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The organizers of the Seventh International Rotavirus Symposium recognize the efforts of the Ministers of Health from participating countries and scientific experts from around the world who demonstrate dedication to children’s health, particularly to easing the considerable burden of rotavirus disease.

Rotavirus can cause severe diarrhea and vomiting, resulting in dehydration that kills 600,000 children a year. Nearly every child in the world becomes infected by the time they are five years old. However, 80 percent of deaths occur in developing countries.

Our goal during the meeting in Lisbon, Portugal, which is reflected in these proceedings, was to review the substantial progress of just the past two years toward safe, effective rotavirus vaccines and to address the challenge of ensuring that they get to the world’s poorest children.

The recent availability and introduction of two new rotavirus vaccines, shown to be safe and efficacious through large-scale clinical trials, gives this document added timeliness.

As we review the pressing scientific, social, and economic issues regarding rotavirus prevention and vaccine introduction tackled by this Symposium, we also eagerly anticipate our next opportunity to convene. For within several years time, we can expect to see epidemiological data that shows the actual impact of these new vaccines on childhood death and disease.

We thank the convening organizations and supporters for making this historic meeting possible.

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The Seventh International Symposium on Rotavirus and Rotavirus Vaccines, held in Lisbon, Portugal, demonstrated that opportunity can indeed arise out of crisis. The crisis came seven years ago, when a newly licensed childhood vaccine for rotavirus, known as RotaShield, was abruptly withdrawn from the United States market in response to reports of an apparent association between RotaShield and intussusception (IS), a sometimes fatal bowel obstruction.

While signalling that U.S. public health authorities placed a high value on vaccine safety, the reaction simultaneously had a sweeping impact on vaccine introduction throughout the developing world. It stopped the motion toward rotavirus vaccine introduction in developing countries, where 80% of the annual 600,000 childhood fatalities from rotavirus take place, and where the risk of dying from rotavirus was far higher than the perceived risk of vaccine-induced IS.

But from this crisis, new initiatives emerged: increased surveillance of the virus to enable robust determinations of the burden of disease and of strain diversity; vigorous pursuit of alternative vaccines by pharmaceutical companies; cost-benefit analysis of the disease and vaccination programs; and in-depth epidemiological analysis of RotaShield and IS in the United States, reported during the 6th International Symposium on Rotavirus, July 2004.

The sum of this activity and commitment on the part of hundreds of scientists, public health experts, physicians, economists, government and business leaders, and donors has born fruit.

Two Years of Enormous Progress

Today, two new rotavirus vaccines, Rotarix (GlaxoSmithKline/GSK) and RotaTeq (Merck and Co., Inc.) are licensed and available in more than 35 countries around the world, after having demonstrated their safety and efficacy in two of the largest pediatric clinical trials in history. RotaTeq reduced severe rotavirus disease by 98%, and Rotarix reduced severe disease by 96% in Europe and by 85% in Latin America. Regarding intussusception, both vaccines actually appear to be protective against the condition, rather than increasing its risk. In another intriguing finding, GSK found that Rotarix appears to reduce hospitalisations for all gastroenteritis, not just for rotavirus.

In addition to the two new vaccines, more than six other vaccines are in development, many by emerging manufacturers in developing countries. These vaccines have the potential to help lower costs, increase competition, and possibly offer improved efficacy in the world’s poorest countries. The World Health Organization is recommending that all of these candidates be brought through clinical evaluation.

The Symposium reviewed advances in rotavirus surveillance: continuation and expansion of hospital-based surveillance in more than 40 countries; 5 regional surveillance networks with data coming in on a regular basis; and laboratory networks in 5 centres around the world.

Participants reported on cost effectiveness studies in Europe, the United States, Bangladesh and Peru, and advances in computing systems and capabilities. Many noted that vaccine costs would be a key determinant in the feasibility and speed of vaccine introduction in both developed and developing countries.

Participants reported on safety monitoring and risk management plans now that new rotavirus vaccines are coming into widespread use. Presenters reported on plans in the U.S., Europe, Brazil and Mexico, including those to be carried out by GSK and Merck.

Researchers presented new data and insights on strain diversity. They highlighted the importance of monitoring diversity for any possible impacts caused by widespread vaccination. Others summarized the most recent insights into rotavirus pathogenicity and the mechanisms of immunity to rotavirus. In particular, scientists presented growing evidence of rotavirus as a systemic infection, commonly present in the blood and reaching extra-intestinal organs.

Finally, two roundtable panels, one of experts from the
developed world and the other of experts from the developing world, discussed issues and next steps in rotavirus vaccine introduction. In each case, it was clear that upcoming decisions by policymakers will determine whether, and how quickly, the new vaccines can begin to control and prevent rotavirus.

To make these decisions, conference co-organizer Dr. Roger Glass noted that a number of countries are waiting for answers to key questions. Perhaps most important is whether the newly licensed vaccines will work as well in the world’s poorest regions as they do in the developed world. The Symposium took an in-depth look at the challenges facing live oral vaccines in developing countries, as well as at the record-to-date of rotavirus vaccines in these settings.

Looking ahead, presenters considered the resources needed to introduce rotavirus vaccines to the poorest countries of the world. They reviewed important questions for post-licensure surveillance: an assessment of vaccine failures, changes in vaccine strain diversity, and ongoing diligence in detecting possible adverse effects. In addition, the results of cost-benefit models run prior to vaccine introduction should be compared to real-life impacts.

“The benefits of the vaccine on children’s health should be measurable within two years of vaccine introduction,” Glass said. “After nearly three decades of anticipation, this incredible public health intervention is about to begin.”

“In the year 2000, we expected it would take at least a decade to get new rotavirus vaccines, and so it is very wonderful to see that six years later we have two new vaccines.”

—CIRO A. DE QUADROS
Albert B. Sabin Vaccine Institute, US
On June 12-13, in Lisbon, Portugal, 280 participants gathered for the Seventh International Symposium on RV and RV Vaccines. They reviewed the last two years of striking progress towards the control of rotavirus disease through vaccines, as well as upcoming challenges in the effort to reduce childhood deaths and disease from rotavirus.

First identified in 1973, rotavirus can cause severe diarrhoea and dehydration. Nearly every child in the world will have suffered from rotavirus by his fifth birthday. In developed countries with strong health services the toll of the disease is largely measured in doctor bills, emergency room visits, hospital stays and parental days of work lost. Sickness is widespread, costs are high, but death is minimal.

In developing countries, the toll of the disease is measured foremost in life lost. There are an estimated 50 deaths per year from rotavirus in the U.S., versus 50 deaths per hour in developing countries.

The Symposium reviewed key progress in the past two years, reflected on the impact of past experiences with rotavirus vaccines, and zeroed in on critical questions now facing researchers and policy makers.

Throughout the Symposium, one thing was clear: rotavirus vaccines are no longer vaccines of the future. They have arrived, and they have the potential to dramatically lower childhood mortality in developing countries. But for that potential to be realized, outstanding questions need answers, resources must be committed, and decision makers must be able to use the tools now at their disposal.

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**Disease Control Priorities Project**

The Disease Control Priorities Project (DCPP) is an ongoing, coordinated effort to assess disease control priorities and produce evidence-based analysis to inform health policymaking in developing countries. In April 2006, DCPP released the second edition of Disease Control Priorities in Developing Countries (DCP2). Dr. Dean Jamison, senior editor of DCP2, summarized its main findings.

DCP2 updates information on the global burden of diseases and estimates the cost-effectiveness and impact of single interventions and packages, addressing everything from tobacco to infectious diseases. It notes that average life expectancy in low- and middle-income countries increased dramatically in the past half-century and that improved health has contributed significantly to economic welfare.

Nonetheless, four critical challenges face developing countries today:

- High levels and rapid growth of non-communicable diseases;
- The still unchecked HIV/AIDS pandemic;
- The possibility of an influenza pandemic;
- The persistence in many countries of high but preventable levels of mortality and disability from diseases such as diarrhea, malaria, tuberculosis, and pneumonia.

DCP2 points to a range of very good health buys, with cost-effective health interventions ranging from taxation of tobacco products to inexpensive drugs to treat heart attacks. Also high on this list are vaccines.

According to DCP2: “Vaccination is generally very cost effective. In the best of cases, vaccines are relatively inexpensive and a single dose leads to lifetime immunity. Whenever such an intervention is available for a widespread and potentially fatal infection, it is likely to be cost-effective. The mix of delivery strategies, the price of key inputs (the vaccine itself plus labor, transportation, and cold storage), and the overall scale of the program all affect costs.”

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“The benefits of the vaccine on children’s health should be measurable within two years of vaccine introduction. After nearly three decades of anticipation, this incredible public health intervention is about to begin.”

—DR. ROGER GLASS

U.S. Centers for Disease Control and Prevention
Dr. Umesh Parashar of the U.S. Centers for Disease Control and Prevention and Dr. Andrei Lobanov of the World Health Organization convened this session, which included a collection of presentations from every continent, with new in-depth surveillance data from Europe.

**European Rotavirus on the Web**

Dr. Jim Gray reported on the European Rotavirus Network (EuroRotaNet) and its ambitious plans to monitor rotavirus throughout the region and track the changing diversity of co-circulating strains. The study will encompass at least three consecutive rotavirus seasons prior to vaccine introduction, and three seasons following introduction. It will use complex yet user-friendly computer software for data collection, analysis, and real-time reporting through a web-enabled portal that links multiple countries.

Gray, head of the Enteric Virus Unit at the Health Protection Agency in London, noted that rotavirus surveillance in Europe prior to 2000 reported only the G-types of virus strains, and not the P-types. However, he said that future surveillance will include VP6 and NSP4 strains, which can help detect zoonotic introduction into the human population.

The study will capture the detailed molecular epidemiology of rotavirus infections in Europe and monitor the effectiveness of current genotyping methods.

The European network covers a total population of 336 million living in the countries of Denmark, Finland, France, Germany, Hungary, Italy, the Netherlands, Slovenia, Spain, Sweden and the United Kingdom. Based on each country’s population and expected cases per year of rotavirus, epidemiologists calculated the sample sizes needed to detect viral strains with an incidence of more than 1%, with sample sizes ranging from 470 per year in Denmark, to 959 per year in Germany.

The network has developed a web-based infrastructure to serve as a platform for future surveillance activities, particularly those concerned with evaluating the effectiveness of rotavirus vaccines. The program will be able to track the emergence of vaccine-induced viral mutations, genotypes not included in the vaccine, and reassortant strains. The database includes basic epidemiological data such as age, sex, location, and temporal and geographical data necessary for analyzing the seasonality of rotavirus disease.

Gray gave a detailed description of the database, including its ability to capture unusual data. Access is password protected, and data analyses are updated in real time as the data is entered. Advanced graphic capacities allow researchers to create reports, tables and other data displays.

**Europe’s Burden of Disease REVEAlled**

Dr. Pierre Van Damme from the University of Antwerp, Belgium, presented a multi-center observational study on the burden of pediatric rotavirus infection entitled “REVEAL.” Covering seven European population centers, it determined the annual rate of consultation due to rotavirus gastroenteritis in hospitals, emergency rooms, and doctors’ offices. It analyzed seasonal distribution of the disease and virus serotypes.

REVEAL also analyzed the costs associated with rotavirus. “We evaluated what it means for parents to have a child who is hospitalized for rotavirus infection,” Van Damme said. It found that children are typically hospitalized for 3-5 days, and one-third of parents miss at least one day of work. For children treated in ambulatory care facilities, approximately 20% to 35% of parents stayed home from work.

The REVEAL data will provide a basis from which to evaluate the full economic impact of rotavirus vaccine introduction in Europe, Van Damme said.

**Major Revelations**

REVEAL found that rotavirus is a major cause of pediatric gastroenteritis in Europe. It accounts for 40% of the cases of acute gastroenteritis covered by the study. More than 50% of the hospitalizations were due to rotavirus infections, as were 40-50% of the emergency room visits. Some 95% of rotavirus cases occurred in children older than 6 months of age, with a peak in infections at 12 months of age and during the winter months.

