



Spotlight

Vaccines enter battle against an intestinal virus

New vaccines prevent potentially deadly diarrheal disease in infants

Almost all infants, everywhere in the world, have been infected with rotavirus by age five. This common pathogen can cause a range of symptoms, from mild gastrointestinal discomfort to the diarrheal disease known as acute gastroenteritis that can lead to serious dehydration. And although even the most severe cases of the disease can usually be treated easily with replenishment of fluids or electrolytes, rotavirus kills 600,000 children each year, the vast majority in developing countries where access to healthcare services is limited. This single virus accounts for about 5% of all childhood deaths worldwide.

Yet as organizations such as the Program for Appropriate Technology in Health (PATH), a Seattle-based non-profit organization, meet with policymakers in developing countries to discuss rotavirus, they find many have never even heard of it. These meetings are the first step in preparing governments for the introduction of two new vaccines that may help prevent the tragic consequences of this viral infection.

Despite setbacks with an earlier rotavirus vaccine, which was abruptly revoked over safety concerns, continued efforts by vaccine manufacturers GlaxoSmithKline (GSK) and Merck culminated earlier this year in landmark clinical trials showing that both company's rotavirus vaccines were highly effective in preventing severe gastroen-

teritis in infants, and were not associated with similar safety issues.

"Given the challenges and the enormous resource requirements, it is just amazing that we actually have two new products," says Umesh Parashar, a medical epidemiologist at the US Centers for Disease Control and Prevention (CDC). His enthusiasm for these vaccines is tempered by only one thing. Neither have been tested in efficacy trials in Africa or Asia, so it's unclear if they will be as effective at preventing severe disease in these populations as the already completed Phase III trials indicated in infants from the US, Europe, and Latin America. "That's the biggest scientific question that remains," says Parashar.

Evidence suggests that immune responses induced by orally administered vaccines are reduced in these populations. Trials in developing countries demonstrated the need for additional doses of oral polio vaccine to stimulate equivalent immunity, and both cholera vaccine and earlier versions of rotavirus vaccine performed less favorably in these settings. So it is essential that the new rotavirus vaccines are tested there before rotavirus vaccination programs can be implemented around the world.

GSK has already started two trials in Malawi and South Africa and Merck plans to initiate trials by the end of the year at yet to be identified sites in Africa and Asia, all of which are being conducted in cooperation with PATH. Although data from these studies isn't expected until 2009, organizations like the Global Alliance for Vaccines and Immunizations (GAVI), PATH, the World Health Organization (WHO), and the CDC are already actively engaged in accelerating the testing and introduction of rotavirus vaccines in coun-

tries where the most deaths from severe gastroenteritis occur.

The culprit

Many serotypes of rotavirus are currently in circulation around the globe, but luckily for vaccine developers more than 80% of rotavirus-related disease is caused by just four of these serotypes. Rotavirus is transmitted orally and once inside the body, it can trigger the diarrhea and vomiting that together account for the often rapid and severe dehydration. In developing countries, where prompt access to healthcare services is limited, approximately 1 in 200 children who are infected with rotavirus will die.

The personal toll associated with such a pervasive virus spurred researchers into developing vaccines that would completely prevent infection. However they soon changed course when studies of natural infection showed that children who are repeatedly infected with the virus develop some level of natural immunity that, although not able to prevent subsequent re-infection, can reduce the risk of developing severe disease. After a second infection it becomes unlikely that an infant will ever experience severe gastroenteritis. "Efforts were

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then focused on developing a vaccine to mimic this effect,” says Parashar.

Several vaccine candidates were developed based on different animal strains of rotavirus. One developed by Wyeth called Rotashield was based on a monkey virus engineered to express proteins from the human rotavirus strain. After clinical trials showed this vaccine to be effective it received approval and licensure from the US Food and Drug Administration (FDA). But just nine months later physicians in the US were advised by the CDC to immediately suspend use of the vaccine after a small number of unexpected cases of intussusception occurred in infants who received Rotashield. Intussusception is a serious bowel obstruction that happens when part of the small intestine folds over itself like a collapsing telescope. If left untreated it can sometimes be fatal.

