as academic or non-academic. Non-academic hospitals had to have isolated at least five pneumococcal isolates in order to participate in the survey. A total of 341 questionnaires were returned to the team; respondents were more likely to come from academic vs. non-academic hospitals. The results show that doctors from academic hospitals were more likely to take blood cultures, and CSF specimens; however, doctors from both hospitals believed that blood cultures are not helpful in the diagnosis of respiratory tract
infections. The study team concluded that there was a correlation between rates of culture and the reported incidence of invasive disease, and this has led to an underestimate of disease in those provinces with lower rates of culture.

I.2.10 Tanzania – The serotype distribution of carriage and invasive pneumococcal isolates from children in northern Tanzania (Kilimanjaro Christian Medical College, Tumaini University, Royal Free & University College Medical School)

Principal Investigators:
Ndekya Oriyo (Co-principal investigator)
Kilimanjaro Christian Medical College, Tumaini University
Moshi, Tanzania

Dr. Bambos M Charalambous (Co-principal investigator)
Royal Free & University College Medical School
London, United Kingdom

Summary:
A study site will be established in Moshi to systematically isolate \( S. \) \textit{pneumoniae} from severely ill children. Outputs of the project include information on the number of pneumococcal isolates from blood, antibiotic resistance and serotype distribution patterns.

Goals and Objectives:
The goal of this project is to serotype a representative sample of the carriage isolates (~150) archived from thirteen healthy children during a one year longitudinal study and to compare them with invasive isolates captured prospectively. Non-typable isolates were evaluated by PCR-RFLP analysis of capsulation locus to identify potentially “new” serotypes.
Specific aims included:
1. Setting up a routine blood culture facility to screen febrile patients for bacteraemia and facilitate the capture of invasive pneumococcal isolates.
2. Comparing the serotype distribution of colonizing and invasive isolates.
3. Serotyping non-typable isolates that are not covered by the 23-valent vaccine formulation with a PCR-RFLP method that has the potential to identify new serotype variants in the community.

Status and Results:
This study has received IRB approval and should begin shortly.
I.3 Other Key Research Activities in Africa

1.3.1 Usefulness of Procalcitonin (PCT) and C-Reactive protein (CRP) as surrogate markers of pneumococcal pneumonia in determining the efficacy of a 9-valent pneumococcal conjugate vaccine (PCV) in preventing pneumococcal pneumonia in HIV uninfected and infected children

The South Africa trial:
The Soweto, South Africa trial was a double-blind randomized trial of a 9-valent pneumococcal conjugate vaccine containing serotypes 1, 4, 5, 6B, 9V, 14, 18C 19F, and 23F. Between March 2, 1998 and October 30, 2000 nearly 40,000 children were enrolled in the study and assigned to receive three doses of the 9-valent pneumococcal vaccine or a placebo at approximately six, ten, and 14 weeks of age. Children were followed up for an average of two years to measure outcomes in terms of incidence of pneumonia and invasive pneumococcal disease. Childhood mortality and vaccine immunogenicity were also assessed.

The trial results have been published in the *New England Journal of Medicine* and several other leading journals. This study shows that the 9-valent pneumococcal conjugate vaccine has strong efficacy among children infected with HIV and those without.

Summary and Results:

- The 9-valent pneumococcal vaccine was effective in both HIV positive and HIV negative children:
  - HIV negative children receiving the vaccine had an 83 percent reduction in invasive pneumococcal infections caused by the vaccine serotypes.
  - HIV infected children had a 65 percent reduction in vaccine-type invasive pneumococcal disease.

- Vaccination with a 9-valent pneumococcal conjugate vaccine reduced the incidence of radiologically confirmed pneumonia by 20 percent.

- The vaccine reduced the incidence of invasive pneumococcal disease caused by penicillin-resistant strains by 67 percent, and infection due to strains resistant to trimethoprim–sulfamethoxazole by 56 percent.

PneumoADIP-sponsored ancillary study:
The absence of a highly sensitive and specific tool for diagnosing bacterial pneumonia has been a major limitation in determining both the true burden of disease and the efficacy of conjugate vaccines to prevent pneumonia in children. This study looked at whether C-reactive protein (CRP) and/or procalcitonin levels were useful to measure vaccine efficacy and impact against the burden of pneumonia compared with positive chest x-rays as an outcome. This study was conducted after the conclusion of the trial described above on stored sera of children under two years of age that were hospitalized for lower respiratory track infections (LRTI). Serum from both HIV infected and non-infected children who participated in this trial were analyzed. The results of this study have been published in the Pediatric Infectious Disease Journal in January 2006.
Briefly the major conclusions from this study are:

- CRP in children with LRTI is a useful adjunct marker for measuring vaccine efficacy, yielding higher vaccine efficacy estimates than outcomes such as chest radiograph confirmed pneumonia, clinical outcomes of LRTI alone, and WHO defined severe/very severe pneumonia in both non-HIV infected and infected children.
- CRP and procalcitonin measurements improved the specificity of detecting pneumococcal pneumonia in the absence of the positive chest x-ray for children with clinically diagnosed LRTI.
- For non-HIV infected children with negative chest x-ray, CRP measurements were more useful than procalcitonin measurements to improve the specificity of the outcome. For HIV infected children with negative chest x-ray, procalcitonin levels alone and in conjunction with CRP measurements did not improve the specificity of pneumococcal clinically diagnosed LRTI.

This study suggests an important role for CRP in defining the efficacy/effectiveness of conjugate pneumococcal vaccine in settings where chest x-ray may not be available. These findings pertain to HIV uninfected children in an area unaffected by malaria. The benefit of CRP could not be demonstrated in HIV infected children, possibly due to the high prevalence of other bacterial infections associated with LRTI in those children.

I.3.2 Ancillary studies to the Gambia 9-valent pneumococcal conjugate vaccine trial

The Gambia trial

The Gambia Pneumococcal Vaccine Trial was a randomized, double-blind, placebo-controlled trial. The study evaluated the efficacy of 9-valent pneumococcal conjugate vaccine against pneumonia, meningitis, and sepsis. The four-year study, led by the UK Medical Research Council’s Felicity Cutts was carried out in Upper and Central River divisions of The Gambia between August 2000 and April 2004. All 17,437 infants enrolled in the trial received DTP (diphtheria, tetanus, and pertussis) and Hib vaccines. Children had follow-up visits for two years on average to determine whether the vaccine that had been shown to prevent pneumococcal disease in urban South Africa would also work in the challenging environment of rural Africa.

The results have since been published in the March 26, 2005 issue of *The Lancet*. They show that the pneumococcal conjugate vaccine reduced childhood mortality by 16 percent in children who received the vaccine. This study is the first major randomized, controlled vaccine clinical trial in nearly 20 years to show a statistically significant reduction in overall child mortality.

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Summary and Results:

- The 9-valent pneumococcal conjugate vaccine reduced childhood mortality by 16 percent among children who received the vaccine.

- This vaccine significantly reduced the need for hospitalization: children receiving the pneumococcal vaccine had fifteen percent fewer hospital admissions than those who did not.

- The 9-valent pneumococcal conjugate vaccine was 77 percent effective in preventing pneumococcal infections caused by the vaccine serotypes.

- As a result, there were 37 percent fewer cases of pneumonia in the children who received the vaccine compared with children who received the control vaccine.

PneumoADIP-sponsored ancillary studies:
The PneumoADIP supported five studies added to the pneumococcal vaccine trial. All studies were done retrospectively on data and specimens collected during the trial. The five activities are:

1. Further validation of x-ray classification of pneumonia – In 2006, a WHO panel of two pediatric radiologists read all concordant positive radiographs and an equal number of concordant negative films from the pneumococcal vaccine trial. An assessment was done on the effect of different classifications rules for the diagnosis of radiographic pneumonia on the observed vaccine efficacy in the trial. By doing an analysis on the sensitivity of the diagnosis estimated, the vaccine efficacy estimates could be adjusted from the trial. The results of this study are being prepared for publication and investigators hope to have a manuscript shortly.

2. Analysis of the use of serologic markers of acute inflammatory responses and nasopharyngeal colonization improve diagnosis of likely bacterial pneumonia. This study utilized similar methods to the one conducted in South Africa and allows evaluation of these markers in a different setting than the South Africa trial, namely low HIV prevalence and high malaria rates. The results of this study are being written for publication and writing of the paper will be completed shortly.

3. Analysis of the effect of 9-valent pneumococcal conjugate vaccination of infants on acquisition and transmission of *S. pneumoniae*. – Two colonization studies were nested within the trial. The first was a cohort study of carriage among children enrolled in the trial and the second was a cross-sectional study among their younger siblings not enrolled in the trial. Children recruited in the catchment areas of Basse, Bansang and Gambisara health facilities from January 2003 onwards were invited to participate. The effect of vaccination on carriage among younger siblings of vaccinated and unvaccinated children in the trial is also being assessed, with the aim of detecting an absolute reduction of 30 to 40 percent in carriage of vaccine serotypes among younger siblings aged two weeks to six months. All samples have been cultured and pneumococcal isolates obtained from a majority of nasopharyngeal samples. The results of this study are being prepared for publication.
4. Analysis of the cost-effectiveness of pneumococcal conjugate vaccination in the Gambia. This analysis is ongoing and results are pending.

5. Spatial analysis of the relationship between access to care and pneumococcal disease burden. The relationship between access to care and pneumococcal disease burden is being examined by looking at variables including serotype distribution of carriage, antibiotic resistance, trial outcomes and measles vaccine uptake. The other aim of this study is to investigate the potential variation in vaccine efficacy against the primary and secondary endpoints according to measures of access to Basse and Bansang health facilities. The analysis is still ongoing.

I.3.3 Evaluation of 7-valent PCV impact in The Gambia

This is a four-year project to establish a population-based surveillance system measuring the incidence of invasive pneumococcal disease in both adults and children living in the Upper River Division (URD) before and after incorporation of the 7-valent vaccine into the routine immunization schedule. This project represents collaboration between the Government of The Gambia and the Medical Research Council (MRC). MRC will initiate activities and then transfer coordination for the surveillance system to the government after two years of post-vaccine introduction surveillance. The main study site is a government health centre and a laboratory operated by MRC.

Principal Investigator:
Richard Adegbola,
MRC, The Gambia

Primary objectives:
1. To evaluate the impact of pneumococcal conjugate vaccine on the incidence of invasive pneumococcal disease according to serotype.
2. To evaluate the impact of PCV on radiologically-confirmed pneumonia.

Secondary objectives:
1. To monitor trends in pneumococcal antimicrobial resistance patterns.
2. To monitor case fatality rates for invasive pneumococcal disease.

Specific Aims:
1. Establish surveillance for invasive pneumococcal disease and radiologically confirmed pneumonia in children and adults in the URD;
2. Monitor changes in the incidence rate of vaccine-type, non-vaccine type, and total invasive pneumococcal disease among children and adults in the URD after PCV introduction;
3. Monitor the proportion of all invasive pneumococcal disease caused by vaccine-type serotypes using data from URD;
4. Characterize the serotype distribution of pneumococcal isolates collected.

Current Status:
Full data collection will commence in Q4 2007 and will continue until 2010.
I.3.4 Evaluation of 7-valent PCV impact in Kenya

This project aims to define the total reduction in disease burden that can be attributed to a 7-valent PCV vaccine program. It aims to estimate the impact of pneumococcal vaccine on the incidence of vaccine-type invasive pneumococcal disease and non-vaccine-type disease, as well as its impact on the incidence of all hospital admissions and admissions with radiologically-confirmed pneumonia. Vaccine impact will be evaluated among fully and partially vaccinated children as well as neonates, older children and adults. The cost-effectiveness of the vaccine program will also be estimated and will be based on the costs of vaccine introduction, the costs of treatment averted and the changes in incidence observed.

