

Global immunization of children is an elusive goal of public health officials world-wide. Extraordinary recent funding and organizational initiatives as described by Gustav Nossal have ignited renewed optimism that the stage is finally set to bring this achievement within our grasp.

The Global Alliance for Vaccines and Immunization—a millennial challenge

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Edward Jenner

If an observer from a distant planet was to achieve the triumph of intergalactic travel, she would find much to amaze her on spaceship Earth. In particular, why have the six billion individuals with the most developed brains not learnt to live in greater harmony with one another? The question will also preoccupy most readers of this highly welcome new journal. These readers hold in their hands history's most cost-effective public health tools: the precious legacy of Edward Jenner and Louis Pasteur.

Indeed, it could be argued that access to life-saving vaccines is one of the basic human rights of the child. Striving to bring vaccines, including newer ones, to every one of the 135 million or so infants born each year constitutes a moral imperative.

Human effort usually falls far short of the ideals that inspired it. On this occasion, however, a confluence of circumstances suggests the possibility of an exception. The world has made a new beginning in the field of global



Louis Pasteur

immunization. At the dawn of the new millennium, a challenge known as the Global Alliance for Vaccines and Immunization (GAVI) has been laid down. The purpose of this brief article is to describe its origins and purpose.

Historical aspects

In many respects, this story begins with the glorious achievement of smallpox eradication¹. Although it took 180 years from Jenner's original breakthrough to the final result, the World Health Organization's (WHO) smallpox eradication campaign itself—the planned and coordinated determination to treat the world as a single entity—actually took only 11 years to complete. Apart from the two million or more lives saved each year, and the countless further lives spared the horror of dreadful scarring, smallpox eradication showed the power both of the vaccine approach and of coordinated global action. Emboldened by this success, the WHO embarked on the Expanded Program on Immunization (EPI) aiming to bring six common childhood vaccines (diphtheria, pertussis, tetanus, poliomyelitis, measles and BCG) to all the world's children. Largely due to resource constraints EPI got off to a slow start until in 1984 an historic meeting was held in Bellagio, the delegates of which included representatives of such prominent

organizations as WHO, United Nations Children's Fund (UNICEF) and The World Bank. These key organizations embraced the concept of universal childhood immunization, leading to the unlocking of approximately US\$100 million per year, via UNICEF, for EPI. As the program took off, immunization rates in the developing countries rose rapidly from around 5% of the birth cohort to around 80%. Although it must be admitted that not all 80% were fully immunized, it is estimated that this effort has saved 2–3 million lives each year.

So impressed was the World Health Assembly by the power of this approach that the decision was taken to embark on a global program of polio eradication. It was soon realized that routine infant immunization alone, even with relatively high coverage rates, would not achieve this goal. Accordingly, three further strategies were brought into operation.

The first was the introduction of regular National Immunization Days (NIDs) where, following extensive media publicity and social mobilization, all children aged under five in a particular country were given the oral polio vaccine regardless of previous immunization history. Secondly, in most cases, two NIDs were held a month apart and the program was continued for three years or more. This meant the program reached millions of infants who had previously escaped the routine immunization net and it produced a certain degree of herd immunity so that chains of transmission were broken. NIDs alone, however, would not have sufficed without the third strategy: extensive surveillance and accurate laboratory diagnosis. Intensive searches for cases of acute flaccid paralysis that may have been caused by polio were carried out. Two stool samples were taken from each patient and examined by trained laboratory personnel in order to diagnose the last few polio cases, distinguishing them from patients suffering from other causes of paralysis. Armed with this information, the final phase could begin—namely mop-up immunization campaigns. These were resource and personnel-intensive programs where immunization teams actually brought the vaccine into villages on a dwelling-to-dwelling basis. As a result of this monumental effort, most parts of the world are now polio-free, and the concentrated work going on in the Indian subcontinent and sub-Saharan Africa is progressing rapidly meaning that global eradication may be only two or three years away.