Further analysis showed that most cases of intussusception occurred within two weeks of infants receiving their first vaccination, suggesting Rotashield was the cause. A study by the CDC calculated that the intussusception risk for vaccinated infants was between 1 in 4500 and 1 in 9500. “That level of risk was not considered acceptable in the US,” says Parashar, where only 20 deaths each year are attributable to rotavirus infection. Wyeth soon withdrew Rotashield from the market and stopped manufacturing the vaccine.

This ignited debate among scientists and bioethicists over whether or not the vaccine could still provide benefit in developing countries where the death toll is much higher. In an article bioethicist Charles Weijer of Dalhousie University, Canada said it was “imperialistic to transfer this standard of care to a country in which 1 in 200 children die of rotavirus infection.”

Weijer calculated that even in a worst-case scenario, the intussusception associated with Rotashield would have caused 2000-3000 deaths per year, which is far fewer than the 600,000 deaths caused by rotavirus-induced severe gastroenteritis.

“One of the challenges with this vaccine was that it hadn’t already been tested in Africa and Asia,” says Parashar. Not knowing if the vaccine was even effective in these developing-country settings made it difficult for policymakers to overlook the possible adverse effects. But if Rotashield had been tested simultaneously in developing countries there

may have been greater enthusiasm for the vaccine preventing rotavirus-related death, and possibly even a movement to seek independent licensure.

Small risk, huge trials

Soon after Rotashield’s withdrawal Merck was preparing to take their lead rotavirus vaccine candidate into large-scale efficacy trials. Suddenly the trial plans changed dramatically. To rule out the possibility of intussusception the Phase III trials would need to include 60,000-100,000 infants. Both financially and organizationally this was no small matter. However the company chose to move forward and began a placebo-controlled trial with their rotavirus vaccine, Rotateq, in more than 69,000 infants in 11 industrialized countries. GSK was faced with a similar situation with their vaccine, known as Rotarix, and they too pushed ahead with a trial involving 63,000 children in Finland and 11 countries in Latin America.

These trials are the largest industry-sponsored vaccine trials ever conducted and both showed that the vaccines were highly effective. Rotateq prevented 74% of any rotavirus-related gastroenteritis and 98% of severe cases. The vaccine also reduced the number of hospital visits for gastroenteritis by 86%. Immunization with Rotarix prevented 85% of severe gastroenteritis cases and associated hospitalizations and was 100% effective at reducing the most severe cases of the disease. Just as importantly, neither live-attenuated vaccine was associated with an increased risk of intussusception. “It was likely a Rotashield-specific issue,” says Mark Feinberg of Merck.

A few months after the final data was released, Merck received approval to license and market Rotateq in the US and GSK received licensure for Rotarix from the European Commission. Rotarix is also licensed in Mexico, Brazil, Philippines, and Singapore.

These vaccines were developed without a good animal model and, even after large studies proved their efficacy, researchers have yet to identify exactly what immune response is responsible for protection. This gives hope to AIDS vaccine researchers who are working under similar constraints. Paul Offit of the Children’s Hospital of Philadelphia in the US and one of the co-discoverers

of Rotateq says that in comparison “rotavirus vaccines were much easier to make,” yet it still took a quarter of a century of research and development.

Rolling out vaccines

Before the WHO will recommend rotavirus vaccination for infants in developing countries, where infants are at the greatest risk of developing life-threatening gastroenteritis, the vaccines must be tested in these populations. Despite the experiences of Wyeth with Rotashield, neither manufacturer chose to run efficacy trials with their second-generation vaccines in both developed and developing countries simultaneously. According to Feinberg, Merck decided their large efficacy trial would only be conducted in countries where they were confident all possible cases of intussusception could be detected and treated quickly. “Now that we know the vaccine is highly efficacious and well tolerated we want to move forward as quickly as possible in resource-poor countries,” he says.

This is happening with the help of PATH, whose goal is to reduce the delay between initial licensure of vaccines and availability in developing countries. The first step is talking with policymakers in the 72 poorest countries and educating them about the disease and the vaccines. “If we go to countries right now and say we want to talk about rotavirus, they say ‘What’s that?’” says John Wecker of PATH. These countries know they have a diarrheal disease but are unaware that rotavirus is the cause. “We want to provide a solid evidence base for developing-country governments, and we have a long way to go,” he adds.

