Immunization FORUM

N°1 / NOVEMBER 2004

VVM uptake:

accelerating in international markets but lagging behind in domestic markets.

New data on the introduction of vaccine vial monitors (VVMs) – which are designed to prevent the use of heat-damaged vaccine and avoid waste – reveal that while global uptake has doubled over the past year, there is a big gap between their use in international and domestic markets. Sheila Davey reports.

While VVMs are increasingly supplied on vaccines purchased for the international market through UNICEF, they are not yet available on many of the non-polio vaccines produced in developing countries for domestic markets.

In 2004, almost one-third of the doses of non-polio vaccine purchased and supplied to the international market through UNICEF will have a VVM label attached. By 2005, 100% implementation is expected to be reached on 7 of the 12 vaccines bought by UNICEF (excluding DTP-Hib and meningitis A/C, which are bought in very small volumes). In addition, three others will be at or above 80% implementation, leaving only two with lower implementation *(see Figure 1)*.

The VVM – a label that registers exposure to heat over time – has been available on oral polio vaccine since 1996. However, the implementation of the device by manufacturers was more complicated than envisaged, says Stephen Jarrett, Deputy Director of UNICEF's Supply Division. "As a result, the uptake of the device on other vaccines has been slower than originally anticipated," he explained. "One of the reasons has been that UNICEF is the only committed buyer of vaccines with VVMs."

In 2002, the GAVI Board stipulated that from the beginning of 2004 all vaccines purchased through The Vaccine Fund must include VVMs – a target that will be met this year, with the exception of yellow fever vaccine. Of the 25 vaccine manufacturers prequalified to supply vaccines through the UN – including five suppliers of oral polio vaccine - 16 have now included VVMs (as of June 2004).

A PUBLICATION OF THE GLOBAL ALLIANCE FOR VACCINES AND IMMUNIZATION AND THE VACCINE FUND

The Global Alliance for Vaccines and Immunization (GAVI) is a partnership that brings together major stakeholders in immunization from both the public and private sectors. Partners in the Alliance include governments in industrialized and developing countries, UNICEF, WHO, the World Bank, non-governmental organizations, foundations, vaccine manufacturers, and public health and research institutions. The GAVI partners created The Vaccine Fund to provide financial support directly to low-income countries to strengthen their immunization services and to purchase new and under-used vaccines.

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However, John Lloyd of PATH, which gathered the new data on the implementation of VVMs worldwide *(see Figure 2)*, is concerned that while the international manufacturers have made tremendous progress in the use of VVMs, national manufacturers are lagging behind. "As a result," he says, "a huge proportion of domestically-supplied non-polio vaccines in vaccine-producing countries are still being distributed without VVMs."

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VVMs have been available on oral polio vaccine since 1996.

Manufacturers in Latin America and South East Asia have been especially slow to comply – in some cases because governments have not yet asked them to do so when supplying vaccine for domestic markets. In the Americas, the Pan American Health Organization (PAHO) has not advised countries to make VVMs a requirement.

Developing country manufacturers which supply both international and national markets are now moving towards the wider use of VVMs in domestic markets. However, those producing exclusively for domestic markets are making less progress. The added cost of VVMs remains a barrier, especially in low-income countries where the price of the basic children's vaccines is often relatively low and the added cost of the VVM significantly greater than in industrialized countries, where vaccine prices are higher. UNICEF estimates that in 2004-2006 the VVM will add over 1 US cent on average to the cost of a vaccine dose. While this adds less than 1% to the cost of DTP-HepB vaccine, it represents an 8% increase on the average price of tetanus toxoid vaccine.

UNICEF and WHO estimate that the use of VVMs on the basic vaccines alone could save about US$5 million a year

