Immunization Focus

A quarterly publication of the Global Alliance for Vaccines and Immunization www.VaccineAlliance.org

GAVI

GAVI is a partnership of public and private organizations dedicated to increasing children's access worldwide to immunization against killer diseases.

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Immunization Focus

Immunization Focus is issued quarterly on the GAVI website at www.VaccineAlliance.org

It is intended to provide updates and topical debate about key immunization issues at national and international level. It can also be sent to you by email.

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Letters to the editor are welcome: please write via the GAVI Secretariat, c/o UNICEF, Palais des Nations, 1211 Geneva 10, Switzerland, or Gavi@unicef.org

NEWS

Countries tell GAVI they mean business

LESS than four short months since the launch of the Alliance, more than 50 countries have signed up to participate in its initiative. From Kyrgyzstan to Cambodia and Cuba to Côte d'Ivoire, governments have sent GAVI an emphatic message: they are committed to wider immunization and determined to deliver it. But, like GAVI's partners, they warn that the initiative needs sustained investment to succeed.

Early this year, the Alliance invited all countries with an income of less than US$1000 per capita to express their interest in receiving support from the Global Fund for Children's Vaccines, launched by GAVI with an initial gift of US$750 million over five years from the Bill and Melinda Gates Foundation. More than two-thirds of the countries had responded by early April, detailing their current immunization activities, plans and needs. This month, GAVI is sending countries documents to make their formal proposals, with the first grants to be made later this year. For a map of the countries, see www.VaccineAlliance.org/press/map.html

Part of the Fund is to be spent on newer vaccines such as those against hepatitis B and yellow fever, which many governments are keen to introduce. "We are confident that Ghana has the capacity to deliver the newer vaccines now," says Dr Jama Gulaid, head of the health programme at UNICEF in Accra. Likewise, Cambodia's health ministry has told GAVI that it could introduce hepatitis B vaccine into its programme "as soon as late 2000... if resources become available".

No one is complacent about the challenges ahead, however. Ciro de Quadros, Director of the Division of Vaccines and Immunization at the Pan American Health Organization, warns that more donors to the Fund are needed if the effort is to be sustained beyond 2005, and that countries need support to improve their systems for delivering vaccines. Support for infrastructure is part of GAVI's plans.

Eyes on the future: this winter's babies could be the first to benefit

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The Alliance announced last month that it needed $200 million more per year, on top of the $150 million per year already pledged to the Fund, to halve the number of un-immunized children in poor countries by 2005. ■

For more information see the Report of the Second Board Meeting at www.VaccineAlliance.org/reference/2nd.mtg.rept.pdf

Phyllida Brown

Inside this issue

The right combination

Vaccines that immunize against several diseases at once have obvious advantages. But how many are available for use in developing countries? Lisa Jacobs finds out

THE more diseases an immunization programme can prevent, the better: few health officials would argue with that. But every addition of a separate new antigen into a vaccination schedule requires another shot, another needle and syringe, and extra disposal costs. And, just as important, the extra responsibility on over-burdened health systems may also increase the risks of unsafe injections.

In light of this, the GAVI Board made the decision that – for those eligible countries that seek to introduce vaccines against hepatitis B and/or *Haemophilus influenzae* type b (Hib) – the vaccines purchased by the Global Fund for Children's Vaccines should be combination vaccines. However, there are comparatively few of these combinations available.

The most widely used combination in developing countries is the vaccine against diphtheria, tetanus and pertussis, known as DTP* . Because of its widespread use, ease of administration, and three-dose schedule given in infancy, it has become the foundation of routine immunization coverage. DTP has also become the foundation upon which many of the existing combinations have been built, including those relevant to GAVI:

- Glaxo Smithkline (formerly Smithkline Beecham) has combined DTP with hepatitis B in a four-antigen (tetravalent) vaccine;
- Aventis Pasteur (formerly Pasteur Mérieux Connaught) has combined DTPwith Hib;
- Glaxo Smithkline has combined DTP with both hepatitis B and Hib. This is actually a combination of tetravalent DTP-hepatitis B and freeze-dried Hib that needs to be mixed by the health worker at the time of injection.
- No combination vaccines currently incorporate yellow fever. This is likely to remain a single-antigen vaccine.

Part of the reason why the list is so short is that many high-income countries are not interested in buying vaccines that contain whole-cell pertussis, preferring instead the acellular pertussis (DTaP), despite its higher price. This reduces the incentive for companies to develop combinations containing the whole-cell preparation.

