A healthier climate for the funding of vaccine research

G J V Nossal

Vaccination is a marvel of scientific endeavor that benefits the masses. Yet the laissez-faire economy may not provide a sufficient push for vaccine research and development. The current climate that drives this globally important venture is examined here.

In the launch issue of this journal in July 2000, I made some rather bold predictions about global immunization in the 21st century. I was so impressed by the generosity of the Bill & Melinda Gates Foundation and the dynamism of the Global Alliance for Vaccines and Immunization (GAVI) that I predicted a notable leap forward in the 21st century[1]. No doubt a great deal has been achieved in these three and a half years, but there have also been some serious setbacks. The resurgence of poliomyelitis in North India and the emergence of reassortant strains capable of causing miniepidemics have served as reminders of how gigantic a goal global eradication of this and any other infectious disease really is. The tragedy of 11 September 2001 and the subsequent anthrax attacks have ushered in a new agenda in immunization: vaccines as a defense against bioterrorism. Limitations in both human and physical infrastructure have become apparent in some developing countries, emphasizing the fact that money alone cannot solve all the problems. Yet an undertone of hopefulness remains, particularly as pressure mounts for health to be taken more seriously as a goal for international development assistance. The most dramatic example of this is the Global Fund to Fight AIDS, Tuberculosis and Malaria, where billions of dollars have been mobilized for a great diversity of programs.

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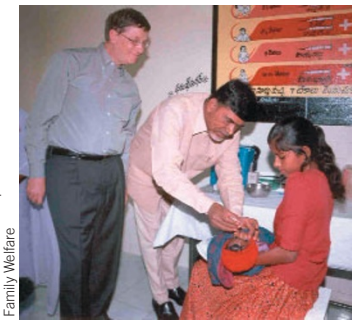
I commented in 2000 that research and development (R&D) were among GAVI's aims in the longer term but that, in the first instance, its funds were insufficient for GAVI to support research directly. The window for funding research by GAVI has now opened (modestly), but here I have the opportunity to discuss the funding of vaccine research more broadly. This commentary is not meant as a compendium of global vaccine research. Instead, it seeks to illustrate by example a variety of vigorous efforts that, as an ensemble, provide a healthier climate for vaccine R&D. As a first step, it is important to dissect the different layers of the R&D spectrum that must precede the wide-scale deployment of a new or improved vaccine.



Andhra Pradesh Department of Health and Family Welfare

The Honorable Chief Minister Chandrababu Naidu immunizing a child against polio in his state of Andhra Pradesh, India. He is accompanied by Bill Gates, cofounder of the Bill & Melinda Gates Foundation.

A great new antigen is not enough

Academic researchers are usually most interested in the definition of a new antigen (or antigens) that might be a vaccine candidate. There is a variety of reasons to predict that an immune response against a molecule might be protective. For example, the antigen might be exposed at the surface of the pathogen and thus the antibody generated is potentially neutralizing, or it might be a peptide exposed on the surface of an infected cell and thus be subject to T cell recognition. Recombinant DNA technology gave this type of research a tremendous 'shot in the arm' and, more recently, the completion of full gene sequencing of many pathogens has given a further boost. Indeed 'genome mining' is providing a rich diversity of new vaccine candidates, with clever computer programs predicting which gene product might be an integral membrane protein, which will not be likely to cross-react with a 'self' constituent and which will have minimal inter-strain variation. High-throughput screening of such gene products through immunization and challenge of laboratory animals has resulted in some fascinating and new leads.

New putative vaccine candidates must be tested preclinically in a variety of species, particularly when dealing with a type of disease (such as malaria or HIV/AIDS) for which no vaccine yet exists. Such testing will frequently involve some new adjuvant and/or immunization protocol such as 'prime-boost' approaches or mucosal immunization[2]. Although aspects of such research can be expensive, such as trials in subhuman primates, this basic research is not nearly as costly as the next phase.

Clinical trials of new vaccines have represented a real bottleneck. There are examples in which an academic researcher can validate a new vaccine preclinically and go straight to an established vaccine manufacturer for clinical development, but this applies mainly to vaccines using established principles and with substantial industrialized country markets. In many cases, the new vaccine's success may depend on new principles, such as induction of cytotoxic T cell immunity, thus making the next steps more risky, or it may relate to a disease (such as bacillary dysentery) problematic only in countries with little ability to pay. This is where special 'mechanisms' must intervene. Phase I and II clinical trials are now often funded by philanthropic foundations. The Gates Foundation's Malaria Vaccine Initiative, coordinated by the nongovernmental organization Program for Appropriate Technology in Health (PATH), is a good example. This is a highly focused vaccine development program with a funding of $150 million that has recognized that traditional market forces are insufficient to give each credible malaria vaccine candidate formulation a reasonable chance of getting into human trials. The Malaria Vaccine Initiative works with a network of nine partnerships spanning five continents, helps to ensure antigens are prepared using Good Manufacturing Practice protocols, identifies and supports clinical trial sites, and facilitates arrangements with both small and large commercial partners. Similar motivations underpin the innovative and successful International Aids Vaccine Initiative and the Wellcome Trust's work based in the United Kingdom. For example, the Wellcome Trust funds the Oxford Centre for Clinical Vaccinology and Tropical Medicine. This academic vaccine testing facility has programs in malaria, HIV and AIDS, tuberculosis, and meningococcal infections, and although the chief focus is on phase 1 trials at present, expansion of this work into phase 2 and 3 levels is planned.

