

Ten years of the Global Alliance for Vaccines and Immunization: challenges and progress

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Diseases preventable by underused vaccines cause the death of approximately 3 million children per year. The Global Alliance for Vaccines and Immunization (GAVI) was launched 10 years ago to tackle this appalling situation.

Approximately 10 million children under the age of 5 die each year. Of those, it is estimated that at least 3 million die of infectious diseases that are preventable with presently available but underused vaccines. These include vaccines against diphtheria, tetanus, polio, *Haemophilus influenzae* type b (HIB) and hepatitis B (HepB). No less important than death in infancy is the legacy of disability and disruption of life, as dramatically illustrated by meningitis in sub-Saharan Africa. It is noteworthy that the death toll of pneumonia and diarrheal disease exceeds that of human immunodeficiency virus (HIV) and malaria combined (Fig. 1a). GAVI was born 10 years ago to address this appalling state of affairs. GAVI can now look back on its first decade and assess whether it has fulfilled its mission “to save children’s lives and protect people’s health by increasing access to immunization in poor countries.” Such an exercise would also prove very useful to GAVI in achieving its strategic goals for 2011–2015 (http://www.gavialliance.org/resources/03___GAVI_Alliance_Strategy_2011_2015.pdf).

The GAVI Alliance

On 31 January 2000, GAVI was launched with the aim of expanding and improving immunization in the developing world. It was formed as an initiative between The World Health Organization (WHO), The United Nations Children’s Fund (UNICEF), the World Bank and the then newly created Bill & Melinda Gates Foundation. Those partners were soon joined by donors from a subset of industrialized countries. From its inception, GAVI has not been an actual organization; instead, it is a private-public partnership between the most relevant stakeholders in the field of vaccines and immunization, including developing and donor countries, international development agencies and financial organizations (mainly WHO, UNICEF and the World Bank), philanthropic organizations (such as the Bill & Melinda Gates Foundation), academia, the vaccine industry in both industrialized and developing countries, and representatives from civil society and the business community.

In our opinion—a position supported by many evaluations of GAVI’s performance in various activities (<http://www.gavialliance.org/performance/evaluation/index.php>)—GAVI has achieved great success during its first decade¹. GAVI has re-emphasized and provided strong evidence of the fact that immunization is one of the most cost-effective ways of saving children’s lives and promoting public health. Moreover, with its

unprecedented track record of being able to mobilize the multibillion-dollar funding needed to fulfill its bold mission, GAVI has ignited renewed optimism that the previously elusive goal of providing universal childhood immunization is within reach.

Over its first 10 years, GAVI received and distributed approximately US\$4.5 billion on a direct contribution basis to procure and buy vaccines for more than 70 developing countries, as well as extending grants from ‘cash windows’ aimed at supporting immunization services and strengthening health systems. As a result, since 2000, over 250 million children have been immunized with GAVI-supported vaccines, and collectively this has resulted in the prevention of more than 5.4 million future deaths due to diphtheria, pertussis, HepB, HIB, measles, meningitis, yellow fever, tetanus and polio (Fig. 1b). GAVI has also accelerated access to new and underused vaccines and has strengthened health and immunization systems in developing countries, resulting in substantially expanded vaccine coverage to over 70% at present in GAVI-supported countries for the trivalent vaccine against diphtheria, tetanus and pertussis, the highest rate of coverage ever experienced in the developing world as a whole.

Importantly, GAVI has taken a very active and successful role in trying to shorten the unacceptably long delays, traditionally 20–30 years, between introduction of new lifesaving vaccines into affluent countries and their subsequent introduction into the developing world. Thus, in 2002, GAVI cre-

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ated an innovative mechanism in the form of focused programs, the so-called Accelerated Development and Introduction Plans, hosted outside the GAVI secretariat but funded and coordinated through GAVI, to promote the development and global uptake of new vaccines for pneumococcal pneumonia and rotavirus diarrhea. In 2005, a similar initiative was added to speed the slower-than-expected uptake of the vaccine against HIB. Those initiatives have been complemented by two highly innovative financing mechanisms (the International Finance Facility for Immunization (IFFIm) and Advanced Market Commitment (AMC); described below), through which donor countries have already pledged future contributions of almost US\$8 billion over the next 5–20 years, largely to support the introduction of new vaccines in developing countries. Together such efforts have enabled GAVI and WHO to make recommendations not only for the global use of vaccines against HIB but also the pneumococcal conjugate vaccine and vaccines against rotavirus. Results on immunization against rotavirus have emphasized the success of these efforts^{2,3}.