Five main circulating strains — G1, G2, G3, G4 and G9 — accounted for 98% of cases. Van Damme noted that G9 was increasingly present but that serotype findings differed amongst the study regions, demonstrating very specific geographic distributions. In Belgium, for example, G1, G4 and G9 strains predominated, while in France, G9 and G3 strains were more common. In Germany, G1 and G4 were most typical while 80% of Italy’s rotavirus infections were identified as G9.
Asian Surveillance at the Forefront

Dr. Tony Nelson, a Professor in Pediatrics at the Chinese University of Hong Kong and a founding member of the Asian Rotavirus Surveillance Network (ARSN), reviewed the history and current work of the ARSN. While the network has collected comprehensive disease burden data from both developed and developing nations in the region, Nelson called for more support of local opinion leaders, greater high-level regional support and more local data on the economic burden of the disease.

Reviewing the history of the ARSN, Nelson recalled that it first convened in Bangkok in February 1999, just after the introduction of a promising rotavirus vaccine, RotaShield, in the United States market. Energized by the prospect of a vaccine, the group gathered to review its own data on rotavirus disease burden, and accelerate its surveillance efforts.

“Six months later, everything went on hold,” with the withdrawal of RotaShield from the U.S. market, Nelson said. But the ARSN regrouped to turn the crisis into an opportunity. Nelson said that the rapid demise of RotaShield set in motion a global effort to determine the burden of rotavirus disease. Simple hospital-based surveillance activities that follow generic WHO protocols were established in many world regions, and Asian countries were in the forefront of this effort.

The ARSN expanded from eight countries in 2001 to 14 countries today: Bangladesh, Cambodia, China, Kyrgyzstan, Indonesia, Laos PDR, Mongolia, Myanmar, Nepal, Pakistan, Philippines, Sri Lanka, Uzbekistan, and Thailand.

Rotavirus Rates in Asia
“Much Higher Than Expected”

Nelson noted that a special supplement of The Journal of Infectious Diseases highlighted rotavirus surveillance in Asia in September 2005. It reported a surprisingly high rate of rotavirus infection: overall, 45% of children hospitalized for acute gastroenteritis had rotavirus. Country-by-country this rate varied: China 50%; Hong Kong 30% (the lowest rate in the region); Japan 58%; Korea 73% (the highest rate in the region); Myanmar 53%; Taiwan 43%; Thailand 43%; and Vietnam 55%.

Human and Economic Burden of Disease in Asia

Nelson reported on a detailed cost study that included 471 children in Hong Kong. It showed that rotavirus disease costs approximately US$1,800 per admission. With an estimated 1 in 24 children hospitalized with rotavirus by age five, the disease exacts a total social toll of an estimated US$4.3 million, including US$4 million in direct medical costs-four times higher than previously thought.

An overall summary of the economic costs of rotavirus in Asia calculated that: 171,000 children die from the disease by five years of age; 1.9 million are hospitalized; 13.5 million are seen on an out-patient basis. The study by Laura Jean Podewils at the U.S. CDC and colleagues found that universal rotavirus vaccination in Asia could avert an estimated 109,000 deaths, 1.4 million hospitalizations, and 7.7 million outpatient visits.

Nelson said that depending on the price of a vaccine, income level, and the standards used, universal rotavirus immunization could be cost saving, as well as life-saving, for Asia.

Latin American Surveillance in the Vaccine Era

Dr. Lucia de Oliveira of the Pan American Health Organization (PAHO) presented the activities of the Rotavirus Surveillance Network of the Americas, including the Adverse Event Sentinel Surveillance Network and Pro-Vac, an initiative designed to help analyze the economic impact of new vaccines, beginning with rotavirus.

Countries in Latin America began surveillance of diarrheal rotavirus in 2003. Current data from 10 countries surveillance indicates that on average 12% of all under-five childhood hospital admissions are for diarrhea, and that 40% of these are caused by rotavirus. Rotavirus causes approximately 75,000 hospitalizations and almost 15,000 deaths annually in the region.

As of June 2006, the network established standardized surveillance of diarrhea in sentinel hospitals in ten countries including Bolivia, El Salvador, Guatemala, Honduras, Paraguay, Venezuela and four English speaking Caribbean countries. The network is also supporting protocols in Argentina and Peru.

Vaccine Introductions and Monitoring of Adverse Events

As of March and April 2006, Brazil, Panama and Venezuela had introduced rotavirus vaccines. de Oliveira said that Nicaragua will soon have a vaccine demonstration project and several other countries are in preparatory phases.

Prior to vaccine introduction, PAHO is working with countries to develop sustainable national EPI programs, cold chain capability, human resource training, strong information systems, and systems for reporting adverse events.

The latter received a large boost in March 2006, when

“EPI managers and decision makers need to answer the question, “What is the most important new vaccine to prioritize in my country?” Pro-Vac will help them decide.”

—DR. LUCIA DE OLIVEIRA
the Pan American Health Organization
representatives from Argentina, Brazil, Mexico, Panama, Venezuela, PAHO and WHO launched the Adverse Events Surveillance Network (SANEVA) in Brazil. Between March and May 2006, SANEVA received reports of vaccine-related adverse events including diarrhea, vomiting, fever, abdominal distension, and intussusception (intestinal obstruction). The reported rates of intussusception were 0.3 per 10,000 vaccines administered in Brazil, and 2 per 10,000 doses in Venezuela.

**The Pro-Vac Initiative: Economic Analysis of New Vaccine Introduction**

Pro-Vac was designed to provide EPI managers with tools to conduct economic analysis of potential new vaccines, including for rotavirus, pneumococcal, HPV and influenza, according to de Oliveira.

“EPI managers and decision makers need to answer the question, ‘What is the most important new vaccine to prioritize in my country?’ Pro-Vac will help them decide,” de Oliveira said. Three essential components of Pro-Vac are simplified tools for economic analysis of all immunization programs, a regional workshop to train immunization managers in economic analysis, and distance learning for long-term support.

**Africa Tackles Surveillance**

Between 110,000 and 155,000 children die of rotavirus-related causes every year in sub-Saharan Africa, reported immunologist Dr. Jason Mwenda, laboratory coordinator of the African Regional Rotavirus Network (ARN) based in Harare, Zimbabwe. Country-specific data show 80-90 children die every day in Nigeria from the disease, 50-60 deaths occur daily in Cameroon, and 10-12 in South Africa.

Continent-wide data indicate that approximately 25-40% of African children hospitalized with diarrheal illness are infected with rotavirus, and by 18 months of age, 83% of children will have contracted the virus.

The Network, which now includes 18 countries, was established in 1998. Since then it has held six workshops and 4 symposia, training more than 40 participants. About 42,000 stool samples have been collected for screening, with some samples genotyped in a reference lab in South Africa.

Mwenda reported that G1 is the most prevalent strain in Africa, accounting for an estimated 50% of cases, followed by G3 at 30%. The G2 strain occurs in “waves” every three to four years; G4 and G8 strains occur in sporadic isolation; G9 is emerging in countries across the continent; and mixed serotypes are increasingly common. Of the P genotypes, P6 is the most common, accounting for 50-60% of cases, followed by P8 (35-40% of cases). An unusual VP4 serotype has also been detected. Mwenda illustrated major changes in circulating rotavirus strains with case studies from Kenya and Ghana.

Mwenda noted that there are still large gaps in data, and in 2003, five African countries and the WHO launched an Enhanced Surveillance Project. The project is trying to improve rotavirus surveillance by integrating it into existing surveillance networks for polio, measles, and other diseases, Mwenda said.

Countries participating in the Enhanced Surveillance Project are tasked with collecting standardized data on the hospital burden of disease (including strain prevalence data); analyzing health facilities utilization; determining disease costs; and working with vaccine trial sites.

In the summer of 2006, Cameroon, Ghana, Kenya, Uganda and Zambia are expected to initiate new surveillance efforts, and the project will also establish two regional reference laboratories, in Ghana and South Africa, with the capacity to support training and other network activities.

“The African rotavirus network intends to carry out sustainable routine surveillance on rotavirus strains and the burden of disease in Africa, providing a formal knowledge base for opinion leaders and policy makers,” Mwenda concluded.

**United States’ Surveillance Past and Future**

Dr. Umesh Parashar from the Centers for Disease Control and Prevention (CDC) reviewed the data presented to the Immunization Advisory Committee in early 2006, prior to its recommendation for use of RotaTeq in the U.S.

Given a lack of active surveillance studies, findings were based largely on existing routine health data collected by the National Center for Health Statistics on mortality, hospitalizations and emergency room visits. According to the findings, in the U.S. children between six months and two years of age are most vulnerable to rotavirus. The disease causes:

- 20-70 deaths a year;
- 55,000 to 70,000 hospitalizations (about one-third of all childhood hospitalizations for diarrhea);
- Between 205,000 and 272,000 emergency room visits;
- 400,000 doctor visits on an out-patient basis;
- Approximately 2.7 million annual rotavirus episodes in a birth cohort of 4 million children.

In addition to the national data sets, since 1990 weekly laboratory surveillance of rotavirus disease has been available from 19 facilities country-wide that report directly to the CDC.

“Rotavirus vaccines are no longer vaccines of the future.”

—DR. JASON MWENDA
African Rotavirus Surveillance Network
U.S. surveillance has focused on monitoring rotavirus hospitalizations, which represent the most severe and costly cases. Beginning in 1992, a specific rotavirus code was introduced that allowed researchers to accurately estimate the fraction of diarrhea hospitalizations due to rotavirus infection.

Since 1996, the CDC has collected rotavirus strain data from 12 laboratories located across the country. Parashar reported that the first seven years of data show that G1 accounts for nearly 80% of U.S. cases, followed by G2 (11.5%). An estimated 82.6% of cases are of P8 genotype.

**Planning Ahead**

The CDC plans to enhance ongoing surveillance efforts in order to monitor vaccine impact.

“While the existing systems were reasonably robust to allow estimates of disease burden, there were some important limitations for estimating vaccine impact,” Parashar said. These include a one-to-two year delay in obtaining national data; a lack of laboratory-confirmed rotavirus cases in national data; and insufficient ability to monitor circulating rotavirus strains.

To overcome these limitations, the CDC has set up active, population-based surveillance of laboratory confirmed rotavirus cases at three sentinel sites. The sites will enable researchers to enroll children under three years of age with acute gastroenteritis, and to monitor rates of rotavirus-related health events over time. Data collected will include hospitalizations, emergency room visits and out-patient visits. To gauge vaccine effectiveness, the CDC will also conduct case-control studies by enrolling healthy children and comparing rotavirus disease episodes in those that are vaccinated to those who are not.

“While the existing systems [in the U.S.] were reasonably robust to allow estimates of disease burden, there were some important limitations for estimating vaccine impact…

So, we have set up active sentinel surveillance and will… evaluate vaccine effectiveness in field settings”

—DR. UMESH PARASHAR

U.S. Centers for Disease Control and Prevention

“The African rotavirus network intends to carry out sustainable routine surveillance on rotavirus strains and the burden of disease in Africa, providing a formal knowledge base for opinion leaders and policy makers”

—DR. JASON MWENDA

African Rotavirus Surveillance Network
Session II: Virology, Pathogenesis, and Immunity

Convened by Dr. Ulrich Desselberger of the International Center for Genetic Engineering and Biotechnology in Trieste, Italy, and Dr. Franco Ruggeri, from Italy’s Instituto Superiore di Sanita, the session walked through an immense area of research on rotavirus diversity, pathogenesis and immunity.

The conveners noted that these topics take on increased relevance as new rotavirus vaccines are broadly introduced. Not only does science inform the composition of the vaccines, but the vaccines themselves may ultimately affect the number and types of circulating rotavirus strains. In addition, further scientific insights are needed to fine-tune vaccine effectiveness in various settings and among different populations.

Strain Diversity in the New Era of Rotavirus Vaccination

A talk by Dr. Jon Gentsch of the U.S. Centers for Disease Control and Prevention (CDC) reviewed the enormous diversity of rotavirus found in both humans and animals, and how the widespread use of Rotarix and RotaTeq vaccines may affect this diversity.

Two proteins on the virus’ outer shell are used to characterize rotavirus diversity. The precise form of the VP4 protein determines the virus’ P serotype, while the form of the VP7 protein determines its G serotype. Both proteins elicit neutralizing human immune responses.