Two studies are proposed in different districts of Kenya. In Kilifi District, existing clinical, microbiological and demographic surveillance will be used to estimate the effectiveness of introducing pneumococcal vaccine through the EPI routine childhood immunization service, accompanied by a catch-up campaign for all children under the age of five years. In Kirinyaga District, the efficacy of the vaccine will be confirmed using a case-control study following introduction of the vaccine into the EPI schedule. In Kilifi District, individual level observations within an existing demographic surveillance system will permit analysis of vaccine efficacy in HIV-infected and uninfected children and among the partially vaccinated. Herd protection will be estimated in unvaccinated age-groups and among children eligible for vaccination but not covered by routine services. With over ten years of microbiological surveillance for *S. pneumoniae*, the Kilifi study site will also be able to detect significant increases in disease caused by serotypes not included in the vaccine.

Principal Investigator:
Anthony Scott

Primary Objectives:
- To measure the total reduction in the incidence of invasive pneumococcal disease of all serotypes in children aged less than five years following programmatic introduction of 7-valent PCV in Kilifi District in Coastal Kenya.
- To estimate the efficacy of 7-valent PCV against invasive pneumococcal disease of vaccine serotypes in a highland area of Kenya among children aged 2-59 months.
- To establish a system of longitudinal surveillance for invasive pneumococcal disease in PCV-immunized populations in East Africa to detect and measure potential serotype-replacement disease over time.

Current Status:
- Surveillance for invasive bacterial disease in children has been ongoing in Kilifi since 1998; surveillance in adults was initiated in 2007. In Kirinyaga District, clinical and microbiological surveillance will be established in 2007 in anticipation of the case-control study to be conducted following vaccine introduction.
Appendix II – Eastern Mediterranean Region

Appendix II lists all PneumoADIP-supported projects including small grants in the Eastern Mediterranean Region (EMR). The section also includes a brief list of non-PneumoADIP activities conducted in the EMR.

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<td>Morocco</td>
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<td>Surveillance</td>
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<tr>
<td>Pakistan</td>
<td>EMRO</td>
<td>Surveillance</td>
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<tr>
<td>Sudan</td>
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<td>Syria</td>
<td>EMRO</td>
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<tr>
<td>Yemen</td>
<td>EMRO</td>
<td>Surveillance</td>
<td>II.1</td>
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<tr>
<th>Country</th>
<th>Participating investigator or organization</th>
<th>Project activity</th>
</tr>
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<tbody>
<tr>
<td>Egypt</td>
<td>WHO/EMRO, Centers for Disease Control – International Emerging Infections Program</td>
<td>Bacterial Meningitis Surveillance Network Identify and control emerging infections via surveillance, research, training and outbreak support</td>
</tr>
<tr>
<td>Jordan</td>
<td>WHO/EMRO</td>
<td>Bacterial Meningitis Surveillance Network</td>
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<tr>
<td>Oman</td>
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<td>Saudi Arabia</td>
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<tr>
<td>Tunisia</td>
<td>WHO/EMRO</td>
<td>Bacterial Meningitis Surveillance Network</td>
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*Please contact PneumoADIP at pneuadip@jhsph.edu to submit any additional research activities in your country or region.
II.1 Eastern Mediterranean Region Bacterial Meningitis and Pneumonia Surveillance Network

With PneumoADIP support, a six-country surveillance network has begun operations in the Eastern Mediterranean region. The countries to be included are Iran, Libya, Morocco, Pakistan, Sudan, Syria and Yemen. This project aims to contribute to the development of a regional epidemiological surveillance network for vaccine-preventable childhood respiratory diseases due to pneumonia and meningitis in the Eastern Mediterranean region. The project will add onto the existing bacterial meningitis network currently operating in the region and will include hospitals and public health laboratories in participating countries.

**Title:** Surveillance of bacterial meningitis and pneumonia caused by *S. pneumoniae* and *H. influenzae* type b in the Eastern Mediterranean region.

**Project leader:** Nadia Teleb, VPI/WHO/EMRO

**Countries:** Iran, Libya, Morocco, Pakistan, Sudan, Syria, and Yemen

**Project Description:** Surveillance for vaccine preventable diseases is a key activity that the Eastern Mediterranean Regional Office (EMRO) of WHO supports in countries of the region. The data collected through such surveillance supports evidence-based decision making on introduction of new vaccines and evaluating the impact of such vaccines once they are introduced.

The Bacterial Meningitis Surveillance (BMS) network was initiated with WHO support in the region in January 2004 to: generate information on burden and trends of meningitis caused by meningococcus, pneumococcus and *H. influenzae*, generate reliable data necessary for evidence-based decision making for introduction of new vaccines and evaluate the impact of such vaccines once introduced, assist in early detection and control of epidemic meningococcal disease, guide clinical management of patients, detect and monitor antimicrobial susceptibility patterns, and build national capacity for long-term laboratory based surveillance in the EMR countries.

As of June 2006, twelve countries (Egypt, Jordan, Morocco, Lybia, Oman, Pakistan, Qatar, Saudi Arabia, Sudan, Syria, Tunisia and Yemen) are participating in the network. WHO/EMRO is fully supporting six countries (Egypt, Jordan, Oman, Qatar, Saudi Arabia and Tunisia) with 31 sentinel sites in addition to supporting five population-based sites in Iran.

At an inter-country meeting to discuss strengthening pneumococcal disease surveillance in the Eastern Mediterranean Region convened by EMRO and PneumoADIP, the participants concluded that surveillance of pneumococcal disease could be improved and should be enhanced to generate data necessary for documentation of pneumococcus as a cause of severe disease and to calculate pneumococcal disease incidence where possible, to identify serotype distribution within the different countries, to assess antimicrobial susceptibility patterns and to establish a system for the measurement of vaccine impact after introduction. For that purpose, the meeting recommended:
Building on the pre-existing Bacterial Meningitis Surveillance network and further strengthening its capacity by:

- Continued support for all existing sites for meningitis surveillance and the addition of new sites and countries to improve country level data and expand regional representativeness.
- Further strengthen the laboratory capacity and data management at participating sites and participating countries.
- Enhance capacity in selected sites to conduct surveillance for other invasive pneumococcal diseases, particularly pneumonia, through investigation of blood culture.
- If possible, conduct population-based surveillance for bacterial meningitis and pneumonia at selected sites.

The Strategic Advisory Group of Experts (SAGE) recommendation to introduce Hib vaccine in all countries drew attention to the delay of Hib vaccine introduction into EMR countries. At the 23rd meeting of the National EPI managers in May 2006, enhanced bacterial meningitis and pneumonia surveillance was recommended in EMR countries to support evidence-based decision-making on introduction of the new vaccines.

**Objectives of PneumoADIP support:**
To build upon the existing bacterial meningitis surveillance network to gather information on the regional burden of Hib and pneumococcal diseases, including serotype distribution and antimicrobial resistance, and to establish a system for assessment of vaccine impact post-introduction by:

1. Sustaining and strengthening the existing regional bacterial meningitis surveillance network and further extending surveillance by adding new countries and sites to obtain more representative data from the region.

2. Enhancing surveillance to include severe pneumonia in children less than five years of age at selected sites in six countries in the region.

3. Conduct population-based surveillance to determine the incidence of invasive pneumococcal disease in one site in the region.

**Expected Outcomes:**
1. Documentation of *H. influenza* type b and *S. pneumoniae* as important causes of meningitis and severe pneumonia in representative populations in the region.

2. Adding to existing regional data on the serotype distribution of pneumococcus and antimicrobial resistance patterns of Hib and the pneumococcus causing meningitis and severe pneumonia.

3. Incidence of hospitalized meningitis and severe pneumonia, and incidence of lab-confirmed invasive Hib and pneumococcal disease in selected populations in the region.

4. Improved data collection at each sentinel hospital through:
a. Improved collection of clinical data through development of standard clinical criteria and training.
b. Individual reporting on patients with laboratory confirmed Hib and pneumococcal disease, including residence, immunization status, key clinical data, and outcome.
c. Case based reporting of culture negative cases by age and diagnosis.
d. Reporting of aggregated numbers of patients with eligible clinical syndromes to assess proportion of eligible patients investigated.

5. Enhancing capacity for surveillance for laboratory confirmed invasive bacterial diseases in participating sites/countries.

II.2 Small Grant Projects: Eastern Mediterranean Region (EMRO)

II.2.1 Egypt - Hospital-based prospective surveillance of severe pneumonia and Bacteremic pneumococcal pneumonia in children one to 23 months old in Alexandria Governorate, Egypt (NAMRU3, Cairo)

Principal Investigators:
Dr. Faoud G. Youseff (Co-principal investigator)
NAMRU3
Cairo, Egypt

Dr. Rana Hajjeh (Co-principal investigator)
NAMRU3
Current affiliation: Hib Initiative

Summary:
NAMRU3 established study sites in Alexandria, Egypt, (El-Shatby University Pediatric Hospital and Alexandria Fever Hospital) to systematically isolate *S. pneumoniae* from severely ill children with pneumonia. Outputs of the project include number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distribution of pneumococcal isolates.

Goals and Objectives:
The primary goal of the project is to obtain information on number of specimens and pneumococcal isolates collected, antibiotic resistance and serotype distributions among pneumococcal isolates associated with pneumonia.

Status and Results:
A total of 518 cases of clinical pneumonia were enrolled over the course of the surveillance period. Four distinct peaks of cases of severe pneumonia were recognized occurring in December, March, June, and September. The majority of cases were less than two years of age. No pneumococci were isolated, possibly because of high levels of prior antibiotic use. This project is now completed.
II.2.2 Lebanon – Establishing a pilot surveillance program for pneumococcal infections in Lebanon (American University of Beirut and partners)

Principal Investigator:
Dr. Ghassan Dbaibo
American University of Beirut
Beirut, Lebanon

Summary:
The American University of Beirut established study sites in six large hospitals geographically distributed over Lebanon to systematically isolate *S. pneumoniae* from severely ill patients of all ages. These hospitals include the American University Hospital and Hotel Dieu de France Hospital in Beirut, Rahhal Hospital in Akkar, Rayyak Hospital in the Bekaa, Ain wa Zain Hospital in the Chouf and Hammoud Hospital in Saida and were already members of a neonatal collaborative research network. Outputs of the project include information on the number of specimens and pneumococcal isolates collected, as well as serotype distribution and antibiotic resistance patterns of pneumococci isolated from normally sterile sites in patients with invasive bacterial illnesses.

Goals and Objectives:
The primary goal of the project was to establish a hospital-based, nationwide pilot surveillance program for invasive pneumococcal disease to facilitate the collection of data, including the number of clinical specimens and pneumococcal isolates obtained and antibiotic resistance and serotype distributions of pneumococcal isolates associated with invasive bacterial illnesses.

1. To establish a pneumococcal pilot surveillance program that will serve as the foundation for future expansion.
2. To determine the serotypes of *S. pneumoniae* causing invasive disease in Lebanon identified by surveillance.
3. To determine the susceptibility patterns and emerging trends of pneumococcal penicillin resistance.