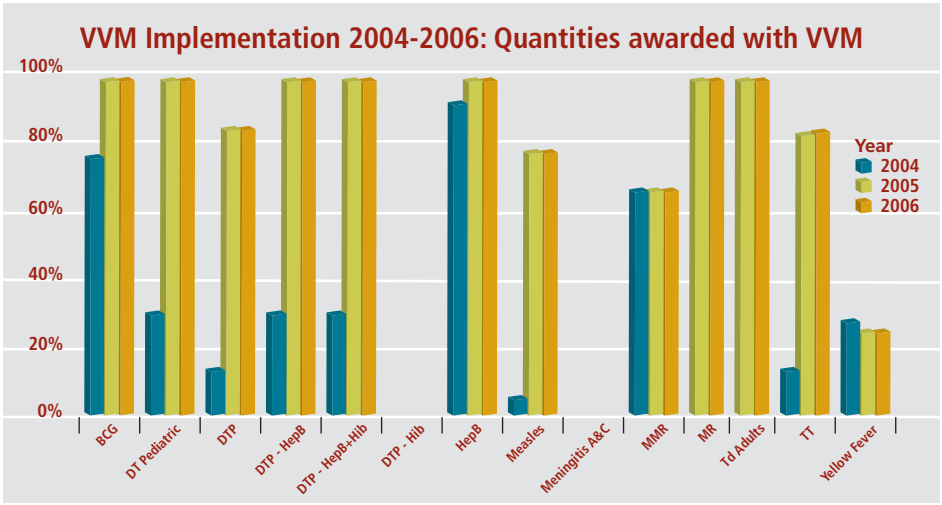

Figure 1: VVMs on vaccines supplied through UNICEF 2004-2006 - Source: UNICEF

UNICEF and WHO estimate that the use of VVMs on the basic vaccines alone could save about US$5 million a year. Their use on more expensive vaccines such as Hib and hepatitis B could generate even greater savings. A study carried out in Bhutan in 1997-98 by WHO and the Government of Bhutan found that when VVMs were used to implement the WHO multi-dose vaccine vial policy they helped reduce wastage on polio vaccine by almost 50%.

However, John Lloyd points out that VVMs are not a panacea. Even when they are supplied on all vaccines, health workers need training on how to use them correctly, including the critical need to monitor vaccine wastage in order to identify problems in the cold chain. "We need to establish proper systems for training, supervision and monitoring in order to make the system work," he warned, "and unfortunately that isn't happening yet."

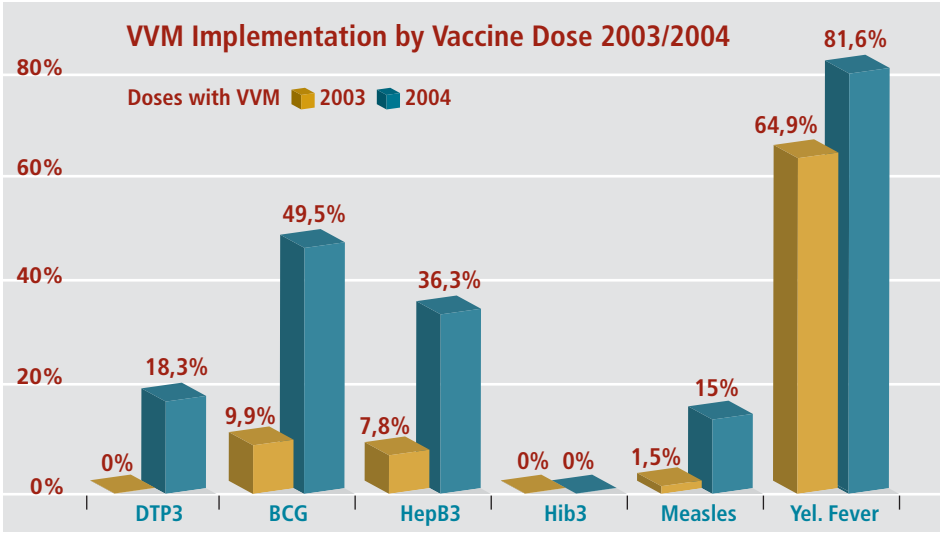

Figure 2: Global VVM implementation by vaccine dose 2003-2004 - Source: PATH/Time Temp, USA

Japanese encephalitis:

an orphan disease comes of age

A lethal disease that threatens 3 billion people throughout Asia and the Pacific is finally getting the attention it deserves, as Dr Julie Jacobson explains.

After years of neglect, efforts to control Japanese encephalitis (JE) have received a major boost with the launch by PATH of a new project to help improve the prevention and control of this 'orphan' disease.

