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Ensuring that Developing Countries have Access to New Healthcare Products: The Role of Product Development Partnerships

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Abstract

Product development partnerships (PDPs) are generating an increasing flow of health products for diseases prevalent in developing countries. Based on past experience, ensuring end-user access to these health products will present a significant challenge following the research and development process. The specific actions required to ensure access, and the time when these actions should be initiated, are becoming clearer based on the experiences to date in various PDPs. This list of activities can seem daunting, but the public health community is already learning how to spread these responsibilities between PDPs and other actors – both public and private, and international and national – such that efficiencies and local relevance are maximized.

Bridging the gap between product development and end users

For many years, there was insufficient development and supply of new health products for diseases prevalent in developing countries. Product development partnerships (PDPs) were formed in response to this market situation, which arose from a perceived lack of financial incentives and abundance of commercial risks for companies. The PDPs, as not-for-profit organizations, could bring together the public, private, academic, and philanthropic sectors to drive the necessary product development [1]. PDPs have been around for decades but, thanks to growing investments from government donors and foundations around the world, their numbers and profile have increased over the past 5 -10 years.

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An increasing number of PDPs are now facing the challenges of ensuring that end-users can access products once developed. Introduction of new tools for various indications has often been associated with a significant delay between global availability and local adoption [2-4], and the process of health technology change has presented significant challenges [5-8]. Frost and Reich (2008) have analyzed some of these challenges and proposed underlying principles for confronting them [9]. PDPs will also benefit from sharing both a forward-looking, time-sensitive menu of specific activities and a set of lessons on how these activities can help ensure access. The term "access" is used in different ways by many organizations, and for the PDPs there was a need to translate this term into an operational definition [10]. This definition can assist in defining what contributions by PDPs and other actors would have the greatest impact on ensuring timely access.

To address this issue, a diverse group of 20 organizations, including donors, NGOs, and 12 PDPs and similar initiatives, met in Geneva, Switzerland, on September 17-18 2008. The PDPs that attended are striving to develop vaccines for HIV, tuberculosis, malaria, dengue fever, meningococcal meningitis, and pneumonia, drugs for tuberculosis, malaria, sleeping sickness, and visceral leishmaniasis, microbicides for HIV, and novel insecticides. This self-convened meeting was the largest-ever gathering of a broad cross-section of PDPs and NGOs to focus on access to newly developed products.

Meeting objectives were to survey PDP experiences, best practices, and challenges in the area of access (in both the public and private sectors, and with comparisons across the access pathways for novel drugs, vaccines, and vector control), to identify the gaps and possibilities for future investigation, collaboration and coordination, and to define the role of PDPs within the overall framework of research, development, and access activities.

The meeting covered four topics: planning and introduction for implementation; manufacturing; pricing, finance, and procurement; and global regulatory pathways for new products. Shared lessons from the meeting can provide a reference for future access discussions and can inform future work. (The agenda, meeting presentations and a meeting report can be obtained from the corresponding author.)

Defining "access"

Participants agreed that, for PDPs, "access" refers to a coordinated set of activities needed to ensure that the products developed will ultimately have an equitable public health impact. Achieving that impact requires products that are available, affordable, and acceptable to end-users, and adopted into developing country health systems. The role of PDPs in addressing these four concepts has varied from doing, to facilitating, to advocating for others to take action. In order to be successful, PDPs need to collaborate closely with developing countries throughout the process from pre-clinical development to product adoption.

Although access activities vary due to differences between interventions (drugs, diagnostics, vaccines, or insecticides) and disease contexts (e.g., presence of disease-specific supporting systems or financing), there is a logical flow of potential access activities according to the stage of product or intervention development. Table 1 lists the activities that participants at the meeting identified as falling under the term "access".

Ensuring local context and ownership

Development of products is best done with a strong and clear understanding, from the outset, of the health system within which they will ultimately be used, the trade-offs that will need to be made and with consideration to the potential impact of the intervention on health systems. National decision- makers need access to sufficient and high quality local, regional, and global data and to be well-informed about the interpretation of data and experiences in other settings. The goal is for national governments to make their own evidence-informed decisions regarding use of interventions in their country. PDPs should seek to maximize country ownership of access activities at all stages, especially as decision-making becomes imminent. Involvement of developing countries in PDP activities helps in achieving this goal.

Table 1: Principal "Access" Activities

a. Pre-clinical:
- Determining stakeholder needs and eventual health system context
- Informing product profiles, including cost constraints

b. Early clinical or pre-proof of concept:
- Analyzing stakeholder perceptions and demand
- Burden of disease studies
- Profitability, return on investment (ROI) and net present value (NPV) assessments
- Refining target product profiles
- Quality control of manufacturing processes
- Identification and allocation of risk, including indemnification and insurance
- Helping to refine the regulatory framework
- Informing contractual "access" agreements with manufacturers
- Planning the fastest possible pathway through the ensuing web of access activities