Status and Results:
Between July 2006 and August 2007, 84 hospitals located throughout Lebanon participated in the surveillance project. They were contacted on a bi-weekly basis to ascertain isolation of pneumococcus, and isolates were transported to the American University of Beirut Medical College for confirmation and antimicrobial testing. A total of 98 isolates were confirmed: 72 from blood, twelve from cerebrospinal fluid, and 14 from other sterile sites. This project has been completed.

II.2.3 Pakistan - Enhanced surveillance for invasive pneumococcal disease in children in Sindh, southern Pakistan (Aga Khan University)

Principal Investigator:
Dr. Anita Zaidi
Aga Khan University
Karachi, Pakistan

Salim Allana
Summary:
AKU established more than fifteen study sites chosen from public and private sector hospitals in Karachi and Hyderabad, the two largest cities of the Sindh region in southern Pakistan. Several laboratories in the private sector were also included in the surveillance network. These sites were responsible for systematically isolating \textit{S. pneumoniae} and other causes of bacterial meningitis from children with meningitis. AKU also passively collected invasive pneumococcal isolates from hospitals and laboratories in Karachi for characterization and serotyping. Finally, the Binax NOW® \textit{S. pneumoniae} antigen test was evaluated prospectively at one of the NICHD site in Karachi. Outputs of the project include information on number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distributions among pneumococcal isolates associated with meningitis and other invasive disease. Additional outputs include data to help evaluate the utility of Binax testing in improving the identification of pneumococcal meningitis cases in Karachi.

Goals and Objectives of the project:
To determine various characteristics of invasive pneumococcal meningitis and to strengthen the existing surveillance system in Pakistan.

Primary objectives:
1. To determine the burden of pneumococcal meningitis in children less than five years of age in Karachi and Hyderabad.
2. To determine the serotype distribution of invasive pneumococcal isolates from children less than five years of age.
3. To determine the utility of the Binax test in identifying pneumococcal meningitis in children less than five years of age with CSF specimens of varying characteristics.

Secondary objectives:
1. To determine the age distribution of pneumococcal meningitis in children in Karachi and Hyderabad.
2. To determine antimicrobial resistance pattern of invasive pneumococcal isolates from children in Karachi and Hyderabad.
3. To determine the proportion of children that present to public sector hospitals with suspected acute bacterial meningitis who do not undergo a lumbar puncture.

Status and Results:
During the study period, 2,690 children less than five years of age were admitted at the surveillance hospitals with suspected acute bacterial meningitis and 2,646 received a lumbar puncture. Pathogens were detected by culture or latex agglutination in 70 specimens (17 percent). Thirty-five of these were Hib (50 percent), 32 pneumococci (46 percent), and three meningococci (four percent). Only fifteen specimens grew pneumococci on culture. Over 80 percent of pathogens detected were in children less than one year old. In addition, 127 pneumococcal isolates from invasive pneumococcal disease from both adults and children have been passively collected by Aga Khan University, of which 50 have been serotyped. Of these, 46 percent of isolates were 7-valent vaccine-type or vaccine-related. The major non-vaccine type strains were serotype 1 (14 percent), serotype 7F (8 percent), and serotype 3 (6 percent).
This project is now completed. The results of the Binax evaluation will be submitted for publication in 2008.

II.2.4 Pakistan – Population-based surveillance for invasive pneumococcal disease in children in rural Pakistan (Aga Khan University)

**Principal Investigator:**
Dr. Anita Zaidi  
Aga Khan University  
Karachi, Pakistan

**Additional contributors:**
Salim Allana  
Asghar Ali  
Ishrat Abbas

**Summary:**
Aga Khan University (AKU) established more than 15 study sites chosen from public and private sector hospitals in Karachi and Hyderabad, the two largest cities of the Sindh region in southern Pakistan. Several laboratories in the private sector were also included in the surveillance network. These sites were responsible for systematically isolating *S. pneumoniae* and other causes of bacterial meningitis from children with meningitis. AKU also passively collected invasive pneumococcal isolates from hospitals and laboratories in Karachi for characterization and serotyping. Finally, the Binax NOW® *S. pneumoniae* antigen test was evaluated prospectively at one of the NICI site in Karachi. Outputs of the project include information on number of specimens and pneumococcal isolates collected, etiologic fraction, antibiotic resistance and serotype distributions among pneumococcal isolates associated with meningitis and other invasive disease. Additional outputs include data to help evaluate the utility of Binax testing in improving the identification of pneumococcal meningitis cases in Karachi.

**Primary Objectives:**
1. To determine the incidence of invasive pneumococcal disease in children less than five years of age in a rural area of Sindh, Pakistan.
2. To determine the serotype distribution of invasive pneumococcal isolates from bacteremic illnesses in children less than five years of age from a rural area of Pakistan.

**Secondary Objectives:**
1. To determine the incidence of severe ARI in children in a rural area of Pakistan.
2. To determine the age distribution of invasive pneumococcal disease in children less than five years of age in a rural area.
3. To determine antimicrobial resistance pattern of invasive pneumococcal isolates from children in a rural area.
Status and Results:
Of 3,938 children residing in the surveillance area, 591 met the study inclusion criteria and were enrolled of which 526 had blood cultures done. One of these cases was culture positive for *S. pneumoniae*. The project is still ongoing.

Appendix III – Region of the Americas (PAHO)
Appendix III lists all PneumoADIP-supported projects including small grants in the Region of the Americas. The section also includes a brief list of non-PneumoADIP activities conducted in the region.

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<td>Dominican Republic</td>
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<td>Guatemala</td>
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<td>Nicaragua</td>
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*Please contact PneumoADIP at pneuadip@jhsph.edu to submit any additional research activities in your country or region.*
III.1 Surveillance of Bacterial Pneumonia and Meningitis: SIREVA II, II+

The Sistema Regional de Vacunas II (SIREVA II) network project aims to contribute to the development of a regional epidemiological surveillance network for vaccine-preventable childhood respiratory diseases due to pneumonia, influenza, and meningitis in Central and South America and the Caribbean. The network includes selected sentinel hospitals, public health laboratories, and epidemiological surveillance units of the health ministries in 21 countries in Latin America. SIREVA II builds upon existing lab-based surveillance in the region by adding clinical and epidemiological components of survival.

Title: *Sistema Regional de Vacunas II* (SIREVA II)

Start Date: December 2006

Project Leaders:
Dr. Jon Andrus, Lead Technical Advisor, Immunization Unit of the Pan American Health Organization (PAHO)
MSc. Lucia Helena de Oliveira, Project Officer, Regional Advisor on New Vaccines
Dr. Maria Tereza da Costa, Project Assistant
Cuauhtémoc Ruiz Mathus, Unit Chief

Support: Primarily from WHO/PAHO, with supplemental support from PneumoADIP

Coordinating Center: Pan American Health Organization (PAHO)

Project description: Surveillance of pneumococcal disease in the Americas dates back to the establishment in 1993 of the *Sistema Regional de Vacunas* (SIREVA) project for surveillance of bacterial meningitis and pneumonia, including pneumococcal disease. The objective of the SIREVA network was to determine the distribution of pneumococcal serotypes causing severe disease and the prevalence and epidemiology of antimicrobial resistant pneumococci. Subsequently, SIREVA incorporated the surveillance for other agents that cause meningitis and pneumonia, such as *H. influenzae* and meningococcus. At present, twenty countries are participating in this network. Countries are reporting cases in children less than five years. In selected sites, the project also measures the incidence rates of radiological pneumonia in children using standardized criteria.

A review of the data was done during the pneumococcal regional workshop in Mexico City, Mexico, in November 2004, organized by PAHO and GAVI’s PneumoADIP. The major limiting factor of the data produced by SIREVA was the inability to merge clinical data to isolates obtained through the lab based network. The following specific recommendations were made for all partners to consider when promoting the introduction of pneumococcal vaccines in the Americas.

- Strengthen laboratory capacity.
- Strengthen the clinical and epidemiological components of surveillance.
- Conduct one or more of the following at key surveillance centers:
  - Economic studies.
  - Surveillance for adult pneumococcal disease.
• Strengthen population based component.

- Support regional coordination for oversight of the surveillance network, including country meetings, mobilization of pediatric societies, and supervisory site visits.

The aim of this project is to implement the recommendations of this meeting continuing to collect facility-based data from all existing sites (SIREVA II) and population-based data in selected sites (SIREVA II+).

**SIREVA II:**

The main objective is to maintain laboratory capacity and strict quality assurance in all the participating sentinel laboratories and to further enhance the data quality by standardized collection of clinical and epidemiological data by improved data management.

SIREVA II aims to maintain the existing surveillance in the existing sentinel sites with enhanced data collection, data reporting, strengthened laboratory diagnosis and susceptibility testing capabilities at sentinel hospital and optimized serotyping at national and regional reference laboratory level. All the participating sites in SIREVA I will participate in SIREVA II. Surveillance is conducted in all hospitalized children less than five years of age with suspected pneumococcal, *H. influenzae* and meningococcal disease. These will primarily include meningitis and pneumonia. The country may decide to also include other invasive diseases likely to be caused by pneumococcus such as sepsis, septic arthritis, peritonitis and osteomyelitis.

Standard clinical algorithms were developed through a small working group convened by PAHO, through adaptation of the definitions and algorithms used by the other PneumoADIP surveillance projects.

Standard operating procedures (SOPs), data collection forms and training modules were prepared for training of all relevant clinicians. Standardization and quality assurance and quality control of the laboratory procedures is maintained through the existing regional and sub-regional reference laboratories as well as continued training, supervision and audit of the participating laboratories.

**SIREVA II+:**

The main objective of SIREVA II+ is to collect population-based incidence data on invasive pneumococcal disease in children at six SIREVA II participating sites. Two sites will also collect incidence data in older age groups.

At the SIREVA II+ sites there will be greater emphasis on standardized specimen collection procedures with an aim to get specimens from greater than 90% of eligible patients within the study population. This will require greater clinician involvement and a syndrome-based trigger to initiate data collection. In contrast to SIREVA II and within this subset of sites, more complete data and individual reporting is performed for all patients meeting the selected clinical criteria for enrolment.

The six sentinel sites selected for SIREVA II+ are Uruguay, Brazil, Colombia, Dominican Republic, Nicaragua and Guatemala. As in SIREVA I, the study will be conducted in all hospitalized children less than five years of age from the defined study area with suspected invasive pneumococcal disease. These will primarily include meningitis and pneumonia, but may
also include other invasive diseases likely to be caused by pneumococcus such as septic arthritis, peritonitis and osteomyelitis. In Uruguay and Brazil, the surveillance will be extended to all age groups, including adults.

**Goals and Objectives:**

1. To build on the achievements of the SIREVA project by maintaining laboratory capacity and strict quality assurance in all the participating sentinel laboratories and to further enhance the data quality by standardized collection of clinical and epidemiological data and by improved data management (SIREVA II).

2. To build on the population-based pneumonia surveillance projects to collect population-based incidence data on invasive pneumococcal disease in children in a few selected sites and data on rates of disease in older age groups in two of these sites (SIREVA II+).

**Specific Objectives:**

**SIREVA II:**

1. Improved data collection at each sentinel laboratory through:
   
   a) Individual reporting on patients with laboratory confirmed pneumococcal disease, including residence, immunization status, presence of selected risk factors, key clinical data, and outcome.
   
   b) Aggregate reporting of culture negative cases by age and diagnosis
   
   c) Reporting of aggregated numbers of patients with eligible clinical syndromes to assess proportion of eligible patients investigated.
   
   d) Improved collection of clinical data of pneumonia and meningitis through development of standard clinical criteria and training.