At present, there are five globally common rotavirus serotypes—P[8]G1; P[8]G3; P[8]G4; P[4]G2; and P[8]G9. A host of additional strains that circulate in humans are either rare, or regionally significant, with quite a bit of variation from one region to the next, Gentsch reported. For instance the serotype P[6]G8 is rare in Europe, but common in Africa, and P[6]G9 is rare in Europe but common in India and Bangladesh. He also noted that animal strains should be included in surveillance as there is increasing evidence that these strains may enter human circulation.

Because widespread vaccination is likely to impact strain diversity, Gentsch emphasized the importance of heightened surveillance in the post-introduction era. Such surveillance could not only ensure that the most efficacious vaccines are prepared, but could also detect:

- Any breakthrough strains that escape the vaccine;
- Any new strains that evolve through reassortment between vaccine strains and wild-type rotavirus either in the gut of vaccinated children or in the environment;
- Any changes of virulence or in the distribution of strains.

“The introduction of two new vaccines gives us a unique scientific opportunity to look at their effect on rotavirus strains.”

—DR. JON GENTSCH
U.S. Centers for Disease Control and Prevention

Rotavirus in the System

Although most virologists have long considered rotavirus a purely enteric disease that infects the villus tip of mature cells in the gut, there is a growing body of evidence that it routinely causes a systemic infection as well. Dr. Harry Greenberg of Stanford University summarized this evidence and presented new data demonstrating the propensity of rotavirus to cause viremia (virus in the blood) as well as to replicate in extra-intestinal organs such as the liver, lung and mesenteric lymph nodes (MLN).

“Rotavirus as a systemic infection has re-emerged as a scientific question,” Greenberg said. Elizabeth Kraft, a virologist who worked in the 1940s and ’50s first suggested this possibility, but her observations were largely dismissed. No longer, Greenberg said.
Since Kraft’s time, sporadic reports have documented children with acute or fatal cases of rotavirus who test positive for rotavirus antigen in various extra-intestinal organs. Other studies have demonstrated that the virus causes systemic disease in severely immunodeficient children and mice. More recently, Sarah Blutt showed antigenemia/viremia occurs routinely in rotavirus infections in mice, other animals and people, implying that infectious rotavirus has access to any cell in contact with blood.

Greenberg’s own research extends these findings. To determine whether rotavirus is replicating in the blood and body organs outside the intestine, Greenberg and his colleagues developed an experimental protocol to detect viral transcription and replication in mice and humans.

Their quantitative reversed PCR assay examined rotavirus replication in feces, the small intestine, blood, lung, liver, kidney and MLN, with the goal of quantifying such replication. It also compared the spread of a mouse rotavirus and a simian rotavirus in newborn mice.

The assay detected rotavirus replication in the liver, lungs, kidney, and MLN—with replication rates highest in the latter. Simian and mouse rotavirus was found in relatively equal amounts in mouse blood. But there was a hundredfold more mouse virus than simian virus in the mice feces, and “a hundred-thousand fold,” more mouse virus in the small intestine, Greenberg said.

The simian and mouse rotavirus replicated at different rates in different organs—indicating that replication was not host-range restricted in all extra-intestinal organs (as they are in the gut). In addition, the findings of rotavirus replication in the lung raise the question of whether rotavirus could be associated with respiratory disease.

Greenberg also reviewed recent research into the role of systemic virus in humans. Pratima Ray and others in New Delhi analyzed the blood of 100 young patients who had rotavirus-induced diarrhoea. She found that 65% of them were antigenemic and viremic within 72 hours of the onset of the diarrhoea, and that G1 strains were more likely to cause viremia than are other strains.

In conclusion, Greenberg noted that rotavirus viremia is common in humans during natural infection. While nothing is yet publicly known about extra-intestinal replication related to the two new rotavirus vaccines, Greenberg encouraged the investigators in the audience to study the issue.

The Redundancy of Immunity

Dr. Richard Ward of the Cincinnati Children’s Hospital compared the immunity of natural infection to that provided by live oral vaccines, and examined questions regarding the mechanisms of immunity.

In the case of natural infection, in general, the best correlate of protection is the total rotavirus antibody titers in serum and stool. However, some studies have shown that protection correlates with the levels of serotype-specific neutralizing antibody, while others have shown that it correlates with heterotypic, or cross-reactive, antibody.

In the case of the new live vaccines, immune responses fail to closely mimic responses after natural infection. Nor do rotavirus antibody titres correlate very well with vaccine protection, Ward said.

Thus far, GSK’s monovalent Rotarix appears to provide the best correlation between antibody responses and protection. Meanwhile, no clear correlate of protection has been found in RotaTeq, Merck’s new pentavalent reassortant. Nonetheless, these vaccines provide good protection against severe rotavirus disease. Scientists do not yet understand why.

Neither do they understand why RotaTeq, and RotaShield before it, were only able to provide consistent protection after their bovine virus backbones were developed into reassortants that contain VP7 or VP4 neutralizing protein genes of human rotaviruses—yet these vaccines still do not appear to elicit serotype-specific correlates of immunity.

Ward suggested several possible explanations; one being that antibodies found in studies of the blood are not representative of antibody in the intestine, the main site of disease.

He also suggested that protection against multiple serotypes could be provided not by neutralizing antibody in the blood, but by antibody being transported through the cells that line the intestine, a mechanism known as intracellular neutralization.

Harry Greenberg first proposed this theory for rotavirus in 1995, and subsequent work has added more evidence. The theory suggests that antibody which is brought into cells lining the intestine en route to the intestine’s interior encounter virus within this cellular environment. Once both antibody and virus are inside the cell, the antibody can bind to any viral proteins involved in replication, rather than just to the surface neutralizing antigens, VP4 or VP7.

“Rotavirus as a systemic disease has re-emerged as a scientific question.”

—DR. HARRY GREENBERG
Stanford University, US
Ward’s own experiments with a genetically modified mouse have bolstered this theory: he found that an immunized mouse that is incapable of transporting antibody across the intestine is susceptible to rotavirus strains that are serotypically unrelated to the vaccine strain.

In summary, Ward noted that while neutralizing antibodies undoubtedly play an important role in protection after vaccination with live oral vaccines, they are likely not the only actors, with a possible role for T cells, and a potentially significant role for non-neutralizing intracellular antibody: all a tribute to the redundancy of the immune system.

**DISCUSSION**

*Capturing non-typable strains*

**Q** How can surveillance deal with the excess of 20 percent non-typable strains?

**A** Gentsch noted that it will be a battle to continuously upgrade primers and systems. While a new laboratory manual being developed by the reference laboratories will help in this regard, technologies are needed for easy use in field laboratories.

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**Epidemics following vaccination**

**Q** What is the likelihood of post-vaccination epidemics, in the absence of adult boosting?

**A** Ward replied that the possibility of rotavirus outbreaks among adult populations exists regardless of immunization status, since re-infection will occur regardless. “A bigger question is: Does immunity wane with time and is rotavirus going to cause severe diarrhoea in adults?” he said. “The facts suggest that adults can have severe rotavirus infections and certainly in the aged it is more likely.”

**Unravelling Immune Mechanisms:**

*Comment:* It has been shown that giving children with diarrhoea immune globulin serum (available commercially) puts an abrupt end to the episode. So while something in the serum arrests rotavirus, it is not likely to be neutralizing antibody, which takes longer to act.

In response, Ward suggested that the immune agent could be directed against the NSP4 protein, which can cause diarrhoea in animals. But there is no hard evidence that this is the case.

“Neutralizing antibodies undoubtedly play an important role in protection after vaccination with live oral vaccines, they are likely not the only actors.”

—DR. RICHARD WARD

Cincinnati Children’s Hospital, US
Session III: Spotlight on New Vaccines

Dr. Timo Vesikari from the University of Tampere in Finland and Dr. Lennart Svensson from the University of Linköping in Sweden convened Session III. It highlighted the dramatic changes in the rotavirus vaccine field. Just two years ago, there were no rotavirus vaccines available for public use. In this session, investigators reported that two live oral vaccines are now being used to prevent disease and hospitalizations in children.

However, the two vaccines are not yet in use in the poorest countries, where their efficacy has to be thoroughly tested in clinical trials. At the same time, alternative new vaccines are being investigated, including by emerging manufacturers in developing countries.

Two New Vaccines

Dr. Béatrice de Vos of GSK reported that universal mass vaccination with the monovalent human vaccine Rotarix has begun in Venezuela, Panama, Brazil, and in the poorest provinces in Mexico. Rotarix is licensed in 25 countries in Europe and in 41 other countries worldwide. GSK is also discussing U.S. licensure with the Food and Drug Administration.

Rotarix is based on the human rotavirus strain G1,P[8]. It is the live, attenuated version of a strain first isolated from the stool of a sick 15-month-old boy by Richard Ward at the Children’s Hospital Medical Center in Cincinnati. Its development was based on the observation that broad protection (against homotypic and heterotypic strains) is accumulated through successive natural rotavirus infections. The use of an attenuated strain in the vaccine confers protection without causing gastroenteritis, de Vos said. The vaccine requires cold storage, and is delivered in only two doses from six weeks of age, at a minimum of four weeks apart. It provides early protection in the first months of life when the risk to develop severe illness is highest.

Dr. Penny Heaton of Merck reported that, in February 2006, the U.S. Advisory Committee on Immunization Practices recommended universal vaccination with the pentavalent human-bovine reassortant vaccine RotaTeq, beginning at six weeks of age. Heaton said that Merck has already distributed more than half a million doses of RotaTeq in the U.S., and the company has filed for licensure in more than 100 countries.

RotaTeq is packaged in a ready-to-use tube, and can be stored refrigerated for 24 months. Three doses are required, the first at age six to 12 weeks and subsequent doses at 1- to 2-month intervals, providing coverage before the peak age of rotavirus hospitalizations.

Clinical Trials that Covered the Field

Both presenters reported on the results of their large-scale Phase III trials. These trials yielded roughly similar high results in the safety and efficacy of their respective vaccines. The trials each included more than 60,000 subjects. (The results of both trials were reported in the New England Journal of Medicine and can be found online at PATH’s Rotavirus Vaccine Program: http://www.rotavirusvaccine.org.)

Merck enrolled 71,799 subjects in its Phase III studies of RotaTeq, 80% of them in the U.S. and Finland, and about 20% in other EU countries, as well as in Mexico, Guatemala, Costa Rica, Jamaica, Puerto Rico and Taiwan, Heaton said.

GSK’s first Phase III trial of Rotarix enrolled 63,225 children in 11 Latin American countries (96.7% of enrollees), and in Finland (3.3% of enrollees). A second, ongoing trial in Europe involves about 4,000 infants randomized into vaccinated and placebo groups. The trial is taking place in Finland, Germany, the Czech Republic, Italy, France and Spain. It is now in its second year, and de Vos reported surveillance from the first rotavirus season.

Are the New Vaccines Safe?

Both companies paid close attention to monitoring for intussusception (IS).

Of the 71,000 plus subjects enrolled in the RotaTeq trial, there were 32 confirmed cases of IS, with more occurring in children who did not receive the vaccine than in those who...
did. Nineteen children who received the placebo developed IS, whereas only 13 children who received the vaccine developed IS. Merck found no clustering of cases during the first week after any dose, Heaton reported.

Of the 63,000 plus children enrolled in the Rotarix trials, 25 developed IS within the first six months of life. Of these, 16 were in the placebo group and 9 were in the vaccinated group. Furthermore, because IS cases during the RotaShield immunization program clustered around children who were vaccinated after they were three months old, GSK looked for any similar clustering of cases, and found none.

Monitoring a subset of children up to one-year-old, GSK found that the older the vaccinated child, the lower his relative risk of experiencing IS (RR 0.28). This suggests a possible protective effect of the vaccine. “It is clear the relative risk is going down, down, and down,” de Vos said.

Overall, in the study of over 60,000 children in Latin America and Europe, at the age of 6 months, the risk difference for IS following Rotarix vaccine compared to placebo was minus 2.23 per 10,000 infants or a relative risk of 0.56.

In addition, both vaccines were well tolerated in respect to all adverse events, including fever, headache or vomiting.

**Reductions in Disease and Medical Cost Savings**

RotaTeq reduced severe rotavirus disease by 98%, and reduced disease of any severity by 74%. Rotarix reduced severe rotavirus gastroenteritis by 85% in Latin America and 96% percent in Europe, where it also reduced disease of any severity by 87%.

