GLOBAL PRIORITIES IN VACCINATION*

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During the past two days, we have had the opportunity to explore a wide spectrum of new approaches to immunization as well as a cornucopia of potential new and improved vaccines. Even so, as you all well recognize, the agenda, full as it has been, does not and could not provide an exhaustive inventory. The point, however, is that the last decade has transformed the potential for immunization and one perceives that prospects are expanding exponentially.

Questions of priorities for vaccine development have been thoroughly examined in a number of publications and by committees of the Institute of Medicine (1) and in NIH's Jordan report (2). These lists have primarily been based on a comparative weighting of the burden of disease problems and the scientific feasibility for development of various vaccines. I could offer my own suggestions as to modifications I would make to those lists but, basically, such suggestions would represent little more than personal quibbles around the fringes of a complex problem of choices.

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I have shared in the optimism and the excitement attendant upon the transformation of this field which some have come to label as "vaccinology." However, what has become apparent to a number of us over very recent years is that there is another critical dimension to be considered in determining global priorities but one which has been studiously ignored until very recently. It is now the critical limiting factor. While research has begun to flourish, subsequent points in the chain--development, scale-up and production--have not. The best vaccines against the most serious diseases are of no value unless they can be produced in sufficient quantities and can be made available at prices which are affordable. This need was clearly pointed out on the occasion of launching the Children's Vaccine Initiative in 1990. However, even then, few appreciated the true magnitude of the difficulty we would encounter in providing needed affordable vaccines and the quandaries in devising appropriate strategies. A brief recapitulation of events may offer some perspective.

When the World Health Organization's (WHO) Expanded Program in Immunization (EPI) was launched nearly 20 years ago, it called for the routine administration of five vaccines--oral polio, measles, DTP, BCG and smallpox. Only smallpox vaccine was then being produced in quantity in the developing countries. That vaccine was closely monitored for potency and purity by WHO international collaborating centers. For non-producing countries

which required vaccine, donations were sought and obtained, the principal supplier being the USSR. This global scheme for vaccine production and quality control did not arise by chance. Rather, it was the product of six years of intensive work and continuing efforts to assure it was maintained. It ceased to function as of 1980.

Internationally provided supplies of the other vaccines were produced in industrialized countries where quality control measures were reasonably good. They were supplied by UNICEF on request of the developing countries. Some countries produced some vaccine for their own use (primarily DPT) but neither WHO nor UNICEF knew where such vaccines were being produced and no efforts were made to assess their quality. The internationally provided vaccines were purchased by competitive bid. Manufacturers were able to offer highly favorable prices, offering them essentially at the incremental costs required for producing modest additional amounts of vaccine in already well-established facilities. For example, the price for purchasing 3 doses each of DTP and polio vaccine as well as one dose each of measles and BCG vaccine was initially less than 40 cents. Ten years ago, UNICEF purchased less than 150 million doses of all the vaccines combined (3); in 1992, 850 million doses were purchased and that quantity will soon surpass one billion doses. To meet this demand, some manufacturers for some vaccines had to expand or add to production facilities and vaccine prices rose to

between 60 and 70 cents. Still, this figure is far less than comparable vaccines purchased under U.S. Federal contracts--now a price of some $40. Even so, as you have read, the U.S. price is considered by manufacturers to be too low to sustain an active research and development program and to realize an adequate return on investment. Prices at this level have dire implications in so far as new vaccines might be contemplated for developing countries.

Even as the Children's Vaccine Initiative was being launched, serious stresses and problems began to occur in the existing system of supply. Vaccine prices started to escalate; demand continued to increase; and donors became increasingly reluctant to make longer-term continuing commitments for vaccine purchase.

As one of its first actions, the CVI Program in 1990 decided to develop a global scheme for long-term supply of vaccine and, preparatory to this, sought to inventory all existing producers and to determine the quality of vaccine produced by non-UNICEF-suppliers. Surprisingly, this had never been done. Much to everyone's surprise, it was discovered that tetanus toxoid is being produced in about 40 countries, DPT in 30 countries and BCG vaccine in 20 others. (4) In fact nearly two thirds of all DPT vaccine is being produced in third world countries. Few of these vaccines have independent quality assurance, and, based on our prior experience with smallpox vaccine production, it is safe to

say that few of these vaccines would meet acceptable international standards.

The accomplishment of EPI in establishing vaccine delivery systems reaching 80% of children in the developing countries is certainly to be lauded. However, the administration of sub-potent or non-potent vaccine accomplishes little in disease prevention. Such has indeed proved to be the case in the limited studies which have recently been undertaken in those areas where locally produced vaccines are being used.

Thus, the single highest priority now for the global program is not a research agenda but rather one of planning and implementing an affordable global vaccine supply and distribution network for the standard vaccines now in use. Vaccine production facilities in many developing countries will need to be upgraded or closed and quality control measures on an international scale will need to be established. Under the most optimistic scenario, this will require at least a five-year effort.

Lower on the agenda are questions of greater interest to you. What of other vaccines? Which should and can be added to the armamentarium? What can be done to improve the quality and heat stability of existing vaccines? What combinations of vaccine in what presentations might be indicated?

