Immunization Focus

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NEWS

GAVI

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Immunization Focus

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An investment for life

IN a signal of their commitment to immunization, government ministers from more than 60 of the 75 countries eligible for GAVI support assembled in Dakar, Senegal for the Second Partners' Meeting last month. The President of Senegal, Mr Abdoulaye Wade, opened the meeting with a call to delegates to redouble their efforts in increasing children's access to vaccines in developing countries. Almost 400 participants – including those from non-governmental organizations, the vaccine industry and UN partner agencies – discussed the progress of the Alliance so far and confronted the challenges ahead.

Ms Carol Bellamy, executive director of UNICEF and chair of the GAVI Board, said that one of the Alliance's greatest challenges is to ensure that countries can assure the sustainability of their immunization services into the future.

Reflecting the importance of this issue, the central political event of the meeting was the signing of the Dakar Declaration on Financial Sustainability by the health and finance ministers of an initial group of 13 GAVI-supported countries. The declaration calls on all governments and partners to recognize that "immunization and the sustainability of immunization is a national priority, a global concern and a shared responsibility" (1).

First results

The presence of finance ministers at a health meeting reflects the seriousness with which countries regard their investment in immunization as a highly cost-effective tool to improve their population's health.

The first six countries to prepare Financial Sustainability Plans for their immunization services – Cambodia, Côte d'Ivoire, Ghana, Guyana, Kyrgyzstan and Mali – presented their plans to GAVI and the Vaccine Fund. The plans set out each country's assessment of their financial needs for immunization in the medium-term future and their plans for mobilizing resources, national and external, to finance these services after the initial period of support from the Vaccine Fund ends.

M. Diop

Political priority: President Abdoulaye Wade arrives to open the meeting

Dr Tore Godal, Executive Secretary of GAVI, summarised the Alliance's progress to date (2) and outlined the tasks ahead. Sixty-four of the 75 eligible countries whose annual income per head is below $1000 have now been approved for support by GAVI and the Vaccine Fund, and 180 million doses of vaccine have been supplied. Some $130 million of funds have been disbursed. Most of this money has been spent on new vaccines but a quarter of the total has gone to improving countries' health systems and infrastructure and $4.5 million has been spent on auto-disable syringes to improve injection safety. Over the five-year initial funding period, more than $900 million of funds have been committed by the Vaccine Fund.

A key achievement in the Alliance's work so far has been the sharp increase ◗

Inside this issue

in access to hepatitis B vaccine, which has now been provided to 10.5 million children. Dr Mark Kane of the Children's Vaccine Program at PATH reminded delegates of the appalling burden of this virus, which causes liver cancer in up to a quarter of all those who become chronic carriers. Epidemiologists estimate that about 1 million deaths could be prevented worldwide each year with wider use of hepatitis B vaccine.

A vaccine to reduce the global cancer burden

During 2002, in a historic agreement between the government of China and GAVI and the Vaccine Fund, a $75-million project began to vaccinate Chinese infants in the poorer western provinces and "poverty counties" against the virus, with half the money coming from the Vaccine Fund and half from the Chinese government. China now plans to extend free hepatitis B vaccination to all infants nationwide (See Box 1).

The impact of the initiative for global health is expected to be dramatic. "After tobacco, hepatitis B is the second greatest preventable cause of cancer," says Kane. "This is one of – if not the – greatest anti-cancer successes in history."

But, as Dr Godal made clear, there is no room for complacency. Countries and their international partners have probably saved about 100 000 lives so far through the GAVI initiative, and this should be celebrated. But a total of 2.6 million deaths could be prevented each year if existing vaccines were reaching all children. The Partners have yet to make much progress if they are to achieve their target of reaching 80% of children in all districts in at least 80% of all developing countries by 2005 with three doses of DTP. And this is just the first part of the challenge.

Key future tasks for the Alliance include:

- Increasing access to immunization over the next 2–3 years;
- Securing sustainable finance over the next 3–5 years;
- Accelerating the development and introduction of newer vaccines, including those against pneumococcus and rotavirus, over the next 5–10 years.

Dr Godal paid tribute to countries that are already increasing their investment in their future immunization services, such as Ghana and Sri Lanka. Increasingly, governments are viewing health interventions as investments in poverty reduction, rather than expenditures. A key challenge is to build immunization services into a broader, strengthened health system.

The Vaccine Fund

Since the initial gift of $750 million from the Bill and Melinda Gates Foundation, the Vaccine Fund has received contributions totalling a further $400 million mainly from governments. The goal, however, is to raise a total of $2 billion over five years and more resources are needed if the Fund is to fulfil its ambitions of becoming a "permanent instrument" to support the activities of GAVI, said Jacques-François Martin, the Fund's President.

