

Policy Analysis: An Essential Research Tool for the Introduction of Vaccines in Developing Countries

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ABSTRACT

To address the unacceptable levels of disease in developing countries and the lack of vaccines to address infectious diseases, the public sector has been expanding its funding for, and involvement in, vaccine research and development. The public sector is becoming a full participant in the spectrum of translational research taking candidates from the laboratory to use in national immunization programmes. As these programmes and the continuing work of the private sector achieve success, an extensive analysis of policy will be needed to support the introduction of vaccines. Based on the early experience with the introduction of hepatitis B vaccine in several developing countries, there is a defined framework for the introduction of vaccines. This framework lays out five essential overlapping and complementary elements of introduction of vaccines in developing countries. Each element requires a clear understanding of policy-related issues. There is a pressing need to include and expand policy analysis on a wide range of topics to ensure that the poor in developing countries can have access to the fruits of modern biotechnology.

Key words: Vaccine; Vaccine development; Immunization programmes; Research; Policy

INTRODUCTION

Despite enormous advances in the prevention and treatment of disease in developed countries and among the rich in developing countries, the poor in developing countries continue to face the ravages of respiratory and diarrhoeal diseases, malaria, HIV, and many other causes of death and illness (1). The private for-profit sector does not allocate significant resources to develop products for these neglected individuals because the potential for profits is dim. The public sector must, thus, take the lead in developing these products. Not since the 19th century, when development of most health products, such as Pasteur's work, took place in the public sector, has the public sector taken an effective leading role in health-technology research and develop-

ment. For most of the 20th century, the public sector focused on supporting basic scientific research and relied on private industry to develop new preventive and therapeutic modalities.

With the advent of the 21st century, some leaders in the public-health sector began to realize that products for the poor would not be developed or provided, if decisions were based on market forces. These individuals recognized that the public sector must be involved in virtually all aspects of product development from basic studies to post-licensure surveillance. We call this comprehensive effort 'translational research'. [The term 'translational research' has been prominently used in cancer research and refers to a more limited activity of taking various treatments from clinical research to clinical application. In this document, we use translational research in the broader sense of translating laboratory findings into products used by people in health programmes, especially in developing countries] (2-4).

This paper deals with an essential component of translational research, i.e. policy analysis. The paper

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also focuses on the role of policy analysis to support the introduction of new and improved vaccines to poor populations—policy analysis for introduction. Policy analysis for introduction is similar to private-sector market research. This component of policy analysis consists of a systematic scientific effort to identify and understand the critical policy issues that will affect the introduction of new and improved health technologies and to identify the means to overcome barriers to successful introduction.

In recognition of the need of the public sector to take a leadership role in translational research, several new donors have begun to support research and development programmes for diseases of importance in poor countries. Of prime importance, the Bill and Melinda Gates Foundation has contributed more than US\$ 700 million to research programmes on health technologies. These product-specific programmes are often referred to as public-private partnerships because much of their work is carried out through collaborative arrangements with for-profit companies. Also funded by the Rockefeller Foundation, the Wellcome Trust, and other donors, such as World Bank and bilateral aid agencies, these partnerships are run by international non-profit groups located in Asia, Europe, and the United States (5). Although the nature of the individual programmes differs, most serve as secretariats that orchestrate a translational research strategy under which they distribute R&D sub-contracts to other groups. Sometimes referred to as virtual R&D programmes (6), they typically do not undertake research on their own. A few have in-house programmes that are complemented by contracts with outside groups for work that cannot be done internally. Examples are the work of the International Vaccine Institute (IVI) on diarrhoeal diseases, the research of the Program for Appropriate Technology in Health (PATH) in diagnostics, and the efforts of the Population Council in contraceptive research and development. These latter partnerships function similarly to biotechnology companies. For any of these partnerships to be successful, they will have to undertake extensive policy analysis for introduction.

Vaccines are among the most cost-effective methods to reduce disease burdens in developing countries (7). Several public-private partnerships are directed to vaccine research and development for diseases of importance in poor countries. As they begin to address the wide range of activities in translational research, they

are finding that policy analysis, in particular, is a neglected area that now requires attention. Indeed, a thorough study of the literature reveals almost no published work in this area with respect to vaccines for developing countries [A summary of recent work conducted on policy analysis is highlighted in the article by De Roeck in this issue of the Journal (8). The work of De Roeck has impact on both development of new vaccines and their introduction]. To illustrate the utility of policy analysis for introduction, we present a case study that has been reported in the literature (9) [This summary is based on both the cited reference and recollections of the author, who was intimately involved in the work].