c. Late clinical:
- Building awareness about the disease and the new products developed to address the disease
- Deriving strategic demand forecasts under specific delivery strategies
- Finalizing target product profiles to ensure alignment with the developing country context
- Modeling impact and cost-effectiveness
- Facilitating disease surveillance mechanisms
- Ensuring manufacturing capacity is in place
- Informing and ensuring adherence to contractual "access" agreements with manufacturers
- Understanding existing market structures and pathways for related products
- Increasing management of risk through indemnification and insurance
- Ensuring quality control of the manufacturing process
- Refining regulatory pathways
- Defining pathways for international and/or regional policy recommendations
- Beginning discussions with financing and procurement agencies
- Supporting activities to develop global, regional and local advocates
- Ensuring that countries understand their role in accelerating access to an affordable and sustainable supply of products
- Supporting the formation of country decision-making mechanisms (as described below)

d. Post-licensure:
- Ensuring implementation of essential operational research, effectiveness trials, demonstration projects, and/or Phase 4 pharmacovigilance studies
- Capacity building to facilitate ongoing pharmacovigilance
- Communicating information on the intervention
- Ensuring that countries and international agencies understand their roles in accelerating access to an affordable and sustainable supply of products
- Supporting leadership and issuance of guidelines by international technical organizations (e.g., WHO) that are mandated to advise on implementation
- Seeking sustainable financing commitments for procurement and utilization
- Serving as an expert resource to international organizations during their policy processes and countries during their decision-making and adoption processes

PDPs can support the expanded involvement of developing country manufacturers when appropriate. For example, developing country manufacturers may be able to improve future access by producing products at lower costs or adding production capacity that contributes to the development of a healthy market with multiple suppliers to help ensure adequate supply is available. As always, sufficient R&D and manufacturing capacity and rigorous regulatory oversight must be ensured.

Agreements with partners

The types of collaborations PDPs enter into with private sector partners and the terms of those agreements should seek a clear commitment to access, a clear understanding of the returns to the private sector partner, a protection of PDP investments and intellectual property (e.g., non-exclusive licensing if an industrial partner stops development), a defined target product profile, and a supply of quality products at affordable prices for countries of the developing world.

If products have significant potential for commercial markets, PDPs can establish contractual terms that allow private sector partners to pursue commercial markets, while also ensuring the investments from PDPs are translated into appropriate benefits for the public sector.

Opportunities for PDPs

PDPs have the opportunity to work with international organizations, national regulatory authorities, and industry to seek innovative regulatory and WHO pre-qualification approaches, potentially getting products to end users years earlier without foregoing rigorous product oversight. Similar opportunities exist with innovative financing mechanisms with PDPs being well positioned to navigate and help perfect these mechanisms.

PDPs can help to reinforce international strategies such as the global strategy and plan of action from the Inter-Governmental Working Group on Intellectual Property, Innovation, and Public Health.

Finally, cooperation between PDPs can increase efficiency and bolster understanding in several areas, including the structure of markets in low income countries, what contractual terms are both favorable for developing countries and fair in development, manufacturing and distribution contracts, and what metrics can be used to determine PDP success in ensuring access.

The evolving role of PDPs in ensuring access

The discussion above reflects lessons on the range of activities PDPs have undertaken when working to address "access." Each of the activities listed in Table 1 has been carried out by at least one of the PDPs. It is clear, however, that each individual PDP cannot cover all of these necessary activities alone. Rather, we see this list as a recognition of the substantial collective effort needed to ensure access to new technologies, and the focus for continued thinking on how this work is best divided among national governments, other national bodies, and existing international organizations. Within PDPs, staffing numbers and skill sets will evolve as activities and stages of product development progress. As today's investments in R&D increasingly produce important interventions in the future, it becomes ever more critical to wisely consider the range of activities that do or do not fall within the "access" remit of varying PDPs and to make sure that the entire pathway from R&D to end users is appropriately addressed.

In this new era of PDPs, we now have several more years experience and many approaches to learn from as we collaborate and strive ever more effectively towards public health goals. PDPs have a unique opportunity to share learning between organizations, which will be critical in decreasing the time between development of products and the realization of public health impact in developing countries.

Author contributions

All authors participated in the meeting where the manuscript originated and contributed to the drafting and revision of the manuscript.

Competing Interests and Funding Sources

ADB, WAW, TDM, RK, RC, TM, LAP-D, AFK, and RTM, are employed by product development partnerships, or similar not-for profit groups, and work on access-related issues.

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Introduction of Hepatitis B Vaccine: Reflections on Innovation

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Abstract

The prevalence of chronic hepatitis B virus infection in Asian populations ranged up to 12% in the 1980s, and chronic liver disease and hepatocellular carcinoma were major public health scourges. In 2010, the prevention of hepatitis B infection by immunization can be seen as one of the great, although unfulfilled, accomplishments of public health. Major reductions in chronic infection have taken place in Taiwan[1, 2], China [3], Korea [Personal communication, H. Margolis, January 2009], and Thailand [4]. The observed reductions in the prevalence of infection are the direct result of immunization with hepatitis B vaccine, primarily to newborns and infants. The introduction and delivery of hepatitis B vaccine in Asian countries is a result of the efforts of many individuals and organizations beginning in the 1950s and continuing to the present day. Perhaps the most salient conclusion to be drawn from a review of the work of the last half century is that developing countries can take leadership in the development, introduction, and use of vaccines that affect the health of their populations.