Vaccine supply and security

Today, the children's vaccine market is changing fast, said Ms Bellamy. Supplies of the so-called "basic" vaccines that form the mainstay of the Expanded Programme on Immunization are becoming more scarce as industrialized countries increasingly switch to "enhanced" vaccines such as DTP using acellular pertussis (see *Immunization Focus*, June 2001 and July 2002). The value of market for the basic vaccines has dropped by 40% while the overall vaccine market has doubled. Not surprisingly, therefore, the number of suppliers has fallen, from around seven in 1997 to as low as three or four in 2002. UNICEF is now buying at least 90% of the total supply of basic vaccines such as whole-cell DTP, BCG and measles, and in 2003, the available supply of tetanus vaccine is expected to fall short of demand. In order to safeguard a secure future vaccine supply, governments, industry and other partners must work together using multi-year plans and accurate forecasting of vaccine needs.

Paul Fife of the Vaccine Provision Project, set up at the request of the GAVI Board last summer to look at all issues of vaccine supply and financing, reiterated the importance of forecasting at country level. Accurate forecasting would be essential to ensure a more predictable vaccine supply, he told health ministry representatives. "The global forecast will only be as good as country forecasts, and this means your ability to do good forecasts is critical." ◗

1: China acts on hepatitis B

Immunization against hepatitis B has long been available in China, but only to those who could pay. In the poorest provinces coverage has been below 40%. As deaths from liver cancer are estimated to be between 280 000 and 400 000, there has long been a need for better protection. China's former minister of health, Dr Chen Min Zhang, now deceased, had said on his deathbed that his greatest wish for China was to see universal vaccination against the virus. His friends formed a foundation and began advocating for his dream.

GAVI and the Vaccine Fund then became involved and, in a joint initiative with the Chinese government (see main text), funded an initiative to immunize children in the poorest areas. The government then decided to extend free vaccination to all Chinese infants. An additional benefit is that the plan has stimulated the growth of an industry to make auto-disable syringes in China, says Kane.

Partners' feedback
Participants used the meeting and its many constituency break-out sessions as an opportunity to swap information and experience. Topics discussed include:

- **Developing countries: a knowledge exchange**
  Ministers from the GAVI-supported countries commended the initial period of work with the Alliance and the broad progress achieved. There had been problems with the shortage of combination vaccines, and more resources will be needed to increase safety with the introduction of auto-disable (AD) syringes and additional incineration facilities. But these problems must and can be overcome with sustained investment. The health ministry must be at the heart of each country's immunization service development to ensure sustainability. All countries would like to see accelerated progress towards vaccines against HIV, as well as more modest gains, such as reducing the costs of AD syringes.

  Health ministers from the GAVI-supported countries agreed that it would be useful for them to pool their knowledge and experiences in the areas of immunization and financial sustainability. Based on feedback from the meeting, *Immunization Focus* will in future include a new feature to foster information exchange among health ministers. Submissions for this feature will be welcomed.

- **Social mobilization**
  Participants discussed how to develop new, innovative and culturally sensitive ways to increase demand for immunization and improve service delivery. "We need to build a better social contract with parents," said Susan MacKay of WHO.

- **Increasing access to immunization**
  Partners discussed ways to reach more of the hard-to-reach, with an emphasis on district planning and preferential targeting of vulnerable children, and the need for partnerships with all stakeholders.

- **'Immunization-plus'**
  Ways to integrate high-quality immunization services into a broader system of health services for children and parents – such as malaria prevention and improved nutrition interventions – were discussed as means to reduce child mortality. ■

2. The state of immunization worldwide
Evidence is now stronger than ever that children's vaccines are an effective investment in reducing poverty, said Dr Gro Brundtland, Director-General of WHO. Launching the latest edition of a key report, *The State of the World's Vaccines and Immunization*, (3) in Dakar, Dr Brundtland said that WHO's Commission on Macroeconomic Development had shown that improved health clearly fuels economic growth in the poorest populations. "Improving health may be the single most important determinant of development in Africa," she said. It is also a humanitarian imperative.

But the report reveals just how many gaps must be closed if vaccines are to deliver their full potential for saving children's lives. In Sub-Saharan Africa, as many as half of all children remain unprotected by the most basic vaccines. Research and development of new vaccines does not, on the whole, address the needs of developing countries. Unsafe injection practices may account for as many as 1.3 million deaths a year. Vaccine supply is unpredictable, and new vaccines are slow to reach those who need them most. WHO, UNICEF and the other GAVI partners are addressing these problems, but substantial additional investment will be needed to enable them to succeed, said Brundtland.