In the European study, Rotarix efficacy against severe rotavirus disease was similar for serotypes G1, G3, G4 and G9 (ranging from 95% to 100%), but somewhat less against serotype G2,P[4] (75%).

RotaTeq reduced the rate of rotavirus hospitalizations by 95%, the rate of emergency department visits by 94%, and the rate of doctor office visits by 86%. These reductions were remarkably consistent across all four G serotypes in the vaccines, as well as for G9, Heaton said.

Rotarix reduced hospitalizations by 85% in its Latin American trial. It also reduced gastrointestinal-related hospitalizations due to any cause in Latin America by 42%, a finding that de Vos described as “an extremely interesting observation from a public health point of view.”

**Future plans**

According to de Vos, GSK will have more data to come from efficacy and safety trials of Rotarix in Asia and Africa; studies of the vaccine in HIV positive infants and pre-term infants; and of possible transmission of live virus between twins—one vaccinated and one not. In addition, they are conducting long-term (two- to three-year) efficacy trials in all regions.

Heaton reported that Merck is continuing post-licensure studies to monitor safety, including a prospective population-based study to assess IS. Merck is currently studying concomitant use of oral polio vaccine and RotaTeq in Latin America. With the organization PATH, Merck is co-planning efficacy and safety studies in Asia and Africa, including in Kenya, Ghana and Guinea Bissau.

**The Future of Alternative Vaccines**

Despite the incredible work done on the two vaccines, from a public health perspective, they are not enough, said Dr. Duncan Steele of the World Health Organization.

Steele framed the need for alternative vaccines in light of the global burden of rotavirus disease and the United Nations’ Millennium Development Goals, which call for reducing child mortality by two-thirds between 1990 and 2015. Globally, 10.5 million early childhood deaths now occur every year, with 60% of these in ten countries centered in sub-Saharan Africa and Southeast Asia.

“Not surprisingly, rotavirus mortality is highest in those same regions, where it kills about half a million children every year,” Steele said.

But the new vaccines have not yet been fully tested in those regions. And, even if they prove effective in poor settings, Steele said that current prices would ensure that the vaccines remain out of reach to most poor countries.

The cost issue is real: “The reality is that even a vaccine for US$7 a dose is out of reach to the countries with the highest rotavirus mortality,” Steele said. This is the approximate price per dose for public health use of Rotarix in Latin America. In the private market, the price is far higher. For example, in the U.S., RotaTeq costs $62.50 per dose, and requires three doses.

Therefore, emerging manufacturers in developing countries and alternatives to the new vaccines have an important role to play. They could help lower cost by increasing competition and production volume, and possibly offer as good or better protection than live oral vaccines in the poorest countries, Steele said.
Vaccines in Development

Duncan Steele reported on a meeting of the World Health Organization in March 2006 that reviewed these upstream vaccine candidates. The first six are oral live vaccines.

**Australian Neonatal Vaccine**, from the laboratory of Ruth Bishop, is now under development by a partnership including the Queensland Institute of Medical Research and Biofarma in Indonesia. The strain used, a G3P[6] originated in a hospital maternal unit where it persisted for more than 10 years. Newborns infected with it were protected for several years from rotavirus disease. Clinical trials are planned for Australia and Indonesia.

**Lanzhou Lamb Rotavirus (LLR) Vaccine**, developed by Lanzhou Biologicals in China, is a monovalent lamb rotavirus from a G10, P[12] strain. It was licensed in China in 2000, but because of concerns about its safety, LLR has not been pre-qualified internationally for Good Manufacturing Practices. It is given as a single oral dose to children up to ten years of age and sells in the private market for about $16 per dose. WHO previously recommended that the company conduct a randomized, double-blinded efficacy trial.

**LLR Reassortant.** Lanzhou Biologicals plans to develop a multivalent vaccine similar to RotaTeq, with human VP7 reassortants.

**NIH Bovine Reassortant** was developed by Albert Kapikian at the NIH in tandem with the development of RotaShield. This vaccine includes bovine rotavirus plus VP7 genes from the G1, G2, G3 and G4 serotypes. It is a “designer” vaccine that could be tailor-made for different regions to include the most prevalent strains. The NIH has licensed it to seven companies in Brazil, China and India, and each will pursue its own development program leading to clinical trials.

**RotaShield (the Rhesus Rotavirus-TV vaccine)** has been acquired by the biotechnology company BIOVIRx, from the National Institutes of Health and Wyeth. Based on a re-analysis of RotaShield and its association with intussusception, BIOVIRx thinks that the vaccine is safe. BIOVIRx has partnered with IDT in Germany to produce the pilot lot for clinical trials in developing countries. They are seeking an FDA license to improve public perception of their product. The vaccine contains rhesus rotavirus (serotype G3) plus VP7 genes from the G1, G2 and G4 serotypes.

**Two Bovine-Human Reassortants** are based on naturally occurring reassortants found in India, and developed through collaboration of the CDC, Stanford University, AIIMS and Bharat Biotech Ltd in India, and funded by PATH. The strains are associated with asymptomatic infection. A Phase I study has shown that the vaccine is safe and gives a strong immune response.

**Parenteral Vaccines:** These include various approaches including a VP6 candidate, virus-like particles and an inactivated vaccine approach. In each case, there are good preclinical and animal studies to show that these might be appropriate vaccines.
WHO has recommended that each of the alternative vaccine candidates now in development be taken forward for clinical evaluation, adhering to a minimum of international standards of safety, production (GMP), and clinical efficacy and safety (GCP).

WHO is working in a variety of ways to reduce vaccine price and condense the decades-long time lags between the introduction of new vaccines in rich and poor countries. It is collaborating with companies on clinical trials and working with other entities to assure developing country markets for vaccines. (See Sidebar, Session V: The GAVI Alliance).

In March 2006, WHO held a meeting of multinational pharmaceutical companies and emerging manufacturers to review the upstream rotavirus candidates. Meeting participants included GSK, Merck, and vaccine manufacturers from India, Brazil, China, Vietnam, Indonesia and other countries.

While keeping in mind that countries have a national prerogative to undertake vaccine development, the WHO meeting issued several recommendations:

- Each candidate should be taken forward for clinical evaluation;
- Minimum global standards should be established for vaccine clinical development to guard against any possible rapid and unsafe development programs that could lead to problems affecting the whole field;
- WHO should ensure solid phase I and II development programs;
- Development of inactivated vaccines should be encouraged.

Steele concluded by noting that two newly created WHO networks—the Developing Countries Vaccine Manufacturers’ Network and the Developing Countries Vaccine Regulators Network—can play an important role going forward.

DISCUSSION

Maternal Antibodies and Dose Regimen

**Q** Are maternal antibodies affecting vaccine efficacy?

**A** Comparing children who received the first dose at six-to-seven weeks of age to those who received it at eight-to-nine weeks, Merck found that vaccine efficacy was nearly identical, implying that there was no interference from maternal antibody, Heaton said.

**Q** Why does the Merck vaccine use a three-dose regimen?

**A** Heaton explained that Merck based its three-dose regimen on data from Dr. Clark and Dr. Hoffet that showed that about 15% to 20% of children do not have a significant immune response until getting their third dose. Their clinical study backs that up: the efficacy of two doses against hospitalization and emergency department visits for rotavirus was 80%, while the efficacy of three doses was 95%.

Intussusception

**Q** Every case of IS should be analysed for possible association with a cold virus to better understand its etiology. Has adenovirus in fact been associated with IS cases in the Merck trial?

**A** Given that adenovirus has been most consistently associated with IS, Heaton agreed that it is an important question to investigate. Merck did find adenovirus associated with two cases of IS, but with so few specimens to look at it was not possible to draw any conclusions.

**Q** It seems that both Rotarix and RotaTeq may be protective against intussusceptions. What is your thinking over the possible mechanism? Could that indicate that a wild type rotavirus is causing IS?

**A** “The only thing we can say right now is that if a child is inoculated with an attenuated virus, it seems to be protected in the long run,” de Vos said. She speculated that although there is no direct relationship known between wild type rotavirus and IS, vaccination could be protective through priming the immune system.

Hospitalisations Down for All Gastroenteritis

**Q** The GSK clinical trial data showing that vaccination against rotavirus has decreased the rate of hospitalisations against any gastroenteritis is intriguing. In European countries, such hospitalisations have declined by 75%. Why?

**A** “That is another million dollar question,” answered de Vos. She said that current surveillance is probably not picking up all cases of rotavirus, so that at least part of the
apparent decrease in all gastroenteritis actually reflects a larger-than-appreciated burden of rotavirus hospitalizations. But, the rotavirus vaccine could also be protecting against diarrhoea caused by other pathogens.

**Viremia**

**Q** Is there any evidence of antigenemia or viremia in vaccinated children?

**A** GSK has not systematically looked for viremia. In an early Finnish trial that had taken blood samples a couple of days after vaccination, evidence of viremia was found in one or two of the samples, de Vos said. But the numbers are too small to extrapolate.

**RotaShield**

**Q** Why were trials for RotaShield stopped in developing countries?

**A** Steele reviewed the thinking at the time. He said that when RotaShield was associated with IS, there were clinical trials ongoing in Ghana, South Africa, Bangladesh, and other settings. All were stopped. The international community was so “staggered” by the finding that it was not ready to grapple with the risk-benefit ratio for the vaccine in developing countries.

**Is there a role for RotaShield vaccine today?**

Steele pointed out that the vaccine landscape has changed. The use of two other vaccines that have been extensively tested and that have a good safety profile would make it very hard to ask a developing country to consider introducing RotaShield.

**Vaccine Approval Process**

**Q** How does a new vaccine receive a WHO recommendation?

**A** To be pre-qualified by WHO, the vaccine manufacturers must provide data and guidelines that show the vaccine is produced under safe conditions, and that it is being developed and approved by a WHO-approved national regulatory authority (such as the EMDA and the FDA). The vaccine must also have been tested for interaction with Oral Polio Vaccine and other standard childhood vaccinations.

Once WHO pre-qualifies a vaccine, a recommendation can go to the GAVI board for the purchase of the vaccine by the UNICEF vaccine fund. Finally, a global recommendation is made by the Strategic Advisory Group of Experts that advises WHO’s Department for Immunization, Vaccines and Biologicals.

That department gave the Merck and GSK vaccines “regional” recommendations (Europe and the Americas), Steele explained. WHO could not give global recommendations without efficacy data in Africa and Asia.

“Should there be any unexpected increase in the risk of IS, we should be able to detect it early. But we are going to ask all our public health advocates to really think about the benefits of the vaccine, and to really look carefully at the data, so unfortunate decisions are not made in haste.”

—DR. PENNY HEATON Merck & Co., Inc.
The real risk is the loss of public confidence in the vaccine due to publicity given to intussusception cases that occur by chance.

—DR. ELIZABETH MILLER
Health Protection Agency, Colindale, UK

Session IV: Challenges to Rotavirus Vaccine Introduction

This session was convened by Dr. Duncan Steele of the World Health Organization, and Dr. Robin Biellik of the Rotavirus Vaccine Program at PATH. It grappled with challenges to rotavirus vaccine introduction, including: safety monitoring, risk management, and cost effectiveness, as well as the issue of efficacy in poorer settings of developing countries.

Safety Monitoring and Risk Management

Governments, manufacturers and public health communities involved in rotavirus vaccine introductions face major challenges to ensure thorough safety monitoring and risk management. Monitoring systems must be able to detect adverse events in real time, be transparent and accountable, with consistency in the process among different vaccines, said the CDC’s Umesh Parashar.

This is especially important given that rotavirus is just one of a number of new or upcoming vaccines. In the U.S., these include vaccines against shingles, human papillomavirus, a combined MMR and varicella vaccine, and vaccines against invasive meningococcus.

In the case of rotavirus, risk management also includes guarding against what Dr. Elizabeth Miller with the UK’s Health Protection Agency called the real risk, “the loss of public confidence in the vaccine due to publicity given to intussusception cases that occur by chance.”

The European Union has recently established guidelines on risk management for medical products. The new guidelines aim to detect and identify risks and to implement strategies that minimize them, said Dr. Luc Hessel, of the European Joint Venture between Merck and sanofi pasteur, which was set up to monitor the safety of RotaTeq. The rotavirus vaccines will be the first to follow these new guidelines.