Funded by an initial US$27 million, five-year grant from the Bill & Melinda Gates Foundation, PATH's Japanese Encephalitis Project (JEP) aims to improve data on the distribution of disease, accelerate the development of diagnostic tests and an improved vaccine, and help countries integrate JE vaccine into immunization programmes in countries in Asia and the Pacific where the disease is found.

According to Dr. Mark Kane, director of the Children's Vaccine Program at PATH, "over the past few decades, JE has extended its grip on countries across Asia and has become the continent's leading cause of viral encephalitis. Recent large outbreaks in India and Nepal are raising fears that JE is spreading even more rapidly than we thought."

Difficult to diagnose – and severely underreported at 30 000 - 50 000 cases a year – the mosquito-borne disease mainly affects children between the ages of 1 and 15 years. About 15 000 deaths a year are reported. Of the children who develop the disease, about 70% either die or suffer some form of long-term neurological disability, including paralysis, movement disorders, mental retardation and behavioural problems. There is no specific treatment for the disease.

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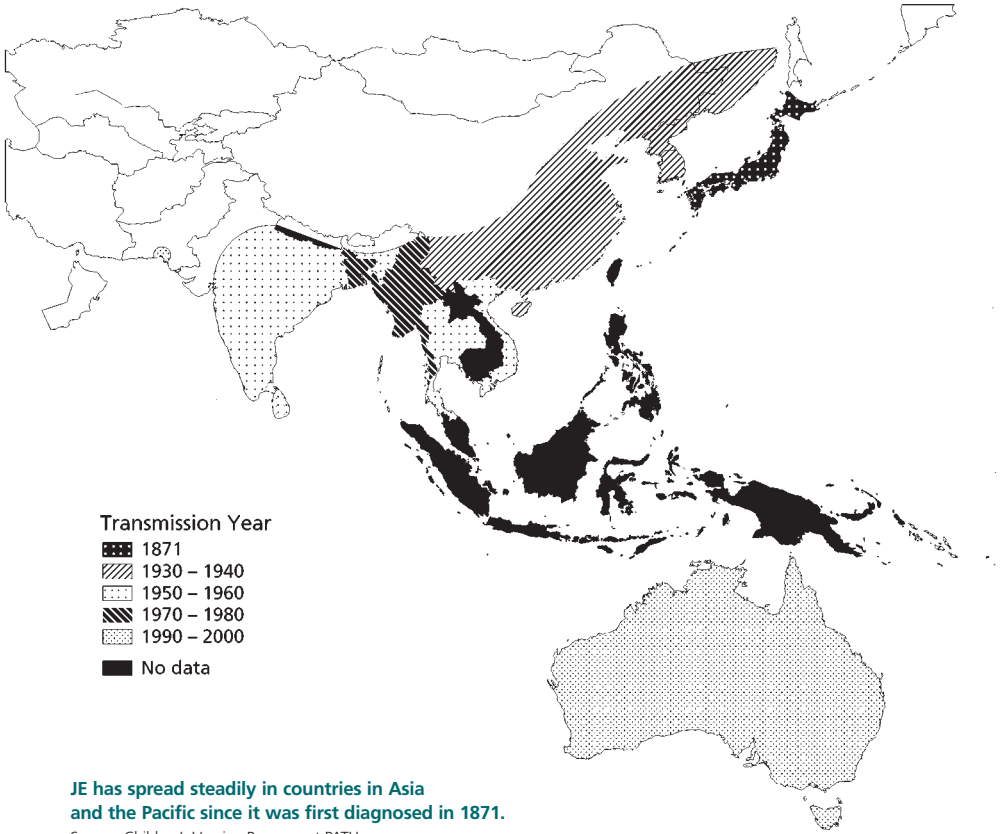
The mosquitos that transmit Japanese encephalitis breed in rice paddies and standing water

Efforts to control JE are hampered by the lack of a safe, effective and affordable vaccine that can be integrated into routine immunization programmes and by the lack of a low-cost diagnostic test for the disease. The new project aims to tackle both of these problems. In the initial phase, the JEP is focusing mainly on support for the development of diagnostics and efforts to improve surveillance.