(1) The full text of the Dakar Declaration is at www.gaviftf.org
(2) The GAVI Progress Report 2002 is at www.vaccinealliance.org/home/General_Information/About_alliance/index.php
(3) *The State of the World's Vaccines and Immunization*. WHO, Geneva. 2002

The GAVI Second Partners Meeting took place from 20–22 November. Presentations from the meeting can be viewed at www.vaccinealliance.org/home/General_Information/About_alliance/Dakar_Presentation_Page.php

Polio: can immunization ever stop?

An article in the last issue examined the progress of the worldwide effort to eradicate wild polio. Here, as the goal comes within sight, Immunization Focus learns about the difficult choices facing countries and the international community

NOBODY said it would be easy to get rid of poliovirus, and the last corners – in India particularly – are proving even harder than expected. But, as the worldwide polio eradication effort comes tantalisingly close to achieving its goal, policymakers face a new set of tough questions. If the world can soon be declared free of wild poliovirus, can countries then stop vaccinating their children against it, or should they continue forever? If they continue, what type of vaccine should they use? Would a world declared polio-free be safer with polio immunization, or without it?

Expect no instant answers. These questions are still being considered by those who advise the Global Polio Eradication Initiative (GPEI), a partnership spearheaded by WHO, Rotary International, the US Centers for Disease Control and UNICEF. But this is not a leisurely academic debate, and policy is evolving fast. Vaccine manufacturers need to know – very soon – what the world's broad requirements are likely to be beyond the next five to 10 years. ◗

Since its launch in 1988, the GPEI's goal has always been to wipe out a crippling disease, such that vaccination could stop. But as the prospect of achieving the first aim comes within sight, the idea of stopping vaccination is increasingly being questioned. Immunization experts disagree, with some advocating a coordinated cessation of vaccination as the safest policy, and others insisting that immunization must continue indefinitely.

Science and politics

While the GPEI continues to work towards the goal of stopping polio immunization after the world is certified polio-free, its leadership acknowledges the uncertainty, and is working to establish an international consensus on what policy should be in what it calls the "post-certification era". "What we need to do is gather the information," says Dr Bruce Aylward, coordinator of the GPEI at WHO in Geneva. "Our goal should be to stop using oral polio vaccine if at all possible. Whether and how we can do so remains a question, but the weight of the evidence currently suggests that we can."

Whether commentators agree or disagree with that view, the reality is that the debate has moved into a more political and public arena in the wake of September 11 2001. The media, especially in the US, have aired concerns that poliovirus could be used by bioterrorists on a non-immunized population in future. Highly influential voices have weighed in, not least Dr D.A. Henderson, who led the global campaign to eradicate smallpox and who now advises the US government on civilian biodefense issues. Henderson is firmly opposed to stopping the use of the oral polio vaccine and argues that those who favour doing so are taking the line of "zealots, not scientists".

So, what are the real issues? Would there be serious risks from an accidental or deliberate release of wild poliovirus into a population no longer immunized against it? What about the risks from the vaccine itself? WHO has set out (1) a framework for analysing and managing the various different types of risk (Box 1) and is overseeing studies to assess their scale. "What we are trying to do is summarise any risks after certification and look at how those risks might change over time," says Dr David Wood, a virologist at WHO who is coordinating the studies.

WHO/GPEI

Living with polio: children at a rehabilitation centre in the Democratic Republic of Congo, 2001

1: If the world is certified polio-free, what are the risks then ?

The WHO and the GPEI identify the risks in the post-certification era as follows:

Risks from oral polio vaccine and viruses derived from it:

- Vaccine-associated paralytic polio (VAPP) cases, estimated at around 250–500 per year;
- Outbreaks of disease due to circulating vaccine-derived polioviruses (cVDPVs);
- The persistence of VDPVs in a small number of individuals with primary immunodeficiency disorders, who can excrete live virus for many years.

Risks from wild poliovirus:

- Accidental release from a manufacturing plant that makes inactivated polio vaccine from wild virus;
- Accidental release of the virus into the environment from a laboratory storing any specimens;
- Intentional release.

The Technical Consultative Group to the GPEI says that the following conditions would have to be met before vaccination against polio could be discontinued:

- All wild poliovirus transmission stopped;
- Effective containment of all laboratory stocks of polioviruses and IPV production sites;
- Demonstration that VDPVs would not circulate for a prolonged period after the cessation of OPV;
- Establishment of a global stockpile and production capacity for OPV to respond to any future outbreak.

