INTRODUCTION

From December 9 - 11, 2013, more than one hundred people met in Cancún, Mexico, for the Regional Meeting on Sentinel Surveillance of Rotavirus, Bacterial Meningitis and Pneumonia. Convened by the Pan American Health Organization (PAHO) in conjunction with the Albert B. Sabin Vaccine Institute, the meeting was significant for its breadth, timing, and its willingness to frankly critique the strengths and weaknesses of the regional surveillance systems for three major causes of childhood disease.

The meeting came at a pivotal time for disease surveillance in the Americas. On the one hand, surveillance systems for rotavirus, bacterial meningitis and pneumococcus have developed and matured. On the other hand, significant gaps in capacity and technical proficiency remain, presenting challenges to the quality and utility of data generated by the networks. As one participant said, the meeting provided a time for reflection, to assess the quality of information generated by the region’s surveillance systems for rotavirus, and for bacterial meningitis and bacterial pneumonia.

It is also a time of global assessment of vaccine surveillance capabilities and performance, as the vaccine community focuses on achieving goals set by the Global Vaccine Action Plan (GVAP). Building off the Decade of Vaccines, GVAP was approved in 2012 by the World Health Assembly, representing 194 member states. GVAP was built on existing strategies, including the Visión y Estrategia Regional de Inmunizaciones, or RIVS, in the Americas.

The GVAP outlines the actions needed through the year 2020 to achieve equality in global immunization. GVAP objectives include the worldwide eradication of polio; the setting of regional, national and local vaccination goals; and the development and introduction of new vaccines in all countries with the overall objective of reducing infant mortality. By 2020 all lower and middle income countries are expected to introduce at least one new vaccine.

In the Americas region, immunization programs are defined as public priorities, public assets and matters of state, and the region has already made significant progress in the
introduction of new vaccines. Sixty percent of births in Latin America and the Caribbean take place in countries where the pneumococcal vaccine is in use, and 87% of births are in countries that use rotavirus vaccine. Even countries that face steep economic challenges are advancing their immunization agendas. Haiti, for example, recently introduced the heptavalent vaccine, and plans to introduce rotavirus vaccine in 2014. Bolivia will soon introduce pneumococcus.

Vaccination coverage in the Americas Region (as measured using the third dose of DPT vaccine as an indicator) is among the highest in the world. The majority of nations in the Americas have coverage above 90%, compared to a global average (162 countries) in 2011 of 83%. However, coverage inside each country varies a great deal when looking at local levels.

Achieving GVAP’s goals—at global, regional and national levels—will require heightened efforts in the development and delivery of vaccines, and in surveillance of vaccine-preventable diseases. With this in mind, the World Health Organization (WHO), and its regional arm the Pan American Health Organization (PAHO), recently conducted strategic reviews of the global and regional vaccine laboratory and surveillance networks for rotavirus, bacterial meningitis and pneumonia. They evaluated the efficiency and needs of the networks, and released recommendations to improve network functioning. Their findings informed the Cancún meeting, enabling participants to consider regional and national experiences within these broader contexts.

With the participation of over 90 National Level New Vaccines Surveillance Managers, laboratory professionals, and other stakeholders, the meeting assessed progress and gaps in new vaccines surveillance in the Americas, and pointed toward critical next steps.
Less than a decade has passed since the introduction of a new generation of vaccines against each of the three pathogens—rotavirus, meningococcal and pneumococcal. Over this time, surveillance networks have also developed, and continue to evolve. Differences between rotavirus and bacterial meningitis and pneumonia present some distinct challenges for their respective surveillance networks.

**Rotavirus** is the most common diarrheal disease among children, and one of the largest causes of vaccine-preventable deaths in the world. Rotavirus has a standard case definition, a specimen that is relatively easy to obtain, and can be detected with the use of a straightforward diagnostic test. However, it is just one of a number of causes of childhood diarrhea.

There are two vaccines against rotavirus available. Rotarix (GSK) is based on a single human rotavirus, G1P[8]. RotaTeq (MSD) is a human-bovine rotavirus reassortant that combines antigens from G1, G2, G3, G4, and P[8]. All data indicated that both vaccines protect against serious disease caused by a wide range of rotavirus strains. The purpose of the rotavirus vaccines is not to end all childhood diarrhea (which has a wide range of causes), but to prevent the majority of severe disease, hospitalizations and deaths caused by rotavirus.

On the bacterial side, *Streptococcus pneumoniae* causes the largest disease burden of the three pathogens. It is the main cause of community acquired pneumonia and meningitis in children and the elderly, and of septicemia in HIV-infected persons. Invasive pneumococcal diseases can cause acute sinusitis, ear infection, conjunctivitis, meningitis, bacteremia, sepsis, and other infections. It is also one of the most common causes of bacterial meningitis in adults, along with *Neisseria meningitidis*. Yet, *Streptococcus pneumoniae* does not have an adequate diagnostic test; and does not have a clear specimen to obtain.

Countries have also introduced the pneumococcal conjugate vaccines (PCV). Currently there are two PCV vaccines available: PCV 10 and PCV 13. These vaccines represent a great advance.
over early vaccines for pneumococcus, in that they are all immunogenic in infants. Prior to introduction of the first PCVs, clinical trials found efficacy of between 23% and 37% against all pneumonia, and an efficacy of between 65% and 94% against invasive disease caused by the vaccine strains.