Some in the public health community worry that, because of the comparative lack of competition, combination vaccines will never be as affordable as single-antigen vaccines. On the face of it, the combination vaccines do look more expensive: for example, DTP combined with hepatitis B may cost up to US$1.07 per dose,

> "When you take all costs into account, combination vaccines are no more expensive than individual antigens"

including the cost of an autodestruct syringe, while DTP and hepatitis B can be given separately for US$0.80, including the cost of two autodestruct syringes.

But these concerns about cost are dismissed by Steven Jarrett, procurement manager for UNICEF, which supplies many developing countries with vaccines and injection materials.

"My calculation is that when you take all costs into account – logistics, labour, compliance issues and the risk of unsafe injections – combination vaccines are definitely not more expensive than individual antigens," he says.

Furthermore, as more of these vaccines are purchased for the developing-world market, prices could drop. There are precedents: when it was first introduced, Hepatitis B cost US$25 per dose; now it is well under US$1. And as recently as 1998, Latin American countries were purchasing Hib vaccine directly from manufacturers for as much US$8.50 per dose. Now the Pan American Health Organization is able to offer the vaccine to its member states for US$3.00 per dose, according to estimates for the year 2000. As demand for these new and under-used vaccines increases, more companies may enter the market.

The process may take some time, however. Combining existing antigens is not a simple development, but poses complex technical and clinical challenges, since the combined product has to demonstrate equivalent safety and immunogenicity. New combination vaccines must undergo extensive clinical trials to ascertain whether the different components, including the individual antigens, stabilizers and preservatives, have had negative effects on efficacy. The regulatory process alone can take three to five years, and adds to vaccine's cost.

"There is no way to avoid combination vaccines in the future and we should be prepared to have more and more of them," says Jacques-François Martin, CEO of Parteurop. "But making things easier also makes things more complicated. Acompany that holds the market position today could lose everything tomorrow if it does not include a particular antigen in its combinations. Market forces will no longer be able to dictate future vaccine needs. We will have to agree on certain orientations today in order to provide the world with vaccines they can use in the future." ■

*Two versions of DTPare available: the 'whole-cell' pertussis and 'acellular'pertussis (DTaP), approved for use because of minor side effects that can occur with whole-cell pertussis.

Lisa Jacobs is Communications Officer for the GAVI Secretariat

Rotavirus vaccines: what next for the countries that need them most?

The withdrawal of a vaccine against a major diarrhoeal disease has raised the stakes for vaccine developers everywhere. Phyllida Brown reports

ROTAVIRUS is one of the biggest killers among diarrhoeal diseases, with an estimated death toll of 600,000 a year – more than one child every minute. A vaccine against the disease was licensed in the United States in 1998. But in October last year the vaccine was withdrawn by its marketing company, Wyeth-Lederle, after it was linked with cases of intussusception, a serious and occasionally fatal blockage of the bowel, in U.S. infants. The consequences – both for those who need rotavirus vaccines and for those who make them – have been profound. Trials of all rotavirus vaccine candidates have been held back and made more complex and costly, forcing back the timeline for reducing the global burden of the disease by years. Here, *Immunization Focus* finds out what happens next, and what other vaccines are in the pipeline.

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Diarrhoeal dehydration: treatment is good, but prevention would be better

Where does the U.S. decision leave developing countries?

The vaccine, known as RotaShield® or RRV-TV, had been tested for efficacy in the United States and Finland before its licensing, but, aside from a successful trial in Venezuela, little was known about whether it could protect children in developing countries where children are typically infected earlier in life and with a wider range of rotavirus strains. So trials had been planned in several countries with a high rotavirus burden, including India, Bangladesh and South Africa. Those trials were put on hold when the data on intussusception emerged in the United States (1,2).

Doctors and researchers from developing and industrialized countries met earlier this year at the World Health Organization to agree how to move forward (3). They called for trials of new candidate rotavirus vaccines as soon as possible. Importantly, they said that wherever possible, these trials should be done concurrently in low-income and industrialized countries. But they also left the door open for trials of RRV-TV itself, under two specific conditions: that trials would monitor babies for signs of intussusception and treat them promptly, and that the manufacturer would guarantee to supply the vaccine for general use if the results were good.

In reality, however, the options are more limited. Wyeth-Lederle is not currently distributing RotaShield anywhere, either for trials or for sale. Wyeth's Peter Paradiso says that the company has "not given up" on RotaShield's potential, but neither is it willing to go further without clear indications from regulatory and health authorities in high-burden countries that they would actually want the vaccine following successful trials. "You don't do trials with a vaccine that nobody would ever use," says Paradiso.

What are the benefits and risks of the vaccine?