Introduction

Hepatitis B vaccines were originally developed in the 1970s as a result of the pioneering work of Saul Krugman, Alfred Prince and Baruch Blumberg in New York. Krugman undertook pioneering studies that demonstrated the cause of "serum hepatitis" to be a virus[5]. Prince had been involved in the study of hepatitis from the early 1960s when he carried out studies in Korea and elsewhere to demonstrate the prevalence of an antigen associated with hepatitis in military personnel[6]. He continued this work after returning to the United States and was eventually able to isolate the hepatitis B surface antigen (HBsAg) and show that it was derived from the virus which caused hepatitis B[7]. Blumberg developed methods to use HBsAg as a vaccine[8].

The need for a vaccine against hepatitis B virus was greatly enhanced by studies that showed the association between viral infection and liver cancer. The demonstration that this virus was a cause of cancer was one of the great scientific achievements in epidemiology and virology and was carried out by Palmer Beasley and colleagues in Taiwan in the early 1970s[9]. As Beasley liked to say, "If you have chronic hepatitis B infection and you don't die from something else first, you will die from liver cancer."

Robert Purcell and John Gerin, scientists at the US NIH developed methods for isolating HBsAg from human plasma[10], and their work and that of Blumberg were adopted by Maurice Hilleman[11] at Merck Vaccine Corporation to manufacture the first

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commercially available hepatitis B vaccine which became available in 1981. The NIH work was assisted by James Maynard at the US CDC in Phoenix, AZ[12]. The Pasteur Institute in France developed a similar vaccine and clinical evaluation was carried out at the Laboratory of Virology in Tours, France under Philippe Maupas and Alain Goudeau [13]. The Netherlands Red Cross also developed a small scale facility for producing plasma-derived vaccine[14].

Throughout the 1980s, Hiroshi Nakajima was the director general of the Western Pacific Regional Office of WHO. He, along with colleagues at the Tokyo-based Kitasato Institute, which had also developed a method for making plasma-derived hepatitis B vaccine, and the directors of vaccine production institutes in China, launched a major program to assist these various production facilities to establish production of vaccine. These efforts were successful, and eventually seven vaccine institutes throughout China were producing plasma derived hepatitis B vaccine and supplying immunization efforts primarily in urban areas.

Efforts were also made in Taiwan to secure supplies of hepatitis B vaccine and collaboration was established with Pasteur that included plans for the establishment of production facilities. It is not clear if hepatitis B vaccine was ever produced in Taiwan, but it is clear that nationwide immunization was launched in the early 1980s and has been highly successful.

Two competing biological companies in Korea, Cheil Co (at the time a subsidiary of Samsung Corp.) and the Korea Green Cross (KGCC), also established production of plasma derived hepatitis B vaccine. Cheil obtained its know-how through a licensing arrangement with the New York Blood Center where Prince was undertaking his work. Prince had developed a low cost means of production of hepatitis B vaccine that included a flash heating inactivation step[15]. The KGCC obtained its know-how from a Korean scientist living in Toronto, Canada who had worked at NIH.

Thus by the mid-1980s, hepatitis B vaccine was being produced and delivered in Europe and the United States. In Asia there was production in China, Japan, Korea, and Taiwan. However, with the exception of Taiwan, delivery of hepatitis B vaccine was quite limited in Asia. In China, distribution was predominantly in urban areas and parents were required to pay for the vaccine. In Japan the availability of the vaccine was limited to children born to mothers who were hepatitis B chronic carriers. In Korea the government was only beginning to establish nationwide distribution. In almost all of the rest of Asia, there was little if any availability of hepatitis B vaccine.

Public health leaders in many Asian countries wished to have access to hepatitis B vaccine but the prices charged by Merck and Pasteur were higher than these countries (except for Taiwan) could afford and, unlike today, trade among Asian countries in vaccines was very limited.

Also during this time, uptake of hepatitis B vaccine in developed countries had been quite limited in part because of recommendations by the US CDC that the vaccine be limited to delivery to "high risk" groups including health-care workers, homosexually active men, and children of babies born to Asian parents[16].

There was great urgency among many public health officials in Asia for the introduction of hepatitis B vaccine because of a wide awareness that the hepatitis B virus was a cause of liver cancer.

Thus there was frustration among public health officials in Asia and among hepatitis B medical experts around the world in both developed (e.g. Beasley, Goudeau, Maynard, and Prince) and developing countries who were aware of the potential for hepatitis B vaccine to control a major cause of cancer in the world. These scientists and medical experts had made major contributions to defining the disease, to conceptualizing a vaccine, to developing that vaccine, and to bringing it to market. But it remained largely unused among those who needed it most.

An unlikely new participant

In the mid-1970s two program officers at the Ford Foundation (Gordon Perkin and this author) Gordon Duncan of the Battelle Northwest Research Center set up a non-profit organization addressed to contraceptive technology. This organization, Program for the Introduction of Contraceptive Technology (PIACT), was set up in Seattle, Washington and was established on the simple principle that there needed to be effective communication among scientists developing new contraceptive technologies, companies producing contraceptive technologies, and family planning program managers delivering these tech-

nologies. This author's first assignment was to establish an office in Manila, Philippines and from that base set up programs throughout Asia. Two years later, an office was established in Jakarta, Indonesia.

