Partners for progress
Richard Arnold

The Expanded Programme on Immunization has achieved dramatic results in reducing the toll of its target diseases. Advances in vaccine technology in recent years now offer prospects for practical approaches to extending the prevention of several of the most serious diseases which continue to kill and incapacitate many of the world's children.

On one hand, improved vaccines may be developed to overcome the difficulties of achieving full cover against some of the EPI diseases themselves. Those difficulties may be due to problems of cold-chain maintenance or to the remoteness of some populations, with consequent limited access by health workers. On the other hand, diseases now not covered by EPI could be attacked with new vaccines. But there is a long road to travel between a technical concept and the completion of a successful vaccination campaign. The technical, logistic, economic and sociological obstacles will have to be overcome. This will involve commitment and action by many parties working towards a common objective.

It is for this reason that the Children's Vaccine Initiative (CVI) has been established. The founding agencies, other donors, academic scientists and their institutions, public health authorities and the enterprises which will develop and eventually manufacture the vaccines must all play their part if the effort is to succeed. The vaccine industry has already shown itself very ready to support the Initiative.

Prototype vaccine

The general availability and use of a new or improved vaccine involves a number of steps. Establishing technical feasibility as a first step means proving that a prototype vaccine made in a laboratory can produce immunity in an animal model. Developing a new vaccine is very different from developing a new synthetic drug, where the process starts with the creation of a unique new chemical entity which is the key innovative step, even though the risks and costs are mainly encountered during the lengthy development process before marketing. Vaccines, on the other hand, may be of many types. They may be made from a live but attenuated pathogen, or from a killed pathogen, or they may be made from a fragment of the pathogen or by modifying other organisms involving the use of recombinant techniques. Adjuvants or special formulations may be needed in order for them to be effective. The technology involved may require the use, in part or extensively, of innovative techniques used for other products in achieving the prototype vaccine. Further technologies may be involved when production of the laboratory vaccine has to be scaled up to permit general use.

As in all other aspects of the pharmaceutical field, industrial vaccine research and development can only be undertaken with the safeguard which patents provide for the heavy investment required. In contrast to the conventional pharmaceutical field.
A better measles vaccine

Despite the high coverage with current vaccines, measles continues to exact a tremendous toll on the lives of small children. Even with global vaccine coverage running at around 78%, nearly 1.5 million children continue to die from the disease each year.

At present, measles immunization in industrialized countries is given at the age of 12-15 months, so that the early immunity acquired from the mother does not interfere with the action of the vaccine. Unfortunately, in developing countries where measles transmission can be very intense and the risk of infection is generally greater than in developed countries, the waning of maternal-acquired immunity can expose children to infection long before their first birthday. WHO has therefore recommended that measles vaccinations in developing countries should be administered at nine months.

A measles vaccine that could be effective between the ages of two and six months would be most valuable. It would fill the "gap" that often occurs after the loss of maternal-acquired immunity, and would enable this vaccine to be included in the existing schedules of the Expanded Programme on Immunization.

An ideal measles vaccine should be safe, and should induce lifelong protective immunity in almost 100% of recipients with a single dose administered shortly after birth. It should also be compatible with other antigens dispensed at the same time, provoke mucosal immunity, interrupt wild measles transmission, retain its potency even at 45°C for seven days, and not be much more expensive than the current vaccine.

In supporting the work already carried out by WHO, the CVI has established a Product Development Group on Improved Measles Vaccine, which is to examine the current measles situation and problems with control, including vaccine coverage and vaccine failure. It has received a broad mandate to consider all promising candidate vaccines against measles.

Additionally, the need for vaccines is likely to be a much more complex issue which may require licence agreements with other innovators.

Once the laboratory activity of a vaccine has been demonstrated, its safety, efficacy and suitability for use in humans has to be established. Ways to recognize quality standards and to make it on the scale needed, at an acceptable cost, must be found. Many questions must be answered. What is the level of immunity and for what period does it last? How many and what doses have to be given? What side-effects may be produced? How severe and how common are the side-effects? These are questions which only extensive clinical trials can reveal, and such trials will involve studies in many countries with volunteers from many different types of population, over several years.

While clinical trials are in progress, assuming that they show promise, work will be done to establish a method of producing the vaccine to consistent quality standards and as economically as possible. Whether or not the vaccine can be made in existing or expanded plants or whether a new plant will be required is a fundamental question, to which the answer will also depend on an assessment of the likely demand.

The world has come to expect not only more advanced vaccines but vaccines that are safer and of reliable quality. For many years the commonly used vaccines were available at a few
cents a dose. One of the consequences of low prices and monopoly purchasers in the public sector has been the disappearance from the market of many producers who were unable to obtain a return on their business. While the tendering system may produce the lowest prices for the common vaccines, the situation for a manufacturer who may get all the business one year and none the next is unsupportable. Contraction of the manufacturing sector, the high costs of assuring today’s quality standards, the costs and risks of research as well as the liability risks in the market have inevitably resulted in higher prices for vaccines than in the past.

### New vaccines

New vaccines in the future can never cost a few cents a dose as in the past, and this is an aspect with which CVI and its supporters must come to terms. So too must countries, since there are already signs that the ability and willingness of donors to assure supplies to developing countries are limited in both time and scope. Nevertheless, even at realistic and fair prices the economic as well as the social and humanitarian benefits of vaccination with new and improved vaccines will be seen to far outweigh the costs.

Several vaccine developers and producers are currently working with CVI on the projects already chosen. At present, collaboration involves the earlier stages of technical development, but this will evolve as the projects expand. The CVI will only be considered to have succeeded if the vaccines which emerge from the development process are extensively used in vaccination campaigns among the world’s children at risk. The vaccines must meet internationally recognized standards of safety, quality and efficacy. They must be affordable in the sense that governments and agencies buy them, and they must yield a reasonable financial return to enable the manufacturer to make them. It seems likely that – for established manufacturers and especially the international research-based manufacturers – the most rational form of collaboration will usually involve both development and production of the vaccine.

There are many variations of collaborative arrangements. At one end of the spectrum the achievement of a project may involve collaboration with a series of units or organizations, each taking on a limited task; for example, one may produce and test an experimental vaccine while others will be concerned with developing a production process or with the conduct of extensive clinical trials. At the other extreme, just one collaborator may undertake all stages of development as well as obtaining regulatory approval and finally producing the vaccine on a commercial scale. Whatever the approach adopted, however, the arrangements must be equitable to all parties if it is going to succeed. Commercial organizations must be able to meet reasonable expectations of return on investment to enable the business to continue and to satisfy the expectations of their shareholders. Where the investment may be needed to build or extend production and quality control facilities, all will depend on the extent to which supplies are taken up by purchasers. Funders – whether governments, international agencies or donors – will expect safeguards against paying for tasks not properly undertaken or being charged unreasonable prices.

It is certainly not easy to devise arrangements which meet all these demands. But the prerequisites exist. All the parties, including the vaccine industry, want the Initiative to succeed and all the parties believe that it will.

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[Images of laboratory workers and children vaccinated, with captions: Laboratory control is vital... to guarantee safe and effective vaccinations.]