Prometheus, Vol. 18, No. 1, 2000

The Global Alliance for Vaccines and Immunization—AMillennial Challenge[1]

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ABSTRACT *As the new millennium dawns, a number of factors have conspired to make the outlook for global immunisation truly promising. These include private philanthropy aiming to raise immunisation rates in developing countries; a real head of steam behind the global poliomyelitis eradication campaign; the very recent introduction of several powerful new vaccines; and a 2-year-long effort to make the various elements of the United Nations system work closely together with non-governmental organisations and the private sector in wide co-operation. The aim is to prevent 3–4 million deaths per year. Despite a great deal of heartening progress, there is still need for further research. We have no vaccine for HIV/AIDS or malaria, and the only tuberculosis vaccine, namely BCG, is poorly effective in the prevention of adult pulmonary tuberculosis. However, new resources are bringing new players into the research field as well, so the longer term outlook is heartening.*

Keywords: HIV/AIDS, immunization, polio eradication, vaccines

Vaccines are history's most cost-effective public health tools. The widely-acclaimed World Bank Report on Health for Development has determined that immunisation scores extraordinarily well on the economic measure known as DALY or Disability-Adjusted Life Years Saved for a given expenditure. As a conservative estimate, 5 million lives are saved per year through the vaccines currently in use, and the global eradication of smallpox in 1977 itself added considerably to this total. For this reason, it is exceedingly important that vaccines of public health significance reach the children of the developing countries in a broad and timely manner.

Higher Infant Immunisation Rates

Emboldened by the triumph of smallpox eradication, the World Health Organization launched its Expanded Programme on Immunization (EPI) over 20 years ago, but the Programme really only got going in a major way when UNICEF joined in with a massive injection of about $100 million per annum for vaccine purchase. Initially, there were six EPI vaccines, namely diphtheria, pertussis, tetanus, poliomyelitis, measles and BCG for tuberculosis. Later it was decided to add hepatitis B for countries with a high carrier rate and yellow fever for those countries in which this disease was a threat. By 1990, EPI could be termed a major success with approximately 80% of the world's children receiving reasonable, though perhaps not complete, coverage. This average figure hides a considerable heterogeneity: some of the poorest countries in Africa reporting only 40–50% coverage whereas some countries, both rich and poor, that have accorded vaccination high priority managed consistently to immunise well over 90% of their

ISSN 0810-9028 print; 1470-1030 online/00/010033-05

infants. As a result, there have been major reductions in both morbidity and mortality from these diseases.

Nevertheless, since 1990 somewhat of a plateau appears to have been reached. There are certain signs of 'donor fatigue' and many countries have been unable or unwilling to mount the year by year effort which is required to lift immunisation rates to higher levels. There have also been problems with the maintenance of the cold chain required for some of the vaccines, and the refrigerators originally purchased for this purpose are ageing quite badly. A rededication of effort is needed, and that is what the Global Alliance for Vaccines and Immunization hopes to achieve, as we shall see.

Polio Eradication

The World Health Organization has set itself the ambitious task of the total eradication of poliomyelitis by the end of the year 2000 and it still hopes that this can be achieved although a couple of years slippage would not surprise. Polio eradication rests on four principles which we should briefly describe. The first is a high level of infant immunisation—preferably over 80% of infants to receive three doses in the first 6 months of life and a further dose in the second year. The second strategy is the National Immunization Day or NID. These represent occasions of very great social mobilisation directed at reaching all children under 5 years of age on a particular given day, regardless of previous immunisation history. On the NID concerned, there is endorsement from high political figures (frequently the President of the country or the First Lady), major effort by the health authorities, but also by volunteer groups, of which Rotary International is the most important. The media are approached to ensure that anyone possessing a transistor radio knows what to do. Many volunteers are used, for example it is estimated that on a typical NID in India (where 120 million children need to be immunised) about 3.5 million individuals are required to help! The oral Sabin poliomyelitis vaccine is used, the normal pattern being to have two NIDs in the winter months, a month apart. This massive effort has to be kept up for at least 3 years and frequently longer. In countries that are very intense reservoirs of the infection, it may even be necessary to introduce NIDs in the summer as well to prevent chains of transmission in cohorts of children who have lost their maternal antibodies but have not yet been at an NID. Even though the NID reaches many of the hard-to-reach, e.g. nomadic people, children of itinerant workers, or people of very low socio-economic status, even such an intense effort does not reach everyone. For example, it is estimated that in India after several rounds of successful NIDs there are still 10 million children who have never been immunised! That leads on to the third strategy, namely good disease surveillance. It is necessary to have dedicated medical personnel investigating every possible case of acute flaccid paralysis and reporting these—typically in a polio-free country there should be one report per 100,000 population per year and this is one measure of whether surveillance is working or not. There are various other causes of acute flaccid paralysis including other viruses, Guillain-Barré syndrome, transverse myelitis and so forth. It is therefore necessary to send two stool samples, under good conditions of cold transport, to a properly accredited virus diagnostic laboratory to confirm whether the case is polio or not. It is impossible to overstress the importance of surveillance in a country's effort to eradicate poliomyelitis. The final strategy is 'mopping up' campaigns. As polio eradication nears, there will only be sporadic cases frequently in outlying districts. It is then necessary to immunise house to house, boat to boat, humpy to humpy by sending immunisation teams to where the children are rather than expecting the children to come to a medical aid station. This is a very powerful tool and is usually a necessary feature of completing the job.