The greater the threat of rotavirus in a child's environment, the greater the potential benefit of the vaccine to that child. In India, for example, about 140,000 infants die of rotavirus disease every year, or one in every 200. In Bangladesh, the figure is 20,000, a comparable death rate to India's.

Assuming that RRV-TV had given 80 per cent protection from rotavirus-related death in Bangladesh, it could have saved 13,000 lives a year in the nation's immunization programme alone, even taking account of the fact that not all children would receive the vaccine, estimates David Sack, director of the ICDDR,B Centre for Health and Population Research in Dhaka.

In the United States, rotavirus kills far fewer children – up to 40 a year – although it causes about 50,000 hospitalizations (4). During the period that RRV-TV was available, about 1 million American infants were immunized, and one child died of vaccine-related intussusception. ◗

The final information on the risks of intussusception will not be known until data are complete this summer, but the U.S. Centers for Disease Control and Prevention (CDC) examined the early data and found that the risk was significantly higher in immunized than in un-immunized children within the first two weeks after receiving the first and second doses (2). In the first week after the first dose, the risk was 25-fold higher in immunized children. In a setting where child deaths are rare, this risk was deemed unacceptable, and the U.S. Advisory Committee on Immunization Practices (ACIP) withdrew its recommendation for use of the vaccine. Perhaps surprisingly, there was no formal discussion in the committee of what an acceptable risk-benefit ratio should be, says Paul Offit, an ACIP member and a rotavirus specialist at the Children's Hospital of Philadelphia. The committee did, however, point out that its conclusions might not apply in other countries where the risks and benefits might be different (2).

Box 1: Intussusception

What is intussusception?

A blockage of the bowel in which one segment of the intestine folds inside another – like a shirtsleeve being pulled inside out

Does it kill?

Death from intussusception is rare if people have prompt access to treatment. Data from hospitals in African and Asian countries report that between 3% and 26% of cases are fatal, but the data may be incomplete

What causes it?

"Natural" intussusception may be triggered by infections or developmental factors. No one knows how rotavirus vaccines might trigger the condition, but animal strains of the virus seem more likely to cause it than human strains

How common is it?

Few large-scale studies have been done. In the United States natural intussusception affects up to 70 babies in every 100,000 every year; in developing countries, the existing figures suggest lower rates, though some cases may go undetected

Who suffers from it?

Infants, usually aged between 3 and 9 months; more common in well-nourished infants and in boys

Source: (3)

If a vaccine is not safe enough for the United States, is it safe enough for anyone?

Paediatricians and researchers are split into two broad camps. For some, the death toll from rotavirus is simply too great to allow a rare adverse effect to prevent immediate further and careful testing of a vaccine that might prevent hundreds of thousands of deaths a year. Bernard Ivanoff at the World Health Organization, who is responsible for coordinating the agency's work in vaccine development against diarrhoeal diseases, is personally sympathetic to this view. "Of course, it would be easier for me to say, forget this vaccine," he says. "But it might be five years before we have another one. If we have a vaccine now that can protect people, we could prevent more than 2 million deaths in that time; that's a concrete reality."

Duncan Steele, director of the South African Medical Research Council's Diarrhoeal Pathogens Research Unit at the Medical University of South Africa, was involved in the planning of a trial of RRV-TV that was stopped. "Personally, I think that we should have been allowed to continue, albeit with very careful monitoring for intussusception," he says. Claudio Lanata at the Institute for Nutritional Investigation in Lima, Peru, says that clinicians in the city had said that they would still consider using the vaccine if there could first be a large study to assess the risk of vaccine-related intussusception.

For others, it is inconceivable that a vaccine considered too risky for the United States could be tested anywhere else. Although the mathematics of risk and benefit clearly indicate that the vaccine could benefit Bangladesh, says Sack, the political reality is that it would not be acceptable. Imagine the newspaper headlines, he says: "It was not safe enough for Americans, but it's OK for Bangladesh." Sack gathered a meeting of physicians in Dhaka to discuss the prospects for future trials and the view, he says, was that "there is an urgent need for a successful vaccine, but that it will be difficult to move ahead with RRV-TV".