Before looking at these risks one by one, it is first worth remembering the reasons why the eradication initiative has always aimed, ultimately, to stop vaccination. The mainstay of the eradication initiative has been the oral polio vaccine (OPV), which is based on live, weakened virus and stimulates a strong protective immune response to the wild virus. OPV is a generally safe vaccine but it can, very rarely, cause paralysis. Estimates are still uncertain, but this disastrous outcome may result from about 1 in every million doses given, affecting something like 250 to 500 people worldwide every year. If the burden of wild polio falls to zero, the risks of the vaccine could outweigh its benefits. "The last thing we would want to do is inadvertently paralyse a child," says Aylward.

The risk of vaccine-associated paralytic polio is lower than, say, the risk of severe adverse events that accompanies existing smallpox vaccines. But it is nonetheless too high to be acceptable in many industrialized countries, where the burden of polio is now zero. In these countries, the more costly inactivated polio vaccine (IPV) is increasingly preferred, although there are questions about how strongly this vaccine would protect against polio in tropical developing countries where children are most heavily exposed to the virus. Nonetheless, if the polio burden reaches zero worldwide, the risks from the oral vaccine may be perceived as unacceptable by governments and the public in many more countries.

'Ideally, everybody would love to give up all polio vaccine, but some of us feel we are not in that position'

Another rationale for the goal of stopping vaccination with OPV was economic gain. During the 1990s, WHO estimated that the cost savings of eradicating polio and then stopping immunization could be as high as $1.5 billion a year by 2015. Clearly, those savings would be substantially less if immunization with OPV continued, and costs could even increase if IPV were widely adopted.

Risks from vaccine-derived viruses

Most of the risks from polio vaccine and from wild virus have been known for some time. But the rapid progress of the eradication initiative, and now a set of events in the last three years, have together forced researchers and policymakers to think harder about the impact of stopping immunization. In 2000 in Hispaniola (the Dominican Republic and Haiti), more than 20 individuals were paralysed and two died in an outbreak caused by poliovirus that was originally derived from OPV. The virus had reverted to behave more like the wild form (2). Further smaller outbreaks caused by these vaccine-derived polioviruses (VDPVs) have followed, in the Philippines in 2001 and in Madagascar this year. An earlier outbreak in Egypt is also now known to be due to VDPVs. Experts believe that more outbreaks will be found as surveillance continues in the absence of wild poliovirus and possibly declining immunization coverage.

All of the documented outbreaks arose in communities where immunization levels had slipped dangerously low and where conditions allowed vaccine-derived viruses to first regain the capacity to paralyse and then the capacity to circulate. The strains that had caused outbreaks had even recombined their genetic material with that of other species of gut viruses.

Scientists have long known that the weakened viruses in OPV can replicate in the gut and spread to household contacts of the vaccine recipient. But until 2000, few expected that such strains would persist for long enough to re-acquire both the capacity to paralyse and to spread widely in a community.

Professor Paul Fine at the London School of Hygiene and Tropical Medicine had argued (3), before the outbreak in Hispaniola in 2000, that VDPVs could persist in environments where poor hygiene favoured their spread, and that this could affect policies for stopping vaccination. He took no pleasure in seeing his concerns borne out in Hispaniola. "Ideally, everybody would love to give up all polio vaccine," says Fine, "but some of us feel that we are not in that position." For Fine, and others, the experience with VDPVs underlines the need to keep immunization coverage high enough to prevent their spread.

An alternative argument, expressed in a review article by Dr Walter Orenstein of the Centers for Disease Control and other members of the Technical Consultative Group to the GPEI, is that the recent vaccine-derived virus outbreaks are a strong additional reason for stopping immunization with OPV as soon as possible. While OPV is used, they argue, there will always be a risk that vaccine-derived viruses will emerge and seed new outbreaks of polio in areas where immunization coverage is low (4). If massive, coordinated immunization campaigns are done before withdrawing the vaccine, the population's level of immunity will be high and the risk of VDPVs circulating will be low.

The fact is, no one will know either way until more research has been done. Wood at WHO says that there are some studies under way to monitor whether VDPVs emerge after population-wide immunization campaigns. In Cuba, he says, polio immunization is given in two "pulses" per year, not as a routine service, so a very high proportion of the population is immunized all at the same time. So far, circulating VDPVs have not been found in Cuba – perhaps, says Wood, because the simultaneous immunization of so many people gives any escaping vaccine-derived virus very little time and very few hosts to go to. But how far can these findings from Cuba be generalised to other settings? Wood says that other studies are now under way, for example, in India, to see whether VDPVs emerge after campaigns in communities where routine immunization coverage is very low. However, some observers worry that such studies will be difficult to carry out and difficult to interpret.