Many governments, United Nations (UN) agencies and foundations have contributed to polio eradication, but special mention must be made of Rotary International. In a splendid grass-roots effort Rotary International has not only raised US\$500 million or more, but has also provided extensive volunteer labor, especially on NIDs. This great humanitarian work deserves wider acknowledgement and applause.

The Children's Vaccine Initiative (CVI)

By 1990 some storm clouds had begun to gather over the global immunization effort. It appeared that 80% coverage constituted some

COMMENTARY

kind of plateau: despite much effort the global figure did not rise further and indeed in some countries had started to fall. A degree of donor fatigue had become apparent and a renewed commitment was required. Thus, at the 1990 World Summit for Children held in New York, the CVI was born. Initially this had a heavy research flavor but with the long-term hope of being able to use modern technologies to minimize the number of infant injections through simplified vaccine delivery and more combined approaches. However, it soon became apparent that advocacy and fundraising were also required. To that end, CVI set up a Consultative Group which united all elements of the immunization spectrum including UN agencies, bilateral donors, foundations, industry representatives and developing country experts, and which convened every two years. These occasions for a global sharing of information proved most helpful. CVI also did excellent work in socioeconomic analysis, cost-benefit studies and priority setting. However, CVI did not have adequate resources to make much of an impact on vaccine research, and in the realm of advocacy and fundraising, a certain tension between CVI and WHO became apparent. As a result in late 1993 the then Director of WHO, Hiroshi Nakajima, made some important decisions. While retaining independence, WHO and CVI were to have the same Head, J.W. Lee. Furthermore, they were to be guided by the same Scientific Advisory Group of Experts (SAGE). I had the honor of being named Chairman of this combined group. The major remaining problem was a very severe limitation on resources.

Embryology of a new global approach

The more the work of the SAGE progressed, the more it became apparent that there was a terrible defect in the global approach. New vaccines of great power were coming through the research and development pipeline and had been introduced or were about to be introduced into the immunization programs of industrialized countries, but there appeared to be no prospect of these becoming available as part of EPI. The *Hemophilus influenzae B* (Hib) vaccine represents a good example of this. This carbohydrate-protein conjugate, embodying the principle of T cell-B cell cooperation, was the fruit of extensive research within academia and development work within industry. It was, therefore, considerably more expensive than the common EPI vaccines especially as expiration of patents and thus increased competition had driven the prices of the common EPI vaccines used in developing country to very low levels. The Hib vaccine has been spectacularly successful throughout the industrialized world, exceeding even the most optimistic expectations. Through a combination of wide acceptance by parents and a herd immunity effect, it has led to the virtual elimination of this common cause of infant meningitis in those countries where it is used. But it is only quite recently that some of the richer developing countries have been able to afford to use it. As a matter of fact, even hepatitis B vaccine—now available for mass purchase at around US \$0.50 per dose—is too expensive for many of the countries in which it is needed.

Three events in 1998 heralded the beginning of a new global approach. Firstly the WHO appointed a dynamic new director, Gro

Harlem Brundtland, who was determined to make a major mark and to revitalize the organization. Soon afterwards the President of the World Bank, James D. Wolfensohn, in conjunction with myself as Chairman of SAGE and Richard Feachem as the Senior Health Officer within the World Bank, convened a Vaccine Summit. Held at the World Bank, the Summit delegates included Brundtland; Carol Bellamy, the Executive Director of UNICEF; key industry leaders; senior academics; and various officials who met to forge a new vaccination strategy together. And finally, at long last a major new source of finance was identified. In December of 1998 William H. Gates III, and his wife Melinda French Gates, launched the Bill and Melinda Gates Children's Vaccine Program with an initial pledge of US\$100 million. This proved to be only the first of many gifts they made, and at the time of writing their contribution to the immunization program stands at well over US\$1 billion in donations and pledges.