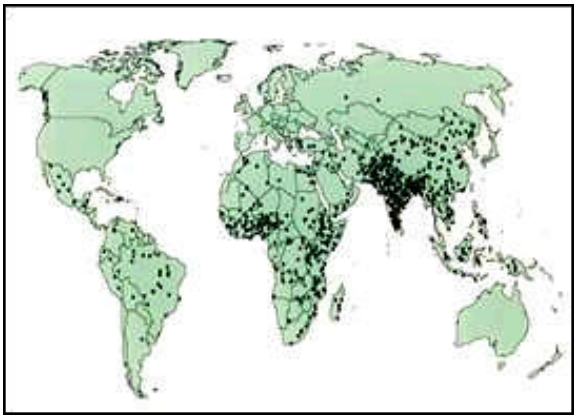
Paradiso at Wyeth-Lederle agrees. "Regardless of risk and benefit, there are concerns about a vaccine that has known side effects," he says. Parents cannot know their own child's absolute risks of getting severe rotavirus disease, he says, but they will know that the vaccine carries a risk, however small.

New vaccines in the pipeline

So far, most candidate vaccines against rotavirus have been based on live, weakened animal strains of the virus. These animal strains were used at first, in part, because they grew easily in cell cultures. ◗

Researchers also had evidence that vaccines based on animal strains would protect against human strains. RRV-TV itself is based on a strain from the rhesus macaque. Merck has a candidate based on a bovine strain known as WC3 (see Table 1). To increase the breadth of protection, these strains have been grown in culture together with the most commonly-found rotavirus strains from humans, to make recombined, or reassortant, viruses that also stimulate specific immunity to these human strains. Merck's candidate has already been tested in Finland and the United States and Timo Vesikari, at the University of Tampere, and others, are involved in plans to test the vaccine in a large trial in these two countries which would monitor both efficacy and safety.

Global distribution of annual rotavirus deaths



Source: (4)

Vaccines based on human strains may now be attracting more interest. Natural rotavirus infection does not seem to cause intussusception, so some researchers reason that vaccines based on human strains may be less likely to cause it. Glaxo SmithKline (formerly SmithKline Beecham), in partnership with Avant Immunotherapeutics, a company in Boston, has a candidate vaccine, 89-12, based on a human strain. Glaxo SmithKline has said that it will consider doing trials of this vaccine concurrently in both industrialized and developing countries, a significant signal that it recognizes the urgency of the problem and the need for data that all countries, including those with a high disease burden, can learn from.

There are many rotavirus strains that infect humans, but four are known to be common worldwide. RRV-TV and Merck's candidate both induce protective antibodies against these common strains. Importantly, in India and Bangladesh, there are additional strains that infect a significant number of children – a finding that may be important for vaccine designers (5). Vaccines based on two strains of rotavirus taken from healthy Indian children are being tested for safety in the United States and have attracted the interest of Indian vaccine manufacturers (6).

However, even with vaccine candidates already under development, it is likely to be around five years and possibly as many as ten years before all the results of trials will be known or before a product can be licensed. Add to this the time that is likely to elapse before prices of any registered products fall to globally accessible levels, and the reasons for paediatricians' frustrations are obvious.

Meanwhile, research on the second generation of rotavirus vaccines continues. The industry is exploring various options for the longer-term future. For example, researchers are considering developing rotavirus vaccines to be delivered through the nose, says Paradiso. It is hoped that these intranasal vaccines will stimulate an immune response at the body's mucosal surfaces – where the virus replicates – without the risk that the virus would also trigger intussusception in the mucosa of the gut. Other researchers are trying to develop vaccines based on a part of rotavirus rather than on the whole, live virus. These would be injected rather than swallowed and would be unlikely to carry any risk of intussusception.

Table 1: Rotavirus candidate vaccines in advanced development

Manufacturer	Vaccine type	Status
Merck & Co.	Oral vaccine based on five bovine-human reassortant rotavirus strains	Safety and efficacy studies in almost 2000 children completed; large safety/efficacy study in Finland and USA is planned to start soon
Glaxo SmithKline (formerly SmithKline Beecham) in partnership with Avant Immunotherapeutics	Known as 89-12 (or "RIX4414") Oral vaccine based on single, weakened human rotavirus strain	Small safety and efficacy studies completed. Proposals for large trials in both industrialized and developing countries are under discussion

Box 2: Paying for vaccines

Compared with the now remarkably low costs of the traditional vaccines such as diphtheria, pertussis and tetanus, rotavirus vaccines are expensive. RotaShield was priced at $38 per dose, putting it beyond the reach of most low-income countries. Nevertheless, says Ivanoff at WHO, a high initial price must not be a reason for delaying product development that is likely, eventually, to benefit high-burden countries. He cites the falling cost of vaccination against hepatitis B, once about $25 per dose, but now below US$1 a dose within the WHO's Expanded Programme of Immunization, as grounds for confidence that prices of future rotavirus vaccines would eventually fall. Companies in high-burden countries, such as India, may produce and market future rotavirus vaccines at lower cost than in the industrialized nations.