Monitoring Rotavirus Vaccines in the United States

Speaking on behalf of Robert Davis, director of the CDC’s Immunization Safety Office, Parashar reviewed the United States’ plans to monitor the safety of all upcoming vaccines, and of RotaTeq, which has already been introduced.

The U.S. uses two main systems to monitor vaccine safety: a passive surveillance system, the Vaccine Adverse Event Reporting System (VAERS), and an active system known as the Vaccine Safety Data Link (VSD).

VAERS allows anybody in the U.S. to report an adverse event through a free hotline or the Internet. The manufacturer of RotaTeq is also required to report any adverse events they detect in countries outside the United States. Researchers at CDC and FDA cooperate to review VAERS reports daily. If any reports of IS or other more serious adverse events arise, they obtain more detailed information. They calculate the reporting rate for adverse events and compare it to the background rates. But because VAERS is a passive system, it may substantially underestimate the true rate of such events, Parashar said.

VSD, on the other hand, covers 3% of the U.S. population, with data generated by eight Health Maintenance Organizations. The data is comprised of computerized vaccination records that can be linked to outcome data at an individual level. It allows calculations of rates of adverse events in vaccinated versus non-vaccinated individuals, but possesses limited power for detection of very rare adverse events.

VSD uses a new application called Rapid Cycle Analysis to detect adverse events, providing a denominator-based assessment of the need for further investigation. To determine how well the system would work, epidemiologists re-visited the RotaShield experience. They crunched nine years of VSD data on intussusception, and detected a signal upon the third case of intussusception—after approximately 9 weeks of vaccine use and at about the same time of the first VAERS reports. Parashar said that these results indicated the system might be up to the task of monitoring the new vaccines.

Considerations in the United Kingdom

In the United Kingdom, the national government makes final decisions about vaccine introductions, purchases vaccines, and administers immunization programs. Vaccines are delivered free, and general practitioners are paid for vaccines given.

Dr. Elizabeth Miller heads the Immunisation Department of the Health Protection Agency in Colindale, UK, which provides data to the Joint Committee on Vaccination and
Immunization (JVCI). The JVCI advises the Department of Health about licensing new vaccines, which in turn advises the Ministers. Miller presented the UK’s position on rotavirus vaccine risk monitoring.

The UK’s health department currently documents rotavirus-attributable morbidity and mortality and is evaluating the cost-effectiveness of mass vaccination. Miller described possible approaches to conducting the safety surveillance needed for rotavirus vaccine introduction in the UK.

Of importance to all new vaccines is detection of the “unanticipated serious adverse events for which there has not been a pre-signal in pre-licensure trials,” Miller said. With rotavirus, this could feasibly include risks posed by the emergence of new reassortant strains that reduce vaccine efficacy.

Because pre-licensure studies show that any potential risk for intussusception would be extremely rare, Miller said the first question to answer is, “how sensitive post-marketing surveillance should be.”

“Would 1 per 25,000 or 100,000 doses be acceptable?” she asked. Miller pointed out that one study in the American Journal of Epidemiology (2001) suggested that parents would accept a risk of 1 in 2,000 if the vaccine were cheap enough. But, in the UK, parents do not pay for the vaccine, “and want a 100% safe vaccine—you can’t do a study that would show that,” she said.

Miller recommended that post-marketing surveillance be based on the analysis of routine data sources, which would probably generate a signal if the risk was 1 in 10,000. If such a signal were detected (from IS or anything else), one could proceed to an analytic epidemiological study.

Routine data sources could be used to conduct an ecological study that looks at trends and incidence of diseases in relation to vaccine usage. Alternatively, the UK could use its passive surveillance system known as “yellow cards,” whereby health practitioners and parents can report any suspected reaction to a pediatric vaccine. The British Pediatrics Surveillance Unit for Clinician Reporting has worked to enhance the system’s effectiveness, Miller said.

However, one limitation with passive reports is that prior knowledge of risk perception strongly affects the relative reporting rate for different vaccines. For instance, when allegations were made about the link between MMR and autism, “We suddenly started to see a signal of autism on the yellow cards,” Miller explained. The same could happen with rotavirus vaccine and intussusceptions.

**GSK’s Plans for Monitoring Rotarix**

Dr. Tom Verstraeten, head of GSK’s clinical safety and pharmacovigilance team, is responsible for risk management planning and all safety strategies at GSK. He presented the company’s plans for post-licensure assessment of the safety of Rotarix.

GSK will continue monitoring vaccine effectiveness, Verstraeten said, along with partners such as the European Rotavirus Network, the CDC, and WHO. GSK will also monitor for genetic stability of the vaccine, and for any impact on serotype distribution in Europe, as well as for potential transmission of the vaccine virus.

To study possible vaccine virus transmission, GSK will follow 100 pairs of twins. One of each pair will be vaccinated, and the study will follow them for six weeks after vaccination. If GSK finds rotavirus in the non-vaccinated twins, it will determine whether it is the vaccine type and check for mutations.

GSK will also investigate the efficacy and safety of Rotarix in pre-term and immuno-compromised infants, including through an ongoing study involving 100 HIV positive infants in South Africa.

Although a large clinical trial found no increased risk of IS following GSK’s rotavirus vaccine, the company will monitor for any IS signals, he said. “Given that we still don’t know the exact etiology of intussusceptions and why they occurred after RotaShield, we cannot presume that any new rotavirus vaccine will not have a problem with IS,” he said.

To look for intussusceptions in post-marketing surveillance, GSK will use its own data collection system. Verstraeten said that so far GSK has distributed about 3 million doses of the vaccine and seen 15 cases of IS. “And, basically, that number is well below the number that we could expect to occur by coincidence following vaccination, based on the natural background rate,” he said.

GSK has planned a safety study in Mexico, the first country to have licensed its vaccine. Mexico is also expected to implement universal mass vaccination for its birth cohort of nearly 600,000 children. With this size birth cohort, GSK estimates that it would take two-to-four years of nearly 100%
vaccine coverage to detect a theoretical risk of IS following rotavirus vaccination smaller than 1 in 10,000.

**Merck’s Plans for Monitoring RotaTeq**

Dr. Luc Hessel is executive director of Medical and Public Affairs Europe at the European Joint Venture between Merck & Co. and sanofi pasteur (the Sanofi Pasteur MSD), set up to monitor the safety of RotaTeq. He described their safety monitoring plans in Europe, noting that it will be taking place during a time of paradigm change.

“We are moving from benefit-risk assessment to prevention of risk, from passive surveillance to active anticipation of risks, and from product safety to patient safety,” he said.

In this new context, Hessel’s group prepared a risk management plan that has been approved by the European Medicines Agency. The plan will monitor a variety of possible risks, including: infectivity; intestinal replication and shedding; safety in the target populations of infants from six weeks of age; possible interferences with other co-administered childhood vaccines; cross protection; potential for strain replacement and the emergence of new reassortants; and intussusception.

Hessel noted that there has been no identified risk between RotaTeq and IS through the clinical trial that involved more than 36,000 vaccinees and more than 100,000 doses. Nonetheless, they plan two major studies:

1. An observational study of 44,000 children in the U.S., aimed at ruling out the relative risk of intussusceptions of 2.5 with an 80% power.
2. A study with the German surveillance system for rare pediatric diseases to establish the annual incidence of IS in children under two in Germany, following a birth cohort of 700,000 children for a minimum of two years.

The sanofi-Merck partnership will study whether the vaccine virus strain is transmitted to close contacts of vaccines. This will include a study of HIV-infected and HIV-exposed infants born to HIV-positive mothers.

Finally, based on the fact that currently identified risks associated with pentavalent rotavirus vaccine are very few and minor, Hessel said that no risk minimisation plan was required “beyond the usual patient information on a health care pamphlet.”

In conclusion, Hessel said, “Monitoring of the new vaccines should contribute to the implementation and acceptability of rotavirus vaccination programs by health care professionals and parents.”

**Will Live Oral Rotavirus Vaccines Work in the Developing World?**

Dr. Martin Friede, a chief scientific officer at the World Health Organization’s Initiative for Vaccine Research Department, reviewed the pros and cons of live oral vaccines, their sometimes spotty history in developing countries, and possible alternative formulations for rotavirus vaccines.

**Oral Vaccines: The Simplest Route?**

Live oral vaccines—such as oral polio vaccine—have been known for their efficacy, ease of use, and low cost. Easy because delivery is needle free; efficacious because it mimics natural infection with replication and acts at the sight of infection in the gut; and cheap—in the past.

But these perceived benefits may be elusive in developing countries, according to Friede. Challenges of live oral vaccines in these settings include: reduced immunogenicity; questions about safety; susceptibility to gastric acid leading to the need for complex formulations and delivery logistics; dependence on cold chains with limited capacity; and the need for multiple doses that could crowd out other vaccines.

**Internal Obstacles**

Friede reviewed a number of oral vaccines that have provided less immunogenicity in developing than developed country populations. These include the Sabin polio vaccine, bovine rotavirus, tetravalent rhesus rotavirus, a live cholera vaccine, a live shigella vaccine, and oral typhoid, which is less immunogenic than injected typhoid in developing countries.

Possible explanations for the difference in immune response
include: maternal antibodies that inhibit vaccine take in infants; underlying medical conditions such as bacterial enteropathies—a feature of children living in areas contaminated by sewage; concomitant parasite infections or diseases such as HIV, TB and malaria; malnutrition, especially vitamin A and zinc deficiencies; differences in vaccine strains; and host factors, such as levels stomach acid that can affect vaccine buffers.

Friede cautioned that preliminary data suggests that the live oral rotavirus vaccines may not perform as well in developing countries. For one thing, first generation rotavirus vaccines, such as RIT and WC3, failed in developing countries.

Furthermore, Friede said that immune responses to the GSK vaccine have been greatest in Finland (more than 90%), intermediate in Latin America (about 70%), and mediocre in South Africa (about 50%) and Bangladesh. Scientists do not understand the reasons for this immune-response gradient, nor whether it correlates with efficacy.

Also unknown is how Rotarix and RotaTeq will compare: will RotaTeq’s poor replication be a plus or a minus? Will its bovine-base better avoid maternal antibodies? Which vaccine will induce better mucosal immunity in these populations?

Social-economic levels also play a role—an important factor in countries such as Bangladesh, which have both rich and poor areas. In the case of live oral typhoid vaccine in Peruvian adults, one study showed that, “the more money you have in the bank, the better your immune responses are going to be.”

**Delivering the Goods**

Friede reviewed logistical concerns based on vaccine formulation. Many oral vaccines need to be reconstituted at the time of use. This presents logistical challenges including the volume that reconstitution components occupy in the cold chain, the weight of the diluent, and the process of reconstitution.

Even if the vaccine works, “The question is how to get it to the children, especially when it has to be carried on the back of a camel or of a donkey for several days over a mountain, during which time it has to be kept cold,” Friede said.

Both of the new rotavirus vaccines are imposing an enormous burden on the cold chain—occupying up to 65% of cold chain capacity—which implies an incremental cost increase for the vaccine programme, “because either we build new cold chain or we stop taking other vaccines, and that is out of the question,” he said.

**Alternative Routes**

Manufacturers of rotavirus vaccines that are still under development may have the opportunity to avoid some of these pitfalls and facilitate logistics, for instance by developing heat-stable vaccines, and vaccines that need a minimal number of doses.

“The ideal is maximum protection with a single dose. Maybe not full protection, but maximum,” Friede said.

Inactivated vaccines may offer other benefits, especially when used with needle-free injection technologies being developed by the WHO and PATH. But these vaccines need powerful adjuvants, which presents a different challenge. And questions remain about their immunogenicity in the presence of maternal antibodies.

In conclusion, Friede noted that some rotavirus vaccines may be more applicable for least-developed country populations than others. To find out, “It is essential that the vaccines are tested in the populations that need them the most — the developing countries. This must be done and must be done very soon.”

“It is essential that the vaccines are tested in the populations that need them the most — the developing countries. This must be done and must be done very soon.”

—DR. MARTIN FRIEDE
World Health Organization
DISCUSSION

**Intussusception**

**Q** What are your plans for collecting both stool and surgical biopsy specimens?

**A** Steele said that WHO had worked with Dr. Joe Bresee to design a generic protocol for obtaining such surgical biopsy specimens. The protocol will be piloted in a number of studies with CDC.