2. Improved data management and sharing of information through web-based portals and publication of newsletters.

**SIREVA II+:**

1. Generate information on incidence rates of invasive pneumococcal disease in children under five years of age through prospective surveillance in defined populations in a few selected sites in the region.

2. Collect information on incidence rates of invasive pneumococcal disease in older age groups in two of the above sites.

3. Collect economic data and data on disabilities caused by pneumococcal disease in selected sites.
Summary of results from SIREVA II:
Five of 13 countries committed to improving surveillance have reported surveillance data, while the remaining countries are scheduled to start reporting by the end of 2007. According to the data of sentinel hospital surveillance reported by Ecuador, El Salvador, Honduras, Guatemala and Paraguay, 145 children died due to bacterial pneumonia and more thirteen children died due to bacterial meningitis during 2007.

<table>
<thead>
<tr>
<th>Total number of cases reported</th>
<th>Number of deaths</th>
<th>Percentage of lethal cases (%)</th>
<th>Number of pneumococcal isolates</th>
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<tr>
<td>2,440</td>
<td>145</td>
<td>5.9</td>
<td>43</td>
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</table>

These five countries also reported data of bacterial meningitis in children less than five years of age as the following: 92 cases of bacterial meningitis, 16 confirmed pneumococcal meningitis cases and 13 deaths.

III.2 Small Grants Projects: Region of the Americas (PAHO)

III.2.1 Dominican Republic - Burden of disease and serotype prevalence in children aged under five years in Santo Domingo (Robert Reid Cabral Children’s Hospital, University of Miami and partners)

Principal Investigator:
Dr. Jesus Feris
Fundación Dominicana de Infectología
Hospital de Ninos Robert Reid Cabral
Santo Domingo, Dominican Republic

Dr. Angelica Floren
University of Miami
Miami, Florida, USA

Summary:
The Fundación Dominicana de Infectología established surveillance at the Robert Reid Cabral Children’s Hospital in Santo Domingo to systematically isolate *S. pneumoniae* from severely ill children. Outputs of the project include information on the number of specimens and pneumococcal isolates collected, antibiotic resistance, and serotype distribution of pneumococcal isolates associated with pneumonia and meningitis.

Goals and Objectives:
The primary goal of the project was to obtain information on case-fatality rates, antibiotic resistance and serotype distributions among pneumococcal isolates associated with meningitis and pneumonia in children in Santo Domingo.

Status and Results:
One-hundred and sixty-five patients with meningitis and 143 with pneumonia were enrolled at Robert Reid Cabral, and ten pneumococci were isolated. This project has been completed.

III.2.2 Guatemala - Incidence of invasive pneumococcal disease in children hospitalized in Guatemala City (Johns Hopkins Bloomberg School of Public Health and University of Guatemala City)

Principal Investigator:
Dr. Neal Halsey
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland, USA

Summary:
Three large pediatric hospitals in Guatemala City were supported to systematically isolate S. pneumoniae from severely ill children. Outputs of the project include information on the number of specimens and pneumococcal isolates collected from children with meningitis, pneumonia, sepsis and other invasive illnesses, the serotype distribution of isolates, and the proportion of disease that could be prevented by current and future pneumococcal conjugate vaccines.

Goals and Objectives:
The primary goals of the project were to obtain information on age-specific incidence and case-fatality ratios of hospitalized invasive pneumococcal disease in Guatemala City and on the serotype distribution of pneumococcal isolates associated with pneumonia, meningitis, sepsis and other invasive bacterial diseases.

Status and Results
During the 2005 surveillance period, 372 children with suspected invasive bacterial disease were identified in the three hospitals. Based on the National Population Census of 2004, the average annual age-specific incidence of invasive pneumococcal disease was 45.9 per 100,000 children one to 11 months of age, and 19.6 per 100,000 children 12 to 59 months of age for children residing in Guatemala City. Of 60 pneumococcal isolates serotyped, the five most frequent serotypes were 2 (20 percent), 1 (11.5 percent), 5 (11.5 percent), 6A (11.5 percent), and 7F (8.3 percent). This project is now complete.
Appendix IV – Europe Region (EURO)

PneumoADIP does not currently support any activities in the Europe region.

<table>
<thead>
<tr>
<th>Country</th>
<th>Participating investigator or organization</th>
<th>Project activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ukraine</td>
<td>Hib Initiative</td>
<td>Sentinel surveillance for bacterial meningitis and x-ray confirmed pneumonia following introduction of <em>H. influenzae</em> type B (Hib) conjugate vaccine into routine childhood immunization schedule and evaluation of vaccine effectiveness through 2009</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Meningitis Research Foundation</td>
<td>Research activities include: vaccine development and candidate evaluation, diagnostics, treatment, prevention</td>
</tr>
</tbody>
</table>

*Please contact PneumoADIP at [pneuadip@jhsph.edu](mailto:pneuadip@jhsph.edu) to submit any additional research activities in your country or region.*
Appendix V – South-East Asia Region (SEARO)
Appendix V lists all PneumoADIP-supported projects including small grants in the South-East Asia Region (SEARO). The section also includes a brief list of non-PneumoADIP activities conducted in the SEARO.

### PneumoADIP-funded projects in South-east Asia region

<table>
<thead>
<tr>
<th>Country</th>
<th>Surveillance network</th>
<th>Project type</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>ICDDR,B</td>
<td>Surveillance</td>
<td>V.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small grant</td>
<td>V.4.1</td>
</tr>
<tr>
<td>India</td>
<td>SAPNA</td>
<td>Surveillance</td>
<td>V.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small grant</td>
<td>V.4.2</td>
</tr>
<tr>
<td>Indonesia</td>
<td></td>
<td>Small grant</td>
<td>V.4.3</td>
</tr>
<tr>
<td>Nepal</td>
<td>SAPNA</td>
<td>Surveillance</td>
<td>V.2</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>SAPNA</td>
<td>Surveillance</td>
<td>V.2</td>
</tr>
<tr>
<td>Thailand</td>
<td>IEIP</td>
<td>Surveillance</td>
<td>V.3</td>
</tr>
</tbody>
</table>

### Non PneumoADIP projects in South-east Asia region

<table>
<thead>
<tr>
<th>Country</th>
<th>Participating investigator or organization</th>
<th>Project activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>Samir K Saha, Dhaka Shishu Hospital</td>
<td>• Observational study to assess the safety of outpatient treatment of severe pneumonia with oral amoxicillin in children aged 3 to 59 months</td>
</tr>
<tr>
<td></td>
<td>International Centre for Diarrhoeal Disease Research, Bangladesh</td>
<td>• Observation of 5 vs 10 days of ceftriaxone therapy for bacterial meningitis in children</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surveillance for influenza and viral etiologies of respiratory illnesses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hospital-based influenza surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hospital mortality surveillance of pneumonia and meningitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Meningo-encephalitis project</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Zinc in outpatient pneumonia as adjunct therapy</td>
</tr>
<tr>
<td>Thailand</td>
<td>Centers for Disease Control – International Emerging Infections Program</td>
<td>Identify and control emerging infections via surveillance, research, training and outbreak support</td>
</tr>
</tbody>
</table>

*Please contact PneumoADIP at pneuadip@jhsph.edu to submit any additional research activities in your country or region.*
PneumoADIP currently supports three surveillance networks in the South-East Asia region:

1. International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B).
2. Invasive Bacterial Infections Surveillance/South Asian Pneumococcal Network Project (SAPNA).

All three of the PneumoADIP networks in the South-east Asia Region build on existing infrastructure and expertise. The ICDDR,B has a long and remarkable history in conducting surveillance. Since 1960, the Cholera Research Laboratory, and its successor ICDDR,B has been recognized globally as a leading international health research centre. Over the past decades, ICDDR,B has expanded its activities to address some of the most critical global health needs and has been working in collaboration with partners from academic and research institutions throughout the world. ICDDR, B has operated health and demographic surveillance systems at a variety of locations in Bangladesh, beginning 35 years ago. Traditionally, health and demographic surveillance systems have been used in rural settings. With PneumoADIP support, ICDDR,B currently undertakes surveillance in hospital, rural, and urban community based settings.

SAPNA builds on the strength and experience of the Invasive Bacterial Infections Network (IBIS). IBIS has been responsible for the development of locally appropriate standard clinical and laboratory protocols for collaborative working group and has productively generated important data on pneumococci and *H. influenzae* in India and has obtained preliminary national data on prevalent serotypes by age and patterns and trends of antimicrobial resistance. With PneumoADIP support, SAPNA/IBIS undertakes surveillance in India, Sri Lanka, and Nepal.

The International Emerging Infections Program (IEIP) is a collaboration established in late 2001 between the Thai Ministry of Public Health (MOPH) and the U.S. CDC, with a core objective of establishing high quality surveillance to inform public health decisions, including the introduction of new vaccines. IEIP launched active, population-based surveillance for radiographically confirmed pneumonia in August 2002 in Sakaeo province of eastern Thailand, and in July of 2003 in Nakhon Phanom province of northeastern Thailand. PneumoADIP supported the addition of laboratory surveillance to the existing clinical surveillance of pneumonia in these provinces.

### V.1 ICDDR,B Surveillance Network (Bangladesh)

**Title:** Burden of Pneumococcal Disease in children in Bangladesh: A Project to Enhance Laboratory Capacity and Create Awareness, and to Prepare for Introduction of Pneumococcal Vaccine

**Date Started:** April 2004

**Project Leaders:**
- Dr. Stephen Luby - Principal Investigator, Centers for Disease Control and ICDDR, B, Bangladesh
- Dr. Shams El Arifeen - Principal Investigator, Rural surveillance, Mirzapur, Bangladesh
- Dr. Abdullah Brooks - Principal Investigator, Urban surveillance, Kamalapur, Bangladesh
- Dr. Aliya Naheed - Project Coordinator, Bangladesh
- Dr. Samir Saha - Principal Investigator, Bangladesh Hospital surveillance, Dhaka, Bangladesh
Additional support provided by:
Hib Initiative
Government of Bangladesh through IHP-HNPRP

Coordinating Centre: International Centre for Diarrheal Diseases Research, Bangladesh (ICDDR,B)

Country: Bangladesh

Project Description: The project is led by the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B) Center for Health and Population Research. ICDDR,B has an extensive list of accomplishments since its inception in 1960. Initially developed as the Cholera Research Laboratory, the ICDDR,B, with support from PneumoADIP, is now affiliated with pneumonia and meningitis surveillance research activities. ICDDR,B coordinates surveillance activities in seven participating hospitals and in two population-based surveillance at two sites (one rural and one urban). The project aims to improve our understanding of the burden of invasive pneumococcal disease in Bangladesh. Surveillance for pneumococcal disease was initiated in early 2004 and has provided significant evidence of the presence of extensive pneumococcal disease across all sites involved.

Project Objectives:
1. Enhance capacity of the local laboratories to isolate and characterize S. pneumoniae and H. influenzae in children.
2. Identify the most common serotypes of S. pneumoniae causing disease in children in Bangladesh.
3. Describe the antimicrobial resistance patterns of S. pneumoniae and H. influenzae causing disease in children in Bangladesh.
4. Estimate the population-based incidence of pneumonia and laboratory-confirmed invasive pneumococcal and Hib disease in children.