As programs were launched and more experience obtained, it became clear that there was a need for similar activities in other areas of health. For example, programs in Oral Rehydration Therapy (ORT) were launched in several Asian countries and had the objective of accelerating the introduction and use of ORT to treat diarrhea. As time passed, a new name was adopted for the organization: Program for Appropriate Technology in Health (PATH). Senior officers of the Ford Foundation maintained a deep interest in the activities of PIACT, now PATH, including the representative in Indonesia, William Fuller, a member of the Fuller Brush Co. family. He and this author met on a number of occasions to discuss the work of PATH. Apparently Fuller was impressed with the efforts of PATH to bridge the gap between the public and private sectors to improve the availability of health technologies. Fuller put this author in touch with senior officials of USAID in Washington DC who were launching a new program under the Reagan administration to enhance the involvement of the private sector in development. This contact led to a major grant to PATH to catalyze collaborative development activities between the public and private sectors in Asia.

The program was begun with a needs assessment and visits were made to senior officials in several Asian countries including the Minister of Health of Indonesia, Dr. Suwardjono, with whom this author had worked while Suwardjono had been the Director General of the Indonesian national family planning program. Suwardjono suggested that the highest priority for the new PATH program could be to assist Indonesia to have access to hepatitis B vaccine including its production at the national vaccine production facility, Bio Farma, in Bandung. Suwardjono was responding to a request from President Soeharto who was dismayed because one of his golfing partners had recently died from liver cancer.

PATH staff undertook a detailed assessment of the field of hepatitis B vaccines and concluded that indeed there was a disconnect between the existence of safe and effective hepatitis B vaccines and their availability to those who needed them most in developing countries. This assessment included extensive discussions with leaders in the field such as Prince and Maynard, who was head of the Hepatitis Branch at the US CDC. It also included discussions with leading health experts in Asia including those in China (Zhi Yi Xu (Shanghai Medical U.), Indonesia (Suwardjono, Leona D'Agnes (PATH)), Japan (Nakajima (WHO), H. Nishioka), and Thailand (Henry Wilde, Supawat Chutivongse and Chaivej Nuchprayoon (Thai Red Cross), Don Douglas (PATH, Thailand), Praphan Phanuphak (Thai Red Cross and Chulalongkorn University) and Supamit Chunsuttiwat, (Ministry of Public Health))[17].

Responding to Suwardjono's request, in the summer of 1986 PATH organized visits for him and other officials of the Indonesian Ministry of Health to hepatitis B vaccine manufacturers in Korea, the United States, and France. By the time the team got to the United States and made a visit to the New York Blood Center, it had become obvious to this author that there was an opportunity to accelerate the introduction of hepatitis B vaccine into developing countries, if only the right intellectual resources and money could be brought together. It was decided to form an "International Task Force on Hepatitis B Immunization" with a core group of Maynard, Prince and Mahoney. This task force eventually involved hepatitis B specialists from developed and developing countries. The other members included Beasley (Taiwan), Goudeau (France), Ian Gust (Australia), Andrew J. Hall (Banjui) , Violet How (Malaysia), Xu (China), and E.A. Ayoola (Nigeria).

To launch the activities of the Task Force, Perkin and this author approached Kenneth Warren at the Rockefeller Foundation who was head of the health program. Warren not only gave a small seed grant of $50,000 to launch the work of the Task Force, but made contact with the president, John Bruer, of the new James S. McDonnell Foundation in St. Louis, Missouri. Eventually, the McDonnell Foundation made grants of more than $7 million to support the activities of the Task Force. A detailed history, entitled, "The War Against Hepatitis B" of the Task Force has been prepared by William Muraskin[18].

Defining the problem and setting the stage for success

As noted, only plasma derived vaccine was available in the early 1980s (recombinant DNA vaccine was licensed in the mid-1980s), and marketing by the large international manufacturers was directed at high risk individuals such as Asian immigrants to the United States, health care workers, and the gay community. These policies were driven to a large extent by the recommendations of the US CDC. The price of the vaccine was $20 upwards per dose. It was difficult for these priority groups to afford the vaccine, and it was impossible for the poor in both developed and developing countries. In Thailand and neighboring countries hepatitis B seroprevalence among the general population was at least twice if not three-times the level among health care workers and the middle class. The highest rates of infection were in childhood mainly from horizontal infection with family members and play mates, but vertical transmission from mother to child also occurred. Unfortunately, infection in childhood held a much greater risk of the individual becoming chronically infected and thus at risk of liver disease. This pattern was consistent with patterns in many other countries including Indonesia, Taiwan, and South Korea.

Both Merck and SmithKline (now GlaxoSmithKline) were developing a recombinant hepatitis B vaccine. Pasteur also developed a recombinant DNA vaccine, but the use of Chinese Hamster Ovary (CHO) cells as the production system resulted in costs of production that were much higher than those achieved by Merck and SmithKline both of which used yeast cells. Merck again focused on the U.S. market, but from the beginning, SmithKline took a very international approach and sought to establish markets in both developed and developing countries. Nevertheless, the price of the vaccine from these two international manufacturers remained too high for developing countries and the poor.