JE has spread steadily in countries in Asia and the Pacific since it was first diagnosed in 1871.
Source: Children's Vaccine Program at PATH

Improving diagnosis and reporting

At present, there are no commercially available diagnostic tests for JE. As a result, doctors and public health officials in the countries affected are often unable to identify JE, which is difficult to distinguish from other diseases that affect the brain and nervous system. To confirm the presence of the virus, doctors have to take a sample of serum and/or cerebral spinal fluid seven days after the onset of symptoms, and these must be tested for antibodies in a laboratory. One week after the onset of illness, almost all samples will be positive. Countries with successful control programmes have usually combined diagnosis of the clinical encephalitis syndrome with laboratory tests in a subset of "sentinel" hospitals – to estimate what percentage of neurological disease nationally is due to JE and monitor the impact of control programmes.

In an effort to improve the diagnosis and reporting of JE, the project is supporting efforts to develop an ELISA diagnostic test for JE, which should become available this year. The project team is also looking into an innovative information system for JE surveillance in India.

The Surveillance Information Management System (SIMS) will enable health workers in the field to report and access disease incidence data via phone or the Internet – providing a model for information sharing that can potentially be scaled up to subregional and national levels.

Preventable – for some

Many countries have tried to curb JE through efforts to control its vector – the mosquito – and its main host – the pig. However, success to date has been limited and costly. The *Culex* mosquitos that transmit JE breed in rice paddies and standing water – making them very difficult and expensive to control in Asia. Insecticide-treated bednets have only limited impact as the mosquitos bite in the early twilight when most at-risk populations are not in bed. Experience in several countries has shown that immunization is the only reliable effective control measure. WHO recommends the use of the currently available JE vaccine in all endemic areas where affordable.

An effective vaccine against JE was developed in 1941 and is used to control the disease in richer countries and to protect travellers, but it has not reached many of the poorest countries in Asia. JE vaccine is routinely used in Japan, Thailand and China, and on a limited scale in Viet Nam, India, Nepal and Sri Lanka. Following the introduction of vaccination programmes in Japan and the Republic of Korea, the disease effectively disappeared in humans - although the virus remains active in animal populations.

Despite the evident successes of JE vaccination, at-risk countries have, for a variety of reasons, been slow to adopt the existing vaccine. For a start, the current JE vaccine is expensive – at US$9 - US$15 for the three doses needed to fully immunize a child. In addition, the vaccination schedule for JE often begins after a child's first birthday and requires three doses at irregular intervals over the next 12 months - making it difficult to integrate the vaccine into routine immunization programmes. These problems are compounded by a vaccine production process that is costly and an end product that is difficult to produce in large volumes. The current supply is insufficient to vaccinate all children in the at-risk countries. As a result, there is now growing interest from the international community in a second-generation vaccine to combat JE.

Experience in several countries has shown that immunization is the only reliable effective control measure

New vaccines needed

To successfully control JE in all affected countries, a new vaccine must be affordable, safe and effective, and fit easily into routine immunization. Several second-generation candidate vaccines that could meet this need are in varying stages of development. China produces three vaccines. Of these, the most interesting is a live, attenuated JE vaccine (SA14-14-2). Available since 1988, it has been administered to over 200 million Chinese children, with good disease control and no reports of serious complications. Studies of the vaccine in use outside China showed the efficacy to be over 95%, with no serious adverse events. However, this vaccine is not yet widely licensed for use internationally and is not pre-qualified by WHO for distribution.

China also produces two other vaccines, available for use only in China. Elsewhere, several manufacturers in the US, Europe and Asia are also working on candidates that would be improvements to the current inactivated vaccine. One promising candidate is a "chimeric vaccine" – so-called because it is made by combining parts of the current yellow fever vaccine with parts of the JE virus.

PATH's JE project is working closely with WHO, the International Vaccine Institute (IVI) in the Republic of Korea, the US Centers for Disease Control and Prevention (CDC), UNICEF and other partners to catalyze more interest in a reliable, efficacious vaccine against Japanese encephalitis. With this new initiative, for the first time there is a real prospect of controlling this devastating disease.

Dr Julie Jacobson is Director of the Japanese Encephalitis Project at PATH.

About the virus

JE is caused by an arbovirus in the *Flaviviridae* family that is similar to West Nile virus. It is spread by mosquitos that lay their eggs in quiet pools such as rice-paddy fields or drainage ditches. The natural transmission cycle of JE is among pigs, wild birds, and mosquitos. Humans and horses are dead-end hosts that do not contribute to the spread of the disease. Pigs are believed to be the source of infection for most human cases. However, birds such as herons and ducks have also been implicated.