The impact on the vaccine industry – down but far from out

No one doubts that rotavirus vaccine developers' jobs have become more difficult because of intussusception. "The experience with rotavirus vaccine will set a new bar on the size of vaccine trials," says Offit. Researchers estimate that at least 60,000 participants will be needed, and possibly as many as 1 million, for trials to be able to pick up the risk of intussusception. To date, field trials of candidate vaccines against other diseases have rarely involved more than 40,000 people, and usually they have been much smaller.

Beatrice De Vos, director of clinical development in the paediatrics unit of Glaxo SmithKline in Belgium, believes the whole framework for developing rotavirus vaccines has now changed. Now, she says, when the data for any new candidate vaccine is on the regulator's desk, "somewhere in the head of the person looking at the dossier will be the data from RotaShield". She believes that, rather than simply proceeding along a standard development plan, companies now have to negotiate the development process with the regulatory authorities step by step.

The impact may spread beyond rotavirus to other vaccine development programmes, says Alan Shaw, executive director of virus and cell biology at Merck. "This has had a profound impact on how we are going to have to conduct trials in future," he says. "You have now got to do your 'post-marketing surveillance'before you market a vaccine, and that is expensive." De Vos agrees that conditions have been made tougher. "It looks as though there is a tendency to go for zero risk with vaccines, and that may be impossible," she says. "A baby is at risk just breathing air." For example, a trial might detect no intussusception in 200,000 infants, but the 200,001st child could be the first to suffer the condition: does that mean the vaccine is unsafe? Nevertheless, DeVos remains hopeful. "We are moving ahead."

Given the expected problems with regulators in the industrialized countries after RotaShield, some public health officials think the best hope lies with researchers and manufacturers in high-burden countries, who may be able to develop their own rotavirus vaccines within approval frameworks that are acceptable worldwide. This would be possible, for example, in India, says Julie Milstien in the WHO's Vaccines and Biologicals division. India already makes and regulates vaccines that are sold to the Expanded Programme on Immunization and its infrastructure for quality control has been fully developed for a number of years.

Paradiso at Wyeth-Lederle says that the cost of developing and testing vaccines has been rising steadily as regulatory requirements have increased. Realistic estimates range between US$200 million and US$400 million for a product, he says, and costs may now spiral further as trials grow larger and their capacity to monitor all participating infants for intussusception is ensured.

Nevertheless, the company has no intention of abandoning its work on rotavirus vaccines. But, says Paradiso, "it seems important for us to move on to new candidates, in addition to evaluating the future of RotaShield. Our overall commitment to vaccine development is still very high, and this has not affected our outlook." That, at least, is good news for tomorrow's children. ■

Key references

1. *Morbidity and Mortality Weekly Report* 48 (27); 577-581 www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4827a1.htm

2. *Morbidity and Mortality Weekly Report* 48 (43); 1007 www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4843a5.htm

3. WHO 2000. *Future directions for rotavirus vaccine research in developing countries.* In press. Contact Dr Bernard Ivanoff for more information: ivanoffb@who.ch

4. Parashar U. and others. Rotavirus. *Emerging Infectious Diseases* 4 (4) www.cdc.gov/ncidod/EID/vol4no4/parashar.htm

5. Ramachandran M. and others. Unusual Diversity of Human Rotavirus G and PGenotypes in India. *Journal of Clinical Microbiology.* 1996 February; 34 (2) 436-9

6. The Jordan Report 2000. *Accelerated Development of Vaccines.* National Institute of Allergy and Infectious Diseases. Available via www.niaid.nih.gov/publications/jordan

Advocating immunization: how health professionals can make a difference

Scott Wittet and Robert Aston offer some practical suggestions

CHILDHOOD vaccines save three million young lives per year. The World Bank has concluded that immunization is one of the most cost-effective health interventions available today and that improved health helps to reduce poverty and boosts national development. Yet the realities of current immunization programmes often fall short of their potential. If you and your staff are involved in promoting immunization in any way, there are steps that you can take to help overcome the common problems. You can advocate for stronger and better immunization programmes. You can advocate for the introduction of new and under-used vaccines against major threats to public health, such as hepatitis B and yellow fever. And you can inform yourself fully about vaccine safety so that you can help parents who may be worried by media "scares". Here are some suggestions:

Learn all you can about overall immunization safety

Become familiar with the evidence that immunization is a very safe and cost-effective way to protect children against suffering, disease, and premature death. If you do not have the time to investigate the literature yourself, take advantage of the short summaries and briefing documents that are available for health-care workers on the web sites of reputable organizations in public health, such as the World Health Organization, the U.S. Centers for Disease Control and Prevention (CDC), and others. If web access is difficult, write to the organizations' public information offices to request paper copies of documents.