At this point, a Korean-American scientist stepped in to make a singular contribution. Seung-il Shin had left Korea as a young refugee from the Korean War. He eventually became a professor at Albert Einstein College of Medicine in New York but had left there to establish a biotechnology company with sponsorship of Cheil. He brought to this biotechnology company a concern for the health of people in developing countries and was involved in the transfer the technology for production of hepatitis B vaccine from the New York Blood Center to Cheil. To implement its model immunization programs, the Task Force needed a supply of affordable vaccine. The Task Force also saw the procurement of this vaccine as an opportunity to break through to a new low price for hepatitis B vaccine. Shin approached the most senior management of Samsung Corp, then the owner of Cheil, and obtained their written agreement to supply hepatitis B vaccine at $1.00 per dose for Task Force programs. This commitment gave the Task Force the confidence that it could undertake model immunization programs with an affordable supply of vaccine. However, wishing to operate within rigorous and transparent processes, PATH undertook a competitive bidding process for procurement of the vaccine. In submitting their bids, the companies were required to commit to providing the vaccine to other public-sector agencies such as national governments and UNICEF at the same price they would offer to the Task Force. This was intended to discourage "promotional" bidding. Cheil submitted its bid at $1.00 per dose, but the winning bidder for the first tender was KGCC, which offered a price of $0.95. The Task Force procured this vaccine for its first model immunization program implemented on Lombok Island in Indonesia. (Shin would later go on to be the intellectual and personal force behind the founding of the International Vaccine Institute in Seoul, Korea).

Despite these promising developments among manufacturers, international organizations such as WHO and UNICEF showed little interest in introducing hepatitis B vaccine into national immunization programs. Indeed, officials of the WHO Expanded Program for Immunization (EPI) and the UNICEF vaccine procurement program actively opposed efforts to introduce hepatitis B vaccine arguing that it would "burden EPI." The argument was that national EPI programs were struggling just to deliver the basic vaccines of polio, BCG, DPT, and measles, and the addition of another vaccine would "burden" the cold chains, record keeping systems, etc.

The Korean companies and SmithKline recognized that entering this market required production of a low-cost vaccine and that the largest market would have to be derived from a combination of high-priced sales in developed countries and lower-priced but still profitable sales in developing countries.

Thus the world was "stuck" between a potential supply of affordable vaccine, on the one hand, and a resistance by international agencies on the other. By this time the U.S. CDC had changed its recommendation and now called for universal immunization of newborns in the United States.

Indonesia and Thailand assume leadership

Indonesia and Thailand became focal points for activities to accelerate hepatitis B vaccine introduction in Asia and indeed the world.

In Indonesia, a collaborative program between KGCC and Bio Farma was established to assess the feasibility of production of plasma derived hepatitis B vaccine in Indonesia beginning with the importation of bulk vaccine for local filling and labeling. PATH (Steve Brooke and Mahoney) undertook a detailed financial feasibility study that showed that Bio Farma could produce plasma-derived vaccine at a price substantially less than $1.00 per dose.

In Thailand, the Thai Red Cross (TRC) also decided to assess the feasibility of production of plasma derived vaccine. This work was launched through a visit made by Wilde to the Netherlands Red Cross. Interest in hepatitis B vaccine had been initiated in the early 1980s by Kaset Sanidwong, then secretary of the Thai Red Cross, Supawat Chutivongse, director of the National Red Cross Blood Center, and Praphan Phanuphak, head of the immunology division of Chulalongkorn University. This interest was given life in a project to collect HBsAg positive plasma in Thailand and ship it to the Netherlands Red Cross to produce a plasma derived vaccine. This work was implemented around 1984, with W.G. van Akens, then director of the Dutch Blood Bank and his associate Henk Reesink. Professor Kaset was the recipient of the first dose of this vaccine. Wilde visited van Aken in 1984/5 and reported to PATH and the Thai Red Cross that a collaborative project between the Dutch and Thais looked technically promising, even though international companies that manufactured a plasma derived vaccines had begun to market their product aggressively in the Netherlands. The original plan was to divide the production output equally for use in Thailand and the Netherlands public sectors. Even though competition from international firms and some difficulties in production (one lot had to be recalled[19]) and the resulting negative publicity in Holland led to the discontinuation of production by the Netherlands Red Cross and the resulting demise of the project, it was the spark that ignited more interest and contributed mightily to the effort of the Thai Red Cross and PATH to search for a hepatitis B vaccine that was affordable for EPI use[20].

Chunsuttiwat, recently returned to Bangkok from a US-CDC fellowship, prepared an extensive analysis of vaccinating infants at birth that showed the favorable cost-effectiveness of such programs. Soewardjono was very receptive to the interests of the Task Force and made arrangements for the Task Forced to undertake a model immunization program on Lombok, located to the east of Bali.

