From 19-20 March 2012, 181 people from 21 countries discussed the strategies needed to prevent and control meningococcal meningitis in Latin America and the Caribbean. Vaccines were at the top of the agenda.

The development of advanced vaccine technologies over the past 20 years has enabled countries to dramatically reduce the burden of meningococcal disease. Conjugate vaccines can now be effectively and safely used in both infants and adolescents, with nearly immediate effect against several of the most common serogroups of meningitis.

Yet major challenges remain, based on the biology of the bacterium itself. Just as a chameleon changes the color of its coat, the meningococcal bacterium can switch its capsular cover, evading immune defenses.

Perhaps most importantly, there is not yet a licensed, broadly acting and long duration vaccine for meningococcus Group B, which predominates in many countries of Latin America and other world regions. Researchers anticipate that advanced investigational vaccines for group B will soon yield new tools in the fight against meningococcal disease.

Although vaccines against four important serogroups are available, and a vaccine against serogroup B is on the horizon, countries still lack critical epidemiological information needed to evaluate and implement vaccine policy for the disease. Yet, countries still lack critical epidemiological information needed to evaluate and implement vaccine policy for the disease.

The Symposium elucidated these challenges and more, advancing the fight against an important and deadly vaccine-preventable disease.
Meningococcal disease is relatively rare but can be absolutely devastating. Untreated, it may cause death or long-term disability in less than 24 hours. Even when treated, the fatality rate can be 10-to-20 percent, and a similar proportion of survivors suffer severe long-term consequences, such as brain damage, hearing loss or limb amputations.

The World Health Organization estimates that 500,000 cases and 50,000 deaths of meningococcal disease occur annually each year. However, meningococcal meningitis can be prevented through vaccination.

The First Regional Meningococcal Symposium for Latin America and the Caribbean brought together the best minds and top experts on meningococcal disease globally and in the Americas, providing a comprehensive and detailed picture of the opportunities and challenges in preventing and controlling the disease, including new data on disease incidence and cost.

At the Symposium, Dr. Marco Aurélio Sáfadi, Head of the Pediatric Infectious Disease Division at São Luiz Hospital, São Paulo, Brazil, reported results from the first major study of meningococcal disease in the region. Reviewing the literature, they found reports of 45,000 cases from 1980 to 2011. Background incidence rates can range from less than 0.1/100,000 inhabitants to 1.8/100,000. Furthermore, “One out of every five people with the disease in Latin America dies” Sáfadi reported.

Dr. José Cassio de Moraes, Faculdade de Ciências Médicas da Santa Casa de São Paulo, Brazil noted that disease rates during outbreaks in the region have reached as high as 43/100,000 for the overall population, with even higher rates among infants.

The costs associated with the disease are also high. Dr. Dagna Constenla of the International Vaccine Access Center at Johns Hopkins University Bloomberg School of Public Health found that costs per patient during a period of endemic disease range from about US$4,500 to more than US$6,000. During outbreaks, costs can easily reach US$16,000 per patient, as urgent efforts are launched to prevent the spread of disease.

Scientists explained the biology behind Neisseria meningitidis, which enters through the nose and throat, and is usually carried asymptotically by about 10 percent of the population. In rare cases, the bacteria not only colonize the nasopharyngeal area but also invade the bloodstream. Speakers elaborated on the molecular mechanisms behind this process, and the human immune response to it. They described a bacteria species of enormous diversity and variability, able to change and recreate itself, nimbly avoiding human immune defenses.

The dynamic nature of the bacterium’s genome has presented tough challenges for vaccine development. Vaccines must be able to protect against one or more of five major serotypes, and be prepared to address rapid changes in serogroups within a population.

“The dynamic nature of the bacterium’s genome has presented tough challenges for vaccine development.”

– Dagna Constenla of the International Vaccine Access Center at Johns Hopkins University Bloomberg School of Public Health
Yet, vaccines have succeeded in greatly reducing disease in many of the world’s countries. Success has come most recently to countries of Africa’s Meningitis Belt, where the disease takes its highest toll. Significantly, experience in a number of countries has shown that high levels of coverage and vaccination of both infants (who suffer the main burden of disease) and adolescents (the main carriers) can reduce carriage and engender herd immunity.

However, at least one outstanding challenge in vaccine development remains, and that is broadly acting, long-duration vaccines against serogroup B. Group B is a major problem globally and in Latin America. However, unlike the other serogroups, its capsular proteins fail to elicit a strong immune response. Thus, researchers have had to develop alternative vaccine approaches.

Today, there is a growing pipeline of investigational group B vaccines, including by researchers in Brazil and Cuba, as well as by Pfizer and Novartis.

Yet, huge gaps remain in the information needed to set policies for vaccine introduction. And, at this time, Brazil and Cuba are the only countries in the region that include meningococcal vaccines in their national immunization schedules.

Dr. Julio Vazquez, National Institute of Health Carlos III, Spain noted several areas in which more and better information is needed, including the age distribution of clinical cases; serotype and subserotype information; and the impact of vaccines on carriage. At the conclusion of the Symposium, Dr. de Quadros urged participants to “move ahead, taking these messages about meningitis forward to other individuals that will also have a main role in this fight against vaccine preventable diseases.”
The First Regional Meningococcal Symposium held in Buenos Aires, Argentina, brought together 181 people from 21 countries, including the heads of national immunization programs, researchers, economists and vaccine experts from across the Americas.

Welcoming the Symposium participants, Dr. Ciro de Quadros, Executive Vice President of the Sabin Vaccine Institute, noted that the meeting will tell us where we are at this moment in regards to meningococcal disease, and the potential of vaccines to effectively combat meningitis in the region.

The meeting reviewed the epidemiology of the disease, its clinical manifestations, sequelae, treatments, the cost of disease and disease outbreaks, and the vaccines available for its prevention. There was a special focus on the development of vaccines for type-B meningococcal disease, a major disease threat globally and in Latin America and the Caribbean.

Representing the Pan American Health Organization (PAHO), Dr. Lucia de Oliveira noted that the region of the Americas has, “the most relevant experience of all world regions in terms of introducing new vaccines.” Its experience could now be applied to assessing the potential of vaccines against meningitis in the region.

“This will be a very important meeting, because it will tell us where we are at this moment in regards to meningococcal disease, and where we could go with vaccines against the disease.”

~ Dr. Ciro de Quadros, Sabin Vaccine Institute, US
“I can assure you that at least some of us in this room are carrying Neisseria meningitidis,” began Dr. Harrison, describing it as “a relatively rare disease that can be absolutely devastating,” causing meningitis (inflammation of the lining of the brain and spinal cord); meningococcemia (systemic blood infection); pneumonia, death in 10-20 percent of cases, and serious disabilities in a similar proportion of survivors. Disabilities include brain damage, deafness, and amputated limbs.

Globally, meningococcal disease causes about 500,000 cases and 50,000 deaths every year. The incidence of disease and the serogroup of the bacteria are highly dynamic and variable, presenting significant challenges to its control and prevention.

Globally, incidence per 100,000 persons ranges from less than 0.1 percent to greater than 1 percent. “And for a highly fatal disease as dramatic as Neisseria meningitidis, one percent is a phenomenal attack rate,” Harrison said.

At any given time, about 10 percent of a population may carry the bacteria, and spread it through respiratory droplets. However, only rarely does it cause invasive disease.

The major risk factor for disease is lack of serum bactericidal antibody, which develops in carriers. Infants who lack meningitis antibody are at highest risk for developing meningococcal disease.

Behavioral risk factors also impact both acquisition and carriage. “Smoking, crowding, kissing, going to pubs and discos, ‘party animal’ behavior are clearly risk factors for invasive meningococcal disease,” Harrison said.

Adolescents and young adults have the highest rates of carriage; infants have the highest rates of disease and the lowest rates of carriage.

Epidemiology of a Dynamic Genome

Underlying these risk factors is the variability and williness of the bacteria itself. Variations in the bacteria’s polysaccharide capsule drive variability, giving rise to 13 different serogroups. Five of these are clinically significant: groups A, B, C, Y and W-135 cause the vast majority of disease. Yet, these serogroups are anything but stable, in both their global distribution and genetic makeup.

Serogroup A is the leading cause of epidemic meningitis worldwide, and the most prevalent group in Africa and China. Group B is a major cause of disease in Europe and the Americas, and the predominant group in infants. No licensed vaccine is available for endemic disease caused by group B.

Two examples of the dynamism of meningococcal epidemiology are found in serogroups W-135 and Y (which is associated with pneumonia). In Colombia, Y first emerged in 2003, and three years later was causing almost half of all infections. In the United States, Y increased from 2 percent of infections in 1989-1991 to 37 percent in 2006-2007. It is also rising in Europe, previously a “Y-free zone.”

A number of factors drive such changes: individual and population factors, environmental factors, meningococcal immunization, and microbial factors. The genome of N meningitidis is highly adaptable, allowing it to avoid population immunity. Among its tricks: meningococci can acquire DNA through horizontal gene transfer with bacteria of other serogroups. This can lead
to capsular switching, and allow pathogenic strains to acquire capsules not recognized by host immune responses.

In 2000, several of these factors came together and gave rise to a virulent strain of W-135, a serotype that had not previously posed a serious disease threat.

**Home from the Hajj**

“W-135 got on the map in a dramatic way in 2000 with the Hajj pilgrimage to Mecca, which led to a global outbreak,” Harrison said. In Mecca, 241 cases of W-135 were reported. “You have this incredible crowding at Hajj,” he said, “and all those pilgrims go home to their host countries,” leading to cases as far away as Argentina and Burkina Faso in West Africa.

The change in W-135’s epidemiology was due to a capsular switch. Genetic scrutiny showed that a hyper-virulent strain of serogroup C had acquired the genes for the W-135 capsule through recombination. Many Hajj pilgrims were vaccinated against serogroup C, but few were vaccinated against W-135, Harrison explained. Therefore, once the C strain acquired the W-135 capsule it was able to evade host immunity. “You had the perfect storm,” Harrison said.

By 2002, the Hajj W-135 clone had caused a meningitis epidemic in Burkina Faso with about 13,000 cases and many deaths. By 2008, the clone was causing a large proportion of the disease in infants in Buenos Aires.

Vaccination strategies are therefore constantly challenged by changes in serogroup distribution and incidence. Indeed, serogroup W-135 is changing the epidemiology in Africa, even as a major vaccination campaign against group A has succeeded in dramatically reducing transmission, disease and deaths from group A meningitis. Harrison reported that since mass vaccination for group A began, W-135 has replaced A as the dominant serogroup in Africa’s Meningitis Belt.

“To make things even more complicated, there are areas that have had periodic problems with serogroup X,” Harrison said, noting that the region will need to closely monitor changes in disease epidemiology, along with vaccine effectiveness, the durability of protection, and carriage.

**New Conjugate Vaccines on the Scene**

The introduction of new conjugate vaccines is having a major impact on disease and epidemiology in other regions as well. In the United Kingdom, introduction of group C conjugate vaccine reduced disease by 95 percent, providing herd immunity to disease caused by group C. However, nearly all disease is now group B, for which there is no broadly applicable vaccine.

Going forward, Harrison noted that major remaining needs for vaccine prevention include:

- Quadrivalent conjugate vaccines for infants starting at two months
- Broadly protective group B vaccines
- Sustained group A conjugate program for Africa’s meningitis belt

In addition, disease prevention strategies and vaccine decisions will need to be based on a country’s careful assessment of disease incidence and serogroup distribution and emergence, which can be gained only through stronger surveillance systems and data.

“Incidence can be as high as one percent, and for a highly fatal disease as dramatic as Neisseria meningitidis, one percent is a phenomenal attack rate.”