*Nisseria meningitidis* causes meningitis, an infection of the thin lining that surrounds the brain and spinal cord. It is a relatively rare but unpredictable and potentially devastating disease. It is also a cause of life threatening blood infections and bacterial pneumonias. The disease has a fatality rate of 10% to 20%, and about 20% of survivors suffer long-term health impacts from the disease. There are a variety of diagnostic tests, but they are complex and the specimen is difficult to obtain.

A number of different types of vaccines are available against different strains of *N. meningitidis*, including a meningococcal A conjugate vaccine, C conjugate vaccines, tetravalent A, C, Y and W135 conjugate vaccines and meningococcal polysaccharide vaccines.

As of December 2013 Fifteen countries and one territory in LAC have introduced rotavirus vaccines with over twenty having established rotavirus surveillance; Twenty have introduced pneumococcus conjugate vaccines;
After vaccine introductions, surveillance networks began to face new challenges related to monitoring the vaccines’ impacts on public health and pathogen behavior. After a country has introduced a vaccine, surveillance should be able to answer at least three of the four questions:

1) What is the vaccine impact on public health?
2) How does strain distribution for that pathogen change?
3) What is the impact of strain changes on vaccine effectiveness?
4) How should the detection of unusual strains be interpreted?

In order to answer such questions, the surveillance system must collect consistent data both on strain genotypes, and on the vaccine status of patients; their age; and the clinical severity of their disease. Such data collection requires increased capacity and resources.
For the region as a whole, data indicates that since rotavirus vaccine introduction, there has been a 25% decrease of rotavirus in children less than five years of age. Epidemiologists suspect that this decrease is much higher in children under two, however the data is not available yet. Recently countries started to desegregate information by age.

But the lack of age desegregated data underscores a problem in the system, as it is just one of many shortfalls in the availability of quality data, which limit the usefulness of surveillance efforts. The conference examined the challenges to improved surveillance in some detail.

One of the challenges to improving surveillance is learning how to utilize the collected data to measure disease impact. It is important to use quality tools while collecting surveillance data in order to generate consistent information. Otherwise, it’s not worth spending resources to collect unreliable data that cannot be used properly.

The next sections will look at the surveillance of each disease in more detail, from the global to regional and national levels.

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**Real-World Decline in Childhood Diarrhea Deaths after Rotavirus Vaccination in Mexico**

![Graph showing decline in childhood diarrhea deaths](image)

*Gastanaduy Pediatrics 2013*
PAHO reported on a strategic review conducted on the global laboratory network for rotavirus that was done by outside experts for WHO.

Begun in 2008, today the global rotavirus network includes 153 laboratories that confirm suspected cases of rotavirus. The Global Reference Laboratory is at the Centers for Disease Control and Prevention (CDC) in the United States, in Atlanta. The network includes nine Regional Reference Laboratories, including one in Brazil for Latin America and the Caribbean (the LAC region); 36 National Laboratories, and 107 Sub-national Laboratories that work out of sentinel hospitals.

The goal of the review was to determine if the network was working in the most efficient and effective ways, and meeting its original goals of understanding the presence of disease; monitoring disease trends over time; and determining genotype distribution.

**20 LAC countries that monitor for rotavirus, and the year surveillance began:**
- **2005:** Bolivia, El Salvador, Guatemala, Guyana, Honduras, Paraguay, Suriname, Venezuela (begun in 2005);
- **2006:** Nicaragua, St. Vincent and the Grenadines
- **2007:** Chile
- **2008:** Ecuador, Panama
- **2009:** Brazil, Colombia, Peru
- **2012:** Anguilla, Dominica
- **2013:** Dominican Republic, Haiti

**PROGRESS AND PROBLEMS IN ROTAVIRUS SURVEILLANCE**

**Strategic Review of the Global Rotavirus Network**

In 2008, the global rotavirus network includes 153 laboratories that confirm suspected cases of rotavirus. The Global Reference Laboratory is at the Centers for Disease Control and Prevention (CDC) in the United States, in Atlanta. The network includes nine Regional Reference Laboratories, including one in Brazil for Latin America and the Caribbean (the LAC region); 36 National Laboratories, and 107 Sub-national Laboratories that work out of sentinel hospitals.

The goal of the review was to determine if the network was working in the most efficient and effective ways, and meeting its original goals of understanding the presence of disease; monitoring disease trends over time; and determining genotype distribution.
The review determined that overall, the laboratories were meeting these goals, and that the quality control and assurance program was adequate. However the review also identified overarching issues in need of attention and improvement. These are:

- Strengthen global network cohesion, while maintaining needed regional individuality
- Ability to use data for real time monitoring of site or lab performance needs to be improved, including through:
  - The collection of case-level data in standard format
  - The linking of laboratory results with the clinical and epidemiologic data
- Resources are insufficient for a network of its size, and need more strategic allocation, especially in the areas of:
  - Resources for network data management and analysis
  - The capacity of Reference Laboratories need to match the number of sentinel sites supported
Regional Rotavirus Surveillance Network

Rotavirus surveillance in the countries of the Americas began in 2004 in just three countries (El Salvador, Paraguay and Venezuela), and vaccine introduction began in 2005. As of 2013, surveillance had begun in 15 countries and one territory. Today the regional network consists of one Global Reference Laboratory (at the CDC in Atlanta); one regional reference laboratory in Brazil; and 14 national laboratories in Latin America and the Caribbean. Of the later, eight can do genetic sequencing and six can only detect the viral antigen using ELISA.