Ten years ago, Sir Gustav Nossal, who was actively involved in the establishment of GAVI⁴, noted that the substantial increase in immunization coverage in the 1970s and early 1980s was followed in 1990 by stagnation and, in many areas, falling rates of coverage, due to donor fatigue. At the 1990 World Summit for Children in New York, the Children's Vaccine Initiative (CVI) was created, but it progressively became clear that for various reasons, CVI could not mobilize sufficient financial resources and other commitments needed for its mission. Moreover, in the realms of advocacy and fundraising, a certain tension between CVI and WHO also became apparent.

Therefore, on the basis of consultations and analyses by a working group drawn from WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation and the Rockefeller Foundation, a meeting in Bellagio, Italy, in 1999 concluded that CVI should be replaced by a successor body that, in contrast to CVI, would not be independent but would be governed by its main sponsors. That is, sponsors needed to be involved at the highest levels to maximize each organization's commitment and provision of resources toward a partnership able to generate results beyond the capacity of each organization alone. Thus, GAVI was born and launched at the World Economic Forum in Davos in January 2000, directed by Tore Godal (Norway), who brought with him years of experience from

WHO. Initially, mainly for financial and legal reasons, GAVI fundraising was achieved by a separate legal entity, the Vaccine Fund (subsequently renamed the GAVI Fund), but since then, the initially founded GAVI and the Vaccine Fund have been fused into a single entity, the GAVI Alliance.

Since its inception, the main priorities for GAVI have been to increase routine immunization coverage and safety, and to accelerate access to underused or new lifesaving vaccines for children in the world's poorest countries. Countries eligible for GAVI's support were identified as those with a gross domestic product per capita of less than US\$1,000, a clear commitment to immunization (as shown by coverage of at least 50% of the birth cohort with the six traditional vaccines of the Expanded Program on Immunization) and a population of less than 150 million inhabitants. Thus, at the time, China, India and Indonesia were excluded, but the last two were subsequently included among 72 eligible countries. This will change when a new policy enters into force in January 2011. An annual review of eligible countries (a threshold of US\$1,500 gross national income has now been set) and subsequent rules for a gradual application of new eligibility criteria will apply. It soon became clear that to fulfill the first obligation, it was necessary not only to support eligible countries by procuring vaccines (through UNICEF and other agencies) but also to contribute to strengthening the capacity of eligible countries' existing health systems to deliver immunization and other health services in a sustainable manner. Likewise, the goal of accelerating access to underused or new lifesaving vaccines, initially vaccines against HepB and HIB and later also the pneumococcal conjugate vaccine and vaccines against rotavirus, called for special initiatives. In this context, the Accelerated Development and Introduction Plans and HIB initiative mentioned above were important for promoting evidence-based advocacy (and for the vaccines against pneumococcus and rotavirus, also vaccine development and availability), and for preparing for and credibly predicting the future markets in developing countries for these newer vaccines.

A major success of GAVI has been the unprecedented rapid uptake of the vaccine against HepB (from <20% to >70% in GAVI-eligible countries over a 10-year period) and, in the past few years, also of the vaccine against HIB (Fig. 1b). Together it has been estimated that these have prevented more than 3 million deaths. In addition, the GAVI Alliance has confronted recurrent emergen-