~ Dr. Lee Harrison, University of Pittsburgh
**EPI IN THE REGION OF THE AMERICAS**

**Dr. Cuauhtémoc Ruiz Matus**, Pan American Health Organization (PAHO)

The Pan American Health Organization works for public health for the population of the Americas, which numbered 935 million inhabitants in 2010. Dr. Matus reviewed the history of PAHO’s work on immunization, and the incredible progress made.

In 1977, the PAHO Board of Directors, representing all its member countries, established the Expanded Program of Immunization (EPI). Its goal was to reduce morbidity and mortality, equitably and sustainably, in vaccine preventable diseases, Matus explained.

“And the first person responsible to generate that program was Dr. Ciro de Quadros, who has been a hero in the immunization field, and a hero in the public health field, for all of us,” Matus declared.

To fulfill its immunization mission, PAHO has promoted and coordinated technical cooperation and built strategic alliances between the academic, public, private and social sectors. In addition, 24 countries have passed immunization laws to secure national funding for the program. And in 1979, at the initiative of Dr. de Quadros, the PAHO Revolving Fund for the purchase of vaccines was created.

“The Fund is a mechanism that we, the Secretariat, operate on behalf of the countries,” Matus explained. The Fund purchases vaccines in bulk at the lowest market price on behalf of the countries. “The Revolving Fund enables us to have a prompt supply of quality vaccines, WHO pre-qualified, at low prices,” he said.
Across the region, there is access to vaccines, and each country has an EPI director responsible for the immunization program. In its 34 years, the program has initiated everything from “Calm Days,” used to vaccinate children during the Civil War in El Salvador, to the annual Week of Vaccination.

Three Strategies for Immunization

PAHO’s immunization program has three strategic areas: Protect the Achievements; the Unfinished Agenda, and Meet Future Challenges.

“We must not take a single step back,” Matus said, elaborating on the first strategic area.

“We must not take a single step back in the eradication of polio, in the eradication of measles, in the eradication of rubella, in maintaining diphtheria and pertussis under epidemiologic control.”

Regarding the Unfinished Agenda, he stressed the need to achieve at least 95 percent coverage levels in all countries and municipalities.

To Meet Future Challenges, Matus focused on introducing new vaccines, including rotavirus, pneumococcus and HPV, as well as an anticipated vaccine for MenB and for dengue. Already, 16 countries have incorporated rotavirus vaccine into their universal vaccination schedule, and 21 countries and territories have introduced pneumococcal vaccine. Six countries have introduced HPV vaccine as part of their universal vaccination program, while another eight countries are piloting the vaccine.

But the vaccination program is not only about administering vaccines, Matus said. It is also about strengthening epidemiological surveillance, understanding strain behavior and drug resistance.

To generate evidence-based information that can guide public health decision makers, PAHO started the ProVac Initiative. It promotes studies on burden of disease, cost effectiveness, and cost-benefit. The ProVac approach has now been replicated in other regions, expanding to become International ProVac through a collaboration among WHO, AMP, PATH and the Sabin Vaccine Institute.

Maintaining Financial Sustainability

As PAHO advances its immunization strategy, Matus noted an outstanding issue that remains to be resolved: financial sustainability.

“From 2007-2008, we can see that 99 percent of the cost of the immunization program was paid with national funds,” Matus reported. “Therefore, any introduction of a new vaccine… affects directly the available resources that the countries have to sustain this program.”

The budget for vaccines in the region is reflected in the growth of the Revolving Fund. From its creation in 1979 to 2011, the number of antigens purchased increased from 6 to 28; the number of participating countries increased from 8 to 30; and the vaccine purchase cost increased from US$2.3 million to around US$400 million. “As you can see, this has enabled the growth and the introduction of new vaccines,” Matus said.

Continued success depends both on the growth of broad, effective and genuine partnerships and, fundamentally, “on the day-to-day work of thousands of public health workers, who make it possible for vaccine to reach the end user, the population of the Americas,” Matus concluded.
34 Años del PAI

1977  2011

Consejo Directivo de OPS establece el PAI

Nominación de jefes PAI en los países
Creación del Fondo Rotatorio
Creación de metodología de evaluación
Immunización y Salud Primaria
Planes de Acción
“Días de Tranquilidad”
Se declara meta de erradicación de polio
Se crea Grupo Técnico Asesor del PAI
Creación de CCI
Último caso autóctono de polio en Perú
Región certificada libre de polio
Se declara meta de eliminación de sarampión
Se acelera introducción de vacunas SRP, Hep B, Hib
Three different bacteria are the most common causes of meningitis: Neisseria meningitidis, Haemophilus influenzae and Streptococcus pneumoniae. To understand the epidemiology of N. meningitidis, one must first be able to diagnose it, distinguishing it from other possible sources of its clinical manifestations. Diagnosis is further complicated when a patient is already on antibiotic treatment, as the treatment makes it far more difficult to detect the bacterium in the blood or cerebral spinal fluid (CSF). Yet, antibiotic therapy is essential when the disease is suspected.

Session I reviewed the current epidemiology of meningococcal disease in Latin America, its surveillance, and diagnosis, and the information still needed to establish vaccination policies.

CURRENT SITUATION OF MENINGOCOCCAL DISEASE EPIDEMIOLOGY IN LATIN AMERICA

Dr. Marco Aurélio Sáfadi, São Luiz Hospital, São Paulo, Brazil

Dr. Sáfadi reported on the first major study of meningococcal disease in Latin America and the Caribbean, conducted by the Sabin Vaccine Institute with the goal of providing guidance to Latin American policymakers regarding the introduction of meningococcal vaccines. While the work is ongoing and the findings are still preliminary, they provide the clearest picture yet of the disease epidemiology in the region.

The researchers reviewed and analyzed the literature on meningococcal disease in Latin America in the last 20 years. A search of nine electronic databases yielded 238 citations in English, Spanish and Portuguese, published between 1980 and 2011. Of these, 106 studies were used to create a new data base used in the final analysis. The studies provided insights into the:

- Incidence and case fatality rates of meningococcal disease by age group
- Serogroup distribution and molecular characteristics of isolates
- Evaluation and management of outbreaks

Argentina, Brazil, Cuba and Uruguay generated the majority of the data. There were about 45,000 cases of meningococcal disease reported region-wide throughout the period. However, nearly 40,000 of those were in Brazil; 2,300 in Argentina; 1,400 in Cuba; and a smattering in other countries.

Only in Brazil was there enough data to analyze incidence across the whole time period. The country reported 2 cases per 100,000 people in 1980, and incidence peaked in the 1990s, with a preponderance of group B.

**Disease Incidence and Mortality**

The study shows N. meningitides is the leading cause of bacterial meningitis in many Latin American countries, with incidence rates ranging from less than 0.1 per 100,000 people to 1.8 per 100,000.

While overall there has been a downward trend in disease incidence over the last few years, inconsistencies in the quality of information suggest that the disease has been underestimated.
As an example, Sáfadi pointed to two Brazilian studies with quite different conclusions. One national study was based on clinical and laboratory findings, while a second study in the state of São Paulo used PCR to identify the cause of meningitis in patients.

The national study found about 2,900 cases of N. meningitidis in the country in 2010, and almost 2,500 cases of meningitis in which the etiological agent was unknown. The more scientifically exact PCR study narrowed the group of disease with an indeterminate cause, resulting in a significant increase in positive findings for N. meningitidis.

Extrapolating the results from the PCR study to the national study would increase the burden of meningococci meningitis disease in Brazil to almost 5,000 cases in 2010. “So this gives a more precise idea of the scope of the disease,” Sáfadi said.

Another indication that the disease is being substantially underreported came from Mexico, which on an annual basis has recently reported 50 to 70 cases per year, suggesting a very low rate of meningococcal disease. However, a study using PCR at the Mexico/US border found three cases for every 100,000 children under age 17.

Data also revealed the mortality rate from N. meningitides in Latin America. Region-wide, it was 18 percent, about double that in the United States.

“One out of every five people with the disease in Latin America dies,” Sáfadi said.

**Age Distribution**

In endemic situations, the highest incidence rates were in infants and young children. Unlike in Europe and the United States, there was no second peak among adolescents. However, this changes during outbreaks, with adolescents and young adults suffering the greatest burden of disease. This pattern held true for Brazil, Argentina, Chile and Venezuela.

“If you observe in your jurisdiction an increase of cases among adolescents and young adults, watch out, because this could translate into a possible outbreak,” Sáfadi warned.

**Dominant Groups**

The most recent data indicate that groups C and B are responsible for the majority of cases, but groups Y and W-135 are on the rise. No cases of group A have been reported in the last few years. When Brazil is taken out of equation, half the cases are B, 14 percent are C, 27 percent are W135 and 8 percent are Y.

“The epidemiology is ever-changing, it is dynamic, so it is important to have an idea of what is currently happening,” Sáfadi said.

However, change is constant. For example, group B was the main type in Brazil up until about 2005, and today group C is responsible for about 75 percent of cases. Distribution in Venezuela and Colombia is similar to that in the United States, with about one-third B, one-third C and one-third Y. In Uruguay, about 90 percent of the cases are B.

To fight this disease, Latin American countries have begun to introduce vaccines against meningitis. Brazil introduced C-conjugate vaccine into its routine vaccination program in 2010, and Cuba has been using an Outer Membrane Vesicle (OMV) vaccine for more than 20 years.

In conclusion, Sáfadi noted that a main finding from the preliminary evaluation of the data is that meningococci is a significant cause of bacterial meningitis—indeed its main cause—in many countries of Latin America.

The research was coordinated by the Sabin Vaccine Institute in partnership with the Pan American Health Organization (PAHO), the International Vaccine Access Center (IVAC) at Johns Hopkins University and the US Centers for Disease Control and Prevention (CDC).
Dr. Oliveira described the value of epidemiological surveillance, stressing that it requires the systematic gathering, analysis, and diffusion of data. The object of monitoring disease trends and distribution is to both create a plan for disease control and to enable the accurate evaluation of control measures such as vaccination.

“We must carry out adequate, continuous and systematic surveillance of the data so that … decisions can be reached,” Oliveira said.

Oliveira defined the various forms of surveillance:

- Passive surveillance that depends on reporting by the National Health Services
- Active surveillance that gathers data from the source; carries out specialized polls to search for cases; and gathers supplementary data to obtain a fuller disease profile
- Sentinel surveillance that collects sample data on reference groups, with the goal of early detection of emerging trends.

To carry out sentinel surveillance, PAHO recommends selecting a specific region and its population. The data generated by health centers in the targeted region can then be used to estimate the national load of the disease. Such surveillance becomes even more important during an outbreak, as it allows tracking of geographic distribution and serogroups.
Oliveira pointed to PAHO’s practical field guide: Surveillance of Bacterial Pneumonia and Meningitis in Children Aged Under 5 Years. It is available in several languages on the PAHO website. It describes standard criteria to select sentinel hospitals, and standard case definitions and diagnosis to allow comparisons within and among countries.

Across the region, ten countries are systematically sending data on meningococcal disease in children under five years of age to PAHO, using the agreed-upon standards and definitions.

“We must carry out adequate, continuous and systematic surveillance of the data so that … decisions can be reached.”

~ Dr. Lúcia Helena de Oliveira, Pan American Health Organization

INTEGRATION OF REAL-TIME PCR INTO ROUTINE PUBLIC HEALTH SURVEILLANCE OF BACTERIAL MENINGITIS: THE BRAZILIAN EXPERIENCE

Dr. Lucila Fukasawa, Adolfo Lutz Institute, São Paulo, Brazil

Dr. Fukasawa described the incredible power of real-time PCR in diagnosing the disease agent responsible for meningitis. Between 2002 and 2006 in Brazil, half of the cases of meningitis were of unknown origin. In 2006, about 28,000 cases of meningitis were reported nationally, with about 40 percent of bacterial origin. However, in half of these the responsible bacteria could not be identified.