GAVI awards
for top-performing countries

Ugandan Vice-President Prof. Gilbert Bukenya receives an immunization award from Dr Tore Godal, Executive Director of GAVI.

Five countries have received special awards from GAVI for outstanding performance in increasing immunization coverage. Immunization Forum looks at some of these success stories.

A country emerging from almost a decade of conflict has received a special award from GAVI for out-performing its own targets for immunization in 2002. Sierra Leone succeeded in reaching 30 000 more children than anticipated – boosting DTP3 coverage from 44% in 2000 to 62% by 2002.

In addition to receiving additional funding from GAVI – a US$20 payment for each additional child immunized – Sierra Leone has received a plaque in recognition of its exceptional performance.

Dr Mercy Ahun, Head of Country Programmes at GAVI, said Sierra Leone's achievement was outstanding. "To emerge from a period of such instability and increase immunization coverage like this is remarkable," she said.

Four other countries – Mali, Pakistan, Uganda and Tajikistan – were also awarded plaques for outstanding performance during 2002. The awards were presented in Geneva earlier this year, when government representatives were attending the World Health Assembly.

So how did they do it? And what can other countries supported by GAVI and The Vaccine Fund learn from their experience?

For Sierra Leone, the initial focus (not GAVI-funded) was on restoring health facilities destroyed during the conflict. When the conflict began in 1991 there were 741 Peripheral Health Units throughout the country. By 2002 only 450 of these were still functioning. Today the country has 600 fully functioning Peripheral Health Units.

Funds provided through The Vaccine Fund to help strengthen immunization services were used to provide cold chain equipment and generators, to distribute vaccines and other supplies for immunization, and to cover the cost of vehicle maintenance and the expansion of outreach activities at district level (including the payment of transport costs for the health workers involved).

Efforts to increase immunization coverage included training EPI staff and establishing monthly targets to help motivate them. Each health facility was ranked at district level and districts were ranked at national level – in a bid to encourage health workers to increase coverage. Another key strategy was the use of community mobilization to increase demand for immunization and the use of Village Development Committees to trace immunization drop-outs.

The emphasis on targets and ensuring recognition for high-performing health centres and districts was repeated in the other award-winning countries as well. Mali established a system of performance contracts signed between decentralized districts, the Ministry of Health and community partners. In Uganda (which boosted DTP3 coverage from 53% to 72% in 2000-2002), best-performing districts were recognized and rewarded (with prizes including bicycles, financial awards, certificates and plaques) in national award ceremonies. At the other end of the spectrum, districts performing badly received extra supervision and focused support.

In both Pakistan and Uganda, the introduction of a new vaccine, hepatitis B, was believed to have been a key factor in increasing demand for immunization. In Uganda the introduction of the pentavalent vaccine (DTP3-HepB-Hib) was given a high-profile launch at the national level by President Yoweri Museveni. Cultural and religious leaders helped promote immunization, while at the grassroots level parish mobilizers registered children for immunization and followed up on those who dropped out. In Pakistan, EPI Programme Manager Dr Rehan Hafiz, said the new vaccine had served as a "promotion tool" to help increase the uptake of existing vaccines. In addition, training in the use of the new vaccine had helped re-motivate the country's 8000 EPI vaccinators.

Other key elements in these success stories included efforts to expand access – both through increasing fixed delivery points and outreach services and through community mobilization to increase demand for immunization - and an emphasis on training, planning, monitoring and evaluation.

Dr Ahun said all five countries had worked extremely hard to increase coverage to the present level. "The challenge now is to maintain it," she said. ■

Sheila Davey

Children immunized

against measles and polio in Darfur

© WHO / Christine McNab

Children who are malnourished are especially vulnerable to measles

Immunization campaigns have continued to target children in the troubled region of Darfur in western Sudan in an effort to prevent outbreaks of measles and polio. In September, mass immunization campaigns against measles and polio were held in remote areas currently controlled by the Sudan Liberation Movement (SLM). Meanwhile, the Sudan has been participating in the largest-ever, synchronized cross-border polio campaign in history, involving 23 countries in sub-Saharan Africa and targeting 80 million children aged under five.