Based in part on the work of Chunsuttiwat and the sponsorship of Suwardjono, the Task Force undertook a wide range of activities including several pilot projects in Kenya, Indonesia, the Cameroons, and Thailand that demonstrated hepatitis B vaccine could be delivered successfully within EPI at an affordable cost. The execution of these model programs was greatly facilitated by the presence of PATH Field Offices in Indonesia and Thailand under the direction of Leona D'Agnes and Don Douglas, respectively. PATH Indonesia secured the capable guidance of Anton Widjaya in dealing with the Indonesian Ministry of Health in Jakarta and Lombok, and stationed a young medical epidemiologist, B. Otto, on Lombok where he provided invaluable liaison between the outstanding Indonesian investigators and PATH.

Subsequently, Indonesia and Thailand began the process of integrating hepatitis B vaccine into their national EPIs. A key factor in launching these programs was the publicly stated commitment of KGCC, Cheil and later SmithKline to provide vaccine at or below $1.00 per dose.

Global impact

These successes culminated in the late 1998 with a grant by the Bill & Melinda Gates Foundation of $100 million to launch the Children's Vaccine Program (CVP) at PATH. The CVP set hepatitis B vaccine introduction as one of its highest priorities. Thereafter, the Foundation made a grant of $750 million to a

newly-established Children's Vaccine Fund, one of whose first priorities would be to buy and distribute hepatitis B vaccine. This grant was made out of the Gates Global Health Program managed by Perkin, who had left the presidency of PATH to take on this challenging post, and on the recommendation of Mark Kane[21], who had come to PATH to run the CVP from the U.S. CDC where he had been a protégé of Maynard. These funds were used by the Global Alliance for Vaccines and Immunization (today, GAVI Alliance). GAVI, with its close affiliation with WHO and UNICEF, which, it will be recalled, had strenuously opposed the addition of hepatitis B vaccine to national immunization programs, became the lead mechanism for promoting hepatitis B vaccine globally. Unfortunately, much work remains to be done. On global scale only 27% of children born in 2006 received a birth dose of hepatitis B vaccine[22].

The private sector

Private companies played a very significant and essential role in the development and introduction of hepatitis B vaccines in developing countries. This is best illustrated by the work of three companies: SmithKline, LG Chem in Korea, and Shantha Biotehnics in India.

SmithKline was a particularly influential force. With the launching of Task Force activities, visits were made to numerous developing countries to assess their interest in hepatitis B vaccine. Without exception, Task Force members found that staff of SmithKline had already been working in the country for quite some time and had been undertaking discussions with the staff of the ministry of health, private physicians, and others to plan for the introduction of hepatitis B vaccine. Of course, SmithKline's goal was to develop profitable markets among individuals who could afford to pay a private sector price. Nevertheless, SmithKline engaged in discussions with ministry of health officials to explore ways in which the vaccine could be made more widely available. In the early days of Task Force activities, there was an understandable level of suspicion and mistrust between the two organizations. Normally, in these years, the public and private sectors worked quite independently of each other on the introduction of vaccines in developing countries. For example, a SmithKline marketing strategy was to subtly raise questions about the possible safety concerns of plasma derived vaccines and indicated that its recombinant DNA hepatitis B vaccine did not have the same concerns. Task Force staff and staff of SmithKline met in the headquarters city of SmithKline, Rixensart, Belgium to discuss this matter. In the course of a very long conversation that went into the early morning hours, the Task Force argued that even an indirect attack on the safety of plasma derived vaccines was not in the interest of anyone who was interested in introducing these vaccines into developing countries because the first job was to get people interested in the vaccines whether made from plasma or yeast cells and then have the countries choose which vaccines to procure. SmithKline staff argued that it was only fair of them to point out the differences between their vaccine and the plasma derived product, but Task Force staff argued that there were no validated scientific studies confirming safety concerns about plasma derived vaccines. At the end of the conversation, SmithKline staff agreed to modify the marketing strategy of the company. Task Force staff left the meeting somewhat skeptical of this agreement, but in fact the marketing strategy was modified and SmithKline never again raised in its marketing materials any questions about the safety of plasma derived vaccines. This interaction contributed to a greater sense of trust between the two groups and eventually SmithKline became the supplier of vaccine at no cost for a Task Force model program in Kenya. Perhaps SmithKline's greatest contribution to the introduction of hepatitis B vaccines was its foresight in building its production facilities. Its first facility was capable of producing 120 million doses per year and this capability was determined in part by SmithKline's recognition that it should be in a position to supply the markets in both developed and developing countries. Also SmithKline took leadership in establishing tiered markets for hepatitis B vaccine in which it charged one price in developed countries and another substantially lower price in developing countries.

The significant contribution of two of the Korean manufacturers, Cheil and KGCC is described elsewhere in this paper, but there was a third Korean producer, LG Chem which made an important contribution. LG Chem went directly to the development of the recombinant DNA hepatitis B vaccine

and was very aggressive in marketing this vaccine throughout Asia and the Middle East. This company also was a leader in reducing the prices for recombinant DNA hepatitis B vaccine which helped to drive down prices from all manufacturers. There was almost no interaction between LG Chem and the Task Force probably because LG Chem had access to the global marketing capabilities of its parent company while both Cheil and KGCC were primarily domestic vaccine companies[23].