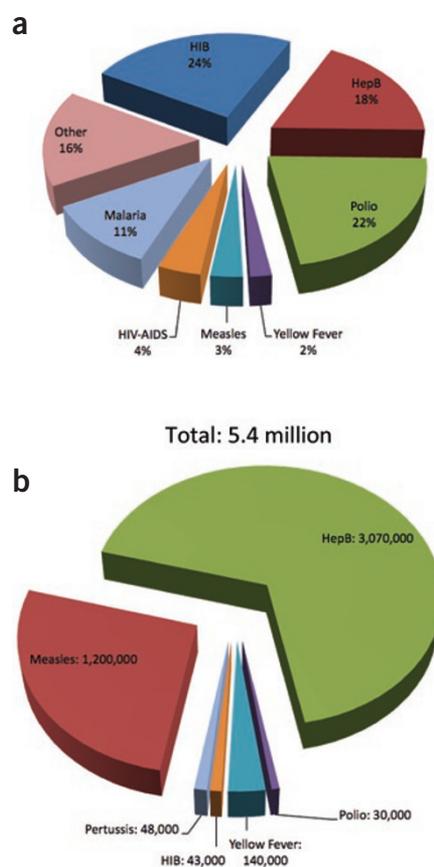


Figure 1 Vaccine-preventable deaths and the effect of GAVI. (a) Causes of death for children under 5. (b) Estimated future deaths to be averted by GAVI: 5.4 million total deaths.

cies of yellow fever and meningitis in GAVI-eligible countries by stockpiling vaccines and making them available. Countries in sub-Saharan Africa are plagued by recurrent meningitis epidemics, with devastating effects in terms of deaths, disability (for example, deafness), and disruption of social and economic life⁵. GAVI's planned support for the introduction of a glycoconjugate vaccine against meningococcus A into routine immunization programs has made a meningitis-free future a realistic dream for sub-Saharan Africa.

Innovative mechanisms of financing

A tenet of GAVI from the beginning has been to harness market forces to cope with the health needs of the poorest children. Indeed, the appearance of a reliable robust buyer has resulted in a substantial change in the scenario of vaccine producers, with an ever-increasing role being played by producers in developing countries. Vaccine prices have dropped considerably (for example, 18% for the pentavalent vaccine against diphtheria, tetanus and pertussis plus HIB and HepB). However, the drop in vaccine prices was not

as great as originally predicted, a failure that may affect the sustainability of the program.

Since 2006, innovative financing mechanisms such as the IFFIm have provided GAVI with additional resources that have allowed considerable expansion of its immunization programs and have enlarged the donor base of the alliance. IFFIm was launched by the UK, France, Italy, Spain, Norway and Sweden (South Africa and The Netherlands joined later on) to meet the need of frontloading and the predictability of resources in a long-term effort. 'Vaccine bonds' issued by the IFFIm (the World Bank assures the financial management) draw financial resources from bond markets, and this enables the planning of interventions on immunization on a long-term basis. Indeed, the inception of the IFFIm changed GAVI's financial landscape by doubling the existing resources in the years 2006–2015. So far, the IFFIm has raised US\$2.6 billion in the world's capital market, guaranteed by legally binding long-term (up to 20 years) commitments of participating donor countries, which has provided reliability and predictability in the vaccine market.

A second innovative financial instrument is the AMC pilot program for pneumococcal disease⁶. This was officially launched in Lecce, Italy, in June 2009, but the underlying concept had been devised many years previously in academic circles and subsequently received a strong political input by the G7, which translated the idea into practice. Its main purpose is to stimulate a market for vaccines that are not developed because of a lack of demand and therefore a subsequent lack of private investment. To achieve this, AMC donors have pledged to create a market (US\$1.5 billion from Italy, UK, Canada, the Russian Federation, Norway and the Bill & Melinda Gates Foundation) for producers to generate innovative new vaccines tailored to the needs of eligible countries, including epidemiologically relevant strains, at a sustainable, predefined price. After extensive consultation, the pneumococcal vaccine was chosen as a pilot because of its potential effect (~800,000 deaths per year) and feasibility. Together with the World Bank and UNICEF, GAVI worked on this project and was given the task of implementing it. The success of the AMC approach (<http://www.vaccineamc.org/AMCAnnualReport10.html>) may have profound consequences in terms of research-based innovative efforts to eliminate diseases that plague the poorest countries.

A moving frontier

A brighter financial scenario in 2008 allowed GAVI to expand on the already developed

vaccine portfolio to include typhoid, human papilloma virus, Japanese encephalitis and rubella. Various elements must be considered in prioritizing areas for intervention. For example, vaccination against human papilloma virus to prevent cervical cancer represents the first sex-specific vaccine available, although at present the price is very high. Cervical cancer, with a total death toll of over 250,000 in poor countries, is the leading cause of years of life lost for young women in sub-Saharan Africa. At the other extreme, typhoid causes between 200,000 and 600,000 deaths a year, mostly among children. Inexpensive vaccines against typhoid are available and have proven to be active in the appropriate context⁷. Moreover, new vaccines are in the pipeline.