CASE STUDY: INTRODUCTION OF HEPATITIS B VACCINE IN INDONESIA

This work addressed the policy-analysis needs with respect to a vaccine that had already been developed and was widely used in developed countries. The work was pioneering in that it was the first major effort to introduce a new vaccine in developing countries since the launching of the WHO's Expanded Programme on Immunization (EPI) in 1974. The work in Indonesia involved assessing policy issues from the highest levels of the Government to individual mothers in small villages. The policy analysis was conducted to support a model immunization programme carried out on the island of Lombok and was a collaboration between the International Task Force on Hepatitis B Immunization hosted by PATH (Program for Appropriate Technology in Health, Seattle, Washington) and numerous colleagues in Indonesia, particularly staff of the Ministry of Health in Jakarta and Lombok. Here, we describe several key insights of policy analysis:

- **Support by high-level political figures.** In 1984, PATH received a significant grant from the U.S. Agency for International Development (USAID) to promote the involvement of private companies in health in developing countries, including Indonesia. PATH retained a consultant who had been a long-time advisor to the Indonesian Minister of Health to meet the Minister to identify high-priority activities. The Minister of Health requested PATH to undertake work in hepatitis B because a golfing friend of the President had recently died from liver cancer and the President asked the Minister to do something about this infection (Saunders L. Personal communication, 1984).

Based on this request, PATH sought a technology that could be introduced and thus identified the newly-developed hepatitis B vaccine. This request by the Minister suggested that a programme concerned with hepatitis B would have high-level support.

PATH proposed to the Minister that he personally review the available hepatitis B vaccines by visiting the existing producers in Korea, the United States, Belgium, and France. During the trip, the Minister stopped at the New York Blood Center (NYBC) when this author met with Dr. Alfred Prince of the Center and Dr. Seung-il Shin of Eugene Tech, Inc. [A private biotechnology firm supported by Cheil Sugar & Co., a subsidiary of Samsung Corp., Seoul, Korea]. Eugene Tech, Cheil, and NYBC had an agreement to transfer Prince's plasma-derived hepatitis B vaccine-production methodology to a new facility south of Seoul. Shin did not become a member of the Task Force. While a member of the Task Force, Prince foreswore his portion of royalties from Cheil to NYBC. This meeting (and a later meeting with Dr. James Maynard of the Centers for Disease Control and Prevention) was the founding of the International Task Force on Hepatitis B Immunization (Task Force) (10). The Minister's tour was a strong contributing factor to the eventual cementing of relations between Indonesia and the Korea Green Cross Corporation for use and manufacture (see below) of vaccine.

- **Establishing consensus in the Ministry of Health.** The Task Force asked the Minister to select the province in which to conduct a model immunization programme of a hepatitis B vaccine. The Minister designated the rural province of Lombok just east of Bali. This step helped reinforce strong political support from ministry of health officials at all levels—national, provincial, and local.
- **Assuring long-term supply of vaccine.** The Indonesian government policy accorded high priority to producing most important vaccines in-country at Bio Farma in Bandung. The Task Force launched a collaboration with Bio Farma to support its efforts to establish production of hepatitis B vaccine. A study on the feasibility of producing vaccine from human plasma was carried out [Hepatitis B vaccine made with recombinant technology had

entered the market by this time, but the Task Force believed that the cost of production of this advanced-technology vaccine would be much greater than for plasma-derived vaccine. This belief seems questionable today in light of the current (2004) cost, US\$ 0.30 per dose, of recombinant DNA hepatitis B vaccine procured by UNICEF, although scale of production has a profound effect on marginal vaccine-production costs. At the time, the Task Force was procuring plasma-derived vaccine for US\$ 0.95 per dose, the lowest in the world] (11). This study, which was essential both for technical and cultural reasons, concluded that Bio Farma could produce hepatitis B vaccine at a cost of approximately US\$ 1.00 per dose. The study also addressed the possible impact of the general Moslem prohibition against using body parts—in this case, blood—for medical purposes. The study helped clarify that the Indonesian Red Crescent Society [IRCS conducted its own study on this topic in addition to the work of the Task Force] could establish and implement policies for the collection of plasma that could be used for vaccine production.

- **Consensus building among medical and scientific personnel.** At the provincial level, the Task Force addressed a number of policy issues. For example, key medical and scientific personnel wanted serum samples of individuals who had been vaccinated to be tested for antibodies in a laboratory in Lombok. The programme, therefore, provided equipment, supplies, and training for Indonesian scientists and technicians to carry out this work.
- **Formulation of vaccine-delivery policy.** At the community level, it was important to understand what led to a decision to be immunized or to have a baby immunized. Policy research revealed the great importance of the Village Headman in establishing community norms about appropriate behaviour. Thus, the programme exerted great efforts to include the headmen in the work and to obtain their support in every village. At the individual level, the programme realized a special concern would be that hepatitis B vaccine does not have a directly-identifiable benefit, i.e. it prevents liver cancer that may occur 30 years later. Further, children might be infected with hepatitis A virus which could cause jaundice and other symptoms of liver infection, so it was not easy to