Shantha was established by Varaprasad Reddy with the support of his mother who gave him the necessary initial capital on the promise that he would contribute 10% of his production to the poor. Reddy had been running a company producing batteries for the Indian Air Force but he happened to attend a meeting in Geneva in the early 1990s of the Children's Vaccine Initiative in which a representative of a European vaccine manufacturer gave a talk in which it was claimed that only European or US companies could produce modern high-technology vaccines. These comments greatly invigorated Reddy and committed him to showing that, at least in India, people were capable of making the most modern vaccines. His initial project was to develop recombinant DNA hepatitis B vaccine. He succeeded and his company has become a global supplier of this vaccine. The work of Shantha followed the work of the Task Force but was critical in the effort to make hepatitis B vaccine available to the poor.

The power of individuals

The Task Force was only one element in the global effort to introduce hepatitis B vaccine, but it did play an important role. PATH provided a secretariat for the Task Force and managed the grant funds that were made available to it. Maynard and this author shared overall responsibility for the management of the secretariat. The members of the Task Force were internationally recognized experts in the field with long careers of substantial achievement. There was agreement between PATH and the Task Force that the Task Force deserved a high level of autonomy in its operations. The Task Force approved the appointment of the PATH secretariat director and reviewed his performance. It also reviewed and approved annual budgets and formed various subcommittees to address both administrative and technical matters. The Task Force met two or three times per year.

Perkin, as president of PATH, demonstrated exceptional leadership. PATH had both fiduciary responsibility and reputational exposure for the work of the Task Force, but Perkin allowed the Task Force great leeway in developing, implementing, funding, and overseeing its activities. By maintaining collegial and respectful communication between himself and the members of the Task Force, it was possible to have a relationship in which the institutional needs of PATH were met while allowing the Task Force to undertake a wide range of risky, experimental, and politically aggressive initiatives. These included the launching of model immunization programs, the convening of national and international symposia to promote the introduction of hepatitis B vaccine, and the publishing of papers challenging widely held views. One of these papers analyzed in detail the cost of production of plasma derived hepatitis B vaccine and showed that in large quantities in a single facility, the marginal cost of production of hepatitis B vaccine would be less than $0.20 per dose[24]. Up to the publication of this paper, some representatives of private vaccine manufacturers had been arguing that hepatitis B vaccine could never cost less than several dollars per dose.

But the Task Force could be seen more as an activist group pushing and prodding. It is the view of this author that the most important ingredient in the success of the introduction and use of hepatitis B vaccines in developing countries has been the leadership of individuals in those countries. Without the foresight and perseverance of individuals such as Suwardjono and Chunsuttiwat, progress would have been much slower and many individuals would now be facing certain death from liver cancer who are now free of this worry. Without the drive of Korean and Indian vaccine company managers, the success also would have been more slowly realized.

Other factors in this success were the combination of flexible and wise leadership, flexible funding from foundation donors, the commitment of a small group of highly qualified and motivated individuals with the freedom to operate in a highly entrepreneurial manner, and a collegial and respectful atmosphere of communication among all parties.

As described, for-profit vaccine companies were invaluable in this effort. Without their willingness to

recognize the need in developing countries and provide vaccine at an affordable price, little could have been achieved.

With the expanded procurement of hepatitis B vaccine under GAVI, and the later entry of Indian manufacturers, the price of hepatitis B vaccine fell even further and today is obtained by GAVI at less than $0.30 per dose. All of this reduced chronic carrier rates of hepatitis B virus in many Asian countries to about 1%.

This author's career in vaccines began with the work in hepatitis. With the lessons learned there, there have been a number of additional opportunities to work on vaccine introduction including those against Haempohilus influenzae b, cholera, Japanese encephalitis, rabies and, most recently, dengue. The work in dengue has been under the egis of the Pediatric Dengue Vaccine Initiative (PDVI) at the International Vaccine Institute, Seoul, Korea. The PDVI is the brain child of Scott Halstead, one of the field's foremost leaders and has been funded by the Rockefeller Foundation and the Bill & Melinda Gates Foundation. We present below a brief discussion of how the lessons of hepatitis B are being applied to dengue.

Applicability to other vaccines

The PDVI is undertaking a wide range of activities to accelerate the development, evaluation and introduction of dengue vaccines in endemic countries. A major component of its activities has to do with ensuring "access" to dengue vaccines by the poor in developing countries. The framework for this access work derives largely from the experience of the International Task Force on Hepatitis B Immunization[25, 26] and includes substantial emphasis on collaboration with private sector vaccine companies involved in the development and manufacture of dengue vaccines. In addition, the PDVI has been managed, with great technical skill and programmatic vision, by one of the leaders of the hepatitis B effort, Dr. Harold Margolis, who served as the head of the hepatitis branch at U.S. CDC following Maynard.