For general information for health professionals on the benefits of immunization:

- The "Resource Center" of the Bill and Melinda Gates Children's Vaccine Program, PATH, 4 Nickerson St, Seattle, Washington 98109 USA:
www.childrensvaccine.org/html/resources.htm
- The World Health Organization, 1211 Geneva 27, Switzerland:
"Six Common Misperceptions about Vaccination":
www.who.int/vaccines-diseases/safety/prof/misconcept.htm
"Immunization Safety Priority Project":
www.who.int/vaccines/aboutus/newweb/immunizationsafety.htm
"Professionals":
www.who.int/vaccines-diseases/safety/prof/prof.htm
- The South Australian Health Commission, via the Australian Government Publishing Service, GPO Box 84, Canberra ACT 2601:
"Immunization: Myths and Realities":
www.health.gov.au/pubhlth/strateg/immunis/myths.htm
- The Centers for Disease Control and Prevention, National Immunization Program, Information Center, 1600 Clifton Road, NE , Mailstop E34, Atlanta, GA 30333, USA (or call +1 404 639-8226):
"Six Common Misperceptions about Vaccination - And How to Respond to Them":
www.cdc.gov/nip/publications/6mishome.htm
"What Would Happen If We Stopped Vaccinations?":
www.cdc.gov/nip/publications/fs/gen/WhatIfStop.htm

Learn about your local immunization programme

Try to determine how "healthy" it really is. Are children being fully immunized and are they receiving the vaccines at the right age? Are the injections safe? Has the risk of accidental needle-sticks been minimized? Is the cold chain adequate? Is there adequate surveillance of vaccine uptake, adverse events, and disease incidence? Are public relations and health education efforts effective? Is there a working system to counter anti-vaccine rumours and misinformation? If not, alert those in charge of the programme and urge them to make some changes.

Reputable sources on injection safety and the implementation of safety surveillance include:

- The Safe Injection Global Network (secretariat based at WHO, address as above):
www.injectionsafety.org/
- The Institute for Vaccine Safety at Johns Hopkins University, Baltimore, Maryland, USA:
www.vaccinesafety.edu/
- Relevant papers in a special issue of the *Bulletin of the World Health Organization* devoted to immunization safety:
www.who.int/bulletin/tableofcontents/2000/vol.78no.2.html

Know your local disease burden

If you think that hepatitis B or *Haemophilus influenzae* type b (Hib) disease are problems in your area, find out what is known about the disease burden. Contact your health authorities, the WHO representative, and the local UNICEF office. Determine if there are research projects in which you could participate or that can share relevant data. Investigate what is known about the burden of these diseases in neighbouring countries.

- For WHO statistics on disease burden by region see the World Health Report:
www.who.int/whr/1999/en/disease.htm

Fight ignorance and misinformation

As the success of immunization programmes reduces the immediate threat of disease in some countries, it is increasingly common to find individuals and groups who criticize immunization and claim that it is harmful. For example, anti-immunization groups have recently revived claims of a link between the combined vaccine against measles, mumps and rubella (MMR) and autism. There is to date no evidence of a causal relationship between the vaccine and autism, but many parents have been worried by what they have heard. They have a right to accurate and informed advice from their healthcare workers.

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Crucial contact: healthcare workers have a duty to give informed advice to parents

- For help in responding to parents' concerns, see the CDC's website for a briefing on this topic, with links to other resources:
www.cdc.gov/nip/vacsafe/concerns/autism/
- For briefings on other current "hot topics" on vaccine safety in the media, see:
www.who.int/vaccines-diseases/safety/hottop/hottop.htm
and
www.cdc.gov/nip/vacsafe/concerns/gen/default.htm

In general, be sceptical about rumours and sensational media reports claiming dangers from modern vaccines; they may be based on misinterpretation of the evidence. As the feature on rotavirus vaccines on pages 3 to 6 of this issue shows, vaccine safety concerns that are genuine are promptly publicized.

Remember that vaccines are far safer than the diseases they prevent. Severe adverse effects of vaccines are very rare. The diseases themselves are much more likely to harm children. Remind colleagues and patients about the horrors of those diseases. Counter allegations of vaccine-damaged children with reports of disease-damaged children.

Don't sit on the fence

Health professionals do not help parents if they simply hand out brochures or articles and expect people not trained in medicine to make sense of confusing, and sometimes contradictory, data. Healthcare providers are trained to form balanced, evidence-based judgments and to share their recommendations with patients. Doctors or nurses who do not assist patients with healthcare decisions may be shirking their responsibilities. If you believe in the value of immunization, say so.