argue that hepatitis B vaccine would prevent these symptoms. This raised the question of the appropriate policy for explaining the value of the vaccine to individual mothers and fathers. Focus-group discussions were conducted with parents. The Task Force found that an effective message was "hepatitis B vaccine is like other vaccines that your baby receives and will help ensure the baby lives a long, healthy life." Also at the individual level, it was necessary to have means to know when a child was born so the first dose of vaccine could be delivered soon after birth—a requirement for effective hepatitis B immunization. A policy was established by which midwives notified the immunization programme of a birth. This birth notification system worked very well and was essential to the success of the programme.

The Task Force undertook wide-ranging policy analysis on issues that would affect the formulation of effective policies for the involvement of health workers, immunization personnel, record-keepers, and others.

While these efforts may, in retrospect, seem obvious and essential, the difference about the Lombok Hepatitis B Model Immunization Programme was that there was a systematic and well-funded effort to address the full range of policy issues from the beginning. The issues were anticipated and dealt with systematically in advance rather than addressed reactively as they arose.

GENERAL FRAMEWORK OF POLICY ANALYSIS

Overview

Based on the experience of the Task Force, Mahoney and Maynard constructed a general framework for the introduction of new vaccines in developing countries (12). The framework lays out the following five essential overlapping and complementary elements of successful introduction of new vaccines in developing countries. Each element concerns one or more aspect(s) of policy analysis to support the formulation of effective policy. Most of these elements can be seen in the preceding summary of the work in Indonesia.

- a. Measurement of disease burden and computation of vaccination cost-effectiveness
- b. Conduct of large-scale vaccine-introduction trials (model programmes)

- c. Establishment of international and national consensus on need for vaccine along with recommended practices for use
- d. Assurance of adequate and competitive supply
- e. Creation and sustenance of funding mechanisms for procurement of vaccine

Measurement of disease burden and computation of cost-effectiveness are essential for national and international policy-makers to determine the priority to be accorded to various vaccines. In the context of scarce resources, these policy-makers need to decide the relative priority of various vaccines, such as hepatitis B, *Haemophilus influenzae* type b, Japanese encephalitis, and others. Large-scale vaccine-introduction trials are essential to determine appropriate policies for the delivery of vaccine at the community, provincial and national levels (11). Establishment of international consensus and recommended practices are needed to ensure that critical agencies, such as WHO, UNICEF, the World Bank, and others can assist developing countries in the introduction of vaccine in a consistent and effective way. Assurance of adequate and competitive supply depends on the establishment of effective cooperative policies between users and producers. Producers need to know projected levels of use at various price levels. By encouraging and fostering competition, public-sector policy-makers can help insure lower yet sustainable prices. Finally, global purchase systems, such as those of the Global Fund for Children's Vaccines and the Global Fund to Fight AIDS, Tuberculosis and Malaria, are essential to meet the needs of poor countries which face extraordinary challenges in mobilizing the required resources to purchase vaccines. These global funds operate on the basis of a complex set of policies involving many important issues, including such controversial matters as respect for intellectual property rights.

Recent reports concerning meningitis vaccine illustrate the importance of these policy issues and the implementation of the five-element framework (13-14, and Jodar L. Personal communication, 2003).

Meningitis Vaccine Programme

The Meningitis Vaccine Programme made efforts to involve private-sector firms in the development, production, and introduction of a meningitis A vaccine for African countries. The Meningitis Vaccine Programme is a 10-year US\$ 70 million effort to develop and intro-

duce a vaccine in nine African countries representing a high prevalence of the disease and known as the meningitis belt. The programme, jointly administered by WHO and PATH, addressed the following five elements of introduction:

Measurement of disease burden and computation of vaccination cost-effectiveness: The programme began with an assessment of epidemiology of the disease in the target countries and determined a need for at least 25 million doses per year. After a detailed study of the probable cost of producing this amount of a meningitis vaccine, the programme determined that the cost would be about US\$ 0.40 per dose and with a profit margin of US\$ 0.50 per dose, the vaccine would be priced at less than US\$1 per dose. It had concluded that a price of less than US\$ 1.00 per dose would make a meningitis immunization programme cost-effective. The programme has a continuing effort to strengthen meningitis surveillance in the target countries and supports the production of weekly reports. An epidemiologist has joined the team to document the expected benefits from widespread vaccination.

Conduction of large-scale vaccine-introduction trials: The programme anticipated the need for both clinical evaluations and introduction trials. It contracted a group of experts in clinical research, who submitted plans for clinical studies.