Parashar noted that CDC is encouraging both clinical specimens and pathological specimens, and that it is easier to collect clinical specimens through the active surveillance population than through passive systems like VAERS, because VAERS reports are often delayed.

**Comment:** Since the implementation of rotavirus vaccination in Venezuela last November, a pediatric gastroenterologist reported seeing three non-vaccine related cases of IS. All were in children with adenovirus. A rectosigmoidoscopy performed on each child, with a very thin scope and without sedation, found a 25–30 cm severe lymphoid hyperplasia in the rectum. The doctor reduced the IS and, upon examining the rest of intestine, found it normal. The doctor suggested that every case of IS should be tested for other viruses using PCR, and that an endoscopy should be done on every child with IS.

**Risk Communication**

**Q** What information will be included in risk communication for the public and for general practitioners?

**A** Miller replied that the UK will only address that question if and when it finds that rotavirus vaccine is cost effective, and decides to introduce it. “But, as a result of this conference, my enthusiasm has grown and it is looking very promising,” she said. If rotavirus vaccine is introduced, there would have to be information for health care professionals about the probability of chance association with rare adverse events such as sudden infant death and IS.

**Alternatives to Live Oral Vaccines in Developing Countries**

**Comments:**

- I have perceived a lack of urgency about the development of the injectable rotavirus vaccine. There are concerns about the potential efficacy of the oral vaccine in the places where it is going to save lives. If we are not working now for the development of the injectable vaccines and overcoming their associated problems, we run the risk of delaying dealing with rotavirus mortality by 5 or 10 years.
- That message [the importance of injectable vaccines] has to be taken to PATH. With novel delivery systems coming out, it is appropriate to revisit the experiences in the last 20 years of oral polio vaccine.
- Safety is an issue with injectable vaccines. As much as 25% of HIV transmission in certain African countries is due to the use of contaminated needles. This is an issue that WHO and partner agencies take very seriously.

**Efficacy of Live Oral Vaccines in Developing Countries**

**Comments:**

- The near eradication today of polio could never have been achieved without the oral polio vaccine in developing countries. This is proven beyond any doubt.
- The figure presented by Friede for Rotarix immunogenicity in Africa cannot be compared as such to the other regions, because only in Africa was Rotarix being co-administered with OPV. In addition, in two GSK studies in Africa, the result for immunogenicity when co-administered with OPV was between 44% and 60%. Another study outside of Africa has shown that “in no case have we seen an efficacy rate lower than the seroconversion rate.” Therefore, GSK expects at minimum an efficacy of 60% for Rotarix in Africa, although studies in South Africa and Malawi are ongoing.

**Costs and Savings from Rotavirus Vaccination**

Four speakers presented the results of recent cost effectiveness studies done in a variety of regions—with a variety of results.

**United States: Costs and Benefits**

Dr. Marc-Alain Widdowson, with the CDC's National Center for Immunization and Respiratory Diseases, presented a cost-effectiveness study for the U.S. It assumed the use of a three-dose regimen of RotaTeq, now priced at $62.50 per dose.

Widdowson’s study followed a fictitious cohort of 100,000 children from birth until five years of age, counting the number of rotavirus disease outcomes. For each outcome, the investigators calculated the medical costs, the non-medical costs (such as parental days of work missed, travel, extra diapers, and special foods), the cost of the vaccine program and of any potential adverse reactions.

The results were then compared to those from the same cohort, but assuming that the children were vaccinated at 2, 4, and 6 months of age with RotaTeq. Using Monte Carlo modelling they calculated the reduction in outcomes and costs, the cost effectiveness ratio per life-year saved, and per case averted.

Widdowson reported that with 70% vaccine coverage in the U.S., a routine rotavirus immunization program would
prevent: 13 deaths; 44,000 hospitalizations; 137,000 ER visits; 256,000 office visits; and 1,100,000 rotavirus episodes requiring home care.

The study found that assuming a $10 per dose cost of vaccine administration and a $12 per dose cost of vaccine, vaccination would likely be cost savings from a health care perspective. From a society perspective (taking into account indirect costs), “A vaccine up to $27 a dose would definitely be cost saving. Up to about $42 a dose it is likely to be cost saving, and after that it is increasingly less likely to be cost saving.”

“In conclusion, based on a $62.50 dollars per dose cost, rotavirus vaccination will not be cost saving from the health care perspective. It is unlikely but yet possible, that it would be cost saving from a society perspective,” Widdowson said. Nonetheless, the vaccine may be considered cost-effective compared to other health interventions.

**Europe: Balancing the Budget?**

Dr. Carlo Giaquinto, a pediatrician at the University of Padova, in Italy, presented a cost-effectiveness analysis of rotavirus vaccination in Europe from the perspective of both the health payer and of society.

He noted that the study used real data on disease burden gathered by REVEAL (Rotavirus Gastroenteritis Epidemiology and Viral Types in Europe Accounting for Losses in Public Health & Society. See Session I for more on this study.) Its efficacy data was based on RotaTeq.

To quantify the consequences of vaccinating versus not vaccinating, the model incorporated efficacy, coverage, and costs of the rotavirus vaccine program.

It showed that in Italy, a 90% vaccine coverage rate would yield a 75% reduction in the burden of gastroenteritis, amounting to “a major reduction in cost,” Giaquinto said. However, he noted that the calculation only includes workdays lost. It includes neither vaccine cost nor information on family impact, Giaquinto said.

He concluded that a rotavirus vaccination program could have a major impact in reducing the cost of rotavirus disease and that the price of the vaccine would have to be balanced to allow cost-savings at the country level.

Dr. Baudouin Standaert, the Health Economics Director of GSK, presented a second study on cost effectiveness in Europe. Standaert prefaced his talk cautioning that even when cost effectiveness data is available, an important obstacle to vaccine introduction is lack of knowledge of budget impact.

GSK’s study used the QALY as the effect measure. Standaert explained that a QALY combines two elements: principally time, expressed in life years, but also the value of time (or quality of life). For universal mass vaccination against rotavirus disease to be cost effective in the EU, cost would need to remain under the threshold of 50,000/QALY, Standaert said. The study determined that Rotarix would meet this threshold.

Standaert described his model as a “process driven by health stages.” It included data on breast feeding, seasonality of infection, and non-rotavirus related gastroenteritis hospitalization. Looking specifically at France, the model found that introducing a vaccine against rotavirus in two doses and with high efficacy would reduce disease costs from 76% to 93%.

**Bangladesh and Peru: Cost Effectiveness v. Affordability**

Dr. Colin Sanderson at the London School of Hygiene and Tropical Medicine reported on a study done in Bangladesh and Peru. It used a micro simulation model that would allow countries to compare the relative cost effectiveness of rotavirus, hepatitis B and Hib vaccines.

“If you save a life from one disease, it doesn’t help if they then ‘get got’ by something else shortly afterwards,” Sanderson said. “Looking at each vaccine separately may not give you the whole story.” It can depend on the age-specific incidence of other diseases, and the extent of cost-sharing between different elements of vaccine programs.

The study used data on populations, natural history, vaccine effectiveness and health care utilization from the UN, WHO/UNICEF, DHS, National Statistics, literature reviews

“If you save a life from one disease, it doesn’t help if they then ‘get got’ by something else shortly afterwards. Looking at each vaccine separately may not give you the whole story.”

—DR. COLIN SANDERSON
London School of Hygiene and Tropical Medicine
and expert consensus, as well as primary data on costs of vaccination and vaccine-preventable diseases based on field studies, facility surveys, patient record surveys and interviews with physicians and patients.

The results were based on a simulated time period from 1995 to 2029, with rotavirus introduced in 2010 to a population of 250,000. Looking specifically at rotavirus, the study projected the cost effectiveness of 1 and 2 doses of GSK vaccine, and 2 and 3 doses of the Merck vaccine, at $5 and $7.50 per dose.

Comparing the two- and three-dose schedules, the model found that the improvement in benefits from the second to the third dose in a three-dose schedule was small relative to the increased costs, making the third dose less cost-effective.

For Bangladesh, the model suggested that because the health care costs of vaccine-preventable diseases were low, they did little to offset the costs of a vaccination program. In fact, devoting significant effort to gathering data on the costs of vaccine-preventable diseases was not an efficient use of research funds. “We can imagine it would be a different story in wealthier countries,” where more is spent on health care, Sanderson said.

In summary, Sanderson said that the rotavirus vaccine looked cost-effective in both countries, “but whether it is generally affordable is another question.”

He also advised against presenting model outputs as “results”. Policy makers were demanding simple models, but simple models could be misleading. Meanwhile, modelers want to be useful, but without risking their future credibility. “This is just one of the modeler’s dilemmas,” Sanderson said.

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**DISCUSSION**

**Questioning Parameters**

*Q* When one has data on an annual birth cohort, as in Mexico, is it necessary to have the information broken into rural and urban areas, and to include seasonality data?

*A* Sanderson replied that their model distinguished between urban and rural areas because some parameters are affected by this distinction. This includes demographic parameters, vaccine coverage rates, treatment and costs. “We wanted to capture that and offer the option of looking at things more selectively in different areas.”

*Q* Did you find a difference in mortality figures between the national and UN data sets? Did you consider using any national data on mortality? How well do these estimates represent the true picture?

*A* Sanderson replied that they looked at both sets of figures, and did find differences in death and fertility rates. They were advised to use the UN figures. In some age groups, differences were by a factor of two. The fertility rates were important because the model needed to bring in new babies to get vaccinated.

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**Comment:** There is a strong argument for using the marginal cost of producing, packaging and distributing the vaccine in the social cost effectiveness analysis. So, instead of several hundred Euros for a vaccine course, the cost would be less than a tenth of that. The rest is the monopoly price accorded to the manufacturer that represents a transfer of resources from society to the manufacturer. It is a transfer that has strong social purposes as it will presumably be used in substantial part on other drugs or vaccines.
Dr. Ciro de Quadros, President and CEO of the Albert B. Sabin Vaccine Institute and Dr. Bernard Ivanoff, international consultant, convened Session V. It featured two panels of experts, one from developed and one from developing countries.

Opening the first panel, de Quadros noted that the development of rotavirus vaccines has taken surprising turns. He recalled a meeting organized with Dr. Roger Glass at WHO in February 2000, just after the withdrawal of RotaShield vaccine. Its purpose was to reactivate research on the rotavirus vaccines for developing countries. “In the year 2000, we expected it would take at least a decade to get new rotavirus vaccines, and so it is very wonderful to see that six years later we have two new vaccines,” de Quadros said.

Panel I: Decision Makers from Industrialized Nations

Decision makers and scientists from five industrialized countries presented a range of opinions regarding next steps and the prospects for introduction of the new rotavirus vaccines. At one end of the spectrum, the United States and Austria have each already recommended universal rotavirus vaccination for children. At the other end of the spectrum, Portugal questions its importance from either a public health or cost/benefit perspective. France, as well, requires more data before making a decision.

Price is a factor in introductions in industrialized nations. Vesikari stressed the need for affordable prices: “Nobody expects national immunization programs to be purchasing the vaccine at the private market price,” he said.

Panelists expressed divergent views on the role of cost-benefit studies. While some stressed their importance, both Mutz and Vesikari cautioned against over-reliance on such studies. Vesikari objected to reducing vaccine-introduction decisions to “cost-benefit calculations and cold numbers. ... I want to emphasize the human side of this: it is a question of the distress of the babies; the anxiety of the families-and this is something that we need no longer tolerate.”

The United States

Dr. Kathy Neuzil of Seattle-based PATH described issues considered by the CDC’s Advisory Committee on Immunization Practices (ACIP), prior to its unanimous decision to recommend universal childhood vaccination with RotaTeq in the U.S. Much of the discussion focussed on safety issues. Although the RotaTeq clinical trial data showed no association with intussusception, to address any lingering concerns, Neuzil said that the ACIP recommended a very strict vaccination schedule, with infants receiving the first dose at no later than 12 weeks of age (before the age of higher risk of natural IS in infants). The ACIP made this recommendation knowing that it would lower coverage rates by about 10%, Neuzil said.

The ACIP also debated whether to recommend rotavirus vaccines to children with immune deficiencies. A review of the science showed that immune suppression from HIV is minimal in infants, and, therefore, wild-type rotavirus does not appear to be either more common or severe in HIV infected children. This led the ACIP to recommend that HIV-positive status be considered a precaution rather than a strict contraindication to rotavirus vaccination.