Long-term carriers of vaccine-derived poliovirus

Most scientists see VDPV outbreaks as a serious concern. But there are other risks to consider. One is that people with certain rare inherited forms of immunodeficiency may continue to excrete VDPVs for years after immunization. So far, in the 40 years that the vaccine has been in use, only 19 such individuals have been identified worldwide, the majority in industrialised countries, and only four are known to be excreting virus today. No excretors of wild poliovirus have been identified.

According to the Technical Consultative Group (4), congenital immunodeficiency disorders occur ◗

in no more than 1 in 10, 000 births and of these at most 1% are likely to become long-term carriers of VDPVs. None have yet been documented in developing countries where conditions for the spread of polio are most favourable, despite some attempts to find them. Presumably such individuals would be unlikely to survive long after birth in environments where they are constantly exposed to infections. Importantly, people with acquired immunodeficiency disorders, such as AIDS, do not seem to be affected. But, as Wood points out, even if long-term excretors with primary immunodeficiencies are rare, the risk that they could seed new outbreaks is "not zero". Henderson argues that there are "undoubtedly many more of these long-term excretors out there", and compares the search for them with the search for a needle in a haystack. Aylward insists that they have been looked for, and not found. Monitoring studies continue.

2: Did he really say that?

On 27 October 2002, the influential leader of the former global campaign to eradicate smallpox was the subject of a provocative press report. "The worldwide eradication of polio is unachievable and efforts should be abandoned, a senior federal health official said Saturday", the story in the New York Times began.

Dr D.A. Henderson, the official in question, is known to have strong concerns about stopping immunization after wild polio is gone. What surprised many about the press report, however, was that Henderson now appeared to be advocating abandoning the struggle to get rid of the virus, when the number of countries where the virus is still spreading is lower than ever before. Even other researchers who have expressed doubts about stopping vaccination in the post-certification era, such as Professor Paul Fine at the London School of Hygiene and Tropical Medicine, were dismayed. "We are almost there," he says.

Henderson explained his position to Immunization Focus. "I believe the polio eradication initiative deserves our full support," he said. "We must do all we can to assure that it succeeds." What he had intended to convey was that the World Health Assembly is now committed to the eradication of just two diseases, guinea worm and polio, and, given the problems and costs of both efforts, he is opposed to considering the eradication of any other disease for the foreseeable future. He is also anxious to distinguish between polio eradication and stopping polio immunization. "It is important to bear in mind that the Assembly's commitment was to the eradication of polio, not the eradication of polio vaccine," says Henderson. "These are two quite different goals and should not be confused." The aftermath of the eradication of smallpox, he argues, has taught us important lessons. As the effort to eradicate polio continues, he argues, "We must begin to look more critically and realistically towards the longer term future to assure that we are providing for protection against polio, whatever the outcome of the eradication effort." Meanwhile, the strenuous activity under way in India, Nigeria and Pakistan should continue, said Henderson. "Let us do our very best."

Risks from wild poliovirus

There are also threats from the wild virus in a post-certification era. First, could a virus escape by accident from a laboratory? Absolutely. The last person to die of smallpox was infected by an accidental release of the virus from a laboratory in Birmingham, England, in 1978, a year after the last known indigenous case of the disease. If polio immunization ceased, a growing population would be at risk of infection in such an event. Aylward believes that the containment of laboratory stocks of wild poliovirus is "a major issue", but the issues related to poliovirus are very different from those surrounding smallpox, because of the nature of the virus itself and the strategies for protecting populations from it.

In 1999 the World Health Assembly unanimously agreed to a containment policy for all poliovirus stocks. Countries agreed to list and survey all biomedical laboratories. Within the agreed policy, biomedical institutions will keep complete inventories of all infectious or potentially infectious materials; they will destroy any stocks that are non-essential, and store any essential stocks of scientific value in secure, approved laboratories. Some experts question whether such conditions can be achieved in every lab in the world. "Fecal samples, collected for many different reasons and held in freezers worldwide, may be inadvertently contaminated with wild or vaccine-derived polioviruses," wrote Fine and Neal Nathanson in a commentary in the journal Science (5). But Aylward believes that, with careful attention to oversight mechanisms and proper independent validation, effective containment can become feasible. Wood adds that many laboratories in resource-poor settings are now choosing to destroy stocks rather than attempt to store them.