Overall, the regional laboratory network is being strengthened. Individual countries reported the improvement of capacity over time. For example, Venezuela began sentinel surveillance in 2004, giving it a solid two years of data prior to rotavirus vaccine introduction in 2006. This has enabled accurate measurement of vaccine impact. The success is motivating, and Venezuela has been working hard to integrate the work of surveillance. Each sentinel hospital has three components: epidemiological, clinical, and laboratory, and the three are in constant communication, in addition to the central national reference laboratory.

For the regional network overall, quality assessments and quality control are also improving, and some countries have been able to improve their rotavirus genotype data, enabling important observations, including on vaccine impact and on genotype change.

Surveillance Findings: Tracking Genotype Change

One critical role of the regional surveillance system is to determine how rotavirus genotypes are changing, and whether changes in genotype distribution are related to vaccine introduction. Regarding this topic, the US CDC reported on conclusions and recommendations of the Experts Meeting on Rotavirus Genotypes in the Region of the Americas.

Rotavirus genomes can recombine through genetic reassortment (like flu virus), and the available genotype data reaffirms that genotype distribution changes continuously,
and in different ways in countries with and without vaccine introduction. It also varies among sub-regions, within countries, and with regional annual variability. However, no particular patterns are associated with the use of either rotavirus vaccine. The changes appear to reflect natural variation over time.

However, others pointed out the severe limitations of genotype data in the Americas. There is an overall paucity of this data, and when it does exist, it is rarely linked to information regarding the related patient’s age, sex, origin or onset.

These gaps affect the usefulness of surveillance and genotype data in other ways as well. Ideally, genotype data would assist in providing insights into the significance of a variety of disease events, including outbreaks; rotavirus in older children, adults and the elderly; circulating vaccine reassortant strains; circulating animal related strains; and apparent vaccine failures.

Identification of Group A Rotavirus (RVA) Genotypes Pre- and Post-Introduction of Rotavirus Vaccine (Rotarix –G1P[8]) in Brazil

Fiocruz reported on the impact of Brazil’s national rotavirus vaccination program, begun in 2006. After the introduction of the rotavirus vaccine, Brazil had 1,500 fewer deaths under five due to diarrhea (2007-2009). Detection of RVA in subjects with acute diarrhea declined significantly from 2010 to 2013. At the same time, detection of Norovirus increased. Since introduction of the vaccine, there has also been a clear shift in RVA genotype distribution, especially between 2010-2013. Among these changes, on a national level G1 declined from more than 50% before vaccine introduction, to less than 5% after. G2 increased from less than 5% before to about 80% after. Within this broad picture, there was a huge amount of regional variation. In addition, a study by John Patton at the US National Institutes of Health (NIH) concludes that the shift in rotavirus genotype distribution may have positively influenced the performance of Rotarix due to a reduction in the prevalence of heterotypical strains.
Regional Rotavirus Surveillance Network Challenges

The Regional Rotavirus Surveillance Network does face some challenges, including:

- Inconsistent capacity for and consistency of genotyping rotavirus specimens
- Lack of or inconsistent use of case identification
- Limited linkage of laboratory data with clinical and epidemiological data (including vaccine status of patient)
- Inconsistent reporting of genotype data to national Ministries of Health and to PAHO
- Lack of robust laboratory teams at sentinel sites
- Lack of funding to support capacity building within the Regional Laboratory Network

Country representatives addressed specific examples and concerns. It was noted that there is currently very little commitment from clinicians to support surveillance. The network has therefore developed a plan to provide incentive through acknowledgement of and feedback to their work, with the goal of fostering a culture of feedback for clinicians, so that they will know the value of the information they monitor and provide.

Countries are also experimenting with different strategies for filling data gaps, including the vaccination status of sick children. It was noted that an episode of rotavirus is alarming, and that when the mother rushes the child to hospital, she often forgets the child’s vaccination card. To address this, Nicaragua is working with local health centers to support the collection of individual vaccine histories, and hospitals in Venezuela have set up a system for follow-up contact with the mother reminding her to bring in the card.

Recommendations for Rotavirus Surveillance

A number of recommendations to improve the Regional Rotavirus Surveillance network were discussed, including:

- Prioritize data quality over quantity of samples
- Report genotype data 2x per year (minimum requirement for members of WHO’s global laboratory network)
• Standardize sample selection for genotyping; Examine country-level genotype distribution
• Compile information on patient age, disease severity, and vaccine status; link strain and epidemiology data
• Increase Regional Reference Laboratory support for country rotavirus surveillance through training and capacity building; improved quality assurance; generating feedback and support in problem resolution
• Improve national supervision of hospitals
• Hospitals should conduct monthly reviews of surveillance data; strengthen teams at sentinel sites, such that each includes (at least one clinician, one person in charge of surveillance, and one in charge of labs); and improve training of personnel
• Incorporate the Strategic Advisory Group of Experts (SAGE) on Immunization and Technical Working Group (TWG) recommendations in the Regional Rotavirus Lab Network

Overall, it is more beneficial to have a fewer number of sentinel hospitals that are collecting quality data than many sentinel hospitals that are collecting unreliable data.