In the event, all of Europe, all of the Americas, all of Oceania, most of Asia and the Western Pacific and much of North Africa are now polio-free. The last case of polio in the Americas occurred in Peru in September 1991 and the last case in the countries adhering to the Western Pacific Regional Office of WHO occurred in Cambodia in March 1997. China is to be congratulated on achieving polio eradication in 1997 largely through the use of vaccines manufactured in that country itself. The remaining problem is sub-Sahara Africa and the Indian subcontinent. India has recently raised its attention to surveillance and has embarked on a cycle of mid-year National Immunization Days. Many African countries are also mounting major campaigns. Even those countries in which there is civil unrest or warfare have called 'Days of Tranquility' to allow the immunisation work to go forward.

The polio eradication initiative will have effects beyond just eradicating a leading cause of disability. For example, in many cases it has been possible to combine the polio vaccine with the administration of vitamin A for the prevention of blindness. In other cases it has been accompanied by a major measles immunisation effort. In general terms, it has been shown that countries working hard on polio eradication also manage to lift their game with respect to routine immunisation with the other vaccines. Health infrastructure has benefited through the surveillance system and the laboratory networks created with polio diagnosis in mind. In order to mount a sturdy polio eradication campaign, countries have had to improve their performance in health planning, management and evaluation. The 'culture of prevention' and the social mobilisation involved have all served to put a better perspective on the health sector. Finally, it should not be forgotten that success in this venture would have enormous economic implications for the richer countries. For example, when the United States is able to stop polio immunisation, the savings would be $1.5 billion (US) per year. The cost of the work of the last decade or more would be very rapidly repaid!

Introduction of New Vaccines into the EPI

In a world which appears to be getting increasingly selfish, bilateral and multi-lateral development aid funds have been shrinking in the face of an expanding need. This has created a situation where the UNICEF funding for vaccine purchases is fully stretched in making the six traditional vaccines available to the poorest countries. The introduction of the two new vaccines (hepatitis B and yellow fever) mandated more recently has therefore been very slow. The yellow fever vaccine via public tender purchase costs only US$0.17 per dose. The hepatitis B vaccine is more expensive, rock-bottom prices being around US$0.50–0.60 per dose. It has taken a great deal of effort from WHO to bring the proportion of children receiving hepatitis B to 40% in those parts of the world where the vaccine is required. The yellow fever story is worse—there simply has not been the national will to give these vaccines in countries where it is badly required.

The problem is compounded by the recent development of some important new vaccines, for example the *Haemophilus influenzae B* vaccine for meningitis, pneumonia and scepticaemia; the *Streptococcus pneumoniae* conjugate vaccine which has performed brilliantly in Northern Californian trials; and the tetravalent reassortant rotavirus vaccine which is effective against severe rotavirus diarrhoea, though this last vaccine has run into some possible side reactions which are currently being extensively investigated. At least until the research and development costs of these newer vaccines are recuperated, they will certainly be considerably more expensive than any of the vaccines mentioned to date.

The Bill and Melinda Gates Children's Vaccine Program

Late in 1998, the William H. Gates Foundation took a major step in creating the Bill and Melinda Gates Children's Vaccine Program, generously supported in an ongoing way by the Gates Foundation and administered by the Seattle-based non-governmental organisation Program for Appropriate Technology in Health (PATH). The governing assertion of the Children's Vaccine Program relates to the difficulty of getting these new vaccines into the poorer countries. The governing assertion states that the basic problem related to making needed vaccines available to the world's children without temporal or geographic discrimination is financial not technical. It is realised that routine immunisation is the bedrock of EPI and it is important to recognise that new vaccines do not burden EPI. In fact, these must be added in logical and stepwise fashion. The Gates Program believes that the false distinction between new and traditional vaccines must cease to exist. In that regard, the Gates Program will take a special interest in hepatitis B, Hib, pneumococcus and rotavirus and in terms of vaccines of regional significance in Japanese B encephalitis and yellow fever. The work funded by the Foundation will initially relate to sorting out the roadblocks to vaccine introduction which will include epidemiological and field research, trial vaccination campaigns in poorer countries, a great deal of work in the advocacy field, strengthening of the relevant United Nations Agencies, and in the longer term it is hoped to make a contribution to a Global Vaccine Fund for actual vaccine purchase.