That first World Bank Summit drew attention both to the beckoning opportunities and to the dimensions of the funding gap, so a working group drawn from the WHO, UNICEF, the World Bank, the Bill and Melinda

Gates Foundation and the Rockefeller Foundation engaged in an extensive series of studies and consultations, the results of which were brought back to a second Summit meeting held in Bellagio in March, 1999 (ref. 2). This meeting concluded that the CVI should be replaced by a successor body that was not independent but rather totally dependent on the major sponsors, who needed to be involved at the highest level—Chief Executive if possible. It also created task forces in three important fields: advocacy, financing and within-country coordination. Shortly afterwards a fourth task force on research and development was created. Tore Godal, the distinguished Norwegian immunologist and long-serving Director of the WHO's Special Program for Research and Training in Tropical Diseases, was recruited as Coordinating Secretary of the CVI's successor group, which became GAVI. The new program was ceremonially launched at the World Economic Forum in Davos, Switzerland, on 31 January 2000. But before describing the mission of GAVI in detail, it is necessary to say a little more about the Bill and Melinda Gates Foundation.

The Bill and Melinda Gates Foundation

The Bill and Melinda Gates Foundation is now the largest charitable foundation in the world—valued at US\$21,800 million. Its two main areas of concern are information science and health. I have the great honor of chairing the Strategic Advisory Council of the Bill and Melinda Gates Children's Vaccine Program, which at the moment has two major arms. The first, funded to US\$100 million, is devoted to the introduction of four vaccines of global significance (hepatitis B, Hib, *Streptococcus pneumoniae* conjugate and rotavirus) and two vaccines of regional significance (yellow fever and Japanese B encephalitis). An extensive series of disease burden studies and field trials is under way, aimed at setting priorities and identifying possible barriers to widespread introduction. The second major arm is the Malaria Vaccine Initiative (MVI). With funding levels of US\$50 mil-



Community involvement.

UNICEF

lion, this program has just started. Its main brief will be to bridge the gap between preclinical research on malaria vaccines—which has identified promising candidate antigens and/or new vaccine approaches—and the quite different world of clinical trials. Amongst other things, the MVI will facilitate the manufacture of trial vaccine lots under Good Manufacturing Practice conditions. It will also help to identify suitable trial sites and to coordinate clinical studies according to world best practice protocols.

These two programs are implemented by a non-governmental organization known as PATH (Program for Appropriate Technology in Health). PATH has extensive experience in vaccine field trials and has a number of offices in developing countries. Although the Strategic Advisory Council will supervise the strategic elements of the program, each subprogram will have its own technical advisory group comprising of the very best experts in the world on the particular disease concerned.

Other Bill and Melinda Gates Foundation benefactions in the vaccine field include contributions to the polio eradication campaign, contributions to the International AIDS Vaccine Initiative and a new tuberculosis vaccine effort. One particularly imaginative applied research program, currently financed by the Foundation to the tune of US\$40 million, is called Diseases of the Most Impoverished (DOMI). DOMI is based at the new International Vaccine Institute in Seoul, Korea, under the directorship of John Clemens. Its work is focussed on diseases such as typhoid, cholera and shigellosis or bacillary dysentery.

But the largest Bill and Melinda Gates Foundation donation is to the global Children's Vaccine Fund (CVF): the pledge stands at US\$750 million. This is absolutely central to the GAVI project.

Further mobilization of public and private sectors

The extraordinary generosity of the Bill and Melinda Gates Foundation is meaningful not only because of the huge sums involved but also because of the leverage it confers on the CVF. There is no doubt in my mind that it has helped to galvanize other public and private sector efforts. Two initiatives are worthy of special mention.

On 2 March 2000 the President of the United States, Bill Clinton, convened a White House meeting devoted to this program and related aspects of global health. At this meeting he revealed that he was seeking from Congress not only a concrete contribution to the CVF, but also tax credits for companies prepared to invest in this general area and in other aspects of health in the developing world. Although the details remain to be worked out, we could be talking about as much as a further US\$1 billion.