Regional Challenge Up Close: Rotavirus Genotyping

The conference paid considerable attention to the issue of genotyping specimens. Currently, only a fraction of confirmed rotavirus specimens in the region are genotyped. In one Latin American country, the percentage of specimens genotyped fell from 73% in 2008, to a low of 12.8% in 2009, and as of 2012 only one-fifth of specimens that had been positively identified as rotavirus through sentinel surveillance are genotyped. Meanwhile, the percentage of untypable specimens had increased dramatically, and represented 75% of all rotavirus specimens in one country in 2012. But some samples that appear non-typable in a sentinel laboratory, are typable at a regional reference laboratory.

One important function of the surveillance network is to identify new genotypes as they emerge, and enable other laboratories in the region to look for them. A regional exercise held in 2013, tested the networks capacity to do so, and its overall expertise in antigen detection, genotyping, and response time.
Of 14 laboratories that did the ELISA antigen detection test, all got a score over 80% with an average of 97.3%. Of those that did the genotyping test, all responded, and four got a score over 80%. Five were penalized for being tardy.

Despite these generally high scores, the exercise was a challenge for the laboratories. They had trouble detecting the mix of genotypes, especially one that was new and unexpected.

This raises the question of how to prepare to face new strains.

The region continues to work on improving genotype identification, encouraging sample preservation, use of kits for RNA extraction and RT-PCR, and quality control in the Regional Laboratory Network. Last March the surveillance network held a training for 10 countries to increase capacity in virus genotyping.

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**El Salvador’s Road to Ending Rotavirus-Related Deaths**

An outbreak of childhood diarrhea in 2000 and 2001 highlighted diarrhea as a cause of under-five deaths. After an investigation demonstrated that rotavirus was present in 58% of the samples taken from children hospitalized for diarrhea at Zacamil Hospital during the outbreak, the country began sentinel surveillance for childhood diarrhea in 2002 in five hospitals. Based on surveillance results, El Salvador initiated free and universal vaccination against rotavirus in October 2006.

Since then, the country has strengthened its technological capacity for surveillance, including through acquisition of PCR molecular techniques and implementation of RT-PCR technique at the national reference laboratory. In 2009, El Salvador implemented a web-based data capture tool that collected all the data from sentinel sites and laboratories. In 2011, surveillance was extended to 11 sentinel units.
These changes have enabled tracking of vaccine impact, showing a steady decrease in suspected rotavirus hospitalizations. Prior to vaccine introduction, rotavirus positivity was at 62%. After vaccine introduction, the rate decreased to 49% in 2007, with vaccine coverage of 58%, and to 16% percent in 2008, with vaccine coverage of 83%. But positivity climbed up again in 2009, due to a shortage of funds to purchase vaccines.

Surveillance has also measured vaccine impact rotavirus-related deaths. 2009 saw the countries last three deaths—none have been reported since. Among the challenges ahead is consolidating the development of the integrated sentinel surveillance system through incorporating additional tools and data protocols. “It is a fairly expensive task, and it’s one of our main challenges, along with the sustainability of the national reference laboratory. Having all the necessary resources and technology for maintaining this surveillance will be a big challenge.”
The Global Laboratory Network for Surveillance of Bacterial Pneumonia and Meningitis has grown quickly over the past five years, along with demand for its data and the commitment of National Ministries of Health. Starting with 36 countries in 2009, by 2012 it included 58 countries. Today, the network’s 142 participating laboratories includes: two Global Reference Laboratories; nine Regional Reference Laboratories (two of them in the LAC region); 27 national laboratories; and 104 Sub-national Laboratories.

The network recently participated in a global strategic review which evaluated how effectively it is able to support surveillance, and whether goals set in 2008 were being met. Those goals were: to document the presence of disease and describe disease epidemiology; provide data to help estimate disease burden; have a system to measure vaccine impact; track circulating serotypes; and track antibiotic susceptibility.

The review noted several achievements and limitations at the global level:

- A functioning global network, with high levels of training and a strong external program for quality evaluation and quality control
- Overall, regional reference laboratories functioning at a high level, but with some variation regarding technical rigor
- Limitations include that the size of the network currently exceeds its capabilities to provide consistently high management and supervision
- The quality of data is inconsistent, particularly the linkages between laboratory and clinical and epidemiological data
- Two of the six WHO regions have no case monitoring system that allows linking of clinical, laboratory and epidemiological information
- Sentinel sites have uneven capacity to microbial agents; and may not rigorously apply criteria for case definition
– Limited ability in many settings to analyze cerebrospinal fluid and determine whether meningitis cases are associated with bacterial infection
– Serotype data is insufficient for meeting surveillance objectives

Another challenge for the global network is to do a better job of communicating the data to countries, to donors, and to the public.

As more countries prepare to introduce new vaccines, it becomes even more important to have strong functioning surveillance networks. One key conclusion of the strategic review was the need to narrow the number of sites and improve the quality of data each provides.