“We hope that the decision to be more permissive with HIV-infected children will have a positive effect in the developing world, where the prevalence of HIV is much higher than it is in the U.S.,” Neuzil said.

Neuzil also acknowledged that the licensing of the GSK vaccine is likely to present a challenge: “The ACIP will have to make a decision. They are different vaccine constructs, so it will be interesting. It will be a nice problem to have.”

Europe

Vesikari noted that if there is any generalization to be made about European countries, it is their concern about safety. “So,
being a bit behind the U.S. will allow the European countries to watch the ongoing human experiments that are starting with RotaTeq in the U.S. and with Rotarix in Latin America,” he said. This will also give European countries access to post-marketing data to inform their decision-making, said Vesikari, who developed the first rotavirus vaccine in the 1980s.

Regarding the likelihood of broad introduction of the vaccines across Europe, Vesikari emphasized that the EU is a patchwork of countries, with no way of introducing vaccine on a pan-European schedule. Nonetheless, with hopes of facilitating the process, a group of European experts is being convened to develop regional guidelines. These would be endorsed by key European pediatrics societies independent of regulatory authorities.

**Austria**

Austria was among the first countries to recommend universal rotavirus vaccination, a decision it made in 2005, while updating its overall immunizations recommendations. “We had to take into consideration the impending registration of rotavirus vaccines in 2006,” said Dr. Ingomar Mutz, a leading Austrian pediatrician.

The burden of disease in Austria includes about 3,800 children a year admitted to hospitals with diarrhoea. Fatality, on the other hand, is very low, between 0 and 3 deaths each year. At the time Austria recommended vaccination, the price of the vaccine was unknown. “But the cost-benefit ratio was not our primary concern,” Mutz said. “Children are entitled to optimal medical care.”

**Portugal**

The situation in Portugal is different. Annually, rotavirus causes about 500 hospitalizations, with a fatality rate near 0%. “This is not seen in our country as a serious problem,” said Francisco George, Portugal’s Director General for Health.

So, although Rotarix vaccine has been authorized for private use on the commercial market, RotaTeq is expected to be as well, “we cannot say whether the vaccines will be approved as part of the EPI schedule,” George reported.

In Portugal, where EPI vaccines are free of charge for families, George said there is a need for more data, including on cost effectiveness, as was done prior to the introduction of vaccines for hepatitis B and meningitis C.

He noted that it took 10 years for hepatitis B to be approved as part of the EPI schedule, but only a couple of months for approval of meningitis C vaccine. The main factor affecting approval of both was pressure from the media. With meningitis C, “The pressure from TV and newspapers was incredible,” he said.

### RETROSPECTIVE: THE ROTA SHIELD DECISION

*Excerpts of a talk by Dr. Jon Abramson, Chair of the CDC’s Advisory Committee on Immunization Practices (ACIP)*

I will take you back to 1999 and through a little bit of what happened when we decided to discontinue the RotaShield recommendation. The vaccine was approved in 1998 by the FDA, the ACIP, the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP). In 1999, I had just become chair of the American Academy of Pediatrics’ Committee on Infectious Diseases, when I received an emergency call from the CDC telling me that there was a problem with the rotavirus vaccine related to intussusception.

When we looked at the RotaShield data, it was quickly very clear to us that IS was related to vaccine doses 1 and 2, and the risk was fairly high. There was a near unanimous decision by AAPC, the ACIP, and the AAFP that we should stop using this vaccine, based on its safety issues.

And clearly the message was: ‘We are concerned about safety - we will not use a vaccine where the benefit does not clearly outweigh the risk.’

However, we also made the point that the decision in the U.S. was based on 20 to 40 childhood deaths from rotavirus a year—and that the risk-benefit ratio in developing countries was very different. We were only making the decision for the U.S. But, clearly, we knew the impact our decision would have on developing countries in negatively impacting the implementation of the rotavirus vaccine. I consider that was unfortunate.

After we made the decision, we were asked a very difficult question: ‘If we would not accept an IS rate of 1 to 10,000, then what would we accept?’ We could not agree on a number. The companies made the point that you needed 60,000 children in a clinical trial to determine if the IS rate was less than 1 to 10,000, and going beyond that would be nearly impossible.

But much to the companies’ credit, new vaccines were pursued. We thought it would be very difficult to do studies in the U.S., but it wasn’t! Parents were still willing to let their children get a rotavirus vaccine. And last February we approved the Merck rotavirus vaccine for universal use in children in the U.S.

To this day, no one knows for sure what caused the increased risk of IS with RotaShield. But, at the end of the day, because we were so careful and clear about our message that safety is very important to us, we have been able to come back to a point where we have a new universally recommended rotavirus vaccine.
France
Dr. Catherine Weil-Olivier, a leading pediatrician in France, noted that the country needs more clinical and virologic data before the new rotavirus vaccines could be approved. This includes data on changes in strain prevalence, including in neonates. Other data gaps include the vaccine’s impact on chronic digestive tract disorders and on immune-compromised children, and the herd effects of immunization, especially in day care centres. In addition, she stressed the need for a simple diagnostic test, usable at the bedside, in order to eliminate under-diagnosis of the disease.

Weil-Olivier noted that the rotavirus vaccines are introducing new concepts in vaccine policy. Currently, 98% of any developed country health budget spending goes to curative drug therapies, versus 2% that goes to preventative vaccines. “The new vaccines are trying to gain some of that 98 percentage,” she said.

In addition, “In the old times, introducing a vaccine was mostly dedicated to preventing childhood deaths. Today, as disease deaths have decreased, newer vaccines aim to decrease the incidence of disease and its consequences.” She said that this puts more emphasis on the societal benefits of vaccines.

Weil-Olivier noted the importance of cost-effectiveness models in the decision-making process, and urged that they be evaluated for accuracy after introductions take place. She stressed the need for a multi-year, multi-vaccine introduction strategy, noting that, “A lot of new vaccines are at the door, and we have to decide why one and not the other. This is a problem for every country.”

Panel 2: Decision Makers from Developing Nations
Panelists from Brazil, China, Mexico, Nigeria and Thailand presented their differing perspectives on the benefits and difficulties of rotavirus vaccine introductions. They reviewed the current status of childhood immunization, the burden of rotavirus disease, and the role of the private sector. In addition, Michel Zaffran, Deputy Executive Secretary of the GAVI Alliance, reviewed his organization’s work in developing countries and its plans to support future introductions of rotavirus vaccines.

Brazil
Dr. Jarbas Barbosa da Silva Jr., Secretary of Brazil’s Public Health Surveillance Department at the Ministry of Health, shared Brazil’s experience with rotavirus vaccine.

While the overall incidence of diarrhoea in Brazil has dramatically decreased in the last two decades, it remains very high in the poor regions. Nationally, Brazil has an estimated 3,800,000 cases of childhood rotavirus each year, leading to 6,000 hospitalizations and 850 deaths.

Brazil decided to introduce rotavirus vaccine in 2005. Three factors led to the decision: a thorough review of the vaccine and disease burden data; Brazil’s established successes in new vaccine introductions (hepatitis B nationwide in 1997; Hib in 1999; influenza for elderly people in 1999; a new MMR vaccine in 2003); and an increase in the Ministry of Health budget. Barbosa said that this increase was dedicated to the introduction of rotavirus vaccine among the poor people in the north and northeast of Brazil.

Brazil’s total vaccine budget for 2006 is around US$350 million. Of this:

- 16% is being used to buy rotavirus vaccine at US$7 per dose;
- US$5 million is being spent in an ongoing effort to improve the cold chain;
- US$100,000 is being used to train health workers to administer the vaccine.

In addition, US$1 million has been used to adjust the delivery schedule to deal with problems related to vaccine volume. For example, some states that were receiving vaccines every three months now receive them every two months.

Brazil launched its rotavirus vaccination program in March 2006, and has already applied 372,000 doses. The national surveillance system has reported seven intussusception cases in immunized children, giving “a very low incidence .20 per 10,000 doses applied,” Barbosa said.

A major challenge lies in communications, given Brazil’s decentralized system of more than 31,000 health care centres that deliver vaccinations. A second challenge is to strengthen laboratory capacity as part of building a system to monitor vaccine impact.

“Finally, we are investing in national production of rotavirus vaccine at the Butantan Institute in São Paulo,”
Barbosa said. The Institute has received technology for the NIH bovine vaccine, and plans to have a national vaccine available in 2008. It is adding the G9 strain to try to improve efficacy.

“An affordable national vaccine will not only give us a sustainable rotavirus vaccine program in Brazil, but it may also allow us to export this vaccine to other Latin American countries,” Barbosa concluded.

Thailand

“Although Thailand is much smaller than Brazil, we share something in common, and that is we are proud of our immunization program and we love to introduce new vaccines,” said Dr. Supamit Chunsutthiwat, the senior expert in disease control at the Ministry of Health in Thailand, and Secretary to the National Vaccine Committee.

Chunsutthiwat noted that in the past decade and a half, his country had introduced four new vaccines: hepatitis B, combination DTP hepatitis B, MMR and Japanese Encephalitis (JE).

“But with rotavirus we may need to take careful steps and go slowly,” he said. “We are optimistic, but we need to observe reality.”

Chunsutthiwat noted that improved surveillance has recently clarified the burden of disease in Thailand. Data shows that among 1 million reported cases of diarrhoea every year, one-third are in children under five, 12% of them are hospitalized, and about 40% to 50% of these cases are caused by rotavirus.

But before introducing a new vaccine, the country must consider alternative ways to prevent and control diarrhoea, he said. These include through improved sanitation and water supply, personal hygiene, breast feeding and oral rehydration therapy. The later has already dramatically reduced under-five mortality from diarrhoea.

Cost is a major issue. The national budget fully supports childhood immunizations, “so any additional vaccine will come from the same source,” he said. The basic EPI vaccines used today are inexpensive, ranging from $.50 to $1.50 per dose.

“The viability of a new vaccine introduction is based on cost effectiveness and cost benefit, which is determined primarily by the cost of the vaccine,” he said.

Furthermore, Thailand will need to choose from a long list of existing and potential new vaccines that include Hib, influenza, HIV, malaria, dengue, JE, pneumococcus and rotavirus, Chunsutthiwat said.

Thailand is encouraging rotavirus vaccine introduction by the private sector, recognizing that this can serve as a bridge to public sector use. Private sector uptake is itself determined primarily by the awareness of the parents and professionals, so good communication “should be encouraged and promoted,” Chunsutthiwat said.

Next steps for a possible rotavirus vaccine introduction include:

* A good cost benefit analysis that compares vaccination to other measures to reduce mortality;
* An improved system for surveillance of adverse effects;
* Concerted international and multi-sectoral collaboration to improve the supply of rotavirus vaccine.

“It is good news to learn that Brazil is going to locally produce rotavirus vaccine,” Chunsutthiwat concluded. “This kind of collaboration to improve supply and lower the cost of the vaccine will ultimately help to make this vaccine available to children in developing countries.”

—DR. JARBAS BARBOSA DA SILVA JR.
Ministry of Health, Brazil

—DR. SUPAMIT CHUNSUTTHIWAT
Ministry of Health, Thailand
Nigeria

“First of all, let me remind you that developing countries account for 93% of the world’s disease burden, but only 18% of its income, and only 11% of global health spending,” began Dr. Adenike Grange, President of the International Pediatrics Association and a Nigerian pediatrician. This has led to a “vaccination gap” between developed and developing countries.

In Nigeria, only 30% of children receive basic childhood immunizations—down considerably from past levels. Grange laid the fault at the door of politics, as well as on funding gaps in health service delivery, infrastructure and human resources.

“We are struggling with basic vaccines—so why do we want to talk about the new vaccines?” Grange asked. “We have to, because we need the new vaccines, and the global environment is suitable now for us to get our coverage up.” Grange said that Nigeria has recently regained the support of the GAVI Alliance, raising the prospects for faster progress in immunization.

In addition, Grange said that the national environment for new vaccine introductions is favorable because management of the health care system is improving. For example, the Ministry of Health once again controls immunization services (the Presidency had controlled these services for five years). “The Ministry of Health is quite accessible to health professionals, so we now have access to decision making,” he said.