PATH

A woman with her child awaits vaccination at a clinic in India.

In the US, there are several Vaccine Testing and Evaluation Units funded largely by the National Institutes of Health (US Public Health Service). One of the most interesting of these is the Center for Vaccine Development in the School of Medicine of the University of Maryland, Baltimore, under the direction of Myron Levine. It was established in the mid-1970s as one of the first facilities to evaluate vaccines in community volunteers, and it seeks to span the whole R&D spectrum from basic science to experimental vaccine development, clinical evaluation and field studies.

Phase 3 trials, which must involve thousands of subjects and multiple trial sites, represent a very special problem. Such trials can cost from $50 million to $300 million and typically take 3 years or longer to complete. What if industry is unwilling to sponsor such trials? This is really still an unresolved problem and will have to be tackled on a case-by-case basis. A possible role for developing country manufacturers is discussed below.

Countries' vaccination priorities

The final, and in some ways most challenging, R&D 'layer' comes in the area of national and international decision-making when a given vaccine has been shown to be safe and effective. National governments and the global community cannot prioritize vaccines for the developing world without reliable disease-burden and cost-effectiveness data. Nor can politically 'saleable' decisions be reached without determining community and professional attitudes toward a disease. There may be times when an extended education program is necessary. For example, it took a great deal of time and effort before the full scale of the burden of hepatitis B was realized. Because hepatitis B causes chronic liver disease and liver cancer many years after first infection, its total influence on morbidity and mortality was not appreciated. Many share the credit for gradually changing perceptions, but chief among them are James E. Maynard of PATH, Mark Kane, then of the World Health Organization (WHO), and Ian Gust, then of CSL, Australia. One of the great triumphs of GAVI is the much wider distribution of the excellent hepatitis B vaccine, which certainly will be followed by a considerable lowering of the incidence of hepatocellular carcinoma[3].

David Mercer

GPS location data and standard record-keeping are used to track Hib disease on the Indonesian island of Lombok.

The International Vaccine Institute in Seoul, South Korea, has developed a fine reputation for research in this field. Under the direction of John Clemens, and with financial support now chiefly from the government of the Republic of Korea and from the Gates Foundation, it has established a good record of accomplishment of multicountry, multidisciplinary 'downstream' or translational research, generating evidence for rational accelerated vaccine introduction. For example, its DOMI program (for 'Diseases of the Most Impoverished'), funded at $40 million by the Gates Foundation, concentrates on enteric diseases such as cholera, typhoid and bacillary dysentery (shigellosis). It has already shown that a killed oral whole-cell cholera vaccine is effective and, equally important, cost-effective when the vaccine comes from a Vietnamese manufacturer (with some technical assistance from Sweden). A very exciting series of studies of *Haemophilus influenzae b* (Hib) meningitis in several centers in Asia, some in collaboration with PATH, produced unexpected and important results. It has been generally believed that Hib is much less of a problem in Asia than in Africa or indeed in industrialized countries and thus that universal infant immunization against Hib may not be warranted. The research showed that the incidence of Hib disease was indeed low in some areas of Asia but considerably higher in others. It was concluded that the real value of immunization might, in some cases, be revealed only by vaccination studies with rigorous population-wide follow-up. One such study has just been completed on the Indonesian island of Lombok. Hib immunization reduced the incidence of purulent meningitis by 50% in children under 2 years of age (a reduction from 134 cases per 100,000 person years in unimmunized children to about 67 per 100,000 in those immunize against Hib). However, many meningitis cases are diagnosed as 'clinical meningitis' without spinal tap. If all individuals with meningitis are included in the analysis, including those who were never tapped, the number of meningitis cases prevented by Hib immunization more than doubles, from 67 to 158 per 100,000 child years. This figure represents more than 20% of all clinical meningitis cases seen in this age group. Concurrently, Hib immunization prevented a very large number of pneumonia cases on Lombok. However,

because the rate of pneumonia in this population is extremely high, the proportion of pneumonias prevented by immunization was lower than expected (S. Wittet and D. Mercer, personal communication). Such population-based studies will have to be repeated in many different countries. The Children's Vaccine Program at PATH is now conducting a major Hib program in the Ukraine.