Establishment of international consensus on need for vaccine, along with recommended practices for use: The programme is jointly administered by WHO and PATH, thereby ensuring ready access to the mechanisms of developing international consensus and recommended practices. The programme convened an expert advisory committee at WHO, including representatives of ministries of health in African and eastern Mediterranean countries. The committee reviewed and approved the programme's strategy. It has an ongoing programme of collaboration with key groups in the target countries.

Assurance of adequate and competitive supply: This was the main activity of the programme. The programme found that large vaccine producers in developed countries were not interested in producing a marginally-profitable vaccine. Their reluctance was based primarily on considerations of opportunity cost. The companies felt that they could make a higher return on investment with other vaccines. The programme then implemented a novel approach that involved forming a con-

sortium of developed- and developing-country firms with the Serum Institute of India agreeing to produce the final vaccine. Under this arrangement, the final product would cost less than US\$ 0.50 per dose.

Creation and sustenance of funding mechanisms: The programme has a major commitment to communications, advocacy, and resource mobilization. Because of the long-term nature of the vaccine-development programme, it is too early to begin mobilizing funds for procurement; however, because of the work already accomplished, it is straightforward to compute the resources that will be required.

In summary, the Meningitis Vaccine Programme represents an excellent example of how a public-private partnership in vaccine research and development, and including the eventual goal of introduction, is applying policy analysis to facilitate its work.

Because policy analysis related to public-sector vaccine research and development is yet a new field, there is much to learn.

PRIORITY ISSUES FOR FURTHER STUDY

Embedded in the five elements of vaccine introduction are a large number of policy issues that need to be addressed for the successful introduction of new vaccines. We have illustrated some of these by reviewing the experiences with hepatitis B and meningitis vaccines.

We have recently examined key issues with respect to one of the five elements: assurance of adequate and competitive supply. These issues have to do with the global movement towards a uniform system for the management of intellectual property rights as embodied in the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS). Under TRIPS, by the end of 2004, most developing countries must have in place intellectual property management systems comparable to those in developed countries [Least-developed countries will have until 2016 to implement the provisions of TRIPS fully]. These systems will have several implications for ensuring an adequate and competitive supply of vaccines for developing countries. Developing countries will have to issue product patents for vaccines rather than the previous common practice of issuing only process patents or of not issuing patents for vaccines at all. The countries will also have to treat foreigners who obtain patents equally with national inventors.

A key event in the introduction of hepatitis B vaccines was the establishment of production of these vaccines by the Korean manufacturers. These manufacturers were able to produce plasma-derived and eventually recombinant DNA hepatitis B vaccines in part because the key patents were not filed in Korea and in a group of other developing countries that together comprised an interesting market for the Korean companies (unpublished data of author). It is not at all clear what will happen after 2004 with respect to the ability of second comers to establish production and distribution of new vaccines and thereby provide an important competitive pressure to the international market. In addition to Korean companies, producers in Brazil, China, India, and Indonesia are able to produce vaccines to meet international regulatory standards and are actively exporting their vaccines. If a company in a developed country were to bring to market a vaccine against HIV, for example, and held dominating patents that it had filed not only in Europe and the United States but also a large number of developing countries, would it hold a virtual global monopoly? What opportunities would there be, through competitive pressures, to obtain this vaccine at low cost for the poor in developing countries? Would developing-country producers be able to obtain patent licenses from the primary producer so they could produce in their country? Would other producers be able to 'invent around' the dominating patents by coming up with modified antigens or different expression systems? These and numerous other questions call for detailed policy analysis in intellectual property, procurement, production strategies, etc.

In recognition of the growing importance of policy analysis, WHO has established an Accelerated Vaccine Introduction Priority Project. WHO describes the Project as follows (15):

The objective of the project is to implement a mechanism for accelerating introduction of new and underused vaccines of public-health importance in the developing world.... Barriers to new vaccine introduction in developing countries include lack of efficacy, burden and cost-effectiveness information for developing-country settings, the need for technical assistance with introduction, logistics, supply and quality-control issues, and lack of funding for vaccines. The AVI project was developed in early 1999 to focus on critical points in the vaccine evaluation and introduction contin-

uum at which WHO activity can make a substantial difference. The project involves activities in each of [the WHO Vaccine and Biological's Programme] teams and addresses the following areas—efficacy, burden and cost-effectiveness, vaccine quality, vaccine supply and financing, and introduction into immunization programmes.

CONCLUSION

As the public sector becomes more engaged in the full spectrum of translational research to bring vaccine candidates from the laboratory to use in national immunization programmes, there is a concomitant necessity to engage in a wide range of policy analyses. To date, the scholarly literature in vaccine policy analysis for introduction of vaccines is limited. Further policy research will surely help in the quest to enhance health in developing countries.

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