Moving forward, careful consideration needs to be given to which sentinel sites are best poised to receive intensified support.

**PCV Challenge: Measuring vaccine impact**

Measuring PCV impact was recently the topic addressed by the global International Immunization Technical Advisory Group (ITAG) meeting in Geneva. The global ITAG addressed the over-riding question of whether more impact studies are needed and came to general agreement that the efficacy of the PCV vaccine has already been demonstrated through numerous studies, showing a clear impact on disease. Indeed, the experts agreed that every country does not need to conduct a formal impact evaluation, and that it can be appropriate to bridge data from one setting to another and/or use models that predict impact.

Nonetheless, there are good reasons to measure the impact of vaccines. First, vaccine behavior in the real world can vary in different contexts, and may differ from the results of early clinical trials. These were mostly conducted using the PCV7 vaccine, whereas most countries are now using either PCV10 or PCV13. In addition, natural changes over time affect the distribution of circulating strains, and may affect vaccine effectiveness.
Furthermore, in order to maintain and build support for vaccination programs, it is important to show policy makers and other partners both the direct benefits of the vaccine to children and the indirect benefits to non-vaccinated populations who are less frequently exposed to disease. Showing the benefit of vaccination programs can justify their costs—which can be high. Indeed, the ITAG agreed that cost-effectiveness analysis at the country level is likely to become key for the sustainability of vaccine investments, and for communicating with policy makers.

But demonstrating impact is complex, and presenters discussed the pros and cons of different approaches, including studies of nasopharyngeal carriage; comparison of pre- and post-introduction data; and the role of case studies.

The ITAG group had focused on the usefulness of studies of nasopharyngeal carriage, which can be seen as a proxy for the impact on vaccine-type disease. Studies conducted before and after introduction of vaccine will virtually always see a fall in vaccine-type strain carriage, which can be helpful data for convincing skeptics of the value of vaccination. On the other hand, carriage studies also show that non-vaccine strain types tend to increase. But this information has limited value in evaluating PCV impact. Indeed, it can be misleading in terms of assumptions made about “replacement disease,” since increases in carriage of non-vaccine strains does not mean there is an increase in disease caused by those strains.

Nasopharyngeal carriage studies not only present challenges in monitoring impact but they are also logistically complicated and expensive. On the whole, the expert group found they are not a satisfactory end point for monitoring impact.

Another way to measure impact is to compare changes in disease burden before and after PCV introduction. Theoretically, a number of factors could be measured, including invasive diseases, pneumonias, and deaths. Another advantage is that it measures population impact rather than individuals, meaning it is not necessary to know individual patient’s vaccination status—information that is frequently unavailable.
However, there are disadvantages with this method as well. ITAG considered studies that evaluate the impact of vaccines on pneumonia from any cause. But because not all pneumonia is caused by pneumococcus, results pre- and post-vaccination can be complicated to analyze. To start with, they require a baseline of at least two years of good quality consistent data prior to vaccine introduction, and five years of follow-up monitoring, often covering a large population.

Additionally, a number of major factors independent of vaccine introduction can impact disease. These include use of antiretroviral therapy (which reduces the risk of pneumonia), and changes in population, migration, nutrition, health services, payment plans, and factors related to the bacterium itself. To understand disease impact, such factors must also be taken into account.

One study which was cited as illustrating this complexity, was a study of an indigenous population in the United States with a high risk of pneumococcal disease. The study initially found a very significant decrease on the incidence of invasive disease after universal introduction of PCV7. Upon further scrutiny, however, researchers realized that the decrease began before vaccine introduction. Teasing out the reasons for this, including changes in clinical practices, made it difficult to interpret the study results with confidence.

Finally, the diagnosis of pneumonia syndrome is itself riddled with complexities. Chest X-rays are the best tool for identifying severe hospitalized pneumonia. But x-ray interpretation is imperfect, and two different clinicians may interpret the same x-ray in opposite ways. This ambiguity can impact findings of vaccine efficacy as well. One study that used chest x-rays as the endpoint in assessing efficacy against pneumonia performed two different sets of x-ray readings. The reading that used the WHO standardized protocol found 30 percent vaccine efficacy; while the other reading found just 20 percent.

Case control studies were also discussed as an approach to measuring vaccine effectiveness. They do not require a baseline of data prior to introduction, and are not affected by trends. They also give the opportunity to evaluate things that were not investigated in the
original clinical trial, such as efficacy against individual serotypes. On the other hand, case control studies entail rigorous preparation and planning. As an observational study, confusion and errors almost inevitably arise.

Presenters highlighted the many tradeoffs in designing impact studies, and the need to recognize the strengths and limitations of each. The key point was to be aware of the methodological complexity of any impact study, in order to interpret surveillance and other tools as accurately as possible.

Assessing the LAC Regional Surveillance Network for Bacterial Pneumonia and Meningitis

The regional network is aligned with PAHO’s SIREVA II system, which monitors the three bacterial agents responsible for the great majority of pneumonia and meningitis in the region: S. pneumoniae, H. influenzae and N. meningitidis. SIREVA II works with sentinel laboratories in hospitals to monitor the trends of the strains over time and to track pathogen susceptibility to antibiotics. The SIREVA network has two regional reference centers: The National Institute of Health in Colombia and the Adolfo Lutz Institute in Brazil. There are 20 countries of participating laboratories. Within countries, the SIREVA network depends on and reports to national Ministries of Health.