Participating Institutions:
- Dhaka Medical College Hospital - 1,400 bed government hospital (45 pediatric beds)
- Sir Salimullah Medical College Hospital - 600 bed government hospital (36 pediatric beds)
- Institute of Child Health - 80 bed hospital in the Mirpur area of Dhaka (all pediatric beds)
- Kumudini Hospital - 750 beds (85 pediatric beds) in rural Mirzapur
- Chittagong Medical College Hospital - 500 bed government hospital (100 pediatric beds)
- Chittagong Maa Shishu O General Hospital - 200 beds (all pediatric beds)
- Dhaka Shishu Hospital - 349 pediatric beds in Sher-E-Bangla section of Dhaka
- ICDDR,B – International Center for Diarrheal Diseases Research, Bangladesh

Details of Surveillance Activities:
Hospital-Based Surveillance:

Hospital-based surveillance is conducted through a network of seven hospitals including four hospitals in Dhaka, two hospitals in Chittagong (the second largest city in Bangladesh) and a large NGO-operated hospital in Mirzapur that serves a rural population of 400,000 people. Three of the seven hospitals that make up the network are pediatric hospitals. On average, hospital surveillance collects 4,500 blood cultures per year.

The hospitals participating in the surveillance network are diverse in location and in the populations they serve. Prior to PneumoADIP support, blood cultures were not routinely performed at six of the seven participating hospitals. This project provides clinical laboratories with the capacity to isolate \textit{S. pneumoniae} and other pathogens. Isolates are then sent to a central laboratory in Dhaka Shishu Hospital (reference laboratory) for confirmation, drug susceptibility testing and serotyping. Results of blood culture drug susceptibility testing are provided to clinicians at each of the hospitals, in real time, for use in clinical decision-making. The training and continuous quality control provided by the Dhaka Shishu Hospital reference laboratory to the hospitals within this network enhances the capacity of each laboratory to culture blood and cerebrospinal fluid specimens.

Urban, Population-Based Surveillance:

Kamalapur is an impoverished urban area located in the southeastern sector of Dhaka consisting of 40,000 households. This active population-based urban surveillance project utilizes a cohort of 5,000 households, each with at least one child under five years of age (about 22,500 people), approximating a birth cohort of about 675 children and 2,200 children less than two years of age.

Households are visited on a weekly basis by field research assistants who have been trained to query about whether any child less than five years of age is experiencing any of the symptoms relevant to the case definitions (including fever, cough, difficulty breathing, chest indrawing, stiff neck, and altered consciousness). For children meeting the case definition of pneumonia or sepsis, a chest radiograph and blood for culture are obtained at the local clinic. Treatment is provided to the child based on the diagnosis made by the medical officer. Information is recorded on a standardized case report form. Blood is sent to the Clinical Pathology Laboratory at ICDDR,B’s Dhaka hospital for culture. Pneumococcal isolates are then sent to Dhaka Shishu Hospital Microbiology Laboratory for serotyping.

Rural, Population-Based Surveillance:

Rural population-based surveillance is conducted in Mirzapur, a rural sub-district of Bangladesh, located about 60 km north of Dhaka. The birth, infant and child mortality rates (26/1000 population, 70/1000 live births and 100/1000 live births, respectively) of Mirzapur are similar to national averages.

Weekly household surveillance is conducted by 75 village health workers (VHWs) each serving a cluster of 1,200 people. The VHWs make household rounds to identify children with suspected pneumonia or meningitis and refer them to Kumudini Hospital, hold group meetings with mothers of young children, and encourage mothers to seek help from VHWs, if their children are sick and experiencing any signs and symptoms of meningitis or pneumonia. The
families in the surveillance area may also go directly to Kumudini Hospital. For children who visit Kumudini Hospital and meet the case definition of pneumonia or sepsis, a chest radiograph and a blood culture is obtained. Cerebrospinal fluid and blood are collected from patients meeting the meningitis case definition.

ICDDR, B – Summary of Main Findings

Data Collection Period: April 2004 – March 2007

Specimens and isolates:
- > 3,772 CSF specimens collected from seven hospitals and rural surveillance activities
- > 29,349 blood specimens collected from seven hospitals and rural and urban surveillance activities
- 335 pathogens isolated, of which 207 were *S. pneumoniae*, 111 *H. influenzae* and 17 *N. meningitidis*
- The specimens and isolates were collected from meningitis, pneumonia and sepsis cases and thus represent the broad spectrum of invasive bacterial illness in Bangladesh.
- Because pneumonia is more common among children than meningitis, more blood specimens were collected than CSF specimens. Therefore, significantly more bacterial isolates were obtained from blood than from CSF.

Yields:
- *S. pneumoniae* was the most common cause of bacterial meningitis in Bangladesh, followed by *H. influenzae* and *N. meningitidis*.
- The ~1 percent pneumococcal yield from blood and ~2 percent yield from CSF (by culture only) are similar to yields observed in other regions such as East Africa (see section reporting on the netSPEAR network)
- The bacterial isolation rate from CSF is one to five times higher than the isolation rate from blood, depending on the age group considered.
- Given the high rates of prior antibiotic use and infrequent bacteremia associated with pneumonia in Bangladesh, many cases cannot be identified by bacterial culture. Inferences of invasive pneumococcal disease based on culture alone are underestimates. Use of more sensitive diagnostic techniques such as latex agglutination or PCR in CSF leads to significantly higher yields.
- The prevalence of confirmed pneumococcal and Hi cases among patients with suspected meningitis, pneumonia and sepsis decreased with age: infants were more likely to have a pathogen identified from CSF or blood than older children.

Vaccine Serotypes:
- Serotype data collected by the Bangladesh network has improved our understanding of pneumococcal serotype distribution in this country and will allow local decision-makers to evaluate the utility of existing and upcoming pneumococcal conjugate vaccines (PCV) for their population.
- Serotypes 1, 2, 5, 12A, 14 and 45 were the most common serotypes detected and represent ~ 50 percent (82/165) of pneumococcal isolates from all Bangladesh surveillance activities. The licensed 7-valent PCV provides protection against 25.5 percent of isolated pneumococcal serotypes, while the 10-valent PCV would provide close to 50 percent coverage.
- Given the high incidence of pneumonia and pneumococcal disease in Bangladesh, the 7-valent PCV could prevent a large number of cases and deaths despite relatively low serotype coverage. Both 7-valent and 10-valent PCVs may become available through GAVI and would have a significant impact on child survival in Bangladesh.

Antibiotic Resistance:
- Pneumococcal resistance to cotrimoxazole and gentamicin was high, at 75 percent and > 89 percent, respectively.
- No resistance to penicillin was observed.
- Continued monitoring of antimicrobial resistance is important for prescribing physicians working in areas where empirical use of antimicrobial agents is common.
V.2 SAPNA - South Asian Pneumococcal Network Alliance (SAPNA)

Title: South Asian Pneumococcal Network Alliance (SAPNA)

Date Started: April 2004

Project Leaders:
Dr. Kurien Thomas – Co-Principal investigator for SAPNA; Christian Medical College, Vellore, India
Dr. Mark Steinhoff – Co-Principal investigator for SAPNA; Johns Hopkins Bloomberg School of Public Health
Dr. Andrew Pollard – Principal investigator for Patan Hospital, Katmandu, Nepal; Oxford University
Dr. Pushpa Raj Sharma – Principal investigator for Kanti Children’s Hospital, Katmandu, Nepal
Dr. Aparna Singh – coordinator, Kanti Children’s Hospital, Katmandu, Nepal
Dr. Nihal Abeysinghe – Principal investigator for Lady Ridgeway Hospital, Colombo, Sri Lanka
Dr. Andrew Pollard – Principal investigator for Patan Hospital, Katmandu, Nepal; Oxford University
Dr. Neelam Adhikari – local investigator, Patan Hospital, Katmandu, Nepal
Dr. Stephen Thorson – local investigator, Patan Hospital, Katmandu, Nepal

Coordinating Centre: International Clinical Epidemiology Network (INCLEN)

Countries: India, Nepal and Sri Lanka

Project Description: PneumoADIP funding has enabled the South Asian Pneumococcal Alliance (SAPNA) to initiate pneumococcal surveillance in Nepal and Sri Lanka and resume the work of a previously existing surveillance network in India, the Invasive Bacterial Infections Network (IBIS). SAPNA builds on the strength and experience of IBIS while PneumoADIP support promotes integration and coordination of SAPNA and IBIS activities.

IBIS provided preliminary national data on *H. influenzae* and *S. pneumoniae* disease in India, including prevalent pneumococcal serotypes by age and antimicrobial resistance trends. Based on this experience, it was decided that IBIS should be responsible for the development of locally appropriate clinical and laboratory protocols. PneumoADIP provides assistance to three IBIS network hospitals supported by the Indian Council of Medical Research (ICMR).

PneumoADIP funding links IBIS with additional surveillance sites in Nepal and Sri Lanka and has increased the number of participating hospitals from five to a total of eight. There are five hospitals in India, two in Nepal and one in Sri Lanka, including one of the world’s largest children’s hospitals, Lady Ridgeway Hospital in Colombo, Sri Lanka. The expanded surveillance network allows the close coordination and standardization of activities between the three countries, thereby improving the comparability of data across sites. Surveillance for invasive bacterial disease is improving our understanding of the disease epidemiology in the region and will serve as evidence for accelerated introduction of pneumococcal conjugate vaccines into South Asia.
Project Objectives:
- To generate local data in India, Sri Lanka, and Nepal on invasive pneumococcal disease, serotype distribution and antimicrobial resistance.
- To strengthen local capacity for national surveillance of vaccine preventable diseases.
- To assist the development of national policy regarding control of pneumococcal disease.

Participating Institutions:

Nepal:
- Tribhuvan University, Katmandu
- Ministry of Health, Nepal
- Patan Hospital, Katmandu
- Kanti Children’s Hospital, Katmandu

Sri Lanka:
- Ministry of Health, Sri Lanka
- Lady Ridgeway Hospital (LRH), Colombo

India:
- Christian Medical College (CMC) of Vellore
- King George Medical University (KG MU), Lucknow
- Government Medical College (GMC), Nagpur

Coordinating Center - project coordinators are based at the following institutions:
- Clinical Epidemiology Unit of Christian Medical College, Vellore, through the International Clinical Epidemiology Network (IN CLEN Trust)
- Johns Hopkins School of Public Health, Baltimore
- University of Oxford, England
SAPNA – Summary of Main Findings

Specimens and Isolates:
- >1,200 CSF specimens collected from six hospitals
- >5,620 blood specimens collected from six hospitals
- 129 pathogens isolated, of which 95 were *S. pneumoniae*

Data Collection Period:
- Nepal: November 2004 – April 2007
- India: April 2006 – April 2007

Yields*:
- Nepal: S. pneumoniae yield: 11.3% from CSF, 1.5% from blood
  - N. meningitidis yield: 0.2% from CSF, 0% from blood
  - H. influenzae yield: 0.8% from CSF, 0.1% from blood
- Sri Lanka: S. pneumoniae yield: 2.2% from CSF, 0.8% from blood
  - N. meningitidis yield: 0.2% from CSF, 0% from blood
  - H. influenzae yield: 1.6% from CSF, 0.8% from blood
- India: S. pneumoniae yield: 1.6% from CSF, 0.4% from blood
  - N. meningitidis yield: 0% from CSF and blood
  - H. influenzae yield: 0% from CSF and blood

Vaccine Serotypes:
- Nepal: Most common serotypes: 12A, 2, 16, 7F and 19B
  - 7-valent pneumococcal conjugate vaccine (PCV-7) and PCV-10 provide protection against 8.3% and 50% of pneumococcal serotypes among children under five, respectively
- Sri Lanka: Most common serotypes: 19F, 14 and 6B.
  - PCV-7 and PCV-10 provide protection against 63.6% of pneumococcal serotypes among children under five
- India: No serotype data available

Antibiotic Resistance:
- Nepal: Cotrimoxazole: 100% Penicillin: 100%
- Sri Lanka: Cotrimoxazole: 82% Penicillin: 0%
- India: No data available

Key Findings:
- Isolates from these sites are representative of the broad spectrum of pneumococcal disease, including pneumonia, meningitis and sepsis.
- As is typically observed, pathogens were isolated at higher rates from CSF than from blood. This is probably in part the result of prior treatment with antibiotics, which prevents the growth of organisms in blood cultures but to a much lesser degree in CSF. Antigen detection tests are also available only for CSF and enable identification of pathogens that did not grow in cultures.
- Inferences of invasive pneumococcal disease based on culture alone are underestimates. Use of more sensitive antigen detection diagnostic tests in CSF lead to significantly higher yields.
- The prevalence of confirmed pneumococcal and Hi cases among patients with suspected meningitis decreased with age: infants were the most likely to have a pathogen identified
from CSF.