The President of The World Bank, James D. Wolfensohn, stated that he would be seeking a replenishable fund to the order of US\$1 billion, so that the IDA (a branch of the bank that specializes in soft money loans at concessional or zero interest) could lend for health purposes, chiefly in the field of vaccines and drugs.

Although this initiative is also not yet finalized it represents a magnificent further step forward. It appears certain that the overseas development aid agencies of industrialized countries will take note of these developments and will pitch in either to the Global Vaccine

Fund or, more likely, to efforts in particular developing countries of interest to each donor. To what degree other large foundations or rich individuals will respond to the challenge remains to be seen. President Clinton has, on a number of occasions now, called on them to imitate Bill Gates to whatever degree they find possible.

The position of industry

The pharmaceutical industry, including the major companies involved in vaccine production, has been party to all of the above discussions and represented at many meetings either at Chief Executive level or via the Internal Federation of Pharmaceutical Manufacturers Association (IFPMA). As a result, some very serious pledges have been made. In summary, industry wants to help and is prepared to do so. They are prepared to make vaccines available to developing countries at prices far below those charged in industrialized countries. However, they would like certain understandable concerns addressed.

Firstly, they would not wish to see their quite considerable private markets threatened or undermined in the larger developing countries in which a substantial middle class already exists. In cases of technology transfer to vaccine manufacturers in developing countries, they would like their intellectual property rights to be respected and to have, therefore, normal joint venture and licensing processes observed. They are concerned to ensure that every step be taken to avoid contraband or black markets, so that vaccines intended for the poorest countries and made available at the lowest prices do not find their way back to richer countries and undermining the existing markets there.

Most of all, they wish to see the public sector guaranteeing the purchase of large and defined volumes of vaccines, preferably for a number of years. This could potentially break the "chicken and egg" situation that currently exists. (That is, when volumes are low, prices are high, and while prices remain high, the countries potentially capable of absorbing large volumes cannot afford to purchase.) As soon as the CVF reaches a sufficient size, high volume purchases of the newer vaccines could be guaranteed.

Industry has also said it would be prepared to invest in the research and development of vaccines of interest solely or chiefly to developing countries and here attention must be given to both "pull" and "push" mechanisms of incentive. "Pull" would mean promises of purchase. "Push" might represent public sector involvement in the initial and risky phases of research and development. This is an area in which one can foresee bold and sizable developments in the future.

The three-fold mission of GAVI

The imperative priority for GAVI, and the first drain on the CVF, will be the provision of newer vaccines for the poorest countries of the world. Hepatitis B and Hib will be in the forefront. Initially the program will be targeted at countries meeting three criteria: a gross domestic product per head of population of less than US\$1,000; a clear commitment to immunization (as shown by at least a 50% coverage of the birth cohort with the six traditional EPI vaccines) and a population of less than 150 million. Of course, it is not the intention



Jet gun administration of vaccine

M. Hillman

COMMENTARY

that China, India and Indonesia be denied access to GAVI. Rather, it is believed that the best way of helping these countries is, initially, to upgrade their existing substantial indigenous vaccine-manufacturing capability. To that end, discussions between GAVI and these three countries have already begun.

About 50 nations—with a combined birth cohort of about 40 million—fitted the three criteria when the program was announced, and it is clear that this number will increase as countries make plans to improve their immunization performance. It is highly encouraging that, at the time of writing, 47 countries have already indicated to GAVI their wish to participate in the program. But it cannot be stressed sufficiently that such a program can only succeed if there is a full and effective partnership between GAVI and the developing country itself. To that end, each country will be encouraged to create a national immunization coordinating committee involving the Ministry of Health of the country concerned, the relevant United Nations agencies, all interested non-governmental organizations and, where appropriate, one or more indigenous vaccine manufacturers. The intention is to avoid any semblance of paternalism in the arrangements and to create a within-country situation where the programs become so successful that, after an appropriate number of years, the government itself assumes responsibility for financing them. As external sources of funding are unlikely to last forever, this is the only way to ensure long-term sustainability. Since programs will be tailored to each country's needs, there will be some variation in which vaccines are added and in what order; decisions will be informed by continuing research on disease burden and field efficacy.