External performance reviews conducted under the SIREVA II framework have been a critical component of monitoring and improving laboratory performance. Within the laboratory network, the Reference Laboratory in Colombia is responsible for supervision and quality control for 11 countries in LAC, while the Brazil reference laboratory is responsible for nine countries. The two reference laboratories also conduct international external evaluations. In 2013, it began conducting direct audits of network laboratories with partner laboratories in Canada, England, Spain, and South Africa.

External performance reviews assess several parameters regarding the three micro-organisms under surveillance. These include identification, serotyping, sensitivity to antibiotics, and interpretation of the results. SIREVA reports the results back to the laboratories, allowing for continuous education, and the identification and solving of laboratory problems.
In order for external performance reviews to function properly, both the reference and regional laboratories and all of the countries need to comply with the timeline of activities and carefully review lessons learned from the results.

Colombia’s first hospital-based sentinel surveillance center, is scheduled to start functioning in January 2014, with the assistance of committed hospital staff and a professional exclusively dedicated to the site. Its objective is to have continuous, systematic surveillance of bacterial pneumonia and meningitis in children under five, generating timely, valid information used to orient prevention, surveillance and control measures.

However, it was noted that significant gaps still limit the effectiveness of the regional network. In the Americas last year, there was no serotype data associated with surveillance. Limitations within individual countries can also affect the region as a whole. For example, only 11 countries in the region conduct surveillance in sentinel sites for both bacterial pneumonia and meningitis.

But countries also reported on progress. Nicaragua, for example, reported that since initiating surveillance for bacterial pneumonia and meningitis in June 2011 at two sentinel hospitals in the capital city of Managua, the surveillance system has succeeded in putting in place national quality control of regularly submitted data, which is shared with other countries in the region.

Among the challenges noted in the regional network:

- Contamination is a major problem in regard to surveillance for *streptococcus pneumonia*; in one study, 700 of 2,300 strains could not be identified because of contamination
- The surveillance network is missing serotype data for groups linked to sentinel surveillance
- External performance evaluations of laboratories are irregular
- Expectations for case identification are inconsistently met; those expectations include that 80% to 100% of suspect cases have x-rays; that 80% to 100% of probable cases have blood culture specimens; and that there is bacterial contamination in no more than 3% to 5% of culture specimens in probable pneumonia cases
Regional Challenge Up Close: Specimen Contamination

It was noted that the SIREVA laboratory network is high quality, but data from sentinel hospitals is riddled with problems originating in their hospital laboratories. Overall, the number of isolates is very low, and contamination rates are extremely high. Participants felt the high-quality platform of SIREVA is not being reflected in the sentinel sites.

Others stressed that SIREVA and sentinel surveillance are not two separate entities, they are integrated. Sentinel surveillance has the SIREVA network as its laboratory network. If the SIREVA network is working well within a country, theoretically hospitals with sentinel surveillance should have a laboratory component that also functions well.

But the reality is that often the isolates that arrive from the sentinel site to the reference laboratory are not viable. Therefore, serotype data is not available to be analyzed and interpreted. The problems seem to be in rooted in handling and processing the original sample, with contamination occurring in the laboratory.

Steps for strengthening regional surveillance include:

- Strengthen the technical and response capacity in network laboratories
- Strengthen the role of the national reference laboratories within the regional surveillance network
- Include sentinel laboratories in global external performance evaluations
- Increase capacity to include other bacterial causative agents of vaccine preventable diseases, especially pertussis

11 LAC countries that monitor for pneumococcus, and the year surveillance began:
2007: Ecuador, El Salvador, Guatemala, Panama, Paraguay
2008: Bolivia, Honduras, Brazil (only for Meningitis)
2009: Venezuela
2010: Peru
2011: Nicaragua
The problems being experienced by the sentinel sites are the same that SIREVA experienced when it first started 20 years ago. These are problems of sample collection, transportation of the samples, and the low number of blood cultures. SIREVA has had 20 years to work on and improve these problems. Many of the sentinel sites are just beginning, and it requires years of work to improve quality.

A key to tackling the contamination problem is through continuous training of people who collect blood samples, including nurses, especially given the high turnover rate among hospital personnel.

There is also the need to recognize the value of feedback to sentinel sites from SIREVA laboratories, stressing that the only way doctors will adhere to the surveillance process—given the constraints on their time—is if it provides them with information that they find useful for the clinical care of their patients.

Another factor contributing to contamination and quality control problems has been the privatization of hospital laboratories, because the private companies do not give public health officials access to their facilities or data.

In the field of public health, information is necessary in order to act; otherwise systems begin to break apart.
Current Research on Pneumococcus and Meningitis in LAC

- The impact of the Anti-pneumococcal Decavalent Vaccine against Pneumococcal Disease in Colombian Children. The goal of the study is to examine effectiveness of PCV-10 in the routine vaccination program against invasive pneumococcal disease caused by the serotypes included in the PCV-10 vaccine. The study began in May 2013 and will last about two years.
- Chile and Peru are conducting PCV impact studies on hospitalization and mortality due to pneumonias after the introduction of the vaccine.
- Invasive Isolates of *Streptococcus Pneumoniae* Serotype 19A. The goal of the study is to determine clonal populations in every country in the region and determine the relational structure of streptococcus isolates for serotype 19A collected from patients with invasive disease in several countries in Latin America and the Caribbean. It aims to determine the clonal populations in the region and determine if they are associated with hypervirulent clones and clones with high antimicrobial resistance.