- *S. pneumoniae* was more commonly identified than *H. influenzae* and *N. meningitidis* as the cause of bacterial meningitis in Nepal and India, but more sensitive tests were used for *S. pneumoniae*. In contrast, Hi was more frequently identified in meningitis cases in Sri Lanka.

- The serotype data collected by SAPNA are some of the first reported in Nepal and Sri Lanka and enable evaluation of the value of existing and upcoming pneumococcal conjugate vaccines (PCVs) for the first time in each of these countries.

- The evaluation of antimicrobial resistance in Sri Lanka uncovered previously unknown resistance of pneumococcal strains to cotrimoxazole and penicillin in hospital patients, resulting in changing the medical practice in all Sri Lankan hospitals from prescribing these antibiotics.

- Currently licensed PCV-7 may be appropriate for use in Sri Lanka, while a pneumococcal vaccine with broader serotype coverage may be preferable in Nepal.

- However, vaccines with relatively low serotype coverage can have a significant impact on morbidity and mortality in a setting where pneumococcal disease incidence is extremely high, as is likely to be the case in much of South Asia.

*Cases of *S. pneumoniae* were identified by culture, latex and Binax while cases of *H. influenzae* and *N. meningitidis* were identified by culture only.*
V.3 International Emerging Infections Program (IEIP), Thailand

Title: Population-Based Surveillance for Pneumonia with Detection of *S. pneumoniae*

Date Started: May 2005

Project Leaders:
Dr. Leonard Peruski - Chief, Laboratory Section, International Emerging Infections Program, Thailand MOPH-U.S. CDC Collaboration, Thailand  
Dr. Henry Baggett - Chief, Epidemiology Section, International Emerging Infections Program, Thailand MOPH-U.S. CDC Collaboration, Thailand  
Dr. Somsak Thamthitiwat - Senior Scientist, International Emerging Infections Program, Thailand MOPH-U.S. CDC Collaboration, Thailand  
Dr. Somrak Chantra - Deputy Director, Sa Kaeo Provincial Hospital, Sa Kaeo Province, Thailand  
Dr. Peera Areerat - Deputy Provincial Chief Medical Officer, Sa Kaeo Province, Thailand  
Dr. Supamit Chunsuttiwat - Senior Scientist, Department of Disease Control, Ministry of Public Health, Thailand  
Dr. Kumnuan Ungchusak - Director, Bureau of Epidemiology, Ministry of Public Health, Thailand  
Dr. Susan Maloney - Director, International Emerging Infections Program, Thailand MOPH-U.S. CDC Collaboration, Thailand

Coordinating Centre: International Emerging Infections Program, Thai MOPH-U.S. (Centers for Disease Control Collaboration)

Country: Thailand

Project Description: Consistent with PneumoADIP’s strategic approach of building on existing capacity, the primary objective of this project was to add microbiologic diagnostic capability to an ongoing, population-based surveillance system for pneumonia in both children and adults. The Thailand International Emerging Infections Program (IEIP) began conducting active, population-based surveillance for hospitalized pneumonia in two provinces with a catchment area of 1.2 million persons approximately five years ago. Surveillance was initiated first in the eastern province of Sa Kaeo, which borders Cambodia, in August 2002. A year later, in July of 2003, surveillance was established in the northeastern province of Nakhon Phanom, which borders Laos. With the support of PneumoADIP, in May 2005, IEIP completed key laboratory upgrades, such as the installation of state-of-the-art automated blood culture systems, and began routine blood culturing among hospitalized patients with suspected pneumonia and sepsis. Currently, the Sa Kaeo surveillance laboratory supports all eight public hospitals in the province while the laboratory in Nakhon Phanom province provides support to all twelve of its public hospitals. Results from these provincial laboratories are confirmed by an extensive quality control network of reference institutes affiliated with the Thailand MOPH. Approximately 10,000 blood cultures have been performed annually on specimens from patients with pneumonia, sepsis, and other severe diseases from both of these sites combined. Linkages with local providers have ensured that laboratory results are quickly made available to clinicians to inform real-time decisions about patient care.
Project Objectives:

- To add microbiologic diagnostic capability to ongoing population-based surveillance for hospitalized pneumonia and sepsis in patients of all ages in Sakaeo and Nakhon Phanom provinces of Thailand.

- To improve clinical care by developing laboratory capacity to detect and identify bacterial pathogens, including pneumococcus, in blood at all acute care hospitals in each province.

- To estimate the incidence and burden of pneumonia and bacteremia among pediatric and adult patients and to estimate incidence of invasive pneumococcal disease.

- To describe the serotypes and antimicrobial resistance patterns of invasive pneumococcal isolates in the two provinces with active surveillance in place.

Participating Institutions:

Currently Active Sites:

- Ministry of Public Health (MOPH), Kingdom of Thailand
  - Sa Kaeo Provincial Health Office, Sa Kaeo, Thailand
  - Nakhon Phanom Provincial Health Office, Nakhon Phanom, Thailand
  - Bureau of Epidemiology, Nonthaburi, Thailand
  - Department of Disease Control, Nonthaburi, Thailand
  - National Institute of Health, Nonthaburi, Thailand
  - Bamrasnaradura Infectious Disease Institute, Nonthaburi, Thailand
  - National Tuberculosis Reference Center, Bangkok, Thailand

- Centers for Disease Control and Prevention (US - CDC)
  - International Emerging Infections Program (IEIP), Nonthaburi, Thailand
  - National Center for Preparedness, Detection and Control of Infectious Diseases, Atlanta, Georgia
  - National Center for Immunization and Respiratory Diseases, Atlanta, Georgia
IEIP – Summary of Main Findings

Data Collection Period: May 2005 – December 2006

<table>
<thead>
<tr>
<th>Specimens and isolates</th>
<th>Total</th>
<th>Children less than 5 years old</th>
<th>Children and adults 5 years of age and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of blood specimens collected</td>
<td>16,273</td>
<td>5,035</td>
<td>11,238</td>
</tr>
<tr>
<td>Number of pathogens isolated from blood</td>
<td>2,317</td>
<td>613</td>
<td>1,704</td>
</tr>
<tr>
<td>Number of S. pneumoniae isolates obtained from blood</td>
<td>45</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>Number of H. influenzae isolates obtained from blood</td>
<td>11</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

- The blood specimens were collected from pediatric and adult patients in all 20 hospitals in two provinces participating in surveillance for hospitalized pneumonia
- Many agents uncommonly identified in blood cultures from western nations were found, including *Burkholderia pseudomallei*, *Mycobacterium tuberculosis*, and nontyphoidal *Salmonella* species, suggesting that these agents play significant roles in community-acquired pneumonia and sepsis in this population

<table>
<thead>
<tr>
<th>Yields</th>
<th>Total</th>
<th>Children less than 5 years old</th>
<th>Children and adults 5 years of age and older</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em> isolation rate (%)</td>
<td>0.3</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td><em>H. influenzae</em> isolation rate (%)</td>
<td>0.07</td>
<td>0.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- The 0.3% isolation rate of *S. pneumoniae* from blood is slightly lower than the 0.5-1.3% yield from blood observed in most of the other PneumoADIP-funded sites
- *H. influenzae* isolation rates are also lower compared to other surveillance sites
- The relatively low isolation rates of *S. pneumoniae* and *H. influenzae* may be related to the high prevalence (~33 percent) of antibiotic use before blood culture

Vaccine Serotypes:
- Serotypes 1, 6B, and 23F represent 34 percent of isolated pneumococcal serotypes.
- The serotypes included the currently licensed heptavalent pneumococcal conjugate vaccine (PCV7) cover 58% of pneumococcal isolates found in blood specimens from children and adults with pneumonia, sepsis or other severe disease.
- Prior to vaccine introduction, estimates of vaccine serotype coverage can provide
estimates of the potential impact of PCV7 or other pneumococcal conjugate vaccine.

**Antibiotic Resistance:**
- Around 50% of serotyped isolates had reduced susceptibility to penicillin, cotrimoxazole, or tetracycline
- Continued monitoring of antimicrobial resistance is important for prescribing physicians working in areas where empirical use of antimicrobial agents is common

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**V.4 Small Grant Projects: South-East Asia Region (SEARO)**

**V.4.1 Bangladesh – Follow-up of pneumococcal meningitis cases to determine long-term impact (Dhaka Shishu (Children’s) Hospital, Johns Hopkins Bloomberg School of Public Health and partners)**

**Principal Investigator:**
Dr. Samir Saha
Dhaka Shishu Children’s Hospital,
Dhaka 1207, Bangladesh

**Summary:**
Dhaka Shishu Hospital conducted two cohort studies, one retrospective and one prospective, involving a total of 110 children to estimate the frequency and extent of neurological impairment in children and the risk of developing sequelae following *S. pneumoniae* meningitis.

**Goals and Objectives:**
1. To estimate the short- and long-term morbidity and mortality following discharge of pneumococcal meningitis patients from hospital
2. To determine the predominant type of sequelae and their relation with clinical presentations and duration of illness prior to hospital admission.
3. To elucidate the impact of the infecting organism’s antimicrobial susceptibility and treatment on the outcome of the disease.

**Secondary objectives:**
To assess the social and economic impact of long term morbidity associated with pneumococcal meningitis on the households.

**Status and Results:**
Of 1,538 children screened prospectively during the study period, 372 had suspected meningitis and 70 were confirmed as pneumococcal. Fifty-one of these 70 were followed for 30 to 40 days after discharge. Seventeen had hearing loss (33 percent), four had vision loss (eight percent), 21 had mental delay (41 percent), and 25 had psychomotor delays (49 percent). In addition, 70 children who had meningitis were located for the retrospective study. Fifty-one were followed-up between 6-18 months after discharge: nine had hearing loss (18 percent), eight had vision loss (four percent), 21 had mental delay (41 percent), and 18 had psychomotor delays (35 percent). This project is now complete.
V.4.2 India – Risk factors and consequences of \textit{S. pneumoniae} colonization in the nasopharynx of infants in Vellore, India (Christian Medical College)

**Principal Investigator:**
Dr. Sara Bhattacharji
Christian Medical College
Vellore, Tamil Nadu, India

**Summary:**
A community-based longitudinal study in urban Vellore was established to collect nasopharyngeal specimens from volunteers at regular intervals and isolate \textit{S. pneumoniae} from these specimens. Outputs of the project include information on the risk factors of pneumococcal colonization and the morbidity and growth consequences associated with colonization.