The CVF will sit within UNICEF but will be supervised by an independent board. GAVI itself will have a high profile board, initially chaired by Brundtland, with senior representatives from the other major partners, and several outside directors of the highest standing. Obviously, GAVI will have access to scientific and technical expertise from SAGE, the Gates Strategic Advisory Council and whatever other national or international expert body it seeks to consult. The aim is not to create a vast new structure or to introduce costly overlaps. Rather, GAVI represents an unincorporated and relatively unstructured joint venture between the committed parties.

The second aim of GAVI will be to repair the deteriorating vaccine infrastructure in the poorest countries and to ensure the greatest possible safety of vaccine injections. This will involve rejuvenation of the cold chain, introduction where possible of auto-disabled single-dose syringes, and the safe disposal of syringes and needles using suitable packaging with eventual incineration. The issue of safe injection is of paramount importance in countries where unauthorized re-use of syringes and needles is common, and where HIV and hepatitis B and C are present in substantial numbers of people. It turns out that the extra costs of disposable injection equipment are relatively minor with appropriate mass production technology.

The third long-term aim of GAVI is to encourage research on new and improved vaccines for use in developing countries. The prospects for truly important new vaccines have never been brighter³. Newer approaches including mucosal immunization, nucleic acid



Jenner and the first vaccine trial

vaccines, vectored vaccines and even edible vaccines are making rapid progress. To move such initiatives from preclinical research on laboratory animals to real-life practice will be a monumental task. For vaccines as for pharmaceuticals, the applied research and development, including clinical trials, are far more expensive than the basic research. Furthermore, the skills for this vital development work lie not within academia, but within industry. No matter how well disposed industry leaders may be to furthering the long-term ambitions of GAVI, in the end commercial realities dictate that they do not embark on too many loss-making ventures. For diseases like HIV/AIDS or even malaria, arguments can be mounted that there will be a substantial market for a successful

vaccine in industrialized countries. But for diseases like bacillary dysentery this becomes much more difficult. Thus there is room for a "fourth window" within GAVI, dealing with vaccine research and development. How soon this window can be opened will depend significantly on how the world as a whole reacts to the challenge laid down by Bill Gates and President Bill Clinton. Simple arithmetic will show that a fund capitalized at US\$1–2 billion will not have the capacity to do all that is asked of it. But in the context of a world where health is approximately a US\$3 trillion industry, one could envisage GAVI being much bigger a decade from now.

Conclusions

One of the great glories of immunology is that it manages to span a huge spectrum of endeavor. From the most fundamental probes into the molecular genetics and cellular physiology of immune responses, to more applied endeavors in vaccinology, autoimmunity, allergy, transplantation biology and other branches of immunopathology, it extends not only into clinical medicine, but epidemiology and public health. Within this great spectrum, there are literally no discontinuities.

In the years 1950–1980 (as the foundations of new immunology were laid and the field became a dominant force in biomedicine) the high priests and priestesses of the discipline concerned themselves more with the academic end of the spectrum and less with the community-oriented approaches which actually had given birth to immunology. Things have changed now, and over the last two decades it has been wonderful to see this imbalance being redressed, with some of the best minds in immunology now heavily concerned with the practical end. Thus the academic community has played its part in creating a balanced structure.

But if spaceship Earth is really to derive maximum benefit, the most recent immunization debate—started in January 2000 at the World Economic Forum—must be widened and deepened to involve the whole global community. As this story unfolds, GAVI should become the most effective public health program in history.

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