TAG RECOMMENDATIONS FOR USE OF MENINGOCOCCAL VACCINE

Brazil, Chile and Cuba are among the few countries in the region that have introduced a vaccine for *N. meningitidis*, an unpredictable disease for which little data is available in Latin America and the Caribbean.

Meningococcal disease affects all age groups, with the highest incidence in children under five years of ages, and especially children under one. Peaks of incidence also involve adults, and adolescents who generally also have the highest rate of carriage. While occurring predominantly in winter, the disease is sporadic and outbreaks occur at irregular intervals. The high fatality rate of the disease generates fear and large social mobilizations to protect public health.
Case rates vary by world region: they have been as high as 1,000 per 100,000 in Africa’s Meningitis Belt (but where a conjugate vaccine for meningococcal A is lowering the rate of disease), to rates ranging from 0.3 to 4 per 100,000 people in the Americas. In the United States, the majority of cases are serotypes B, C and Y; in Latin America the majority are B and C.

Data on meningococcal disease is inconsistent among countries in Latin America, and there are few published papers. Every country uses different case definitions. In general, incidence appears to be increasing in young adolescents. Serotype changes include the disappearance of type A, and the emergence of serotype W135.

A severe outbreak of W135 in Chile last year caused numerous cases of invasive meningococcal disease, 73% of which developed into life-threatening sepsis. The fatality rate was 28% to 30%. In the course of a single day, a patient could go from being diagnosed to dying. The high fatality rate was not only in children under five, but also in 20 to 22 year olds.

Two types of vaccines are available: the polysaccharide and the more immunogenic conjugate vaccines. Both types are available for serotypes A, C, W135. Vaccine efficacy rates vary over time, and many are of relatively short duration. But two quadrivalent vaccines, licensed in 2005 for children 9 to 23 months old, and for adults up to age 55, maintain efficacy of 80% to 85%, three-to-four years after application.

Given this overall situation, TAG made several recommendations for the LAC region—all of which focus on improving surveillance as the essential tool needed for decision making for both routine and outbreak vaccination. The recommendations include:

- Improved surveillance in all countries to learn the full magnitude and exact profile of the disease, including through better use of laboratory techniques such as PCR
- Establishing sentinel surveillance for age groups over five years old
- In-depth study of outbreaks prior to making control decisions
• Countries that introduce conjugate vaccine as part of routine childhood immunization should include catch-up campaigns for adolescents.

Recent experience has shown the danger of relying on “common wisdom” about meningococcal disease, rather than facts on the ground. For example, a study of carriage of W135 came up with the surprising finding that carriage among people 10 to 20 years of age was extremely low, with a prevalence of 0.2%. This contradicts conventional wisdom based mainly on data from North America, which has found that carriage is highest among adolescents.

This discrepancy prompted many participants to emphasize the need to develop and rely on national data, rather than conclusions based on data from other regions. Furthermore, limited data can portray a misleading picture. Mexico, for example, appears to be practically free from meningococcal meningitis. The question, however, is whether the rate is actually so vanishingly low, or whether the cases have simply not been reported.

Furthermore, meningococcal disease is a challenging topic among decision makers, since its epidemiology is highly dynamic and outbreaks cannot be predicted ahead of time.
Emerging from the two days of discussion was a strong awareness of the need to improve the quality of information and laboratory performance. This involves a review of sentinel hospitals, and placing a priority on strengthening those that are already doing the best work. In this way, the surveillance systems should be able to ensure that information coming from sentinel sites is accurate, and will therefore lead to the best decisions about resource allocation and actions to control disease.

The United States has one surveillance system with six sites, and Brazil has five active surveillance sites. Smaller countries with more limited resources should keep this in mind. Maintaining four or six sites for a long period of time, and collecting quality data, is very resource-intensive, and may be impossible for smaller countries.

Moreover, it was recommended that resources and efforts be focused in hospitals that meet criteria for the global network of sentinel surveillance; that surveillance only continue in hospitals with adequate human and logistical resources for long term sustainability and a high institutional commitment; and that few sentinel hospitals with better quality data is preferable to many sentinel hospitals without reliable information.

Over the course of the conference and in its wrap up the importance of improved quality not only for country decision making and disease prevention, but also for continued participation in the global WHO surveillance network was emphasized.

Other aspects of improving laboratory function include: the establishment of external performance reviews and quality control; continuous training; improving the integration of clinical, laboratory and epidemiological information; and reporting on serogroup, serotype and genotype information at least twice a year.
Regarding funding, it was noted that most countries in the region have developed surveillance based on their own funds and resources. This is an important—and costly—achievement for both vaccine-preventable diseases and general epidemiological surveillance. In many countries, budgets for sentinel hospital laboratory supplies are minimal or nonexistent.