In the first round of a mass immunization campaign against measles in June, over 2.2 million children were targeted – many of them already malnourished and therefore especially vulnerable to measles. A second round of immunization was held in July in an effort to reach about 200 000 children who missed the first round.

The campaign – led by the Sudanese Ministry of Health, WHO and UNICEF in coordination with other national and international organizations – was also used as an opportunity to provide vitamin A supplements and to immunize at least 90% of children under five against polio. In May, a child was paralyzed by polio in the Darfur region – the first case of polio in the Sudan for three years. Since then, the spread of polio in the Darfur region and to Khartoum have highlighted the potential for rapid spread of polio in the Sudan, compromising the major progress which had been made toward polio eradication. The virus involved has been genetically linked to poliovirus endemic to northern Nigeria, where polio immunization was suspended late last year in Kano State following a local controversy about the safety of the polio vaccine used. Since then, wild poliovirus has spread from northern Nigeria into 12 previously polio-free countries in west and central Africa. Polio immunization resumed in Kano State in July.

In Darfur, the first round of a polio immunization campaign was held in late July. A second round in late August targeted 1.4 million children under five. ■

Campaign

for child immunization launched in Germany

A scientific conference and gala dinner were held in Frankfurt, Germany, on 12 November in an effort to garner support from the German business and political communities for The Vaccine Fund's global Campaign for Child Immunization. The one-day event — organized by The Vaccine Fund and the Stiftung Präventive Pädiatrie, a leading German foundation which advocates child immunization worldwide — highlighted efforts to raise an additional US$400 million a year over the next three years to immunize children in the world's poorest countries.

© The Vaccine Fund

Dr Rita Süssmuth, a member of The Vaccine Fund Board, speaking at the Berlin launch of the Child Immunization Campaign.

The event follows the German launch of the campaign in Berlin on 30 June involving the German Government, Members of Parliament, the media, industry leaders and NGOs, in a one-day event which was supported by Queen Rania of Jordan and the German Minister for Economic Cooperation and Development Heidemarie Wieczorek-Zeul. The aim of the campaign, first launched in London on 27 February, is to save the lives of one million children by 2006. ■

Michel Camdessus, Rita Süssmuth and Jocelyn Davis join The Vaccine Fund Board

Three new members have joined The Vaccine Fund Board, bringing the current membership to 18. They are Michel Camdessus, former head of the International Monetary Fund (IMF), Dr. Rita Süssmuth, former President of the German Bundestag (Parliament) and Jocelyn Davis, President of Nelson Hart L.L.C, a US-based financial services consulting company.

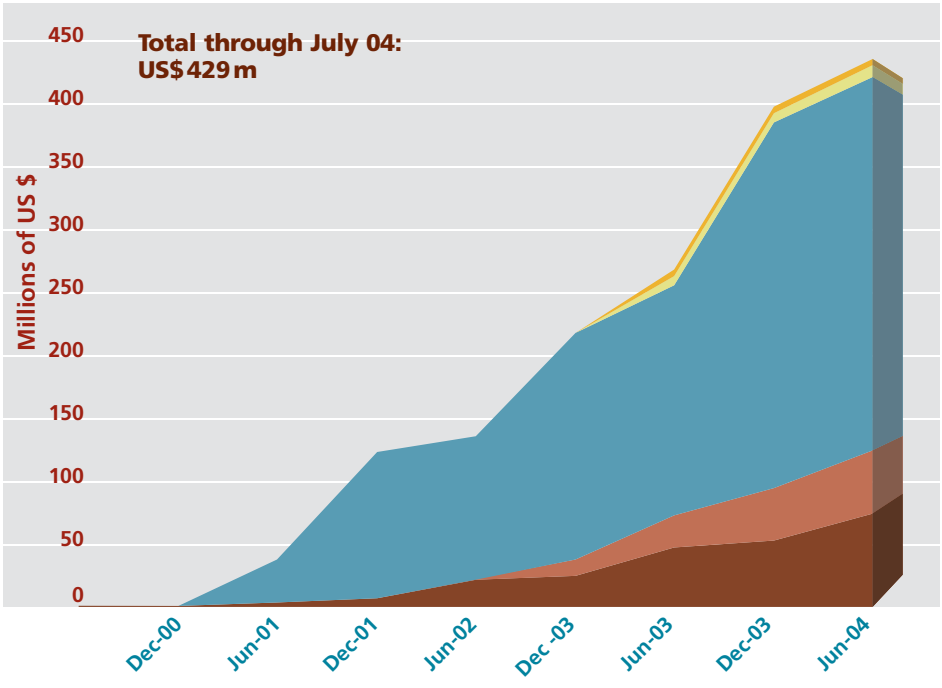
Mr Camdessus, a former Governor of the Bank of France, was Managing Director of the IMF from 1987-2000, where he served three terms in office. He is President Chirac's Personal Representative on Africa and was recently appointed as the French representative for the New Partnership for African Development (NEPAD).