Unfortunately, dengue (like hepatitis in the 1980s) has not been accorded a high priority in the global health community. There are two key reasons for this low priority. First, dengue has a low level of mortality with only about 24,000 deaths per year. Many global health programs use mortality as a key indicator of priority. But dengue is associated with a very high level morbidity with at least 70 million cases of dengue fever occurring annually. It is estimated that over half of the world population lives in areas affected by dengue[27]. Second, dengue was first recognized as a public health problem at a time when its impact was quite limited geographically. Since the 1970s dengue has spread throughout the tropical world and epidemiological studies find it difficult to keep up with this rapid spread.

Despite the low priority often accorded by the global health community to dengue, senior health officials in endemic countries accord a very high priority to the disease. Therefore, the PDVI is undertaking a dual program of seeking to enhance the priority accorded to dengue by the global health community, but also building on the already existing high-priority in endemic developing countries. Unlike the attitudes of WHO and UNICEF in the 1980s with respect to hepatitis B vaccine, there is no active opposition to the introduction of dengue vaccines and, indeed, WHO has been a valued and an essential partner for the work carried out by PDVI. The collaboration between WHO and PDVI includes the development of guidelines for conduct of clinical trials, development and evaluation of diagnostic tests, the assessment of challenges for regulatory review of dengue vaccines, and the preparation of regulatory guidelines for the production of dengue vaccines. In 2008, GAVI Alliance (of which UNICEF is a key partner) conducted an assessment of new and underused vaccines to determine which should be included in the GAVI Alliance programs. Dengue was given thorough consideration and it was determined by the GAVI Alliance that dengue could be included in its programs at the time of first licensure of a vaccine. This is an important step in placing dengue at a higher level of priority within the global health community.

The global health community must deal with the competing needs, and programs to deal with HIV, malaria, and tuberculosis most often receive the highest priority. Individual developing countries do not necessarily look at the global burden of disease but look at a complex and interrelated set of factors to establish priorities for their country's national

health programs. PDVI is undertaking a program of research to assess the attitudes of health policymakers in endemic developing countries. Preliminary results of studies conducted in India and Sri Lanka indicate that upon the availability of safe and effective and affordable dengue vaccine, these countries will take steps to encourage the wide scale use of the vaccine. Policymakers in Sri Lanka state that they would mobilize the resources needed to procure and deliver the vaccine, at least for the early stages[28].

To help develop an enabling environment to assist and encourage the priority accorded to dengue by endemic countries, PDVI has established two Dengue Prevention Boards, one in Asia Pacific and one in the Americas. These boards consist of independent experts from many countries in their regions who meet on a regular basis to consider important issues with respect to dengue vaccines. The boards are issuing reports on diagnostics, surveillance, and other issues. During 2009, the boards met to consider the issues related to the introduction and implementation of dengue vaccines.

Production in developing countries of hepatitis B vaccines played an important role in encouraging more use of the vaccine because of the availability of lower-cost products. Efforts are underway in Brazil, India and Vietnam to establish production of dengue vaccines. The PDVI supports these initiatives and, for example, is working closely with the Instituto Butantan in São Paulo, Brazil to assist it in its efforts to establish production of a dengue vaccine that it has obtained through a license from the US NIH.

Both GlaxoSmithKline and sanofi pasteur have programs to develop dengue vaccines. Both companies can draw on their extensive experience with hepatitis B vaccines for their work on dengue vaccine. The PDVI has established collaborative agreements with both companies and accords high priority to facilitating their efforts to develop safe and effective vaccines. For example, the PDVI is working very closely with sanofi pasteur to undertake an expanded Phase 2 study (Phase 2b) of dengue vaccines in Ratchaburi, Thailand. This study was launched in early 2009 and results should be available in about two years. The study is carried out in a field site which is under the direction of the Faculty of Tropical Medicine, Mahidol University and Prof. Arunee Subchareon serves as the principal investigator. Many institutions in Thailand including the Ministry of Public Health have worked hard to provide the necessary resources to ensure the effective conduct of this trial. Thailand is prepared to be one of the first adopters of the dengue vaccine should trials prove successful. Again, Thailand is proving to be a leader in the development, evaluation, and introduction of new and important vaccines.

Comparison with the experience with hepatitis B vaccines leads to several observations:

- Because of the priority system used in the global health community (primarily mortality), dengue is not accorded high priority by that community.
- It seems likely that the strongest force for the introduction and use of dengue vaccines will emerge from endemic countries themselves. The lessons from hepatitis B will be important to facilitate this work.
- Companies involved in dengue are very aware of the hepatitis B experience and will use that knowledge to help ensure wide availability in developing countries through mechanisms such as tiered pricing.
- Developing country manufacturers are likely to play a key role in ensuring availability.
- The positive attitude and strong intellectual/policy contributions of WHO will help accelerate introduction of dengue vaccines substantially.
- Highly motivated independent groups of professionals are having substantial impact on raising awareness and building commitment to dengue vaccines.

A focused team of professionals at an international health institution can drive a comprehensive and flexible program given sufficient resources.

Final comment

This paper mentions many individuals and certainly omits many more who have made significant contributions. The success in accelerating the introduction of hepatitis B vaccine is the result of the efforts of thousands of individuals around the world. Therefore, this paper should be taken only as the perspective of one individual who had the honor to join in this work.

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