Discuss, publish, teach, advocate

Write articles for the local newspaper. Make yourself available as a guest on radio and television programs. If vaccine-preventable diseases are in the news, use the opportunity to call for increased political commitment to immunization. Discuss your concerns with government officials. Introduce yourself to programme managers at UNICEF and non-governmental organizations such as Save The Children or Médecins Sans Frontières. Become active in national paediatric and medical associations and encourage them to formally recommend use of new vaccines against diseases that are major public health problems.

Sustain the momentum

Emphasize that vaccination is necessary even when disease levels diminish in your community. Global travel is now so common that infections can be spread between continents in a day. Not until a disease has been eradicated worldwide can immunization against it be discontinued safely. Only smallpox has been eradicated so far, and that was achieved through continuing, and thorough, immunization.

Global immunization is the greatest public health success in history. In little more than a decade, a massive effort raised coverage rates from 5 per cent of children worldwide in the late 1970s to a reported 80 per cent in 1990. But as new health issues were given priority, some of the energy and excitement about immunization dwindled. Fortunately, that trend is now being reversed.

You can be part of the process. It may seem that immunization issues are being addressed at the national and international levels. But change often comes from the community, and public demand for stronger immunization programs can influence public policy. That demand can be encouraged by individuals, single voices, persistently making themselves heard, then joining with others to create a chorus that cannot be ignored. ■

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Note: This is a shortened and adapted version of an article first published at www.ChildrensVaccine.org

R&D briefing: news from the Third Annual Conference on Vaccine Research

LEADERS in public health and industry told researchers that they were entering a new era for vaccine development as they met earlier this month at the Third Annual Conference on Vaccine Research in Washington, DC to hear updates in strategies against HIV, malaria and other diseases.

On the one hand, the time for vaccine development has never been better, said Sir Gustav Nossal, of the University of Melbourne, Australia. Knowledge of the genomes of major microbes and parasites is increasing rapidly, enabling new approaches to design. Policy-makers and new donors are also recognizing the value of vaccines as cost-effective tools in the fight against poverty. On the other hand, the industry is facing spiralling costs for product development. And in some societies, from Asia to North America, people appear to be more afraid of vaccines than of the diseases they prevent.

Michel De Wilde, deputy executive vice-president for R&D for Aventis Pasteur, warned that the industry must set priorities. Despite expansion in recent years the vaccine market accounts for just US $5 billion, or 1.6 per cent, of the pharmaceuticals market overall. Four major companies account for three-quarters of this market. De Wilde said that increased regulatory pressures and higher technical demands were resulting in "skyrocketing" development costs. Four products have been registered with the US Food and Drug Administration in the past eight years, and development costs have been estimated to be $300 million to $400 million per product. "This is becoming an increasingly difficult business to be in," said De Wilde.

Nevertheless, new-generation experimental vaccines and vaccine delivery systems were in plentiful evidence at the conference. Among them:

● HIV

Scientists in the United States and Italy are testing an ingenious but relatively simple approach to immunization that stimulates an aggressive immune response against the virus. If the approach proves successful in further studies, it might eventually be used both to control HIV in people who are already infected and also to prevent the virus from establishing infection in the first place. In animals, the prototype vaccine is stable at room temperature and can been given without needles simply by painting it onto shaven skin.

Julianna Lisziewicz of the Research Institute for Genetic and Human Therapy in Washington, DC, and colleagues, made an artificial construct of HIV genes, a plasmid DNA, that cannot integrate itself into cells or replicate. The researchers then attached this gene construct to a chemical called polyethylenimine mannose, a mix of a polymer and a sugar, which has a unique ability to dock onto dendritic cells, a key group of cells of the immune system whose job is to introduce other defence cells to microbial antigens. Unlike other cell types, dendritic cells have a specific receptor for mannose. Once docked on this receptor, mannose activates the dendritic cells, which start to alert other defence cells. In the laboratory, the team found that dendritic cells were activated by exposure to the solution, and that when the dendritic cells were cultured with T cells, these made strong responses against the virus.

Just as important, they found, very large numbers of dendritic cells in the skin of mice and pigtail macaques were activated when the solution was painted onto shaven skin. The activated cells have been shown to travel to the animals' lymph nodes where they trigger strong T-cell responses against HIV. Lisziewicz and her colleagues now plan to test whether their potential vaccine can protect rhesus macaques against deliberate challenge with an HIV-like experimental virus, SHIV. The team is also discussing with the Italian regulatory authorities a small trial of the experimental vaccine as an immune therapy in people with HIV in Italy. Nossal, of the University of Melbourne, said the approach was interesting and warranted further study and support, particularly to find out how the solution penetrates the skin.