**Goals and Objectives:**
The primary goal of the project was to implement a community-based prospective study of infant pneumococcal colonization and obtain information on the serotype distribution of colonizing pneumococci, individual and environmental risk factors for carriage and morbidity and growth consequences carriage.

**Status and Results:**
This study is still ongoing. Results are not available at this time.

V.4.3 Indonesia – Pneumococcal Serotype Distribution in children with Pneumonia in Indonesia (a collaborative project of The University of Colorado Health Sciences Center and The Children’s Hospital, Denver, Colorado, USA and RS Hasan Sadikin General Hospital and Padjadjaran University, Bandung, Indonesia)

**Principal Investigators:**
Dr. Eric A.F. Simoes
The University of Colorado Health Sciences Center and The Children’s Hospital
Denver, Colorado, USA

Dr. Cissy Kartasasmita
RS Hasan Sadikin General Hospital and Padjadjaran University
Bandung, Indonesia

Dr. Ron Dagan
Soroka University Medical Center and the Faculty for Health Sciences
BenGurion University of the Negev
Beer-Sheva, Israel

**Summary:**
Study sites were established in West Java, Indonesia to obtain information on antibiotic resistance and serotype distribution of pneumococcal isolates collected during a cotrimoxazole trial and a newborn nasopharyngeal colonization study. A prospective case-control study was also carried out to determine which pneumococcal serotypes were frequently found in the nasopharynx of children with pneumonia.
Goals and Objectives:
The primary goal of the project was to determine the most common pneumococcal serotypes carried in the nasopharynx of Indonesian children less than the age of five years with non-severe pneumonia.

Primary Objectives:
1. To determine pneumococcal serotypes carried in the nasopharynx of over 1,000 children with WHO-defined pneumonia.
2. To compare the serotypes of these children with serotypes from control children who have no respiratory disease.
3. In the context of a cotrimoxazole therapy trial (a randomized double blind placebo controlled trial of three days vs. five days of oral therapy) to determine the serotype of pneumococci colonizing the nasopharynx in relationship to the antibiotic resistance pattern and outcomes.

Status and Results:
This project is currently ongoing.
Appendix VI – Western Pacific Region (WPRO)
Appendix VI lists all PneumoADIP-supported projects including small grants in the Western Pacific Region (WPRO). The section also includes a brief list of non-PneumoADIP activities conducted in the WPRO.

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<tr>
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<td>Identify and control emerging infections via surveillance, research, training and outbreak support (not yet started)</td>
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<tr>
<td></td>
<td>Determine the proportion of hospitalized pneumonia cases in children associated with 7-valent type pneumococcal disease</td>
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</tbody>
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*Please contact PneumoADIP at pneuadip@jhsph.edu to submit any additional research activities in your country or region.
VI.1 Overview of International Vaccine Institute (IVI) – Viet Nam

**Title:** Surveillance for Invasive Pneumococcal Disease in Hospitalized Children, Khanh Hoa Province, Viet Nam – A Pilot Study

**Date Started:** April 2005

**Project Leaders:**
- Dr. Dang Duc Anh, National Institute of Hygiene and Epidemiology
- Drs. Paul E. Kilgore, Nyambat Batmunkh, and Luis Jodar, Division of Translational Research, International Vaccine Institute, Seoul, Korea
- Dr. Le Huu Tho, Khanh Hoa Health Service, Nha Trang, Viet Nam
- Dr. Mary Slack, Respiratory & Systemic Infection Laboratory, Health Protection Agency, London, UK
- Dr. Chong Chia Yin, Department of Infectious Diseases, KK Women's and Children's Hospital, Singapore

**Coordinating Center:** Division of Translational Research, International Vaccine Institute, Seoul, Korea

**Country:** Viet Nam

**Project Description:**
Viet Nam is a country of 82 million in Southeast Asia with a large population of children less than five years of age who suffer from a substantial burden of acute respiratory infections documented through national syndromic surveillance. Despite these data, there are limited data on the burden of invasive pneumococcal disease among children or adults in Viet Nam. The National Institute of Hygiene and Epidemiology, located in Hanoi, Viet Nam, is a leading national reference center for public health programs and research. Together with the International Vaccine Institute (IVI), located in Seoul, Korea as well as the Respiratory & Systemic Infection Laboratory, Health Protection Agency, London UK and the KK Women’s and Children’s Hospital in Singapore, local investigators led by the Khanh Hoa Health Service initiated the first prospective study of invasive pneumococcal disease encompassing detection of pneumonia, meningitis and sepsis. This pilot study was initiated in April 2005 and continued through August 2006. In this study, children with severe disease who were hospitalized in the provincial-level hospital, Khanh Hoa General Hospital (located in Nha Trang), were enrolled using standardized screening criteria and each underwent collection of blood and CSF as appropriate to their condition. Because of the hospital catchment area that includes the city of Nha Trang and outlying districts in semi-mountainous areas, this study enrolled children living in both urban and rural environments. Access to health-care for the Nha Trang population is very good due to the presence of national child health care program provided by the national government and a well-developed transportation infrastructure. The IVI, HPA and KK Women’s and Children’s Hospital have provided technical assistance to Khanh Hoa Health Service and Khanh Hoa General Hospital staff in the areas of epidemiology, microbiology and pediatric infectious diseases to build capacity for systematically and routinely isolate *S. pneumoniae* and other causes of invasive bacterial disease from severely ill children.
Project Objectives:

Primary Objectives:
- Identify hospitalized children with invasive pneumococcal disease (IPD) including meningitis, bacteremia (with or without a focus), sepsis, pneumonia and other clinical manifestations using classical microbiologic culture methods.
- Describe clinical & epidemiologic characteristics among hospitalized children with IPD including spectrum of clinical complications and/or death.
- Characterize invasive *S. pneumoniae* strains by serogroup and serotype contained in pneumococcal conjugate vaccines currently available or in development.
- Describe antimicrobial susceptibility profiles for invasive isolates of *S. pneumoniae* found among hospitalized children.

Secondary Objectives:
- Collaborate directly with regional and central offices of the WHO to utilize pneumococcal disease burden data for estimation of the global pneumococcal disease burden
- Identify key national, regional and sub-regional opinion leaders with expertise in bacterial diseases to maximize utility of information obtained in surveillance system
- Establish training opportunities using sub-regional linkages that will support establishment of high-quality national pneumococcal reference laboratories
- Conduct quality assurance/quality control testing to ensure accurate and consistent identification, serotyping and MIC testing for pneumococcal isolates

Participating Institutions:
- Division of Translational Research and the Division of Laboratory Sciences, International Vaccine Institute, Seoul, Republic of Korea
- National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam
- Office of Health Research, Khanh Hoa Provincial Health Service, Nha Trang, Viet Nam
- Respiratory & Systemic Infection Laboratory, Centre for Infections, Health Protection Agency, London, United Kingdom
- Division of Infectious Diseases, KK Women’s and Children’s Hospital, Singapore
IVI – Summary of Main Findings

Data Collection Period: April 2005 –August 2006

Specimens and isolates:
- 987 blood and 26 CSF specimens collected from Khanh Hoa General Hospital.
- Seven culture-positive blood specimens: one *S. pneumoniae*, two *H. influenzae*, one *S. typhi*, two *S. aureus* and one *E. cloacae.*
- Four PCR-positive blood specimens: two *S. pneumoniae* and two *H. influenzae.*
- Four culture-positive CSF specimens for *H. influenzae.*
- Two PCR-positive CSF specimens for *S. pneumoniae.*

Yields:
- 0.0% and 15.4% culture isolation rate in CSF for Sp and Hi, respectively.
- 7.7% and 15.4% overall identification rate including culture, Binax and PCR for Sp and Hi in CSF, respectively.
- 0.1% and 0.3% culture isolation rate in blood for Sp and Hi, respectively.
- 1.5% and 0.4% overall identification rate including culture, Binax and isolation rate for Sp and Hi, respectively in blood.
- 29% of patients reported prior antibiotic use.

Key findings:
- Laboratory capacity-strengthening using standardized training programs, implementation of standard operating procedures and external quality assurance (proficiency testing) proved to be critical in supporting local laboratory detection of invasive bacterial pathogens.
- With antimicrobial agents (including cephalosporins and other agents) available to parents without prescription and limited investment in health facility diagnostic laboratories, non-judicious use of antimicrobials remains a continuing threat in Khanh Hoa Province.
- Provincial-level hospital clinical microbiology laboratory staff easily implemented pilot diagnostic testing using the Binax pneumococcal antigen detection test.
- Improved laboratory identification of invasive bacterial pathogens also provided a new diagnostic resource as well as positive feedback and encouragement to clinicians who previously had resorted to empiric use of expensive, broad-spectrum antimicrobial agents.
- Data from this pilot study and previous population-based studies of invasive bacterial meningitis in Hanoi, Viet Nam, suggest that use of non-culture based diagnostic tests add substantial value to surveillance and disease burden studies by increasing identification of clinically severe invasive pneumococcal disease in hospitalized children.
- The Khanh Hoa Health Service and districts of Nha Trang and Ninh Hoa have enumerated the population residing in 33 communes using household visits. The most recent census in 2006 continues to maintain detailed population data in a computerized demographic surveillance system. This system constitutes a critical component of the vaccine trial field site infrastructure first established in 1996.
- Among children less than five years of age living in Nha Trang district, the estimated incidence rate of invasive pneumococcal disease was 48.7/100,000 (95% confidence interval [CI], 27.9 - 85.1) and Hib disease was 22.9/100,000 (95% CI, 10.3 - 51.2).
VI.2 Mongolia Surveillance Network

Title: Bacterial Meningitis and Pneumonia Surveillance Network

Start Date: September 2007

Project Leader:
Dr. Prof. P. Nymadawa, National Center for Communicable Diseases
Dr. Jamsran Mendsaikhan

Coordinating Center: National Center for Communicable Diseases

Country: Mongolia

Project Description: With funding from the WHO, surveillance for meningitis started in February 2002 in Ulaanbaatar and was conducted in six hospitals including four district hospitals and two national hospitals. From February 2002 to 2006, 295 cases of bacterial meningitis were confirmed in Ulaanbaatar. *H. influenzae* type b was the main organism isolated from 65 cases of meningitis. The second most common organism was *S. pneumoniae* with 26 cases. The unexpectedly high results generated by these data prompted the Ministry of Health of Mongolia to introduce the Hib vaccine. After introduction of the vaccine, the overall number of meningitis cases fell dramatically. Funding for this surveillance was initially provided by the WHO; however, funding stopped in 2005 and hospitals are supporting this surveillance. PneumoADIP recognized the importance of Mongolia as an early adopter of vaccines and proposed using the existing surveillance infrastructure to establish pneumonia surveillance in Ulaanbaatar. Over 3,000 children are hospitalized with pneumonia in Ulaanbaatar each year. Health statistics show that acute respiratory infections are the leading cause of mortality and morbidity of children less than five years of age, accounting for 51 percent of hospital admissions and 31 percent of deaths.

Objectives:
- Enhance capacity to isolate and characterize *S. pneumoniae* in Mongolia for documenting the contribution of pneumococci as causes of severe disease in children.
- Provide local information on the most common serotypes causing disease and antimicrobial resistance patterns.
- Continue to monitor the impact of Hib vaccine introduction in Mongolia.