“To reverse these problems and to increase the number of lab-confirmed cases of bacterial meningitis, we introduced into our routine real-time PCR to obtain simultaneous detection of pneumococcal, meningococcal and H. influenzae bacteria,” Fukasawa explained.

The multiplex, real-time PCR was introduced into 12 sentry hospitals across the state of São Paulo and three other Brazilian states in 2007.

The sentry hospitals sent samples from patients with suspected bacterial meningitis to the Adolfo Lutz Institute for testing. When used on samples of cerebral spinal fluid, the technique was 100 percent sensitive for the detection of meningococci, 97.8 percent for pneumococci, and 66.7 percent of H. influenzae. While sensitivity with blood samples were lower, it was still good.

Overall the use of PCR increased the yields for detection of meningococci by 52 percent and the detection of pneumococci by 30 percent, Fukasawa reported. By 2011, only 23 percent of cases were of indeterminate cause, compared to 50 percent before the use of PCR.

Researchers obtained similar results in the city of São Paulo, where 1,540 samples from 1,214 patients were analyzed in 2011.
“The most frequent bacterium defined by the PCR was meningococci, followed by pneumococci, and Haemophilus accounted for less than 1 percent of the cases,” Fukasawa said.

More than 76 percent of the meningococci were serogroup C, followed by group B with 12 percent, group W-135 with 5 percent and group Y with 0.5 percent.

With the success of the program, the Adolfo Lutz Institute is stepping up its training of other institutes in the technique. It has already trained personnel in ten Brazilian state laboratories and two regional laboratories, and will soon train another four regional laboratories.

“*The most frequent bacterium defined by the PCR was meningococci, followed by pneumococci, and haemophilus accounted for less than 1 percent of the cases.*”

~ Dr. Lucila Fukasawa, Adolfo Lutz Institute, Brazil

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**Bacterial Meningitis – Etiology**

São Paulo State (2002 -2010)

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Data: www.cve.saude.sp.gov.br/htm/cve_meni.htm

**Sentinel Program + RT-PCR**

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19–20 March | Buenos Aires, Argentina

**FIRST REGIONAL MENINGOCOCCAL SYMPOSIUM 2012**
THE SIREVA PROGRAM IN LATIN AMERICA: IMPROVING SURVEILLANCE AND CHARACTERIZATION OF MENINGOCOCCAL DISEASE IN LATIN AMERICA AND THE CARIBBEAN

Dr. Ana Belén Ibarz, Pan American Health Organization (PAHO)

PAHO’s SIREVA II network includes 19 national laboratories reporting on bacterial diseases, including *Neisseria meningitidis*, *Haemophilus influenzae* (Hib), and *Streptococcus pneumoniae*. In addition to the national laboratories, the network includes two regional reference laboratories: the Adolfo Lutz Institute in São Paulo, Brazil, and the National Health Institute in Colombia.

Dr. Ibarz described a SIREVA II project to improve monitoring of meningococcal disease in the region, for which she serves as the senior researcher. The project comprises four components:

1. **Establishment of a coordinator laboratory** responsible for implementing and conducting the research program.

2. **Performing carriage studies to describe carriage rates for** *N. meningitidis*, **circulating serogroups and phenotypic and genotypic characteristics of circulating strains**

3. **Conduct studies to evaluate diagnostic tools for meningococcal disease.**

4. **Reinforce disease surveillance both epidemiological and laboratory in the countries:**
   
   4.1 **Organization of a regional data-base linking both epidemiological and laboratory data.**
   
   4.2 **Build a collection of strains obtained from the national reference laboratories.**
   
   4.3 **Perform phenotypic and genotypic characterization of the strains, including antibiotic susceptibility.**

The project is set to launch four regional carriage studies: the first one started in Paraguay in March 2012, and will include 2,600 individuals aged 3-21. This study will allow to whether the age distribution of carriers in the region is similar to that found in Europe and the United States, where most such studies have been carried out.

A second study in São Paulo, Brazil, is collaboration with the Adolfo Lutz Institute. It will sample 1,200 people between 11 and 19 years of age. A third study in Bogota, Colombia, will sample 1,500 people between the ages of 15 and 21. The fourth study in Argentina will include at least 675 university students between 18 and 21 years of age.

These studies will allow to determine the phenotypic and genotypic characteristics of *N. meningitidis* strains circulating among asymptomatic carriers, and compare them to those of disease-causing strains. The carriage studies will also examine capsular expression. Ibarz explained that this is of interest because a high proportion of *N. meningitidis* circulating among asymptomatic carriers switch off the expression of the polysaccharide capsule to avoid recognition by the host’s immune system. Additionally, carriage studies from Europe have shown that 16% of carried meningococcal strains present a mutation that inactivates the capsule gene, and therefore these strains are theoretically unable to cause disease. These strains generally belong to two clonal complexes: ST-53 complex and ST-198 complex, which are highly prevalent among carried meningococci by hardly ever seen among isolates obtained from patients. Intriguingly, ST-198 complex meningococci have been detected among the disease strains characterized in Argentina and Cuba.
Within the SIREVA II project, a protocol to perform a retrospective evaluation of bacterial meningitis surveillance at three levels: (i) clinical diagnostic and sample collection at bed side, (ii) laboratory processing and ability isolate and identify the pathogen, and (iii) reporting to the compulsory notification system. This will allow the authorities to identify weaknesses and implement the necessary corrective measures along the process from the arrival of patients to the emergency guard, laboratory processing and, finally, reporting of cases to the Ministries of Health.

Ibarz also summarized serogroup data for all isolates of N. meningitidis reported between 2006 and 2010 within the SIREVA II network, including 19 countries in Latin America, and others in the Caribbean region. The data was grouped into four subregional groups:

- Brazil (which constituted its own region)
- Southern Cone (Argentina, Chile, Paraguay and Uruguay)
- Andean Region (Bolivia, Colombia, Ecuador, Peru and Venezuela)
- Mexico, Central America and the Caribbean (CAREC, Costa Rica, Cuba, El Salvador, Honduras, Mexico, Nicaragua, Panamá, Rep. Dominicana)

Although most countries had very few isolates, the consolidated data revealed distinct regional differences. Group C predominates in Brazil, whereas serogroup B is the most prevalent in the Southern Cone despite the steady increase of W135 isolates from 2008 onwards. The number of isolates from the Andean and the Mexico, Central America & CAREC regions is very low and therefore conclusions should be taken cautiously. In the Andean region, serogroups B appears to have experienced a steady increase during the 2006-2010 period, and serogroup Y prevalence appears unusually high compared to elsewhere in countries located in the Andean region. Serogroups B and C are the most frequently detected among countries in the Mexico, Central America and CAREC region, but no trend can be devised from the data.

Under the scope of the project, meningococcal strains isolated from meningococcal disease patients across countries in Latin America have been phenotypically and genetically characterized. Results have revealed that serogroup distribution is highly heterogeneous across countries. Genetic characterization by MLST has revealed that some of the Clonal Complexes commonly found among disease isolates in Latin America differ from those described in Europe and the United States. Moreover, MLST characterization has identified several strains that had not been described previously. These findings are of paramount importance, as the antigen variants that are currently being investigated as vaccine candidates are being selected on the basis of genetic data, and the presence of new genotypes could also indicate the circulation of undescribed antigen variants that are not being included in the vaccine formulation and therefore render these vaccines less effective in Latin America.

Ibarz concluded with a call to reinforce surveillance at all levels: clinically, in the lab and in epidemiological monitoring as well as mandatory reporting of the disease, and to promote the incorporation of molecular diagnostic and strain characterization techniques into the routine of National Reference Laboratories in Latin America.

“The message to take home is that we need to reinforce surveillance at all levels: clinically, in the laboratory and in the epidemiological monitoring as well as mandatory reporting of the disease.”

~ Ana Belén Ibarz, Pan American Health Organization
Laboratory-based Surveillance of Meningococcal Disease in Latin America and Caribbean Countries, SIREVA II 2006-2010

CARRIAGE AND TRANSMISSION OF *N. MENINGITIDIS*: WHAT INFORMATION IS STILL NEEDED IN LATIN AMERICA FOR IMPLEMENTATION OF VACCINATION POLICIES?

Dr. María Paz Bertoglia Arredondo, Ministry of Health, Chile

Typically, ten percent of a population is asymptomatic carriers of *N. meningitidis*, and these carriers are the source of infection. During epidemics, 70 to 80 percent of the population can become carriers. Some investigations have found 100 percent of carriage in populations, Dr. Arredondo reported.

Carriage and transmission rates can increase in closed or semi-closed populations, such as military units, religious pilgrims, sailors, the incarcerated or extended families. Among university student populations during their first week of classes, studies have shown carriage to be associated with those that consume alcohol and frequent bars or enclosed spaces.

Within a population, the rate of carriage varies by age. Carriage rates are low in children under four. In young people between the ages of 15 and 24, carriage rates go up to 24 to 27 percent. In older groups, rates decline.

Risk factors for carriage include crowding and respiratory tract infections. Lesions in the respiratory tract caused by smoking increases the risk. Carriage rates are higher among lower income and displaced populations.
**Of Capsules and Colonization**

About half of carrier isolates lack a capsule and therefore cannot be serum grouped. Capsular loss aids colonization as it enables the bacteria to evade the immune system. In the past, researchers believed that these capsule-less bacteria lacked pathogenic potential. But studies have since shown that the bacteria can still express their capsule following colonization. The bacteria can activate or de-active capsular production in rapid sequence.

Vaccination and the immune process it evokes can unleash genetic exchange and trigger capsule switching. “This explains why we can observe very rapid changes in the predominant serum types following massive immunization campaigns,” Arredondo said.

Transmission from one individual to another is through direct contact with fluid micro droplets, up to a distance of one meter.

Arredondo stressed the many areas of research still needed in order to create vaccine policy for *N. meningitidis*, including: population studies of carriers to describe specific rates of carriage and serogroup distribution; analysis of natural immunity; a complete understanding of the disease load; and cost effectiveness studies.

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**Bind, Colonize, Invade**

*N. meningitidis* comes equipped to bind to and colonize the human nose and throat. Dr. Arredondo described some of the key mechanisms involved:

**Attachment:** Adhesion molecules called pili attach to receptors on host epithelial cells. Pili are long hair-like filaments that extend out from the micro-organism’s surface and act as anchors in the mucosa. Adhesion leads to a temporary up-regulation of pili production and down-regulation of capsule synthesis.

**Nourishment:** Needing nutrients to survive, *N. meningitidis* possesses receptors capable of binding to human transferrin and lactoferrin, which are sources of iron, an essential nutrient for the growth of meningococci.

**The Best Defense:** Is an offense, and to defend itself against human immunoglobulin A (IgA1) in nasopharyngeal secretions, *N. meningitidis* produces a protease that cleaves IgA1, enabling it to evade these soldiers of the immune system.

After the bacteria colonize the nasal pharyngeal area, there will occasionally be cultures that can cross the mucosa and enter the bloodstream, gaining the ability to create invasive meningococcal disease. However, there is still much to learn about the changes from carriage to pathogenic disease, as well as about the immune response mediated by meningococcal carriage.

“We need many more studies of the immune response as related to carriage. These studies will be very useful to develop immunization strategies, via nasal pharyngeal mucosa, that at some point can turn into an effective control strategy,” Arredondo said.
Discussion spanned issues related to vaccination policy, epidemiologic trends and the uses of PCR.

Asked whether vaccines should be introduced into routine immunization and at what age, Sáfadi referenced the experience in Brazil, where a conjugate vaccine for group C has been introduced for children under two—the group with the highest morbidity. He said that in some circumstances, an outbreak of W-135 disease for instance, a tetravalent vaccine could provide better protection.