Another potential risk is that the wild virus strains used to make inactivated polio vaccine could escape accidentally from a vaccine manufacturing plant. Before inactivation, the viruses that are used to make the existing IPV are virulent and could cause harm. One such escape has been documented: luckily, the person who became infected was free of symptoms. WHO has been working with manufacturers to develop guidelines for safer conditions.

Bioterrorist attack

Finally, there is the risk of bioterrorism. Most researchers think that poliovirus would make a weak bioweapon compared with, for example, smallpox or anthrax. "If your goal is to disrupt the USA, polio ain't the thing," says Fine. "Let's be a bit sensible here." The virus is spread primarily by the faecal-oral route, and in a country with good sanitation, its spread would be limited; what is more, fewer than 1% of infections would be expected to result in paralytic disease, even in a susceptible population (4). However, some virologists and public health specialists argue that, however ineffective poliovirus is as a bioweapon, it could still be an effective means of terrorising a population.

Henderson points out that the terror factor could be especially powerful in an industrialized country where sanitation is good because of the somewhat higher risk of paralytic disease. In "clean" conditions, the probability of becoming infected within a given time is lower than in unhygienic environments, so the average age at which individuals become infected ◗

rises, and older children and adults are more likely to develop paralytic disease than young babies. "Those of us who lived through the 1950s remember the paralytic disease. It was a pretty horrendous time," says Henderson. Aylward agrees, but points out that if polio vaccination stopped, it would take 15 or 20 years before any of the non-immunized cohorts reached early adulthood. Furthermore, should industrialized countries continue using IPV as most currently plan to do, the vaccine would act as a deterrent to any potential bioterrorist and the risk of harm would be far lower. Aylward says it is more important to concentrate on measurable and more predictable risks, such as vaccine-associated paralysis.

Current vaccine options

Given all the different types of risk, it is not surprising that some experts advocate an alternative path: instead of choosing between stopping OPV or continuing OPV, why not switch to IPV? This vaccine contains killed whole poliovirus rather than live virus, so it is associated with fewer adverse events. However, it is by no means a perfect solution. It must be injected rather than given by mouth, making administration more complicated and expensive to do and requiring more trained staff. If it is given to infants in routine immunization, in combination with other vaccine antigens in the early months of life, it may not elicit a strong immune response to all wild polioviruses. It has proved effective in the industrialised countries for routine immunization, but it is not thought to stimulate strong gut immunity. This raises questions as to whether it would protect children in environments where the risk of infection with poliovirus is very high, such as the overcrowded slums of some megacities. IPV is also inadequate for responding to outbreaks; OPV must be used in these circumstances.

Wood at WHO says that studies are under way to monitor the efficacy of IPV in countries that are currently making the switch. So far, these are mainly industrialized countries such as New Zealand, but studies in developing countries are also being planned.

Henderson is concerned that IPV may not be sufficiently protective in the tougher conditions of developing countries, and that its higher cost and more complex administration will eventually lead to a slump in coverage. For these reasons, he strongly advocates continuing to use OPV, arguing that the annual toll of paralysis directly caused by the vaccine is a price worth paying in return for keeping wild polio disease at bay.

Aylward stresses that countries will decide their requirements for themselves. "This is not something that WHO can decide on," he says. Obviously any withdrawal of OPV would have to be internationally coordinated, but a trend to adopt IPV might happen in a more piecemeal fashion. At present, IPV supplies are far below what would be needed if many or all developing countries made the switch from OPV. The cost of the vaccine is also currently several times greater than the cost of OPV, although industry sources will name no figures. The producers would have to increase their capacity sharply to meet a greatly expanded need. The GPEI has now asked UNICEF, one of its partner members and the buyer of vaccines for the Expanded Programme on Immunization, to talk with the manufacturers of IPV – which include Aventis Pasteur and GlaxoSmithKlineBio – about prices and timeframes for scale-up in the event that many countries do decide to make the switch.

Manufacturers confirm that they need to know what the international community wants from them. Aventis Pasteur and GSKBio both make some IPV-DTP combination products. Aventis Pasteur recently announced an investment of around $70 million in increased manufacturing capacity for viral vaccines such as IPV. GSKBio likewise has proposed investments in increased production for IPV, says Dr Walter Vandersmissen. "But [GSKBio] insists on firm guidance and commitment of the public sector as to the future use of polio vaccines… the stakes to increase production are considerable, and cannot be implemented without a full and long-term agreement on the use and purchase of the vaccine."