The Spirit of Bellagio and the Global Alliance for Vaccines and Immunization (GAVI)

In the early 1980s, the Villa Serbelloni, the Rockefeller Foundation's fabled study centre in Bellagio, Italy, was the venue of a historic conference which unlocked a new $100 million per year (via UNICEF) to bring the six common infant vaccines to 80% of the world's children. On the 15–17 March 1999, there was a further Bellagio conference which may well prove to be as significant as the one which set EPI on its successful path. This particular conference had actually been preceded by a World Bank Vaccine Summit 12 months earlier. At Bellagio, the key United Nations Agencies (World Health Organization, UNICEF and The World Bank) met with leaders of the vaccine industry, representatives of bilateral aid agencies, with major foundations including the Gates and Rockefeller Foundations, and with a key group of independent academics to set the agenda for a new global partnership designed to save 40 million lives over the next 10 years, at a cost that could approach $3 billion per year. Since the conference, a number of working groups have been studying matters such as advocacy, fundraising, country co-ordination, research strategies[2] and other key strategic aspects. Not surprisingly, an agenda as ambitious as this has created some curiosity and not a little controversy. Nevertheless, real progress has been made towards forging a Global Alliance for Vaccines and Immunization. A small co-ordinating secretariat has been formed under the leadership of the respected immunologist and former WHO official, Dr Tore Godal. It is physically based in UNICEF in Geneva. There has been one meeting of what has been called a 'Proto-Board' and it is expected that early in the year 2000 there will be a formal launch of the Global Alliance for Vaccines and Immunization and of its Board which will be chaired in turn by the heads of the three key United Nations Agencies. This initiative replaces a former umbrella body known as the Children's Vaccine Initiative or CVI. The purpose is to provide the best possible co-ordination between the partners, including industry. The vaccine manufacturers have pledged to be full and

active partners. They have offered to invest in adequate volumes of production of the newer vaccines. These would be made available to the poorest countries at the lowest possible price, provided efforts were made to prevent 'leakage' of vaccine supplies to richer countries. Industry was also prepared to target more of its research effort to vaccines of predominantly Third World interest if indeed the Global Alliance succeeded in creating a true, worldwide public sector market.[3]

Key to success will be adequate funding. The Gates Foundation has made a magnificent start, but much more will be needed. The World Bank and the bilateral aid agencies have particularly important roles to play, and it is hoped that other private philanthropists will follow the magnificent lead of Bill and Melinda Gates. Indeed, one could regard the right to immunisation as a fundamental human right and UNESCO is taking a great interest in the matter from that point of view. The moral imperative is to create a world where this cheap and cost-effective public health tool is made available regardless of geography, ethnicity or economic might.

GAVI and Research

Given the immensity of the challenge of wide use of the 10 or 12 presently available vaccines of global significance, one could be forgiven for placing research on the back burner. However, this will not be the case within GAVI. Two diseases, HIV/AIDS and malaria, kill 5 million people per year between them and the death toll is rising. For these diseases we have no vaccine presently available but a great deal of research is going on in both areas which needs still further support. The third of the 'big three' diseases is tuberculosis, still killing 3 million people each year. The TB problem is compounded by the emergence of multi-drug resistant strains. While BCG does a good job in protecting infants from tuberculous meningitis and miliary tuberculosis, it clearly is insufficiently effective in the prevention of pulmonary tuberculosis in adolescence and young adults. A new approach is needed here as well. In the first instance, GAVI will not have major resources available for direct support of basic research, but it will play a co-ordinating role and will be a major advocate for an increased effort. Indeed, a gift from the Gates Foundation separate from that for new vaccine introduction will spearhead an increased effort in malaria, and will also help clinical trials for AIDS vaccines. So millennial winds are blowing through the field of global vaccinology and the revitalised partnership which GAVI represents has at least a sporting chance of bringing off the greatest public health achievement of the 21st century.

Notes and References

1. A plenary lecture at the Pacific Science Congress, Sydney, Australia in July 1999.
2. See the following references: G. J. V. Nossal, 'Host immunobiology and vaccine development', *The Lancet*, 350, 1997, pp. 1316–19; G. J. V. Nossal, 'Vaccines', in W. E. Paul (ed.), *Fundamental Immunology*, Fourth Edition, Lippincott-Raven, Philadelphia, 1999, pp. 1387–1425.
3. G. J. V. Nossal, 'Global immunization for the 21st century', Editorial for *Science*, 284, 1999, p. 587.