Participating Institutions:
- Ministry of Health, Mongolia
- National Center for Communicable Disease (NCCD)
- Maternal and Child Research Center (MCRC)
- Songinokhairkhan district hospital (SDH)
- Bayanzurkh district hospital (BDH)
- Sukhbaatar district hospital (SDH)
- Khan-Uul district hospital (KDH)
- Western Pacific Regional Office, WHO (WPRO)
- WR office, Mongolia

Summary of Mongolian Data
Surveillance was initiated in September 2007, but no data is available yet.
VI.3 Small Grant Projects: Western Pacific Region (WPRO)

VI.3.1 Fiji – A cohort study to assess quality of life in young Fijian children with a history of bacterial meningitis (a collaborative project between the University of Melbourne, the Fiji Ministry of Health (MoH), and the Fiji School of Medicine (FSM))

Principal Investigator:
Dr. Samantha Colquhoun
University of Melbourne
Melbourne, Victoria, Australia

Summary:
A cohort study was conducted to assess quality of life in young Fijian children (aged two to five years) with a history of bacterial meningitis. The children in this study all resided in the Central Medical Division of Viti Levu, Fiji.

Primary objective:
1. To document the quality of life of young children with a history of bacterial meningitis in Fiji, with specific attention to children with pneumococcal meningitis.

Secondary objectives:
1. To provide data to enhance the understanding of the impact of this disease in developing countries, and to support future economic analyses of vaccine introduction.
2. To develop generic methods to evaluate the long term morbidity associated with bacterial meningitis in developing countries.

Status and Results:
This study enrolled 37 cases with a history of bacterial meningitis and 148 controls. Results suggest that the quality of life of children with a history of bacterial meningitis in Fiji is diminished compared to healthy peers. Children with pneumococcal meningitis had more severe sequelae than did those with other types of bacterial meningitis. The study has been completed, and further assessments of the neurological consequences of meningitis in this population are ongoing.

VI.3.2 Fiji – Prospective meningitis burden of disease study and rapid assessment of neurological outcomes in children in Fiji: Part 2, extension of laboratory work (Fiji Pneumococcal Project (FiPP) is a collaborative project between the University of Melbourne, the Fiji Ministry of Health (MoH), and the Fiji School of Medicine (FSM))

Principal Investigator:
Dr. Fiona Russell
University of Melbourne
Melbourne, Victoria, Australia

Summary:
Prospective surveillance was implemented at the Colonial War Memorial Hospital in Viti Levu, Fiji, to monitor trends in bacterial meningitis in children aged one month to less than five years old. Outputs of the project include information on number of specimens and pneumococcal
isolates collected, etiologic fraction, antibiotic resistance and serotype distribution of pneumococcal isolates associated with meningitis.

**Primary objectives:**
1. To develop a simple, reproducible system for estimating the outcome of pneumococcal meningitis in a developing country.
2. To determine, in a developing country where universal Hib vaccination is used and meningococcus is rare, the probability that culture-negative, purulent meningitis is due to pneumococcus.
3. To determine the etiology of meningitis in children aged one month to less than five years in the Central Medical division, Fiji.

**Secondary objectives:**
1. To document, over a two year period, the burden of pneumococcal meningitis in terms of short- and long-term morbidity and mortality in children one month to less than five years of age in the Central Medical Division of Vitu Levu.
2. To document the antibiotic susceptibility patterns and serotype distributions of organisms isolated.
3. To document the clinical management of bacterial meningitis in Fiji and the cost involved.

**Status and Results:**
This study is ongoing. To date, 61 children have been enrolled and 50 CSF and 60 blood specimens have been obtained with a total of twenty isolates (eleven from CSF and nine from blood). Fifteen of 72 children who were followed up were found to have neurological deficits.

**VI.3.3 Viet Nam – Socio-behavioral study and healthcare utilization survey of community-acquired pneumonia, meningitis, and sepsis in children of an urban and rural community in Viet Nam (Khanh Hoa Health Service)**

**Principal Investigator:**
Dr. Dang Duc Anh
National Institute for Hygiene and Epidemiology
Hanoi, Viet Nam

**Summary:**
The National Institute of Hygiene and Epidemiology (NIHE) and Khanh Hoa Health Service (KHHS) designed and implemented a study to describe health-care seeking behaviors and health care utilization patterns in one urban and one rural community in Khanh Hoa Province, Viet Nam, based on a socio-behavioral survey of parents of children with pneumonia, meningitis or sepsis.

**Goals and Objectives:**
1. To describe the health-seeking behaviors of rural and urban populations for pneumococcal disease and associated symptoms in children less than five years in Khanh Hoa Province Viet Nam.
2. To assess patterns of healthcare utilization among rural and urban residents of Khanh Hoa Province Viet Nam for pneumococcal disease and associated symptoms in children less than five years of age.
3. To describe the extent to which measurement of disease outcomes may be modified by health-care seeking behaviors and patterns of healthcare utilization.
4. To conduct a comparative analysis of healthcare seeking behaviors and patterns of health-care utilization between urban and rural residents of Khanh Hoa Province Viet Nam.

Status and Results:
This study is currently underway. Standard operating procedures and case report forms have been drafted and data collection has begun.

VI.3.4 Viet Nam – Cost-of-illness associated with invasive pneumococcal diseases in children, Khanh Hoa Province, Viet Nam (Khanh Hoa Provincial Public Health Service)

Principal Investigator:
Dr. Dang Duc Anh
National Institute for Hygiene and Epidemiology
Hanoi, Viet Nam

Summary:
This study collected information on the treatment costs, direct costs and indirect costs of hospitalized and outpatient invasive pneumococcal disease in children in Viet Nam.

Goals and Objectives:
1. To estimate of treatment costs (both private and public costs) associated with hospitalizations for laboratory-confirmed invasive pneumococcal meningitis, pneumonia and sepsis.
2. To estimate indirect costs associated with hospitalizations laboratory-confirmed invasive pneumococcal meningitis, pneumonia and sepsis.
3. To estimate direct costs associated with hospital laboratory-confirmed invasive pneumococcal meningitis, pneumonia and sepsis.
4. To estimate costs-of-illness for children who present to and are treated as outpatients for laboratory confirmed pneumococcal bacteremia in the emergency department of Khanh Hoa General Hospital.

Status and Results:
This study is currently underway. Standard operating procedures and case report forms have been drafted and data collection has begun.
VI.3.5 Viet Nam – A Retrospective Analysis of Childhood Pneumonia Hospitalizations, Nha Trang, Viet Nam (Khanh Hoa Provincial Public Health Service)

Principal Investigator:
Dr. Dang Duc Anh
National Institute for Hygiene and Epidemiology
Hanoi, Viet Nam

Background:
The National Institute of Hygiene and Epidemiology (NIHE) and Khanh Hoa Health Service (KHHS) will be responsible for conducting a retrospective medical record review to describe the distribution of clinical severity for pneumonia in hospitalized children less than five years of age.

Goals and Objectives:
1. To estimate number of hospitalized cases with pneumonia among children less than five years of age.
2. To describe the distribution of patients with clinical pneumonia by age, sex, residence and month.
3. To describe the range of clinical presentations (from mild to severe signs and symptoms) for pneumonia in hospitalized children less than five years of age.
4. To describe the patterns of laboratory diagnostic procedures for patients with pneumonia.
5. To describe the types, duration and cost associated with medical treatment for patients with pneumonia.

Status:
Study is in progress.
VI.4 Summary of other key research from WPRO

VI.4.1 Clinical Trial – Philippines — ARIVAC

The ARIVAC Effectiveness study is the only large-scale population-based pneumococcal conjugate vaccine study in Asia. It was conducted on the island of Bohol, in central Philippines from 2000 to 2004. The product used was an unlicensed 11-valent pneumococcal conjugate vaccine developed by Aventis Pasteur (Sanofi-Aventis). The trial results are important for the pneumococcus vaccine field, even though the vaccine formulation is not expected to be commercialized.

A cohort of over 11,000 infants was enrolled during the trial. The primary outcome of the trial was vaccine efficacy against the first episode of culture-confirmed pneumonia. Secondary outcomes included vaccine efficacy against the first episode of WHO-defined clinical pneumonia and invasive pneumococcal disease. Other secondary outcomes included looking at vaccine immunogenicity and safety.

Results of this study are not published; however, some preliminary results indicate that the vaccine showed protection against radiologically-confirmed pneumonia in children less than two years old.

VI.4.2 Ancillary study

There are two main activities that PneumoADIP supports:
1. Further validation of X-ray classification of pneumonia.

In Activity One, a radiologist will be subcontracted to interpret the chest x-rays according to the WHO standard definitions for use in pneumonia vaccine trials. The radiologist is blinded to the vaccination of the children during the reading.

In Activity Two, a pilot study will be conducted to analyze the use of serologic markers (procalcitonin) in the likely diagnosis of bacterial pneumonia. Though there have been a number of reports evaluating the use of procalcitonin in the diagnosis of bacterial pneumonia, earlier studies did not have the advantage of evaluating the test in samples collected from a vaccine trial where the value of the test in identifying cases of pneumonia prevented by vaccination could be assessed.

A manuscript has been drafted and is under review. We will have preliminary results as they become available.
Appendix VII – Case Definitions Flow Chart

Case definitions used by surveillance networks representing East Africa, West Africa, South Asia and Southeast Asia regions were discussed at the PneumoADIP Investigators’ Meeting held in Mombasa, Kenya in September 2003. Creating standardized case definitions for pneumococcal and Hib disease surveillance was one of the primary objectives of PneumoADIP-funded surveillance. This process started with the request for proposals which required case definitions for pneumonia, meningitis, and sepsis or severe disease. PneumoADIP compiled all of these definitions as well as definitions from other sources including WHO, IMCI, AFRO-PBM into a summary document prior to the September 2003 meeting. At this meeting, consensus was reached on case definitions to be used for data reporting and analysis. The case definitions developed at this meeting were subsequently adjusted to better meet data analysis needs. These definitions are for use in data reporting and analysis, and are not intended to be applied to subject enrollment or clinical case management. Standard definitions and reporting allow rigorous comparison of data between countries and over time within countries.
Tachypnea
- > 50 breaths/min if child is 2 to < 12 months
- > 40 breaths/min if child is 12 months to 5 years

Pneumonia Danger Signs
- Central cyanosis
- Inability to breastfeed or drink
- Vomiting everything
- Prostration/lethargy
- Severe respiratory distress/poor respiratory effort

Indrawing
Difficulty breathing with at least one of the following:
- Supracostal recession
- Subcostal recession
- Subternal recession
- Intercostal recession

CXR Confirmation
Chest radiograph performed and read to have an infiltrate consistent with pneumonia (using the WHO standardized definition for primary endpoint pneumonia — "A dense fluffy consolidation (alveolar infiltrate) of a portion of a lobe or entire lung. This often contains air bronchograms, and may be associated with a pleural effusion.")
**Very Severe Disease Clinical Syndrome**

Presence of at least two danger signs without pneumonia clinical syndrome.

**Danger Signs**
- Inability to breastfeed or drink
- Vomiting everything
- Convulsions
- Prostration/lethargy
- Severe malnutrition
- Hypothermia (≤ 36°C)

Yes:
- Very Severe Disease

No:
- Isolation of bacteria from blood or another normally sterile fluid

Yes:
- Bacteremia

No:
- Other