Stockpile

Even if demand for IPV increases, there will probably always be a need for a stockpile of OPV in the event of any future outbreak of polio. Individuals immunized with IPV take several weeks to develop immunity, whereas OPV triggers a much more rapid immune response, particularly in the gut, and is more effective for outbreak control. Any long-term policy for the post-certification era will require a stockpile of OPV to enable an emergency response to an outbreak.

It sounds straightforward enough, but even a stockpile poses technical, political and economic challenges. Scientists disagree about the length of time that live vaccine stocks could be kept, the feasibility of storing them appropriately, about whether any manufacturer would be prepared to make rolling supplies to replace ageing stocks, and about the willingness of the international community to foot the bill indefinitely. Aylward says these challenges can all be addressed. Henderson is less optimistic. Fine argues that most of the problems can be dealt with if the world has the political will to pay for decent immunization services for all its children.

McNab/WHO/GPEI

Swift protection: a Kenyan girl receives oral polio vaccine

Better vaccines

Ultimately, some researchers believe that the issues would be resolved if there were better polio vaccines. An oral vaccine without the risks of VAPP or mutation to disease-causing strains would be ideal, but, while some scientists believe such a vaccine is feasible, they admit it could take at least a decade to develop one; to prove that it would be safer than OPV would require trials involving, potentially, more than a million people. Another option is inactivated polio vaccine but made with weakened Sabin strains (those used in OPV) instead of wild-type strains. However, such vaccines would need to go through all the usual regulatory hurdles and could take years to bring to market. And the current set of decisions cannot wait that long.

In the meantime, northern India is in the middle of a wild polio outbreak. For Aylward, the interruption of transmission there still has to be top priority. And still, for now, the toughest challenge. ■

Phyllida Brown

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Controlling epidemic yellow fever in Africa

Julie Jacobson, Alya Dabbagh and Gary Ginsberg explain the importance of the GAVI Board's decision last month to support the purchase of a stockpile of yellow fever vaccine

YELLOW fever (YF) is an acute, viral disease transmitted between humans by infected mosquitoes. Many infections are mild, but the disease can cause severe, life-threatening illness. Yellow fever was almost eliminated during the 1950s through intensive vaccination campaigns, but the disease resurged in the 1980s. Now an estimated 200 000 yellow fever cases with 30 000 deaths occur each year, the majority in 33 sub-Saharan African countries, with over 508 million people at risk of infection.

The disease should be a simple public health problem to address—there is a safe and inexpensive vaccine and a single dose protects an individual for life. And the vaccine is effective when given to infants (at the same time as measles vaccine) or to older children and adults. But current YF vaccination efforts are not doing the job. In part this is because YF vaccine is not on the infant immunization schedule in many countries, even though the World Health Organization (WHO) recommends that at-risk countries include it. Another problem has been the lack of a sufficient stockpile of vaccine for routine use, for rapid deployment when epidemics occur, and for preventive campaigns in high risk areas. As a result, the supply of vaccine for routine use has been depleted.

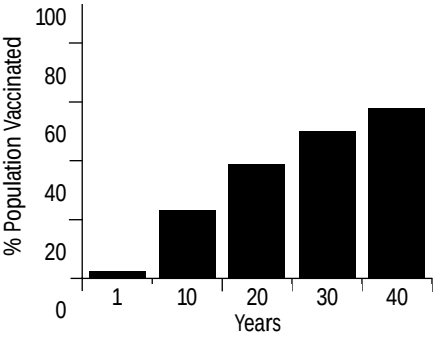
When GAVI was launched in 2000, the Alliance partners agreed to provide financial support, through the Vaccine Fund, for YF vaccine for use in routine immunization programmes in endemic countries. This marked the start of a new era of YF control. However, successful control of epidemic YF requires other changes as well. Weak immunization systems and a lack of YF surveillance and diagnostics have allowed the disease to go unchecked, resulting in frequent outbreaks (such as the current epidemic in Senegal). The unpredictable nature of epidemics and a "fire-fighting" approach to their control repeatedly disrupts routine immunization services and drains human and financial resources.

An effective strategy

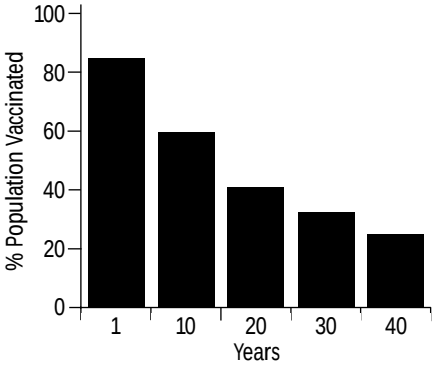
Through extensive review of YF disease transmission and control worldwide, WHO has established a strategy for YF prevention (see Box 1) that has proven effective in Trinidad and The Gambia. The strategy combines the use of YF vaccine in routine infant immunization with preventive campaigns.