Further down the road are vaccines against malaria, HIV-AIDS and tuberculosis. The latter can be used as an example of the challenges ahead⁸. Globally, 10 million new cases of tuberculosis and 2 million deaths attributable to tuberculosis occur annually. Of those, 700,000 women die from tuberculosis every year. Thus, more women die of tuberculosis than all causes of maternal mortality combined. The main burden of disease is in women of childbearing age (15–49 years of age). In addition, tuberculosis is a major cause of death in children younger than 5 years of age. GAVI did a cost estimate for an AMC and came to the conclusion that a new and better vaccine to replace the bacillus Calmette-Guérin vaccine could avert 7.7 million deaths, and a new booster vaccine could further decrease deaths by 40%. The size of the AMC was calculated as US\$360 million for a tuberculosis replacement or US\$3.8 billion for a booster vaccine. At present, US\$500 million per year is spent for tuberculosis research and development.

Stumbling blocks and challenges

A victim of its own success, GAVI now faces formidable stumbling blocks and challenges. Financial woes at present⁹ exacerbate the issue of prioritization and will lead to painful choices, especially in the medium term and long term. Strengthening health systems is key to GAVI's success, but reliable 'read-outs' of effect need to be developed. GAVI has been at the forefront of strengthening health systems, and in this context it has been bolder than other institutions such as the Global Fund and the World Bank. Distortions in vaccine uptake readouts need to be monitored, although these do not affect global estimates of effect¹⁰. Last but not least, the ultimate challenge is reaching the final remote village.

GAVI's financial situation at present places the organization at a crossroads. Although tightened national budgets of donor countries have had an important role in GAVI's shortfall, some have argued that donor fatigue is also an explanation. During GAVI's early history, the GAVI board rejected a research agenda for GAVI in favor of a single focus on the enhanced delivery of vaccines for the world's poorest children. It may now be time to reconsider that position. Indeed, it could be argued that a promising approach for reinvigorating GAVI's existing donors and attracting new donors is to recast the focus of GAVI from an organization dominated by the mission to purchase vaccines and enhance systems for delivery to that of an organization in which that mission is supplemented by a research focus that would generate innovation in vaccines and their delivery. Many years have passed since GAVI considered and then rejected a research agenda to enhance its mission of preventing the unacceptable toll of infectious disease morbidity and mortality among the world's poorest children via vaccination. A new research agenda for GAVI could take many forms and should be subject to vigorous discussion and debate. As a contribution to this debate, we surmise that diarrheal diseases and tuberculosis deserve particular attention. Despite progress in this area^{2,7}, diarrheal diseases continue to pose a formidable challenge that requires the integration of progress in mucosal immunology into vaccine development. Understanding the diversity and polarization of cells of the immune response is key to eliciting appropriate responses to intracellular pathogens.

Vaccinology has long been based on empiricism. It is symbolic that the tenth anniversary of GAVI coincides with the tenth anniversary of reverse vaccinology¹¹. Understanding innate immunity informs the development of innovative adjuvants. The precise characterization of the cells and molecules that guard mucosal surfaces might pave the way to much-needed mucosal vaccines. Structural immunology provides a basis for structure-based design of vaccines. Exploiting these advances represents a major challenge for immunologists and funding agencies around the world and raises the question of whether the power of immunology can be mobilized and deployed for the development of vaccines against diseases of the world's poor. The introduction of glycoconjugate vaccines in the 1980s is only now beginning to be translated into memory-eliciting vaccines to fight meningitis and typhoid in sub-Saharan Africa. Is such a long delay acceptable? Can additional AMC initiatives be foreseen that could raise the bar in terms of innovative research?

Concluding plea

The celebration of GAVI's accomplishments represents an occasion to reflect on stumbling blocks and challenges with a bold vision. Most importantly, it is our plea that the world's poorest children should not pay an undue price for today's financial crisis. As members of the immunological community, and despite the present financial difficulties,

we also plead for innovative and targeted research in support of GAVI's vision.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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