In the future PATH will also have to explain the characteristics that differentiate Rotateq from Rotarix, mainly serotype coverage and dosing schedule, so that representatives from developing countries can choose which vaccine to include in their immunization programs.

But in the end their decisions may be mainly driven by price. PATH is now holding consultations with the manufacturers on pricing. In the US, Merck’s vaccine costs \$180 for the three-dose course, making it one of the highest-priced childhood immunizations. Wecker is confident that financial subsidies provided by GAVI will help reduce the cost burden in developing countries.

Global News

G8 nations pledge support for HIV prevention strategies

In a final report, leaders of the G8 nations who gathered in St. Petersburg, Russia from July 15-17 pledged continued support for HIV prevention, treatment, and care, highlighting in particular the development of AIDS vaccines and microbicides as priorities in the fight against the pandemic. The need for vaccines to prevent other diseases that increase an individual's risk of HIV infection was also emphasized.

Other strategies promoted in the document on infectious diseases, one of the three areas considered during the meeting, included expanding the partnerships with developing countries to bolster capacity for research and development and ensuring that qualified healthcare workers are available in these regions. The leaders also endorsed the Russian proposal to form a regional center in Eastern Europe and Central Asia to promote AIDS vaccine development.

Russia also announced that it would repay US\$270 million that it received from the Global Fund to Fight AIDS, Tuberculosis, and Malaria, to further provision of treatment and care to HIV-infected individuals in developing countries. The Fund is currently in need of \$1 billion to meet its present commitments.

HIV testing programs gather momentum in Africa

Malawi recently launched a nationwide campaign to encourage the country's citizens to undergo voluntary counseling and testing (VCT) for HIV infection (see November 2005 *Primer on Understanding HIV Testing*). The aim of this week-long testing drive, announced by the Health Minister, is to increase access to the available HIV prevention, treatment, and care services, and was initiated after surveys found that only 15% of the 12 million people in the country have already received VCT.

The campaign is expected to reach over 50,000 people. To date 47,000 HIV-infected individuals in Malawi have

received antiretrovirals (ARVs) through the Global Fund, but estimates are that another 178,000 are still in need of treatment.

Malawi's new campaign follows Lesotho's announcement last year of a comprehensive VCT program, which is going door-to-door throughout the country offering testing to all citizens (see June 2006 *Primer on Understanding Home-Based Voluntary Counseling and Testing Services*). Former US President Bill Clinton also recently called for all African governments to actively encourage HIV testing in order to identify those in need of ARVs.

New funding for AIDS vaccine research

The Bill & Melinda Gates Foundation awarded US\$287 million in grants over the next five years to 16 different research teams, encompassing 165 investigators from 19 countries, to support innovative approaches to overcoming the scientific obstacles in AIDS vaccine research and to accelerate the development of new candidates. These grants are the Foundation's largest contribution to date for HIV/AIDS research and bring together many of the leading teams that are currently working to develop an effective vaccine.

Five of the grants are to laboratories that focus on research into vaccines that can elicit broadly-neutralizing antibodies against HIV. The largest of these grants, \$25.3 million, was awarded to Robin Weiss of the University College London in the UK. Among the other recipients was Barton Haynes of Duke University in the US, who leads a team of researchers that was recently awarded a \$300 million grant from the US National Institute of Allergy and Infectious Diseases to form the Center for HIV/AIDS Vaccine Immunology (CHAVI).

Another six grants were issued to laboratories or consortia working on vaccine candidates aimed at inducing cellular immune responses to the virus. IAVI was the recipient of a \$23.7 million grant in this category. Other grantees include David Ho of the Aaron Diamond AIDS Research Center in New York City and Juliana McElrath of the Fred Hutchinson

Cancer Research Center in Seattle.

A main point of these grants was to facilitate cooperation and coordination of data between vaccine discovery teams. The acceptance of this new funding is therefore contingent upon all awardees working through a network of standardized laboratories to test their vaccine candidates. The remaining five grants were provided to researchers who will form these centralized facilities for vaccine candidate evaluation and will be involved in measuring the immune responses generated by candidates developed through the vaccine discovery programs, as well as handling the data collection.



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 23 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to www.iavi.org.

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How does the genetic diversity of HIV affect AIDS vaccine design?