Epidemiological surveillance is very costly; however, immunization programs are incomplete without an integrated surveillance system in place. It is necessary to ensure political, technical and financial support of sentinel surveillance in order for it to be carried out successfully in the Americas.
SPEAKERS

Mary Agocs  
Switzerland  
World Health Organization

Raquel Bolanos  
Panama  
Instituto Conmemorativo Gorgas

Maria Cristina Brandileone  
Brazil  
Instituto Adolfo Lutz

Gloria Carvalho  
United States  
Centers for Disease Control & Prevention

Gustavo Chamorro  
Paraguay  
Ministry of Health

Grettel Chanto  
Costa Rica  
Ministry of Health

Lucia De Oliveira  
United States  
Pan American Health Organization

Carla Domingues  
Brazil  
Ministry of Health

Carolina Duarte  
Colombia  
Ministry of Health

Miguel Ernesto Elas Rodriguez  
El Salvador  
Ministry of Health

Rosabel Gonzalez  
Venezuela  
Ministry of Health

Jose Paulo Leite  
Brazil  
FIOCRUZ

Eyal Leshem  
United States  
Centers for Disease Control & Prevention

Gloria Rey Benito  
Costa Rica  
Pan American Health Organization

Cuauhtemoc Ruiz Matus  
United States  
Pan American Health Organization

Jennifer Sanwogou  
United States  
Pan American Health Organization

Maria Teresa Valenzuela  
Chile  
Universidad de los Andes

Jennifer Verani  
United States  
Centers for Disease Control & Prevention

Alvaro Whittembury  
Peru  
Pan American Health Organization
### Delegates

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>Position</th>
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<tbody>
<tr>
<td>Shalauddin Ahmed</td>
<td>Dominica</td>
<td>Ministry of Health</td>
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<tr>
<td>Angel Manuel Alvarez Valdes</td>
<td>Cuba</td>
<td>Pan American Health Organization</td>
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<td>Pamela Araya</td>
<td>Chile</td>
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<td>Roberto Arroba Tijerina</td>
<td>Costa Rica</td>
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<td>Sonia Arza</td>
<td>Paraguay</td>
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<tr>
<td>Susana Asmat</td>
<td>United States</td>
<td>Pan American Health Organization</td>
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<tr>
<td>Johana Aguirre Balndon</td>
<td>Nicaragua</td>
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<td>Rafael Baltrons</td>
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<td>Julia Blau</td>
<td>France</td>
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<td>Jacques Bonay</td>
<td>Haiti</td>
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<td>Pamela Bravo</td>
<td>USA</td>
<td>Pan American Health Organization</td>
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<tr>
<td>Claire Broome</td>
<td>United States</td>
<td>Consultant to PAHO</td>
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<tr>
<td>Teresa Camou</td>
<td>Uruguay</td>
<td>Ministry of Health</td>
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<tr>
<td>Ana Flavia Carvalho</td>
<td>United States</td>
<td>Sabin Vaccine Institute</td>
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<tr>
<td>Mariana Casas</td>
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<td>Lucia de la Cruz</td>
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<td>Papa Coumba Faye</td>
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<td>Maria Liz Gamarra</td>
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<td>Odalys Garcia</td>
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<td>Gladys Ghisays</td>
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<td>Cecilia Gonzalez</td>
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<tr>
<td>Yippsy Gonzalez Borroto</td>
<td>Cuba</td>
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### DELEGATES

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<thead>
<tr>
<th>Mauricio Gonzalez Elizondo</th>
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<tr>
<td>Patricia Grullon</td>
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<td>Katri Kontio</td>
<td>USA</td>
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<td>Mario Martinez</td>
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| Fabiana Michel           | Peru  |
| Raul Montesano           | Bolivia  |
| Sara Angelica Morales de Santa Gadea | Peru  |
| Yenny Neira              | Colombia  |
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| Claudia Ortiz Duran      | United States  |
| Gilson Paluku            | Haiti  |
| Maritza Patzi            | Bolivia  |
| Jackeline Teresita Pinos | Ecuador  |
| Ana Sonia Quintanilla    | El Salvador  |
DELEGATES

Mabel Regueira  
Argentina  
Ministry of Health

Maria de los Angeles Ribas  
Cuba  
Ministry of Health

Hilda Salazar Bolaños  
Costa Rica  
Ministry of Health

Corvil Salomon  
Haiti  
Ministry of Health

Samia Samad  
Brazil  
Ministry of Health

Jacqueline Sanchez  
Dominican Republic  
Ministry of Health

Sandra Sangradini  
Argentina  
Ministry of Health

Brian Shaw  
United States  
Sabin Vaccine Institute

Jose Orlando Solorzano  
Honduras  
Ministry of Health

Juan Andres Stupka  
Argentina  
Ministry of Health

Eduardo Suarez Castañeda  
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Brazil  
Ministry of Health

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Cuba  
Ministry of Health

Marlene Valcarcel Sanchez  
Cuba  
Ministry of Health

Claudia Valenzuela  
Guatemala  
Ministry of Health

Nancy Vasconez  
Nicaragua  
Pan American Health Organization

Nora Maria Villatoro  
El Salvador  
Ministry of Health

Patricia Vindel  
Nicaragua  
Ministry of Health

Martha Von Horoch  
Paraguay  
Ministry of Health