(Abstract S33)

● Malaria

For years, scientists have recognized an antigen known as MSP-1 (merozoite surface protein 1) on the surface of the blood stage of the malaria parasite, *Plasmodium falciparum*, which they have hoped could form part of an effective vaccine. However, the antigen on its own has triggered only disappointingly weak immune responses and researchers have argued that adjuvants stronger than most of those licensed for human use will be needed to make a successful vaccine (see, for example, 1). Now researchers may have a way around the problem. They are using a natural human protein, C3d, part of the complement system of the immune system, which coats invading microbes and helps to ◗

stimulate defence cells known as B cells to produce antibodies against them. Two or more copies of the C3d protein can increase the antibody response by up to four orders of magnitude, explained Vivienne Cox of AdProTech, the small company based near Cambridge, UK, that makes the C3d under the name of Immudaptin™.

The idea of using C3d as a kind of natural adjuvant was first described in 1996 (2). But now the team has successfully applied the idea in a mouse malaria model. Using the mouse equivalent of C3d and the comparable MSP from a rodent malaria, *P. yoelii*, the team found that three-quarters of all the mice immunized were protected from a lethal challenge with the parasite. The team includes Louis Miller at the National Institutes of Health in Bethesda, Maryland, USA, Anthony Holder at the National Institute for Medical Research in London, and Douglas Fearon at the University of Cambridge, UK.

"The results are very exciting and we are moving immediately into generating the equivalent protein for human immunization against *P. falciparum* and *P. vivax* [the two main human forms of malaria worldwide]," said Cox of AdProTech. The team have contacted WHO and are discussing a collaboration with researchers at the Pasteur Institute in France for these studies.

"This is an interesting and original approach," says Howard Engers, who coordinates malaria vaccine research for TDR, the multisponsor tropical disease research programme based at WHO in Geneva.

(Abstract P52)

(1) Holder, A. (1999). Malaria vaccines. *Proceedings of the National Academy of Sciences*, 96: 1167-69.

(2) Dempsey, P.W. and others. (1996). C3d of Complement as a Molecular Adjuvant: Bridging Innate and Acquired Immunity. *Science* 271: 348-50.

● Needle-free vaccination

Needles might be redundant in immunization programmes sooner than some suspect, judging from the studies presented at the meeting. Several groups reported early work on vaccines delivered nasally, for example against pneumococcus. Meanwhile PowderJect Vaccines Inc of Madison, Wisconsin, USA, has developed a needle-less syringe for single use that uses helium gas to drive powdered vaccines at high speed into the epidermis without causing pain. In mice the existing hepatitis B vaccine, in powdered form, stimulated strong immune responses to the virus when delivered by this route. The small cylinder costs about US$1, says Kathleen Weis of PowderJect. This is clearly more expensive than the conventional equipment used in low-income countries, but may reduce costs in other components, for example in the amount of vaccine used. Weis says that less antigen may be needed with epidermal immunization than with conventional vaccines, as the trans-skin approach may target dendritic cells in the skin (see above). "We are projecting to start a clinical trial next year," says Weis.

(Abstracts P41, 43, 44)

● A practical approach to combination vaccines:

Luciana Leite from the Instituto Butantan in Sao Paulo, Brazil and her colleagues are attempting a tough challenge: to persuade the familiar Bacille Calmette-Guérin, or BCG, a live microbe used to vaccinate against TB, to express antigens against diphtheria, tetanus and pertussis. The advantages are obvious: a single immunization would protect infants against all four diseases, and BCG is an inexpensive vector, already well established for use in humans. Leite's modified form of BCG, which expresses antigens from tetanus, diphtheria and pertussis, has been shown to protect mice against an intracerebral challenege with *Bordetella pertussis*, and to induce antibodies that neutralize tetanus toxin in the animals, and diphtheria toxin in the laboratory. The approach has been investigated before, but few have pursued it. "This is the first report of protective immunity induced by the three antigens of DTP expressed in recombinant BCG," says Leite's team. There is some way to go before human trials could be begun, however, she says.

(Abstract S15). ■

For more information see abstracts of the Third Annual Conference on Vaccine Research, 30 April - 2 May 2000, available by email order from info@nfid.org or by fax at (+1) 301 907 0878 (Price US$45).

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Immunization Focus

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Designed and produced by: Synergy New Media, London N17, UK. www.synergy-interactive.co.uk