One participant noted that there were natural decreases in meningococcal disease prior to vaccination in the United States and in Latin America even without vaccination. Given this downward trend in disease, he asked what levels of incidence would justify massive routine vaccine introduction in terms of cost and benefit.

De Quadros noted that a disease threshold has not yet been established as the basis for vaccine introduction, but the deadly nature of the disease highlights the urgency of vaccination.

“It generates a major panic when one finds an adolescent case that is at school in the morning, and by the evening is in the intensive care unit,” de Quadros said. “When you have this disease in significant numbers in your region, you don’t need to have high incidence rates to consider vaccination,” he added.

Asked whether PCR can help determine which vaccine to use, Sáfadi explained that the importance of PCR is to determine the disease load, which is crucial information for making a vaccine decision. PCR also yields information on serogroup and capsular expression. However, it cannot determine the specific clone complex. “That is why you still need the culture and the isolation techniques,” he explained.
Session II provided a comprehensive review of the epidemiology of the disease; discussed the clinical manifestation, morbidity and treatment of invasive disease and reviewed resistance patterns of the bacteria.

CLINICAL SYMPTOMS OF MENINGOCOCCAL DISEASE

Dr. Eduardo Gotuzzo, Universidad Peruana Cayetano Heredia, Peru

Dr. Gotuzzo urged health workers to keep meningococcal meningitis in their sights epidemiologically and clinically as they use epidemiology to solve diagnostic riddles. He noted that clinical manifestations of meningococci are similar to that of other diseases, which makes diagnosis difficult.

On the other hand, physicians often associate N. meningitidis with a very specific syndrome, Waterhouse-Friderichsen syndrome (massive hemorrhage into the adrenal glands, secondary to severe bacterial infection). This is a mistake, as the syndrome is rare.

"Don't wait for a Waterhouse syndrome case to knock on your door before you think meningococcal disease," Gotuzzo said.

Symptoms of meningitis may be headache, shivers, nausea, stiff neck, and the prognosis and progression of the disease is similar across all serotypes. When these symptoms are present in a case of sepsis in a young child or older adult, a lumbar puncture should be requested immediately, as the first diagnostic procedure. Puerperal syndromes, cyanosis or necrotic lesions around the hands and feet are clear symptoms.

A review of a number of cases from Latin America showed the following conditions associated with meningococcal meningitis:

- Meningitis 47.3 %
- Bacteremia/ meningococcemia 43.3 %
- Pneumonia 6.0 %
- Arthritis 2.0 %
- Otitis 1.0 %

Groups of Concern

Gotuzzo identified several groups for whom N. meningitidis should be considered when they come into a clinic or hospital with typical symptoms.

The first group is children under five. Gotuzzo pointed out the high number of child deaths in the region, noting that some could be caused by unrecognized meningococcal disease. As it is, “In those under five years of age, meningitis is the first, second or third cause of death in many hospitals,” Gotuzzo said.

Diagnosis is complicated by the quick use of antibiotics. “The majority of our patients, up to 80 percent, arrive already under antibiotic therapy and isolating bacterial agents becomes harder as more antibiotics are present.”
A second group is young people who may have recently had contact with large numbers of youth from diverse backgrounds, or young people who are incarcerated or in the military.

A third group is middle-aged adults. “An adult who is colonized by meningococci should almost be an automatic flag of an impending outbreak.” That is because normally, the disease affects the youngest and the oldest, Gotuzzo explained. If you find meningococcal meningitis in a 35-year-old, there should be immediate monitoring of his residence, family and neighborhood.

A fourth group of importance is immuno-suppressed patients. Patients with advanced stages of AIDS develop pulmonary lesions and bacteremia. “Yet, this group of patients has been very little studied in our countries.”

The last group is people over 65 years of age. Many such older patients who develop meningitis or pneumonia never receive an exact diagnosis, and their deaths are not attributed to the right disease, skewing mortality rates.

Fatality rates can range from 7 percent to more than 30 percent, and vary with age. In general, mortality is highest in the youngest. However, one study in Brazil showed that for those over 65, the fatality rate was up to 35 percent.

One-in-five survivors suffer permanent disabilities, including brain damage, blindness, deafness and amputated limbs. In a study of children in Argentina, one in five lost a limb as a result of \textit{N. meningitidis}. “This is not just a matter of aesthetics. It will impact the person’s entire life. When a child loses an arm or a leg, this is a tragedy for that individual and their families,” Gotuzzo said.

In summary, Gotuzzo noted that “Meningococci meningitis is a medical condition that we don’t recognize when physicians are using more and more antibiotics and less and less bacterial studies. The disease requires not just monitoring, but also solid lab work.”

\textit{“In those under five years of age, meningitis is the first, second or third cause of death in many hospitals.”}\nas Dr. Eduardo Gotuzzo, Universidad Peruana Cayetano Heredia, Peru

\textbf{Incidencia y Mortalidad}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{incidence_mortality.png}
\caption{Graph showing incidence and case fatality ratio by age group.}
\end{figure}

Dr. Santos summarized several lessons regarding N. meningitidis. Humans are the sole reservoir of the bacteria, which he described as uniquely "well-adapted, unlike most of them, able to grow in mucous membranes, enabling its transmission to be efficient and on target." He noted that it has great genetic variety, larger than that of most other bacterial pathogens.

Two distinguishing characteristics of N. meningitidis are its propensity to invade the meninges and its ability to rapidly proliferate in the bloodstream—a complex process that can lead to multiple organ collapses.

The natural immunity invoked by colonization may fail to defeat the bacterium. Adaptive immune mechanisms are needed. But between the initial colonization and the production of protective antibodies there is an interval of 7 to 10 days. In the interim, massive infection can occur.

Fortunately, massive infection is infrequent. It requires contact with virulent cultures, the culture needs to colonize and penetrate mucous membranes. Once the bacteria enter the bloodstream, it will replicate in less than 12 hours and can bring disseminated intravascular coagulation.

Santos summarized the natural history of the infection, which typically colonizes a low percentage of the human population. When colonization occurs in over 30 percent of the population, epidemics can emerge.

The main pathogenic agent of N. meningitidis is an endotoxin that comprises about half of its outer capsule. This endotoxin unleashes the body's inflammatory response, activating monocytes, which in turn impact coagulation. The ensuing biochemical cascade can "create capillary diffusion and intravascular thrombosis, a cardiac reaction, and multiple organ failure as characterized by the Waterhouse Syndrome," Santos said.

### Treatment

Santos reviewed the antimicrobial agents available for treatment.

“Even with the appearance of resistant cultures, we still have good therapeutic alternatives,” Santos said. However, they are insufficient when the case is very sudden.

“We have not improved in large part the survival of patients with invasive and fulminating disease,” Santos said.

The cornerstone of treatment is antibiotics, which must be initiated immediately when meningococcal disease is suspected, Santos said.

However, one complication of treatment is that when you inhibit the dissemination of meningococci in the bloodstream, bacterial implantation in the sub-arachnoid space of the meninges can develop quickly into meningitis.

“Patients need multidisciplinary support, preferably in intensive care units,” he said. Patients with more severe disease need wider treatment, including liquids and assisted ventilation.

In addition to antibiotics, Santos noted that a lot can be done to control the body’s inflammatory response. Steroids are used to treat septic shock. Other treatments are being tried but remain controversial, such as the use of fresh plasma and plasma exchange, and immunomodulators.
In the case of acute cerebral edema, physical measures such as hyperventilation, hyperosmolar agents, barbiturates and induced hypothermia should be considered, all for the purpose of reducing intracranial pressure. The use of glycerol has been tested, and its value is still debated. The use of corticosteroids have been tested and found ineffective.

In conclusion, Santos noted, “Despite the growing access to medical care, the mortality rate for invasive meningococcal disease continues to be very high,” which highlights the importance of prevention.

“We have not improved in large part the survival of patients with invasive and fulminating disease.”

~ Dr. José Ignacio Santos, National Autonomous University of Mexico, Mexico

**NEISSERIA MENINGITIDIS ANTIMICROBIAL RESISTANCE: CURRENT SITUATION IN LATIN AMERICA**

Dr. Silvia Gonzalez Ayala, Hospital de Niños Superiorda Sor Maria Ludovica, Argentina

Dr. Gonzalez Ayala reviewed the history and current status of antibiotic resistant N. meningitidis, both globally and in Latin America. Resistance first emerged in penicillin in Spain in 1985. By the 1990s, resistance in this antibiotic of choice for meningococcal disease had spread to the United States, Canada, Italy, Greece, the United Kingdom, France, Israel and Australia. Ultimately, the spread of intermediate penicillin resistance led clinicians to use third-generation cephalosporin for treatment.

Resistance in another antibiotic, chloramphenicol, was found in Vietnam in 1987, and later in Australia and France. Originally considered an alternative medication for people allergic to penicillin, chloramphenicol has been discontinued for the treatment of invasive meningococcal disease.

Rifampicin-resistant meningococci were isolated in the 1960s, and found in the United States, France and Australia. In 2010, two resistant isolates were found in Montevideo, Uruguay. However, “Resistance to rifampicin is absolutely sporadic with very low global frequency”, Gonzalez Ayala said. With such sporadic findings, rifampicin can continue to be used prophylactically in Latin America to prevent disease in the contacts of patients.

The first bacterial isolate with decreased susceptibility to ciprofloxacin was found in Greece in 1992—with additional such findings in Argentina, Australia, Hong Kong, India, Italy and the United States. In Latin America, PAHO recommends that the drug not be prescribed in areas where resistance has been identified.

While resistance to ceftriaxone was reported in India in 2005, Gonzalez Ayala reported that the study has been under intense scrutiny by microbiologists and its credibility is under question.

PAHO’s SIREVA network has been tracking antibiotic resistant N. meningitidis in the region, and in 2010 initiated a project to
improve surveillance and characterization of meningococcal disease. The majority of data on resistance within the network has come from Argentina, Brazil, Chile and Colombia. The highest resistance has been reported in Cuba and Mexico. Although resistant bacteria have been found in a number of Latin American countries, Gonzalez Ayala noted that there are few reports correlating resistance to penicillin and failure of antibiotic treatment. Microbiologists also debate the clinical significance of intermediate susceptibility to penicillin, and some argue that it can be overcome through delivering higher dosages of the drug.

Meanwhile, studies have shown that the emergence of resistance is correlated to the outcome and successful management of close contacts.

“The emergence of resistance demands more study,” Gonzalez Ayala said. While there is no global alert for the spread of resistant N. meningitidis strains, “Continuous vigilance of all isolates is important for study of all medicines included in the treatment and prophylaxis of this disease,” Gonzalez Ayala concluded.

“The emergence of resistance demands more study”

~ Dr. Silvia Gonzalez Ayala, Hospital de Niños Superiora Sor Maria Ludovica, Argentina
COST OF CASES AND OUTBREAKS

The presentation in this session revealed preliminary results from the first-ever study to estimate the burden and costs of meningococcal disease in the region of the Americas. The study was coordinated by the Sabin Vaccine Institute in partnership with the International Vaccine Access Center at Johns Hopkins University (JHU’s IVAC) with the support of the Pan American Health Organization (PAHO), and the US Centers for Disease Control and Prevention (CDC).

COST EVALUATION OF NM CASES AND OUTBREAKS IN SELECTED COUNTRIES OF LATIN AMERICA AND THE CARIBBEAN: PRELIMINARY FINDINGS

Dr. Dagna Constenla, Johns Hopkins University Bloomberg School of Public Health, US

National and regional decision makers and donors need cost information to decide whether to invest in a national vaccine meningococcal program, and Dr. Constenla reported the preliminary results of major study that examined the costs of meningococcal disease in Latin America and the Caribbean.