Grange outlined future steps needed toward adopting new vaccines:

• UNICEF, WHO, GAVI and the government should work more closely with the private sector to address the human resources problem. Currently, private medical practices and civil society organizations (CSO) provide about 40% of health care delivery and services. Therefore, Grange said that CSOs should also receive federal health care funds.
• Nigeria should join the African Regional Rotavirus Network, and improve surveillance to better assess the burden of rotavirus disease.
• All parties should find ways to make vaccines affordable. New funding mechanisms worked out by GAVI for reducing the cost of new vaccines should be supported.

“While we are waiting for these vaccines to become affordable, children are dying and it is really very sad, as a pediatrician, for me to say that we have to wait until vaccines are affordable,” Grange said.

Mexico

Mexico was the first country in the world to license a new rotavirus vaccine.

“Because diarrhoea is one of the five major causes of morbidity and mortality of children under five years of age, the introduction of rotavirus vaccine was considered very important,” said Dr. F. Raúl Velázquez of the Mexican Institute of Social Security. He pointed out that although increased hygiene and sanitary measures had decreased overall diarrheal disease mortality by 80% since the 1990s, the rate of rotavirus disease had not decreased.

Mexico introduced GSK’s Rotarix into the private sector first, and later approved it for public use. Since there was not enough initial funding for universal childhood immunization, the government decided to introduce it to children at higher risk. This has been done in 14 of Mexico’s 32 states, covering states where more than 70% of the population is indigenous.

Beginning in December 2006, the Mexican Institute for Social Security plans to expand this vaccination program to cover some 600,000 children across the country, Velázquez said. At the same time, it will conduct a Phase IV, post-marketing study to confirm the safety of the monovalent human rotavirus vaccine.
China
China’s Extended Program in Immunization has been in existence since 1978. It was recently reformed to increase the types of vaccines delivered and to make some EPI vaccines free to all children, said Dr. Zhou Yuqing, a researcher with the National Immunization Program of the Chinese Center for Disease Control and Prevention.

Early vaccines included those for polio, measles, DPT and BCG. In 2002, a GAVI project on hepatitis B and safety injection was started in China and the hepatitis B vaccine was later integrated into the national EPI schedule. Last year, some provinces added meningitis and JE vaccines.

Every year, 16 million children are born in China. Rotavirus hits hard: annually there are about 2.5 million children outpatients; 580,000 hospital admissions; and 33,000 child deaths.

“So, you can see that rotavirus diarrhoea is a very serious disease in China,” Zhou said. “The introduction of new rotavirus vaccines will have a great meaning for China.”

Steps needed prior to a vaccine introduction include:

• Collection of burden of disease data;
• Collection of cost effectiveness data;
• Clinical trials to demonstrate safety and efficacy of the new vaccines in China;
• Finding ways to lower the cost of the vaccine;
• Government formulation of a new vaccine guideline.

Zhou stressed that data on disease burden and cost effectiveness “is very important for decision makers to be able to integrate this kind of vaccine into the EPI schedule.”

The GAVI Alliance
Mr. Michel Zaffran, Deputy Executive Secretary of the GAVI Alliance, gave a broad overview of GAVI’s work and plans regarding rotavirus and other childhood vaccines.

In 2000, the Global Alliance for Vaccines and Immunizations, now known as the GAVI Alliance, was established to address the vaccination gaps in the world’s poorest countries, those with a GNI of under US$1,000.

Vaccination Gaps
These gaps are stark: Every year, 27 million children do not receive basic vaccines; 1.4 million children die from diseases that can be prevented by basic vaccines; and another one million children die from diseases that could be prevented by the new vaccines for rotavirus and pneumococcus. Ninety percent of these deaths occur in the world’s poorest countries.

GAVI provides catalytic, time-limited support to countries to encourage ownership of programs that strengthen routine immunization and improve vaccine safety. For the last five years, GAVI has focussed its efforts on vaccines that are underused in poor countries, but that have been available for many years in industrialized countries, such as those for yellow fever, hepatitis B and Hib.

With GAVI’s support, in the past 5 years, 15 million more children have received routine immunization services; 115 million children have had access to underused vaccines; and a billion auto disabled syringes have been provided to the 75 GAVI-eligible countries. Zaffran said that today GAVI expends approximately US$200 million a year to support these services.

Rotavirus and Pneumococcus
Since 2002, GAVI has also focussed on vaccines for rotavirus and pneumococcus. After determining that its support for these vaccines could speed their use in developing nations, GAVI established an Accelerated Development and Introduction Plan (ADIP) for each vaccine. The ADIPs aim to increase access to a reliable supply of quality vaccines at affordable prices, and to ensure that countries can make informed decisions regarding vaccine introduction.

“The ADIPs were also a signal to industry, to countries, and to partners that GAVI was moving towards supporting the introduction of new vaccines,” Zaffran said.

Funding Strategies
The WHO estimates that about US$35 billion is needed to help the poorest countries achieve their immunization goals by 2015, in line with the Global Immunization Vision and Strategy (GIVS) and the Millennium Development Goals. Of that amount, an estimated US$20 billion is already available either through the country’s own national budgets or through their traditional donors.

“We still need to find US$15 billion between now and 2015 to actually help promote better immunization, introduce new vaccines and save many lives,” Zaffran said.

GAVI has worked with its partners on two innovative initiatives to raise more resources: the International Finance Facility for Immunization (IFFIm) and Advanced Market Commitments (AMCs).

IFFIm will sell bonds on the capital market to generate income to support development efforts in GAVI-eligible countries. The UK, France, Italy, Spain, Sweden, Norway,
Brazil, and South Africa are so far supporting IFFIm’s launch, with a target of raising US$4 billion. Approximately half of these resources will be used to strengthen immunization services and the other half will be used to introduce new vaccines.

The G8 group of countries has asked the World Bank and GAVI to develop a proposal to launch AMCs, with the goal of addressing the small and risky nature of the vaccine market in developing countries. AMCs would “put resources on the table to guarantee markets, should a vaccine become available,” Zaffran said. It would provide industry with incentives for Research and Development and to build the production capacity needed to supply the developing world. Rotavirus is among the vaccines being considered for use with AMCs.

Zaffran said that GAVI now has a projected income of between US$6.4 and US$8 billion by 2015, and, “We have already committed approximately US$4 billion, which means that between now and 2015 we could have approximately between US$2.5 to US$4 billion available to support new vaccine introductions,” including rotavirus and pneumococcal vaccines, as well as others with potential public health impacts.

**Next Steps**

GAVI’s planned and anticipated steps include:

- In June 2006, the GAVI board will decide whether to help fund clinical trials for rotavirus vaccines for Africa and Asia;
- In November 2006, the GAVI Board will likely review “investment cases” for rotavirus and pneumococcal vaccines that describe the resources necessary to purchase the vaccines for eligible developing countries;
- Success in these efforts and WHO approval of the vaccines would be followed by negotiation with industry and an invitation for countries to submit applications for the introduction of these new vaccines.

With this scenario, Zaffran said that “rotavirus vaccine could be rolled out in the first early introducer GAVI-eligible countries by some time in 2007.”

**DISCUSSION**

**Impact of Withdrawing RotaShield**

**Comment:** The recommendation in 1999 that withdrew RotaShield has its benefits, because we can demonstrate that the surveillance and control system for immunization safety is working and functioning well. And this is a very important argument when discussing the pros and cons of immunization.

**Safety Concerns and Timing of Doses**

**Comments**

- Vesikari said that although he has been a rotavirus vaccine proponent for 25 years, today he is an “advocate of a slow introduction process” in Europe. He noted that there have been isolated examples of IS associated with several rotavirus vaccines, including RotaTeq and Rotarix. “If I could have my way,” Vesikari said, “I would squeeze the immunization schedule towards the lower ages in infants, to avoid as much as possible the peak age of IS.”
- The ACIP working group decided to recommend a restrictive vaccination schedule in order to avoid the perception that any possible cases of natural IS occurring during the age of peak vulnerability were vaccine related. This action was taken because, “We sensed there was a great deal of sensitivity on the part of parents in the U.S., who are very, very safety conscious,” said Penny Donahue, of the Committee on Infectious Diseases of the American Academy of Pediatrics.

**Switching Between Vaccines**

**Q** If two vaccines become available, can children be switched from one to the other?

**A** In principle, the U.S. allows switching of vaccines, although the ACIP expresses a clear preference against doing so. “We don’t make people go back and revaccinate, if they had a different brand of the vaccine,” unless there is data to drive that decision, Abramson said.

“Rotavirus vaccine could be rolled out in the first early introducer GAVI-eligible countries by some time in 2007.”

—MR. MICHEL ZAFFRAN
the GAVI Alliance
Are Two or Three Doses Preferable?

Abramson said that the U.S. is dealing with that question for a second dose of varicela vaccine. After starting a two-dose vaccine program for varicela, the CDC found that the first dose knocked down hospitalizations from 12,000 to less than 200, and knocked down deaths from 200 to less than 20 — thus making the second dose extremely expensive. “So it is going to be a very interesting question for U.S. to try to address,” he said.

Did Austria restrict the timing of the first dose of rotavirus vaccine?

Austria recommends that the last dose should not be given beyond the 24th week of life. All severe side effects have to be registered in Austria and sent to public health agencies.

Role of Cost Effectiveness Studies

Comment: “Cost effectiveness be damned!” was one participant’s point of view. “It is the health of the children that we are really talking about. And I go back to things like mammograms in the U.S., which are very, very costly; they are done because they are important for the health of the women of the U.S. The same is true for the health of the children in the U.S. and the rotavirus program.”

Countries with Greatest Need

Comment: Of the countries from the European Region that became independent during the last decade of the 20th century, 11 are eligible for GAVI support—they belong to the poorest countries of the world, and they should be sitting around this table. If provided with reasonable technical and financial support these countries can achieve success, as seen in some recent introductions there of the hepatitis B and MMR vaccines. In addition, most of these countries have immunization coverage rates that are higher than those in certain industrialized countries. But they lack adequate information about the burden of rotavirus disease.

“I want to emphasize the human side of this: it is a question of human suffering, distress of the babies and anxiety of the families.”

—DR. TIMO VESIKARI
University of Tampere, Finland
“We are the custodians of a powerful new set of interventions for the prevention of childhood diseases and to ensure childhood survival. With all that we know, we must seize this opportunity to make the right decisions and see if we can actually make a difference.”

—DR. ROGER GLASS
U.S. Centers for Disease Control and Prevention

"I am really thrilled to be up here. What we have done in the past two days has been enormous," said Dr. Roger Glass. He summarized the advances highlighted during the Symposium:
- Two new vaccines, their licensure and availability in more than 35 countries around the world;
- Rotavirus surveillance in more than 40 countries, and five surveillance networks with data coming in on a regular basis;
- Laboratory networks with uniform methods in five centers around the world;
- Progress made with cost effectiveness studies and cost-benefit analysis.

Glass noted the significance of Zaffran’s presentation on the resources available for future rotavirus introductions. “We never would have dreamed of such resources being available 10 years ago,” he said. “They will ultimately allow rotavirus vaccines to get to the poorest countries of the world.”

Even more exciting are the times to come: “When we come back here, perhaps in two years, we can expect to see new epidemiological data showing the impact of these vaccines, the decrease on hospitalizations, and what I have called ‘The Golden Studies,’ to show that we can actually reduce mortality from this disease,” Glass said.

Finally, Glass noted that the scientific and policy communities have been challenged to tackle a number of questions:
- Will these live oral vaccines actually work in the developing world?
- How will they work in premature children? In immunocompromised children, and in children with unusual strains of virus or with other infections?
- Will we need to invest in more backup vaccines and backup strategies?
- How can we get the Ministries of Health and of Finance engaged in this and fully knowledgeable of rotavirus?

“We are the custodians of a powerful new set of interventions for the prevention of childhood diseases and to ensure childhood survival,” he said. “With all that we know, we must seize this opportunity to make the right decisions and see if we can actually make a difference.”

Acknowledging Dr. Ruth Bishop, who discovered rotavirus 33 years ago, Glass said, “Perhaps, in two years, when you come back and join us, we will be able to provide you with real data. What you discovered 33 years ago has importance and provided the motto of prevention.”
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Acknowledgements

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