What Are Today’s Orphaned Vaccines?

Henry Wilde
Queen Saovabha Memorial Institute and Department of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand

Development costs for new biological agents are increasing, and the time span from laboratory research to introduction of a product on the world market is becoming ever longer. Complex regulatory requirements add barriers and additional costs to early introduction abroad. This results in reluctance by manufacturers to undertake development of a vaccine that will be used for a tropical disease in only the public sector of a poor country. The chances of recovery of huge investment costs before patents expire are not good, unless such a new vaccine can also be sold at high cost in North America and Europe. These are some of the reasons that we still do not have a modern Japanese encephalitis vaccine or products against malaria and dengue fever. Many tropical countries must find a way to develop their own vaccine production facilities. Innovative help for technology transfer will have to be forthcoming, or many new life-saving products will never bridge the gap between research unit and production.

Have you ever wondered why we do not have a modern tissue-culture vaccine against Japanese encephalitis, a disease that has now spread across most of Asia? Many of us know that the Japanese encephalitis virus grows in Barbour-Stoenner-Kelly, Vero, neuroblastoma, and probably other common tissue-culture cell lines. We also know that several international manufacturers and research laboratories have carried out projects that have revealed that making a tissue-culture Japanese encephalitis vaccine is possible. Is this vaccine really needed, or are we happy with the present-day “dinosaur products” that are made from thousands of suckling mouse brains, which are not entirely free of adverse reactions?

A recent article by Gray et al. [1], followed by an editorial [2], discussed orphaned vaccines and, specifically, the adult adenovirus vaccine made for the military in the United States. This group of viruses usually does not cause life-threatening disease, as does Japanese encephalitis, but the vaccine was made for a select population that is at increased risk of morbidity. Its production was discontinued because it was not profitable to make it for such a small (albeit insured) market. The editorial discusses the lack of interest of the vaccine industry in products that are not profitable and not likely to return investments before patents expire. The editorial neglected to note that this state of affairs is likely to worsen as the development costs become ever higher [2]. Furthermore, this will affect mostly vaccines (and drugs) that are of primary importance for poor tropical countries, which are unable to pay high prices for newly developed vaccines, particularly ones that will be used mostly in the public sector.

One must also sympathize, however, with the international manufacturers that are producing new and innovative vaccines and drugs at ever-higher costs. All of them are responsible to their stockholders, and all are in business to make a profit. Today, development of a vaccine requires anywhere from $300 million to $1 billion in research and development costs. New good clinical practices standards and local regulatory rules are not always rational; they are often made by persons who do not live in the areas that would benefit most from the new vaccines. Many new rules are driven by the litigious environment of North America and Europe and not necessarily by a genuine wish to create a super-safe product. All of these factors add significantly to costs and cause further delays in the introduction of life-saving products. It now takes from 14 to 18 years to bring a new product from the research bench to the market. The money for all this has to come from somewhere, and usually it is not from governments. Further barriers that need to be overcome before a new product becomes widely available are detailed below.
Many countries demand additional local immunogenicity, efficacy, and safety studies for products that have been extensively tested in their country of origin and have been accepted and used there. Such additional tests are often poorly done, and they can add costs and result in long delays before the product becomes available.

Corruption and favoritism in the approval process by local government agencies is a common problem in developing countries. It represents an important venue for extra income for officials who have the final decision in the approval process. They are also subject to pressures from potential competitors, who have a vested interest in keeping out new (and perhaps better) products.

Thus, it is not surprising that a large international company is reluctant to manufacture a new vaccine (or drug) that is to be used mostly in poor developing countries and that is not likely to have a large market in Europe or North America. Such companies much prefer to make a product that can first be widely sold in America and Europe at a price that allows the company to recover research and development costs within a reasonable time, before the patent expires and copies are made by generic-drug firms.

Consider a modern Japanese encephalitis vaccine. In America, Europe, and Australia, it would sell only to a few tourists, missionaries, and expatriates, at a price that would bring in a return for investment costs in a reasonable time span. The main need for this vaccine, however, is in the Expanded Programs of Immunization (EPI) in Asia, where it would have to be sold at <$1 per dose to be affordable to the public sector. It would take >1 decade to recover research and development costs in this manner. Stockholders of large firms do not like this type of product, and this may well be a reason why a modern Japanese encephalitis vaccine does not yet exist on the international market. To what extent this problem will also have an impact on more complex dengue and malaria vaccines is difficult to determine, but surely economics have also had an impact there.

I recently asked a friend in the research division of a large international pharmaceutical firm what will happen with an HIV vaccine, once one is developed. The reply was chilling: “I will give it to my young son and will have to pay several hundred dollars for it.” No HIV vaccine would become available for the poor in Africa, Asia, and South America for decades after it appeared in the West, and then it would be available only if the manufacturers were willing to create a 2-tier price system and if a major “Marshall Plan” were mounted by rich countries to pay for it.

Do we despair that there will be no remedy for all of this, or is there some hope that we might be able to obtain a viable modern vaccine for Japanese encephalitis, dengue, malaria, and HIV infection? Perhaps there is some hope. We might learn from the experience with the hepatitis B vaccine from the late 1980s and early 1990s. This vaccine had been marketed for several years in rich countries, with a sales emphasis on health care workers, persons with certain high-risk lifestyles, and (later) American Indians and Eskimos. The manufacturers and the World Health Organization showed little initial interest in an international effort to include this vaccine in the EPI for developing countries, where chronic hepatitis B is endemic. The picture changed only after the non-government organization-funded International Task Force for Hepatitis B Control was organized and was able to obtain an inexpensive, safe, effective vaccine, manufactured in Asia, for a pilot project in Thailand and Indonesia [3–6]. The international manufacturers of hepatitis B vaccine then managed to reduce prices for the public sector, which created a 2-tier price system, and the vaccine became part of the EPI in many countries [3–6].

The newly founded International Vaccine Institute, at the National University Campus (Seoul, Korea), which is supported by the World Health Organization, several nongovernmental organizations, and a large American foundation, is now endeavoring to catalyze technology transfer from industry and academic researchers to developing countries that need the products and can manufacture them locally [7]. If successful, this might become a conduit for technology transfer for orphaned vaccines. One can thus conclude that there may be some hope, but only if 1 or more of the following happen:

1. A way should be found to curtail, streamline, and rationalize mounting “red tape” that regulatory officials create, which hinders and delays development of life-saving biological agents worldwide.
2. There is already a 2-tier price system in place for many drugs and vaccines, but they are usually devised only after manufacturers have recovered development costs from sales in Europe and America. The interval between introduction of a new product and its appearance in the poor world at a lower price must be shortened.
3. Technology transfer and sustainable funding for local production of important vaccines in suitable developing countries must be made available.
4. Finally, bureaucratic barriers and corrupt practices by regulatory and customs services in many countries need to be curtailed.

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References