“The economic impact can vary widely across countries in the region,” Constenla said. “However, what is clear from our research is that meningococcal disease has significant costs for society and governments.”

Over a four-month period beginning in November 2011, researchers reviewed 51 patient charts in seven hospitals; administered 19 surveys to caregivers and interviewed 40 physicians to develop an estimate of N. meningitidis costs in Chile, Colombia and Panama.

The mean age of the patient population considered was 2.8 years in Chile, 6.7 years in Colombia, and 46.8 years in Panama. Panama also had the longest hospital stays (18.5 days). Total costs estimated comprised direct medical costs, out of pocket expenses and productivity loss.

The total cost per patient in Chile was US$3,785 in Chile; US$5,108 in Colombia; and US$5,327 in Panama. Hospitalization accounted for almost all of the costs of treatment for Panama, Chile and Colombia at 79%, 80% and 94%, respectively. Loss of productivity contributed up to 2.4% of the total cost for meningococcal disease in Chile, in contrast to 1.7% and 1.3% of the total cost estimated in Colombia and Panama, respectively.

“Hospital care costs took the biggest chunk of the total cost, ranging from 82 percent to 92 percent,” Constenla said.

Cost of Outbreaks

Costs associated with outbreaks of meningococcal disease were reported from two recent outbreaks: one in Brazil (Vila Brandina in 2011), and one in Colombia (Cartagena de Indias in 2012). The first outbreak that occurred in Vila Brandina, São Paulo, reported 3 cases that were associated with a total investigation and outbreak management cost of US$34,425 (US$11,475 per notified case), compared to US$735.10 (US$122.52 per notified case) for the 2012 outbreak which reported 6 cases in Cartagena de Indias. These costs correspond to the disease response phase. The difference
in costs among the two outbreaks was due to the type of cost components included in the estimation (for the Cartagena outbreak only personnel costs and chemoprophylaxis costs were captured compared to the outbreaks in Vila Brandina, which included costs associated with personnel, office supplies, gasoline consumption, chemoprophylaxis and vaccination). Differences in costs were also due to the number of cases of an outbreak, the size of the population, the area of exposure, the perspective under consideration, and management practices.

To put these costs into perspective, we compared the costs of an earlier outbreak that occurred in Vila Boa Esperança in 2007. During this outbreak, nine cases were reported and these were associated with a total investigation and outbreak management cost of US$128,963 (US$14,329 per notified case).

For the disease surveillance phase, the costs ranged from US$3,935 (Cartagena outbreak) to US$6,667 (outbreak in Vila Brandina). No costs associated with disease surveillance for the Vila Boa Esperança outbreak were reported. For the Vila Brandina outbreak, the costs of disease surveillance were attributed mainly to meningococcal C conjugate vaccine costs and personnel costs, with 50% and 48% of the total costs, respectively. For the Cartagena outbreak, the costs of disease surveillance were attributed mainly to personnel costs. Costs of vaccine costs were not included in the calculations because the Cuban vaccine strategy (the one that would have been available for controlling the outbreak) was not available and after the identification of serogroup B vaccination it was decided to discard represented a high risk group. In addition, the lack of seasonality of disease in both countries meant that the patient pool was small.

Participants raised questions that will be answered in the second stage of the study, including questions about the cost differential between the public and private sectors. The answers to other questions require data that just is not available. These include questions about cost and effectiveness for each of the different meningococcal vaccines and the costs associated with sequelae.

“No other study of this kind has been undertaken thus far,” Constenla said. “We wanted to establish a reference number for the costs associated with this disease, and its major impact.”

**“Meningococcal disease has significant costs for society and governments.”**

~ Dr. Dagna Constenla, IVAC, Johns Hopkins University, US
SESSION IV:

IMMUNITY AND MENINGOCOCCAL VACCINES

A far-ranging session reviewed the steady advance in the development of vaccines for N. meningitidis, from relatively simple polysaccharide vaccines to the more recent and immunogenic conjugate vaccines. Lessons were drawn from their application in Europe, Africa and Latin America.

HYPO-RESPONSIVENESS AND MENINGOCOCCAL POLYSACCHARIDE VACCINES: IS IT TIME TO STOP USING THESE VACCINES?

Dr. Lee Harrison, University of Pittsburgh, US

Dr. Harrison reviewed the development of vaccines for meningococcal meningitis, and the immune responses they elicit, from the first poorly immunogenic capsular polysaccharide vaccine developed in the 1940s, through to the development of the conjugate vaccines in the early 1990s. The year 2005 saw the use of the first quadrivalent conjugate vaccine in the United States, and, most recently, a conjugate A vaccine was introduced in Africa’s Meningitis Belt in 2010.

Comparing polysaccharide and conjugate vaccines, Harrison noted that the former use purified polysaccharides from one or more serogroups, evoking a limited immune response that wanes quickly over time. Conjugate vaccines attach purified polysaccharide to a purified protein carrier, evoking a broader and more long-lasting immune response that involves helper T-cells for a more robust immune response.

“The addition of the protein carrier might seem like a very, very subtle difference. But it’s not. It’s a monumental change in the characteristics of the vaccine,” Harrison said.

Comparing the two types of vaccines, Harrison noted that unlike polysaccharide vaccines, conjugate vaccines work well in infants, have a long duration, and evoke immune memory.

Also unlike polysaccharide vaccines, conjugate vaccines reduce carriage, leading to herd protection that protects the unimmunized.

Although polysaccharide vaccines are safe and well tolerated, they have many downsides: antibody levels peak between two and four weeks following immunizations, then decline in adults over a period of three-to-five years. This rapid decline in efficacy was demonstrated in a study in Burkina Faso in 1985. It showed effectiveness drop from 85 percent in the first year down to about 67 percent three years later.

In addition, in children under two years of age, the immune response is “very, very meager” and then quickly wanes. To maintain high antibody levels, revaccination is required.

However, “As you give additional doses, the immune response is blunted—you get a diminished response,” Harrison said. This hyporesponsiveness represents yet another down side of polysaccharide vaccines. (The one exception to hyporesponsiveness with polysaccharide vaccine is with serogroup A vaccine).

Harrison explained the immunologic basis of hyporesponsiveness: the polysaccharide binds to immune B cells, which differentiate into
The phenomenon of hyporesponsiveness and other limitations has dampened enthusiasm for polysaccharide vaccines,”

~ Dr. Lee Harrison, University of Pittsburgh, US

Meningococcal Polysaccharide and Conjugate Vaccines: Historical Timeline

1940  First meningococcal capsular polysaccharide vaccines developed
      Poorly immunogenic, probably because of degradation of capsular polysaccharide during purification

1960  New method which allowed purification of high molecular-weight capsular polysaccharide

1980  Development of monovalent (A and C) polysaccharide vaccines
      Development of quadrivalent (ACYW135) polysaccharide vaccines

2000  Licensure of monovalent C conjugate (MCC) vaccines
      Licensure of first quadrivalent (ACYW135) conjugate vaccine

2010  Licensure of monovalent A conjugate vaccine
LESSONS LEARNED AFTER THE LICENSURE AND WIDESPREAD DEPLOYMENT OF MENINGOCOCCAL C CONJUGATE VACCINES AND ITS IMPACT

Dr. Julio Vázquez, Institute of Health Carlos III, Spain

In Canada, 1.6 million doses of polysaccharide vaccines were used in the age group of six months to 20 years old, and the vaccinees were followed for two years after being immunized. Vázquez reported that the study found that the vaccine was not efficacious and that the antibodies had a very limited time duration.

A second large experience with polysaccharide vaccine took place in Spain, following an outbreak in 1996-97 that saw a high fatality rate and incidence rate for group C that reached 2.3/100,000 inhabitants.

This led to the vaccination of the population between 18 months and 19 years in 16 of the country’s 19 autonomous regions. The result was an immediate and dramatic decrease in disease. However, within three seasons the rates of disease were no different in the vaccinated regions than in the unvaccinated regions.

“So we can say that the polysaccharide purified vaccine was a vaccine to stop an outbreak for a short time, but in the long run, this vaccine lost efficacy completely,” Vázquez said.

Currently in Europe, three conjugate vaccines are available. The United Kingdom was the first country to introduce conjugate C vaccine into the immunization schedule, followed by Holland and Spain.

“In the UK, the impact of the vaccine has been tremendous,” Vázquez said. Following the vaccine introduction, there was a large decrease in disease, which continued to gradually fall in subsequent years. Today, there are no more than 4-5 cases a year.

Herd immunity also took hold, as carriage and transmission was reduced. “After the introduction of the conjugate C vaccine, there was a 65 percent reduction in the number of cases in the age groups that didn’t receive the vaccine,” Vázquez said.

A unexpected finding, however, has been the rapid rate at which immunity is lost in the children who were immunized in their first year of life. “After a year they have virtually zero bactericidal activity levels,” Vázquez said. Because of this finding, the country added a booster in the 2nd year of life, which successfully amplifies the immune response.

Holland opted to immunize children only once in the second year of life. However, the strategy also benefited younger children.

“Three years after the vaccine was added to the immunization schedule, the reduction in the number of cases in children under one year of age is 95 percent,” – a result of the herd effect. Benefits to those directly immunized were even greater, with a 99 percent reduction in disease.

Spain’s implementation of vaccination with conjugate C vaccine varied from one region to the next. Both the age group vaccinated and the extent of coverage varied greatly, leading to uneven progress throughout the country.

Nonetheless, the impact has been clear: in 1999, the year prior to vaccination there were 54 deaths from N. meningitidis, reflecting a mortality rate of 13 percent. In 2007, there were 13 deaths, reflecting a mortality rate of 17 percent.
“Therefore, we haven’t done very well, but also not completely wrong,” Vázquez said.

He summarized the main lesson from use of conjugate C vaccine as its impact on reducing the rate of carriage, and thereby providing herd immunity—which raises a critical question.

“The main question that has to be answered… is if we need a booster dose in teenagers to maintain the impact in carriers,” Vázquez said.

The United Kingdom is already moving to a vaccination scheme of a first dose during the 1st or 2nd month of life, a 2nd booster dose at around 12-13 months and a third booster dose during pre-teen years.

“\textit{The main question that has to be answered... is if we need a booster dose in teenagers to maintain the impact in carriers.}”

~ Dr. Julio Vázquez, Institute of Health Carlos III, Spain

**EXPERIENCE WITH THE USE OF TETRAVALENT ACWY MENINGOCOCCAL CONJUGATE VACCINES IN ADOLESCENT PROGRAMS IN US AND CANADA**

Jessica MacNeil, US Centers for Disease Control and Prevention

Dr. MacNeil reviewed the status of meningococcal disease in the US and Canada, and contrasted meningitis vaccination programs in the two countries. She also shared some early data describing the impact of the adolescent meningococcal vaccination program in the US.

In the United States, meningococcal disease has historically been cyclical, with peaks in disease every 10 years. However, rates of disease have also been declining for the past 10 to 15 years – even prior to the introduction of a vaccine in 2005. Current disease incidence is about 0.3 cases/100,000 population in the US and 1/100,000 in Canada.

The two countries also share a similar distribution of serogroups, with group B causing the majority of disease in children under five, while groups C and Y are more common in adolescents and adults. Serogroup W-135 accounts for a smaller proportion of disease.

**Two countries, two strategies**

There are also interesting differences in epidemiology between the two countries. In the US, group Y emerged strongly in the late 1990s. Associated with bacteremic pneumonias in older adults, it is a significant contributor of meningococcal disease in the US. But, more recently in the US, cases of disease have declined for all serogroups, MacNeil said. A similar decline has not been observed in Canada.

But, although the epidemiology of meningococcal disease in the US and Canada is fairly similar, their vaccination strategies are very different.