Dr Süssmuth served for 10 years (1988-98) as President of the German Bundestag. Before that, she was a Minister in the German Government (1986-88) with the portfolio for health, youth, family and women. She is currently serving as a member of the Global Commission on International Migration.

Jocelyn Davis is the President of Nelson Hart L.L.C, a US-based financial services consulting company with specialized expertise in not-for-profit organizations. She is also an Independent Trustee of the Allmerica Investment Trust.

The Vaccine Fund Board, which since 2001 has been chaired by former South African President Nelson Mandela, meets twice a year.

Progress: Cumulative resources disbursed from The Vaccine Fund*

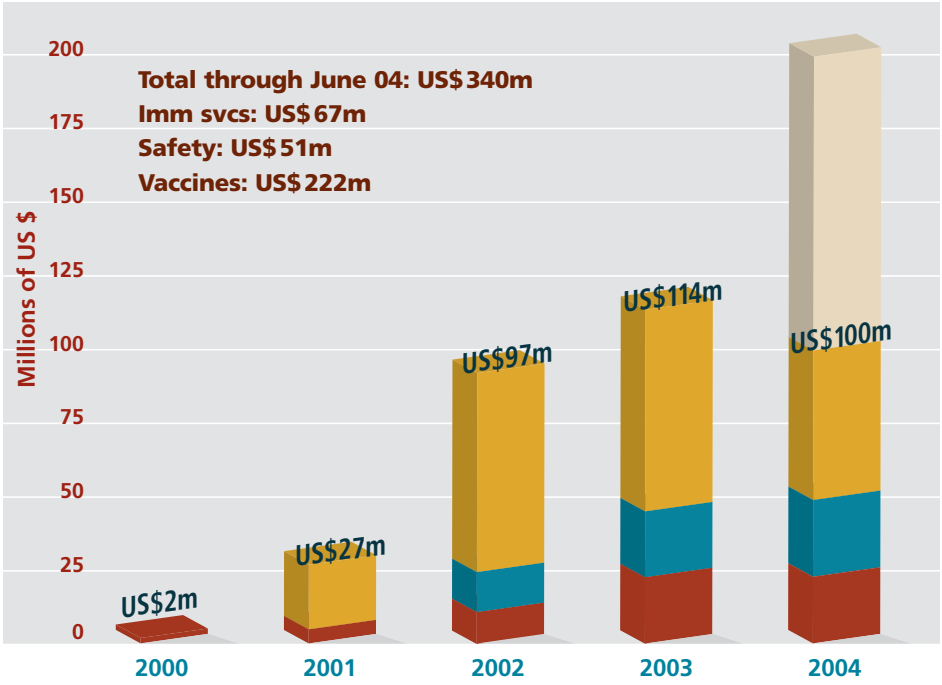


Work plan = US$5m
ADIPs = US$9m
Vaccines = US$297m*
Immunization safety*= US$51m
Immunization services support = US$67m

*Totals do not agree with amount of resources received in countries because this total includes long-term purchases of supplies.

Source: The Vaccine Fund

Progress: Resources received in countries partially or fully funded by GAVI / The Vaccine Fund



Source: GAVI Secretariat

Immunization Forum

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The views expressed in Immunization Forum are not necessarily the views of the GAVI and The Vaccine Fund Boards.
Designed and produced by: Kaolis - Email: sfornairon@kaolis.fr - www.kaolis.fr
Cover: Portrait of a young woman, Ethiopia - Credit: WHO/P. Viro