If YF vaccine were given only in routine immunization, it would take more than 40 years to protect the majority of the at-risk population (see Graph 1). Similarly, a single preventive campaign is insufficient: it helps initially, but soon the effect wanes as new babies are born (Graph 2). However, when used together, a single YF vaccination campaign, plus integrated use of the vaccine in routine immunization, can control epidemic YF (Graph 3). Data from Trinidad and The Gambia have demonstrated that this strategy is effective for at least 20 years, and the simple model depicted in the chart suggests that this strategy is effective ◗

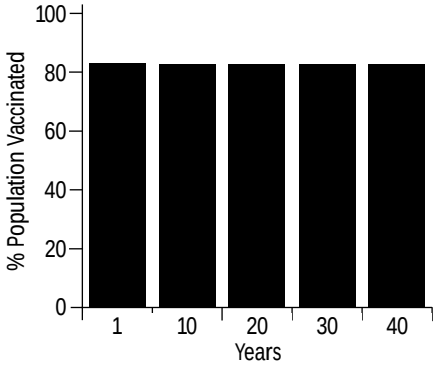
Graph 1: Routine immunization alone (coverage 80%)



Graph 2: Immunization campaign alone (coverage 85%)



Graph 3: Together, preventive campaigns and routine coverage control YF well



for more than 40 years. It must be noted, however, that the effectiveness of this strategy is dependent on additional factors such as maintaining high routine infant immunization coverage.

At the GAVI Board meeting in November, this strategy was discussed and the Board recommended that, in addition to support for routine vaccination, the Vaccine Fund support provision of a YF vaccine stockpile for epidemic prevention and control to allow this strategy to be fully implemented. A rolling stockpile of YF vaccine is to be constituted, for use, in the worst case, in outbreak control. The remaining vaccine from the stockpile, at the end of the year, could be used to supplement existing immunization activities, in preventive campaigns in high risk areas. Although this support will have a significant impact on reducing the death toll due to YF, the stockpile is not sufficient to vaccinate all people living in high risk areas. Efforts to raise funds from additional donors must continue so that sufficient resources are available to ensure vaccination for all high risk areas.

1. WHO recommended strategies for yellow fever control

Outbreak prevention:

- Provide YF vaccine as part of routine infant vaccination
- Organize preventive mass immunization campaigns in high-risk districts – both the routine and campaign coverage should reach at least 80% coverage

Outbreak control:

- Strengthen case-based surveillance, including laboratory capacity to confirm suspected cases
- Strengthen outbreak response

Assistance from GAVI Partners

WHO and the Children's Vaccine Program at PATH (CVP/PATH) have worked in partnership with national governments and EPI programmes to reduce the burden of YF with countries in Western Africa through seven key interventions:

- Establishing an effective (case-based) surveillance system with revised case definition (see Box 2);
- Improving confirmatory diagnostic testing through developing national and sub-regional reference laboratories;
- Strengthening routine immunization systems;
- Ensuring a sustainable vaccine supply through increasing the global production capacity; use of the International Coordinating Group to assess requests for vaccine from the stockpile so that timely distribution is ensured in the event of outbreaks, without depleting routine supplies;
- Providing advocacy and communication support;
- Conducting training in all new areas of YF control and monitoring;
- Creating indicators to monitor a country's success in managing YF programmes (see Box 3).

Significant improvements have been documented in the five countries that have received this support. For example, 80% of the supported countries in West Africa now have functioning labs and reporting systems, compared to only 20% of non-supported countries in the same region. As a result, the supported countries reported 303 cases and confirmed 6 compared to only 34 cases reported and zero cases confirmed in non-supported countries. These results are promising as they show that increased support and attention does make a difference.

2. New suspected yellow fever case definition:

Any case of fever with jaundice appearing within 14 days of onset of symptoms.

3. New national/district indicators to measure progress in the YF program:

- Number of countries/districts with YF/measles coverage gap less than 5%
- Number of districts reporting and taking a blood sample from at least one case of suspected YF per year (target 80% of districts)

This is only a start

To build upon the initial success of the CVP/PATH-WHO collaboration with national governments, lessons must be documented and the new strategy applied in all affected countries. Vaccines provided by GAVI and the Vaccine Fund will support preventive campaigns but funding must also be identified to pay for operational costs and to assure ongoing vaccine supplies for all at-risk populations. Advocacy among partners and Ministries of Health will be essential for long-term sustainability. ■

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Immunization Focus

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