Remember the giants in the field

Nothing illustrates the global upsurge of interest in vaccine research better than the funding patterns of the world's largest medical research provider, the US National Institutes of Health. The overall figures for the last 5 years are presented in **Table 1**. These figures show funding more than doubled over a 5-year period to a total of nearly $1 billion per year. Research into vaccines other than HIV and AIDS leapt between 2002 and 2003. This increase was due to an appropriation of $246.5 million for vaccines for the purpose of biodefense under the guidance of the National Institute of Allergy and Infectious Diseases. The research program includes new and improved vaccines against anthrax, plague, smallpox, botulism, tularemia, hemorrhagic fever viruses and other possible agents of bioterrorism[4]. Although funding for other vaccine research rose, some argue that this effort focusing on bioterrorism is taking away from other more meritorious areas[5].

David Mercer

Indonesian children near a health clinic in Lombok, Indonesia.

The large pharmaceutical firms involved in vaccine manufacture are major research performers; their annual expenditures are estimated at about $700 million per year. Smaller, specialized biotechnology companies are also very active in this field. Vaccine manufacturers from developing countries are a relatively new entrant. For example, a major joint venture between PATH and the WHO, funded by the Gates Foundation, is working with a large Indian manufacturer toward a conjugate *Neisseria meningitidis* serogroup A vaccine to fight the vicious epidemics of meningitis that sweep across the so-called 'meningitis belt' of sub-Saharan Africa every few years. It is hoped that the lower cost structure in India will allow R&D, manufacture and universal deployment at a cost that the philanthropic and public sector institutions can bear.

Challenges of coordinating global efforts

I have by no means mentioned all the initiatives that have revitalized vaccine research in recent years. For example, the Gates Foundation has recently extended its commitment. Apart from the efforts in diarrheal disease, meningitis, HIV and AIDS, and malaria already mentioned, it is active in tuberculosis, Japanese B encephalitis, pneumococcus, dengue fever, hookworm and measles. The last is a particularly provocative $20 million program designed to deliver a 'stealth' measles vaccine mucosally, aimed at protecting children younger than 9 months of age, before the standard injectable live attenuated vaccine is first efficacious. In addition, the Gates Grand Challenges in Global Health program is soliciting proposals of a generic nature cutting across different disease areas[6]. These include new needle-free delivery mechanisms, new adjuvant formulations and stratagems to avoid the need for a 'cold chain' (refrigeration of the vaccine at all times from shipment by the manufacturer to end use at the point of vaccination).

A collaboration be-tween Ian Frazer of the University of Queensland, CSL in Australia and Merck bids fair to produce a vaccine against human papilloma virus, thus potentially preventing cervical cancer[7]. Chiron is making progress toward a vaccine against *Helicobacter pylori*[8]. GAVI has decided recently to devote some funds to research, including for rotavirus and pneumococcal vaccines. How can these various efforts be coordinated?

WHO is making a brave attempt. It has centralized all its vaccine research efforts into IVR, the Initiative for Vaccine Research headed by Marie-Paule Kieny, which seeks to play a global coordinating role. One tool of great value is an annual conference, which unites all the key players from academia, industry, public health, the regulatory agencies and key funding partners. Popularly known as the Montreux conference, this forum rotates between the Geneva area and a developing country and has developed a very special cachet. It is rare to have firms competitive with one another interacting so freely with their regulators (with whom they must have a very formal relationship in general) and to see the academic sector interacting so fully with industry researchers and their necessarily more applied focus. I think the special cachet says much about the moral force of WHO, whose lofty mission can bring people together. Another coordinating effort of a very different kind is an initiative of the US National Institute of Allergy and Infectious Diseases, which is an annual publication known as the Jordan Report[9]. This authoritative volume brings together all recent efforts in vaccine R&D and is punctuated by lively essays from world-ranking figures drawing out the highlights.

Table 1 US National Institutes of Health spending patterns on vaccine R&D

Fiscal year	AIDS	Non-AIDS	Total
2000	232.2	220.2	452.2
2001	269.2	281.7	550.9
2002	329.4	280.8	610.2
2003	413.6	548.4	962.0
2004 (estimated)	456.3	531.9	988.2

Amounts are in US dollars in millions per year.
J. La Montagne, National Institute of Allergy and Infectious Diseases.

Is a fully immunized world possible?

The meeting held at the Villa Serbelloni in Bellagio, Italy, in 1999 initiated detailed consultations, which resulted in GAVI's laboring mightily toward the goal of a fully immunized world[10]. This ideal is still a fair distance away. Although the research community has made great strides, it is not particularly close to definitive success for AIDS, tuberculosis or malaria. Although the costs of discovery research and early stage clinical work are not too daunting, perhaps $10 million for a 5-year effort, the total costs of producing a licensed AIDS vaccine may be in the region of $1 billion (A.I. McMichael, personal communication). Will the world muster enough wisdom, foresight and generosity? I remain hopeful, but the time frames are somewhat daunting.

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