Canada’s meningococcal vaccine program focuses on young children and all provinces have publicly funded universal MenC vaccine programs. Quadrivalent meningococcal vaccine (MenACWY) can be used as a booster dose in adolescents and in high-risk individuals after the age of two years.
In contrast, the US meningococcal vaccine program is designed to protect adolescents through the peak in disease seen in 16-to-21 year-olds. Children age 11-12 years of age are targeted for the first dose—prior to the period of increased risk. After evidence that protection wanes significantly after three years, an adolescent booster was added in 2011. MenACWY is also used for high-risk individuals 9 months to 55 years old.

MacNeil reported that coverage with one dose of vaccine among 13 to 17 year olds in the US has increased slowly, reaching roughly 63 percent in 2010.

**Vaccine impact in the US**

The low burden of disease makes measuring vaccine impact a challenge. Nonetheless, studies have determined that between 2000-2004 and 2005-2009, the incidence of N. meningitidis disease in the US declined 74 percent among 11-14 year olds; 27 percent among 15-18 year olds; and 16 percent among 19-22 year olds.

Vaccination coverage also varies greatly by state (from 26-90 percent coverage among 13 to 17 year olds in 2010), affecting the rate of decline in disease.

But although the program has reduced disease, it has not eliminated it. “We are still seeing an average of 141 cases of preventable meningococcal disease in adolescents in the US each year,” MacNeil said.

The CDC has received over 40 reports of disease in persons who had been vaccinated with the quadrivalent vaccine, with a case fatality rate of 20 percent. An increasing number of breakthrough cases occur in persons two-to-five years after vaccination. In addition, the true number of breakthrough disease cases is thought to be much higher.

While vaccination has lowered disease rates among those who are vaccinated, it has not affected disease rates in children under five or in adults over 25 years of age, “implying that we have not yet established herd immunity in the US,” MacNeil said.

**What about the babies?**

Meanwhile, the next question before the CDC and the Advisory Committee on Immunization Practices is whether an infant meningococcal vaccine program is needed. In the US, the highest burden of disease is among infants.

It is a difficult question to answer given that: the impact of the adolescent program is not yet fully known; disease rates continue to decline in infants in the absence of vaccination; and the high proportion of group B disease in infants makes disease prevention difficult in this age group.

“We are still seeing an average of 141 cases of preventable meningococcal disease in adolescents in the US each year.”

~ Jessica MacNeil, US Centers for Disease Control and Prevention
A girl who migrated to São Paulo from Madera Island yielded the city’s first isolate of N. meningitidis in 1916, “And this is when our fight against meningitis started in São Paulo, and we haven’t defeated it yet,” began Dr. Moraes.

He reviewed the history of outbreaks and approaches to their containment in Latin America and the Caribbean over the past century. Over this time span, disease rates reached as high as 35 and 43 cases per 100,000 inhabitants, in Barbados and Chile respectively. However, there is little in the medical literature detailing reported outbreaks, and there is a general scarcity of guidelines for their control, Moraes said.

The majority of data is from Brazil, and so Moraes focused his presentation on that country’s experience with outbreaks. He noted that the outbreak rate of 10/100,000 inhabitants is easy to reach when considering small population, and that “There is a lot of political pressure for each case to become an outbreak,” which in turn justifies a vaccination program.

In the case of an outbreak, he outlined three essential actions needed:

- Improvement of epidemiological monitoring
- Prophylactic treatment of close contacts of infected patients
- Vaccination based on the situation.

Although there is huge pressure to have the vaccine during an outbreak, Moraes noted that not everyone need be vaccinated. Prophylaxis should go to: household contacts; people who

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**Preliminary Menactra VE Estimates, Case-Control Study, Duration of Protection***

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<thead>
<tr>
<th>Cases (n=147)*</th>
<th>VE (95% CI)</th>
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<tr>
<td>Vaccinated &lt;1 year</td>
<td>79% (46,92%)</td>
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<tr>
<td>Vaccinated &lt;1-2 years</td>
<td>73% (32, 89%)</td>
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<tr>
<td>Vaccinated ≥3 years</td>
<td>43% (-1, 68%)</td>
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*Analysis results based on paperwork received by December 31, 2011.
Controls for smoking status and underlying condition status
PRELIMINARY RESULTS, SUBJECT TO CHANGE. PLEASE DO NOT DISTRIBUTE
live in closed institutions; people who have had close and/or prolonged contact (travel on planes, buses) with patients; childcare workers in contact with pre-school contacts; and health professionals who are exposed to secretions.

In Brazil, serogroup C has been the main source of outbreaks since 2005. And, as of 2011, policy has been to use the conjugate vaccine whenever needed to deal with an outbreak.

Moraes reviewed lessons from an outbreak in an oil refinery with 7,600 employees. There were seven cases and two deaths. Health workers used polysaccharide A/C vaccine to control the outbreak, and six months later compared carriage of N. meningitidis between refinery workers who had or had not been vaccinated. They found no significant difference in carriage rates between the two groups.

“This supports the argument that the best use for outbreak control is a conjugated vaccine,” Moraes said, since it does reduce carriage and provide herd immunity.

Ultimately, the control of several outbreaks in Bahia and Minas Gerais in 2009-2010 with conjugate C vaccine “encouraged the Ministry to introduce the vaccine in the immunization schedule for the entire population,” Moraes concluded.

### Meningococcal Disease in the Americas

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Requejo, HZA meningite meningococica no Mundo
Dr. Marco Aurélio Sáfadi reviewed the experience of Brazil, Latin America’s most populous country, with meningococcal C conjugate vaccine. The country introduced MenC into the national immunization program for children under two in 2010.

With 18 million children under five years of age, and an annual birth cohort of three million children, “When we introduce a vaccine like meningococcal C, (with three doses at the ages of 3, 6 and 12 months), it means about 10 million administered doses per year,” Sáfadi said.

Nationally, Brazil has 1.5 cases per 100,000 inhabitants each year. The state of São Paulo, with about 42 million inhabitants, has an overall meningitis rate of 3.5/100,000. However, the incidence in infants is even higher: 33/100,000.

Prior to 2010, meningococcal C conjugate vaccine was recommended only for high-risk patients and for the control of outbreaks. But in September 2010, Brazil started vaccination of all children under two years of age. However, national immunization does not include a catch up campaign for adolescents, the main carriers of the disease.

When the vaccine program began, group C accounted for about 75 percent of all disease (from a low of about 30 percent in 2000). Group B accounted for about 14 percent (down from its high of over 60 percent in 2000). Other serogroups, including W-135, accounted for the remaining seven percent.

Following the initiation of vaccination in the state of São Paulo, the rate of disease in children under two declined from 30/100,000 in 2001-2010 to 19/100,000 in 2011—a reduction of 27 percent. The proportion of overall cases that occurred in children under two years of age declined by 39 percent between 2010 and 2011.

Children across the country benefitted from a similar reduction in disease after introduction of the vaccine.

However, Sáfadi noted that no impact was observed in other age groups, probably because of the lack of a catch-up program among adolescents, the age group responsible for carriage.
He pointed out that all other countries that had introduced conjugate meningococcal vaccine, including the United Kingdom, Spain and Canada had included a catch-up program. “We learned this morning that an adolescent catch-up program was essential for the success of disease control, wherever this vaccine was introduced,” he said.

Sáfadi also noted a key difference between Brazil’s introduction of conjugate C vaccine and that in European countries, Canada and Australia. In all other regions the vaccine targeted the ST-11 clone of serogroup C, whereas in Brazil the vaccine targets the ST-103 clone that is ubiquitous in the country.

This makes Brazil the first country in the world to introduce a conjugated C vaccine for a clone that is not MenC ST-11 clone, and its experience may yield important lessons, Sáfadi concluded.

“*In 2012 we observed a decrease of 52 percent in the proportion of cases in the vaccinated age group, which is children under two years of age.*”

~ Dr. Marco Aurélio Sáfadi, São Luiz Hospital, São Paulo, Brazil

**Trends in Meningococcal Disease Rates in Children < 2 Years After Introduction of Men C. São Paulo, 2001-2011**

N = 3,347 cases in children aged < 2 years

The rates of MD in children aged < 2 years declined from an average of 25.9/100,000 persons in the pre-vaccination baseline period to 18.8/100,000 in 2011.

- Reduction of 27% (p<0.01) in incidence rates of children < 2 years

**DISCUSSION**

Asked to clarify the role of catch-up vaccination with adolescents, Sáfadi stressed that adolescents are the carriers of N. meningitidis. Therefore, vaccination of this age group is essential to reducing carriage and achieving herd immunity. He pointed to the experience of Spain, which acquired herd immunity only after adolescents were vaccinated.

But the sheer size of Brazil’s population makes it difficult to include adolescents in the vaccination program. “In order to vaccinate [everyone] from 1 to 20 years old, it would be 60 million doses, which is a challenge, no?” he said.
HISTORY, IMPLEMENTATION AND IMPACT OF MENA CONJUGATE ON DISEASE BURDEN IN AFRICA

Marie-Pierre Préziosi, Meningitis Vaccine Project, France

When the dry harmattan wind blows through Africa’s Meningitis Belt, the epidemic season is in full swing. Dr. Préziosi presented the history of meningitis in the area and the development and implementation of a vaccine for the dominant serogroup, group A.

For over a century, outbreaks of meningitis have occurred every year, with major epidemics striking every eight to ten years. The epidemic season lasts through the dry season, from roughly late December to early June. Then the rains come, bringing an abrupt but temporary stop to the disease.

“The epidemic peak was in the mid-1990s, when over a single year, there were more than 200,000 cases reported in the African Meningitis Belt,” almost 80 percent of them in people under 30 years of age, Préziosi said. “And that triggered countries to turn to the World Health Organization, to ask for some help in coping with that major plague.”

Early in 2000, African health authorities and the WHO expert group concluded that the development of a meningitis conjugate A vaccine was the best strategy for control of the epidemics, and in 2001, the Meningitis Vaccine Project (MVP) was created with core funding from the Bill & Melinda Gates Foundation. MVP is a 10-year partnership between the WHO and the US-based nonprofit PATH.

What followed was the rapid development, testing, licensure and introduction of MenAfriVac, the first vaccine developed for Africa’s Meningitis Belt.

Préziosi recounted that story, and the innovative partnerships which enabled its development and production for a cost of less than US$0.50 per dose – making it both affordable and sustainable in the region.

MVP orchestrated a triangular partnership that included SynCo BioPartners, a company based in the Netherlands that initially produced the raw materials for the vaccine; the manufacturer, the Serum Institute of India; and the US Food and Drug Administration’s Center for Biologics, Evaluation and Research (CBER), which developed an innovative conjugation method. That method was transferred to the Serum Institute, which scaled up the method and mass produced the vaccine.

The final vaccine was ready for testing in 2005. It consisted of a PsA polysaccharide protein conjugated to the tetanus toxoid (a PsA-TT vaccine). After a rigorous testing process, the vaccine was licensed in India in December 2009, and certified by WHO in June 2010 for use in 1 to 29 year olds.

“The first introduction took place in 2010, right after licensure. There was no time lost between availability of the product and introduction,” Préziosi recounted.

Burkina Faso, Mali and Niger administered 20 million vaccines, leading to a dramatic fall in disease the following season. “The only confirmed MenA cases were among non-vaccinated individuals,” Préziosi said. In addition, a carriage study being conducted in Burkina Faso has already also shown a dramatic reduction in MenA carriage, she added. No safety issues have emerged, and that surveillance is ongoing.
In 2011, an additional 35 million doses were administered when Mali and Niger finished their country-wide vaccination, and Nigeria, Cameroon and Chad initiated theirs. In 2012, 55 million doses will be given, and four more countries will introduce the vaccine.

The vaccination program has addressed several challenges. “First and foremost is the country co-financing,” she said. The GAVI Alliance is financing vaccine cost and half of operational costs. Countries must fund the rest of the operational costs, which has sometimes been difficult.