A key concern for AIDS vaccine researchers is the tremendous genetic diversity of HIV. The majority of global HIV infections are caused by a single group of virus, which is divided into nine different subtypes, or clades, designated by the letters A through K. Further complicating matters are the viral recombinants that occur when viruses from different clades combine segments of their genome, forming a hybrid. These occur in several regions of the world where more than one HIV clade is circulating.

The advent of clades

The diversity of HIV and the development of clades stems from the ability of HIV to produce billions of viral particles daily. The enzyme involved in viral replication, reverse transcriptase, is not precise and sometimes incorporates mistakes into the viral genome, resulting in genetic mutations. The more HIV replicates, the more likely it is to make mistakes, increasing the potential for genetic variation.

Each of HIV's genes develops mutations at a different rate. The genetic sequence of the envelope gene (*env*), for example, which encodes the HIV surface protein that attaches the virus to human cells, can vary by as much as 35% in virus samples from different clades. Others, such as the *gag* gene that encodes the internal core of the virus, remain more conserved, varying by less than 10% from one clade to another. Overall, the genetic makeup between all clades deviates by approximately 30%.

HIV clades also vary in prevalence throughout the world. For example, HIV clade B is found mostly throughout North America and Europe, while the epidemic in South Africa and India is due to HIV clade C. Researchers are therefore trying to develop an AIDS vaccine candidate that offers the broadest possible protection.

But there are still many unanswered questions about the significance of

viral diversity for AIDS vaccine design. Scientists do not yet know whether immune responses induced by a preventive AIDS vaccine would be able to protect against only one particular HIV clade or against several. Most clinical trials of AIDS vaccine candidates have occurred in communities where the antigen in the vaccine comes from the same HIV clade as the one circulating in the region, a concept known as clade or genetic matching. The key for an effective AIDS vaccine is to elicit the kind of immune response that would be effective against the circulating virus in the region, but this is not well predicted by clade alone. Clade classification refers to the different protein sequences that distinguish the circulating viruses and not the way the human immune system recognizes or reacts to HIV, so the importance of such matching is still in question. Scientists are also still trying to determine the type and magnitude of immune response required for protection, so clinical trials to determine the immunogenicity of vaccine candidates in relevant populations remain critical.

Implications for vaccine design

When the first AIDS vaccine trials were initiated, vaccine development efforts focused mostly on candidates from isolates of HIV clade B, found in North America, parts of South America, Western Europe, and Australia, and currently responsible for approximately 12% of global infections. Later, candidates with antigens from clades A and D, both common in parts of Africa, were brought to clinical trials. Several others were also developed based on clade C, the subtype circulating in Southern Africa, India, and China, which is responsible for over 50% of all HIV infections worldwide.

As more candidates entered clinical testing different approaches to vaccine development have emerged to tackle HIV diversity. One strategy aimed at eliciting cellular immune responses involves the use of the

most conserved regions of HIV or widely recognized protein pieces from different parts of HIV to develop an AIDS vaccine candidate.

A different vaccine strategy that aims to elicit broadly-neutralizing antibodies against several clades uses a combination vaccine with *env* genes from several clades. A third approach, which is not yet in clinical trials, compares the sequences of HIV genomes from different clades to create a computer-generated sequence that best matches the highest number of strains, with the hope that any protective immune response that the vaccine elicits would confer protection against infection by different HIV clades.

Informing the field

Merck and the HIV Vaccine Trials Network (HVTN) are now completing site preparations in South Africa for a second Phase IIB "test of concept" trial with the company's clade B-based adenovirus serotype 5 (Ad5) vaccine candidate, known as MRKAd5. The candidate is currently being evaluated in another Phase IIB trial in North America, South America, the Caribbean, and Australia. The addition of a South African trial marks the first time this candidate will be evaluated in a population where the circulating clade of HIV, clade C, does not match that in the vaccine.

In 2003 the African AIDS Vaccine Programme came out strongly in favor of planning trials to give clear answers about protection across different clades as long as there is evidence that the vaccine candidate induces immune responses against the most commonly circulating virus, regardless of clade classification. Preclinical data for MRKAd5 show reactivity between the vaccine antigens and the predominant virus found in South Africa. The Merck trial therefore offers an opportunity to test this in a "proof of concept" trial that may provide preliminary answers about a vaccine's efficacy while answering crucial questions for vaccine design.