Country preparedness and cold-chain capacity has also been a major problem. “Human resources, coordination, planning, social mobilization, vaccine distribution, waste management is a major task,” she said.

Also critical is continued surveillance to track the vaccine’s effects on MenA disease and on other serogroups, Préziosi said, noting the difficulty of finding funding for surveillance.

“The first introduction took place in 2010, right after licensure. There was no time lost between availability of the product and introduction.”

~ Marie-Pierre Préziosi, Meningitis Vaccine Project, France

**MenAfriVac Roll-out Plan 2010 - 2012**

*Mass vaccination campaigns among 1 to 29 year-olds*

2010

~20 Million vaccinated
Burkina Faso, Mail, Niger
September 2010: Pilot introduction ~1 M
→ passive + active surveillance of serious AEFIs
December 2010: Introduction ~19 M

2011

~35 Million vaccinated
Mali, Niger + Nigeria, Cameroon, Chad
Mali and Niger: country-wide completion
Nigeria, Cameroon, Chad: priority districts/states

2012

~55 Million to be vaccinated
Nigeria, Cameroon, Chad
+ Senegal, Ghana, Benin, Sudan

High vaccine coverage: reached among all age groups in all countries (administrative coverage 92-100%, coverage surveys 63-98%)

No safety concern: serious AEFIs mostly coincidental or when related, anaphylactic or expected.
SESSION V:

PREVENTION OF MENB DISEASE

A vaccine for meningitis B that provides broad coverage, strong protection, and good duration has challenged researchers for more than 20 years. The difficulty lies in the fact that the MenB capsule is poorly immunogenic, and in some ways mimics human proteins, making the capsular proteins a poor target for a vaccine. Presenters in Session V reviewed the specific obstacles to overcome and the unique methods being developed to do so.

CHALLENGES FOR THE PREVENTION OF MENB DISEASE

Dr. Wilfrido Coronell, University of Cartagena, Colombia, GIES group (Group of Research in Health Economics).

In February 2012, a meningococcal serogroup B outbreak struck southeast of Cartagena in Colombia. In two days 3 children died, two with meningococcemia and one with meningitis. One of them died within two hours of admission to hospital, his cousin had died the day before.

“This is a pathology that doesn’t wait,” Dr. Coronell said. “It has a very fast evolution, fatal. A patient can die within approximately 24 hours.” Even with adequate antibiotic treatment, mortality rates are still between five and 15 percent.

A number of vaccines have been developed against N. meningitidis, including polysaccharide vaccines; conjugate vaccines for serogroup C and A; a quadrivalent conjugate for covering A, C, Y and W-135; and outer-membrane vesicle-based vaccines for serogroup B.

However, there is no broad acting vaccine for serogroup B, which accounts for about 30 percent of all cases globally, with great variation from country to country. Serogroup B is responsible for 83 percent of meningococcal disease in Australia, 59 percent in Canada, 67 percent in Argentina, 60 percent in Chile, and 39 percent in Colombia.

Meningococcal serogroup B is also a highly fatal type: in the UK between 1999 and 2006, 19 percent of invasive cases of serogroup B were fatal, Coronell said. It is particularly common in infants, and in the United States it went from causing 0.16 cases per 100,000 infants to 3 per 100,000.

Two traits particular to group B meningococcal have complicated the process of vaccine development: One is the polysaccharide capsule is poorly antigenic, and second its polysaccharide proteins mimic human antigens, raising the risk of an autoimmune response to a vaccine.

To overcome these challenges, researchers have adopted reverse vaccinology, using DNA sequence data of the N. meningitidis to identify novel antigens for a vaccine. Three target proteins have been identified: factor H-binding (FHB) protein, Neisseria adhesin A, and heparin binding antigen, each eliciting significant levels of protective antibodies.

Vaccines based on these proteins could potentially protect against multiple meningococcal serogroups, as the proteins are common to all. Both Novartis Laboratories and Pfizer are working on developing MenB vaccines using such surface proteins.

But vaccine development against serogroup B has not been easy, due in part to the great genetic variation of these proteins. FHB, for example, has 300 different variants, of which three main variants or two sub-families have
been identified. These are: variant 1 or sub-family B, and variant 2 and 3 or sub-family A.

Coronell said that development of a broadly effective vaccine against serogroup B, has important questions still must be answered: “We have to know the distribution of these proteins, their sequence diversity, their antigenic expression, and there capacity to induce serum bactericidal activity.”

A further complication is that the dominant variant differs among age groups. In children under one year of age, variant 2 prevails. In children older than 1 year of age, variant 1 prevails. The variant 2 prevails in carriage in adolescents, while has been found relationship between variant 1 with invasive forms of meningococcal disease. Whereby to choose which variant to work with, vaccinologists need to know at what age the population will be vaccinated.

As work on potential MenB vaccines continues, Coronell reminded the audience of these words from Dr. Stanley Plotkin: “The impact of vaccination on the health of the world’s people is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth.”

**THE CUBAN EXPERIENCE WITH ROUTINE USE OF SEROGROUP B OMV VACCINE**

**Dr. Franklin Sotolongo Padron**, Finlay Institute, Cuba

Dr. Sotolongo described the painful experience with meningococcal disease that led Cuba to develop a group B vaccine. Prior to the mid-1970s, disease was sporadic. But in 1979, disease incidence began to increase, and cases caused by both group C and group B were on the rise. The Public Health Ministry intervened with a polysaccharide A/C vaccine for the population from 1 to 19 years of age.

The result was less than optimal: “The disease kept on increasing, but with a total predominance of serogroup B,” Sotolongo said.

Between 1976 and 1983, disease incidence increased from 0.4/100,000 inhabitants to 14.3/100,000. Among children under 1 year of age, the rate was 120/100,000.

The Ministry of Health made the meningitis epidemic a top priority, and undertook the development of a group B vaccine. Researchers worked with proteins expressed in vesicles shed by the bacterium from its outer membrane. They developed a vaccine containing six high molecular weight proteins, as well as group C polysaccharide.

Pre-licensing efficacy studies of the vaccine, dubbed Va-Mengoc-BC, began in 1987 and included more than 106,000 students 10-16 years of age. Efficacy was 83 percent. A subsequent study in Iceland had similar results—and found increased immunogenicity 20 months after vaccination with two doses.

The vaccine was launched in 1989 with a massive campaign targeting youth from three months to 19 years of age—a population of nearly 2,700,000 people. Within a year, coverage reached 75 percent.

Following introduction, the country implemented routine national immunization of infants with two doses, one at three months and a second dose at five months, and no booster.

The result: a rapid and dramatic decline in meningococcal disease. From 1984 to 1994, the case rate dropped from 14.1 (1,401 cases) to
0.8 (88 cases) per 100,000 people per year. By 2011, the rate was 0.1/100,000 with only 13 cases reported, and a reduction in all age groups.

Researchers subsequently studied the impact of vaccination on strain prevalence in carriage. Between 1982 (prior to mass vaccination) and 2002 (post-vaccination), serogroup B decreased from 68 to 17 percent of all isolates. Non-groupable strains isolated increased from 32 percent to 80 percent; a significant decrease in the hypervirulent strains cc 32 and cc 41/44 and the total absence of N meningitidis serogroup C has been observed as well.

“During more than 23 years, over 60 million doses have been applied, and they have had good tolerability and safety,” Sotolongo reported.

The vaccine has also proven efficacious in some other Latin American countries, Sotolongo said, and it provides protection for disease other than group B.

“During more than 23 years, over 60 million doses of Va-Mengoc-BC have been applied, and they have had good tolerability and safety.”

~ Franklin Sotolongo Padron, Finlay Institute, Cuba

Epidemiological Impact of Meningococcal B-OMV Vaccine in Havana City

DISCUSSION

A participant pointed out that the Cuban vaccine did not show the same efficacy in other Latin American countries, where different subtypes of group B were circulating, as it did in Cuba. He stated that SIREVA data show that meningococcal disease rates are higher in Cuba than in most Latin American countries, and asked whether this could be due to changes in the subtypes of circulating MenB.

Padron responded that rates in Cuba are actually very low: 0.1/100,000 or lower. “In Cuba, meningococcal disease is no longer a problem at all. There are no emerging serogroups, no serotypes or subtypes that occupied the place of the previous one.”

Another speaker clarified that SIREVA does not determine rates, they analyze samples submitted by countries.
SESSION VI:

NEW STRATEGIES TO PREVENT MENB DISEASE

Two major pharmaceutical companies, Pfizer Inc. and Novartis Vaccines and Diagnostics have vaccines in development for MenB. Cuba developed a vaccine more than 20 years ago, however it targets only the one principal clone that has plagued that country. Brazilian scientists are pursuing yet another route to MenB vaccine development. Session VI reviewed all of these efforts, and the challenges yet to be overcome.

PFIZER STRATEGY TO PREVENT MENB DISEASE

Dr. Laura York, Pfizer Inc.

Dr. York described the company’s work with bivalent rLP2086, an investigational vaccine for MenB disease. She said that group B is now the predominant remaining meningococcal serogroup in several parts of the world, including Europe, Australia and New Zealand, Canada and Latin America and the Caribbean.

York noted that adolescents are a group of particular concern, as the disease typically reaches a second peak in adolescents/young adults as they engage in activities that introduce them to new meningococcal strains. In addition, because adolescents and young adults have the highest carriage rate, “There is the possibility of controlling meningococcal disease in all of the population by targeting adolescents and decreasing carriage,” and potentially providing the benefit of herd protection, York said.

Pfizer is, therefore, developing a vaccine targeting adolescents.

To select a vaccine candidate, Pfizer screened for meningococcal antigens with very specific attributes: surface exposed, highly conserved, expressed universally in diverse strains, and ability to induce serum bactericidal activity.

The protein that was the best match was factor H binding protein (fHBP), which Pfizer refers to as LP2086. “We found that the protein induced good killing responses across diverse strain panels,” York said. The protein is important for the survival of N. meningitidis. Expressed during infection, fHBP(LP2086) binds human factor H, protecting MenB from attack by the immune system. Antibodies to fHBP (LP2086) inhibit factor H from binding to bacteria, and kill bacteria in the bloodstream.

Researchers found that the gene for fHBP is present in more than 2,500 invasive strains of MenB. They used genetic sequence data to identify two sub-families of LP2086. Studies demonstrated that the bivalent rLP2086 vaccine induced serum bactericidal activity against 160 epidemiologically relevant invasive strains of MenB, across the diversity of variants in both subfamilies.

Pfizer, therefore, developed a bivalent vaccine incorporating two variants of LP2086—one from each subfamily—to assure immunogenicity and broad strain coverage.

York reported that phase I and II clinical studies have shown the vaccine candidate to be well tolerated and to elicit a broad immune response against diverse strains of MenB. A Phase II study in 11 to 18 year olds in Australia, Spain and Poland found an acceptable safety profile; fevers were rare and generally mild. Based on the data, the vaccine is estimated to give broadest protection when given as three doses; incidence and severity of fever did not increase with each subsequent dose.
York reported that an ongoing comprehensive clinical program will support licensure for use in adolescents and young adults. “We are poised to start our Phase III studies, the large-scale safety and immunogenicity studies in adolescents and young adults,” she said.

Pfizer’s Investigational rLP2086 was Immunogenic in Adolescents hSBA Responses to MnB Bearing Divers fHBP Variants (US Study 2001, Subjects 11 to 18 Years of Age)

% of Subjects with hSBA Titer ≥ 1:4

![Graph showing immunogenicity responses](image)

*MnB strains expressing fHBP/LP2086 variant heterologous to vaccine antigen

Jansen – Pfizer Vaccines Presentation at MRF Conference 2011

MULTICOMPONENT MENINGOCOCCAL VACCINE: AN INNOVATIVE STEP IN THE GLOBAL FIGHT AGAINST SEROGROUP B MENINGOCOCCAL DISEASE

**Dr. Jeffrey J. Stoddard**, Novartis Vaccines and Diagnostics

“We view meningococcal disease very much as an infant disease,” Dr. Stoddard began, noting that the age-specific incidence is much higher in infants than in any other age group. In addition, there are large numbers of cases in adolescents. “So, it would be our view that having a vaccine that would span the age spectrum… really should be the goal of a MenB vaccine,” he said.

The Novartis approach assumes that a single subcapsular protein component would be insufficient, due to the immense degree of genomic plasticity in N. meningitidis.

“This is an organism that has such variability in terms of expression, and such an ability to change itself and recreate itself, that going after a single subcapsular protein component for a vaccine, to us did not make the most sense,” he said.

Novartis therefore set out to identify multiple subcapsular vaccine components to enable broad coverage across a number of strains. Ultimately, the company developed a four-component MenB vaccine candidate, dubbed 4CMenB.
It was the result of 20 years of research. Starting with genomic sequencing, Novartis identified over 2,000 MenB genes. Bioinformatics helped narrow down the candidate genes, whose proteins were expressed in E. Coli. Surface expression was confirmed, as was bactericidal activity, Stoddard explained.

The four components are important for the survival, function, and/or virulence of meningococci. The components are: Neisserial adhesion A (NadA); factor H binding protein (fHbp); Neisseria heparin-binding antigen (NHBA) and a major outer membrane vesicle protein (NZ PorA).

NadA promotes adherence to and invasion of human epithelial cells. fHbp enables bacterial survival by binding to factor H, and is involved in iron chelation and iron transport needed for bacterial growth. NHBA is present in virtually all strains and binds heparin, which is thought to provide meningococci with increased serum resistance. The outer membrane vesicle component is from the New Zealand strain, and was used in the vaccine that ended the 2003 New Zealand epidemic. The vaccine also uses an alum adjuvant.

“Fifty percent of MenB strains tested are covered by more than one of these antigens,” Stoddard said.

He summarized the company’s robust clinical development program that has included six studies in infants and toddlers, and three in adolescents and adults. Some 8,000 people have been enrolled, 6,354 infants and toddlers, and 1,584 adolescents and adults in the European Union, North and South America. Much of the data from those studies are already in the public domain.

Stoddard reported that in the clinical studies, 4CMenB demonstrated a protective immune response in infants, children and adults. Reactions seen after vaccination were similar to those seen after vaccination with other routine vaccines. For example, while fever occurred, it was manageable, short-lived, and predictable.

Novartis developed MATS, a meningococcal antigen typing system, to ascertain whether or not their vaccine would provide coverage in a given region. MATS is based on an ELISA test that measures the presence of the vaccines three recombinant protein antigens in bacterial isolates. Furthermore, “It allows for the determination of the minimum amount of antigen …needed to result in the killing of the organism,” Stoddard said.

Using MATS in Europe, Novartis predicts that 4CMenB would cover 78 percent of strains in five European countries (Norway, England & Wales, Germany, France and Italy). It will soon submit the vaccine to the European Medicines Agency for Authorization. In addition, Novartis is now working with the Adolfo Lutz Institute to assess potential coverage of strains in Brazil.

“There’s not going to be an effective broadly protective capsular-based vaccine for MenB, simply because the capsule looks like human antigen.”

~ Jeffrey J. Stoddard, Novartis Vaccines and Diagnostics
Addressing Dr. York, one participant noted that the benefit of vaccinating adolescents is the herd immunity that comes from reducing carriage. However, it is not yet known whether the group B protein vaccines under development will impact carriage.

In addition, group B incidence rates are actually highest in infants, not in adolescents. He asked whether there is data about the vaccine's safety and immunogenicity in infants.

York replied that Pfizer had tested the vaccine in infants and found an acceptably high rate of fever. “They were mild to moderate, but we didn’t feel it was something that we could take forward into infant immunization where there would be concomitant vaccines,” she said. On the other hand, there is a high disease burden in adolescents, which a protein vaccine could address, while also providing indirect benefits to other age groups. Pfizer also plans to work with the vaccine to make it acceptable for use in children.

Stoddard also fielded questions about the impact of the Novartis vaccine on carriage. He replied that while no data is available yet, a carriage study is underway in the United Kingdom. He said that there is reason to believe the vaccine may reduce carriage, because the NadA protein that it contains is involved in adhesion, and therefore the antibodies it generates could potentially reduce carriage.

Asked what recommendations he would make regarding the Novartis vaccine in Latin America and the Caribbean, Stoddard noted that Brazil had already implemented vaccination for MenC, which, in a sense, has already set a standard. “If the incidence of MenB is about the same, or certainly if it’s higher than the incidence of MenC, then presumably it makes sense to institute a MenB program as well.”

Questioned about the utility of MATS, given that it does not directly evaluate the immune response, Stoddard replied that MATS gives an indirect measure of serum bactericidal activity. “You have to connect the dots, but not very far,” he said. Stoddard also stressed that Novartis does not view MATS as “just a tool to leverage our vaccine,” but rather is sharing it with public health authorities around the world as part of a public/private partnership.
Dr. Martins described the current status of experimental MenB vaccines in Brazil, based on a 20-year effort by Bio-Manguinhos/Fiocruz. He noted the project of the Bacterial Technology Laboratory has several partnerships, including with the Norwegian Institute of Public Health, Instituto Fernandes Figueira, Instituto Adolfo Lutz and Instituto Butantan.

The vaccine combines Outer Membrane Vesicle (OMV) antigens from the two most prevalent strains of MenB in Brazil. The first strain is similar to that used in the Cuban vaccine, and the second is similar to the sub-types in Norway and New Zealand vaccines. The Brazilian vaccine also includes detoxified endotoxin, Martins explained.

In preclinical studies, mice were immunized with different vaccine preparations, and then challenged with a virulent strain of meningococcus B. The best survival was in the animals that received either the OMV vaccine or the Cuban vaccine (Va-Mengoc-BC), which served as the reference vaccine. Taken together, the antigens provide coverage for about 70 percent of the strains that were circulating in Brazil up to 2008.

The vaccine was sequentially introduced in a Phase I clinical trial, beginning with 6.25 micrograms of each strain, with a total of 12.5 micrograms during the first Phase I stage. During a second Phase I stage, 12.5 micrograms of each strain were delivered (total: 25 micrograms), and finally 25 micrograms were delivered during the third Phase I stage (total: 50 micrograms), which is the same concentration as the Cuban vaccine.

The successful Phase I study paved the way to a Phase II study in children 4 to 12 years of age, now underway, using the same sequential methodology and the same doses. Already, 70 children have been inoculated with 3 doses of the experimental vaccine at the lowest concentration (one-quarter the concentration of the Cuban vaccine), and 35 with the Cuban vaccine (full dose). Reactogenicity has been very low, and inoculation with 25 and 50 micrograms is in progress, without any serious adverse reactions, Martins reported. Preliminary immunogenicity results are promising.

An upcoming fourth dose and two subsequent blood collections will give insights on the duration of immunity and the effects of the booster reinforcement, Martins concluded.

**BRAZILIAN EXPERIENCE WITH THE DEVELOPMENT OF MENB VACCINES**

*Dr. Reinaldo Martins, Bio-Manguinhos/Fiocruz, Brazil*

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MODELING THE POTENTIAL IMPACT OF MENINGOCOCCAL B VACCINES IN LATIN AMERICA

Julio Vazquez, National Institute of Health Carlos III, Spain

“My question is: can we really conduct modeling of vaccine impact with the information at hand?” began Dr. Vazquez, who reviewed the information needed in order to model vaccine impact.

Examining the relationship between surveillance and laboratory data, Vazquez stressed that, “In order to design MenB prevention strategies, there is one basic thing that is needed: knowledge about age-distribution incidence.”

Decisions about vaccine introduction can only be made with solid information about the real burden of disease in the region. “In the majority of countries, we don’t know what the burden of disease is, or we suppose it’s not as low as available data suggests,” he said.

PCR and DNA sequencing is needed to fill the gaps in information about age distribution of disease, Vazquez said. But technology alone is not enough. A regional network needs to be organized to facilitate sequencing and engage laboratory clients – regional health systems and hospitals – to submit strains.

Other actions needed include:

- Clear case definitions of meningococcal disease syndromes
- Reform of the current system for selecting trainees for improved laboratory and data analysis
- Audits in hospitals and laboratories for quality control

“It is very important to know if things are being done correctly, if people trust generated data,” Vazquez said.

He attributed the huge variability in disease incidence rates among countries in part on an inadequate disease notification system.

Yet, “In spite of everything, things are being done. Countries are doing a tremendous effort to improve data analysis,” Vazquez said. As an example, he pointed to recent work determining the relationships among three group Y strains in Latin America.

In the past, when vaccines contained only one antigen, it was relatively simple to estimate the coverage it would provide by analyzing the presence of that antigen in disease isolates. The situation is different with the new vaccines, which can contain combinations of different antigens from different strains.

“The new vaccines will benefit us all tremendously, but they have complicated the lives of laboratories,” Vazquez said.

Novartis’ new four component vaccine provides a good example of the challenge now facing laboratories. The Novartis vaccine includes three newly identified antigens and a MenB outer membrane vesicle contained in the vaccine. However, there is a data base for only one of these elements (the fHBP protein), and even that data base is incomplete. “Therefore, reference laboratories don’t have this information right now. This information has to be generated,” he said.

“Latin America should get going at least to have a strain panel that’s representative… it should have at least classical genetic information,” Vazquez recommended. Furthermore, he noted that the strain panel needs to apply to new technologies, such as the Novartis MATS system, in order to evaluate the potential coverage offered by new vaccines.
Vazquez called out several considerations for countries deciding whether to adopt new serogroup B vaccines:

- Potential case coverage based on the knowledge of the strains associated with clinical cases
- Age distribution of clinical cases
- Possibility of adding new doses in current vaccination schedules, including parents’ receptivity to an additional vaccine for their children
- Impact of any new vaccines on carriage

Vazquez noted the latter point as particularly important. “This means herd immunity and an evident improvement in the control and prevention of disease,” he concluded.

“My question is: can we really conduct modeling of vaccine impact with the information at hand?”

~ Julio Vazquez, National Institute of Health Carlos III, Spain
CONCLUDING REMARKS

Dr. Ciro de Quadros, Sabin Vaccine Institute, US

In closing the meeting, Dr. de Quadros framed the greatest challenge facing Symposium participants with a simple question: “What are we going to do with all this information we now have?”

Answering the question, de Quadros presented his take-home messages from the two days of discussion:

First, meningococcus is no longer a forgotten disease in the region. “We get out of here really knowing that we have this disease in the Americas.”

Yet, we do not know the entire burden of the disease in the region. A lot remains to be done in terms of diagnosis and surveillance.

One thing that is clear is that the cost of the disease in the region is enormous. Given the preliminary data, it appears there are at least 10,000 cases every year in the region, at a cost of between US$50 million to US$60 million annually, if hospitalizations, opportunity costs, and long term effects are included.

Vaccines against this disease already exist, and two countries in the region are using them.

Furthermore, there is a pipeline of vaccines against the greatest challenge of this disease: meningococcus B.

De Quadros noted that new MenB vaccines are being developed both by international pharmaceutical companies, and by two groups in Latin American. “This is extremely important because one of the goals we should have is regional self-sufficiency in vaccine production.”

Addressing the participants, de Quadros said, “You are, in my opinion, the main ones responsible for the success of vaccines in Latin America. … In the future, when many more countries are using the meningococcal vaccine, I’m going to remember that this movement started here in this 1st Regional Symposium.”