These questions need to be weighed in the context of what is fiscally and practically possible. At present, there are very few degrees of freedom. A basic reality is that international development funds are, if anything, contracting with no immediate prospects that donors are likely to become more generous in the near term. For developing countries, a critical limiting factor in their expenditures is the severe lack of convertible currencies. This weighs heavily in the planning process. Specifically, it is well recognized that substantial economies can be realized in large scale vaccine production but is this an option? For example, one of the large vaccine producers has stated that it could provide the whole of the world's supply of polio vaccine without substantial change in its production facilities. However, such vaccine even if provided in bulk would require purchase with convertible currencies and donors now indicate that they are neither willing to provide sums of this magnitude on a long-term basis nor are many developing countries prepared to devote limited convertible currencies for this purpose. The only apparent solution is to develop production and/or packaging facilities at least in the larger developing countries.

Difficult questions have arisen as to the nature of such facilities. Is it mandatory that they meet all or most of U.S. or British standards for Good Manufacturing Practice? Such standards, as I'm sure you know, are extremely rigid and costly--

-a cost we are able to afford and willing to pay to provide near 100% certainty of a quality product. If the choice faced by a country is either a technologically advanced production facility which they can't afford or a vaccine with fewer assurances of quality, what choice is possible and who is qualified to help examine options? When an acellular pertussis vaccine becomes available, should all countries be advised to shift to this substantially more costly option? If the industrialized countries make this change, can the developing countries politically decide not to do so.

These appear to be rather elementary bread and butter questions, but how and when these problems are resolved has a critical bearing on which of the many hopeful options for new vaccines will ever achieve effective field use.

The growing realization that vaccines constituted a unique set of products, quite different from pharmaceuticals, and the recognition that vaccines, especially for third world countries, would not realize their potential if left to an ad hoc disjointed private-public sector system, led to a request to the Institute of Medicine to undertake a comprehensive strategy review. Their report was published this summer. (5)

The Committee concluded, as did an earlier IOM group (6), that "the current process of vaccine innovation in the United States

is fragmented and that an integrated process is required to ensure that needed vaccines that lack well-paying markets are developed and manufactured." They assert that this process will depend ultimately on effective collaboration and cooperation among government, universities and, most critically, the private sector."

The IOM committee advised that an entity be empowered "to organize and manage an integrated process of CVI vaccine development and manufacture that not only builds and capitalizes on the strengths of the existing system but also has the capacity and mandate to manage the vaccine development process from beginning to end." Note that the operative word is development and not basic research. Accordingly, the committee proposed the creation of a new entity, a National Vaccine Authority (NVA) "to advance the development, production, and procurement of new and improved vaccines of limited commercial potential but of important public health need." The Committee foresaw six broad areas of vaccine product development:

1. Vaccines used primarily in developing countries.

2. Vaccines for which there are small or limited markets or that are otherwise unprofitable

3. Improvements in existing vaccines which would make them easier to distribute and administer.

4. Development of simple, low-cost vaccine manufacturing technologies.

5. Exploration of vaccine technologies that are non-proprietary and, therefore, of less interest to commercial manufacturers.

6. Adaptation and introduction of currently available vaccines to developing countries.

They foresaw an entity which would have greater flexibility than traditional government structures and which would maintain a balance between its public health mission and its entrepreneurial activities.

Proposed is an up-front capital budget of $30 - $75 million; an annual operating budget of $30 million and a budget of $25 - $45 million for grants, contracts and cooperative agreements.

This is a bold proposal which at least in broad substance, I personally believe to be needed if we are to address meaningfully the unique problems of development and application of the most

effective preventive measures we have. Such an entity would at last give us the opportunity to weigh the complex of problems we face and to develop the intricate road map necessary to expand the scope of immunization. This must be the overriding priority at this time on the global level.

Meanwhile, our national efforts have received unprecedented support what with the decision by the President to support and fund a special immunization initiative as a centerpiece of his domestic policy program. The immediate goal of this program is to modify, expand and motivate the existing infrastructure so as to assure that by 1996, we are fully vaccinating 90% of all children by the age of 2 years. It implies several themes:

1. Strengthening of a now inadequate disease surveillance system.

2. Support toward building a more rational, user-friendly system for well-child care with needed community outreach activities.

3. Creation of a computer-based immunization record system as a development step toward systems needed for health care reform.

4. Augmented support for basic and applied research pertaining to the immune system and immunization.

5. Special support for the global polio eradication campaign.

Over the coming two years, financial support for immunization will be greatly expanded. Under deficit reduction legislation which has just been passed, vaccines will be purchased through Medicaid beginning in October 1995 for all children receiving Medicaid support, all children who have no insurance coverage, all children vaccinated at federally qualified community healthy centers as well as all Native American children. Additional vaccines may be added on the recommendation of the Secretary.

Next year's appropriations are still before the Congress with the House mark approximately $100 million above this year's budget of some $340 million and the Senate committee mark, approximately $200 million greater. These added funds will be directed primarily toward strengthening of state and local infrastructure, for the development of vaccination registries, for improvements in surveillance and for expanded purchase of vaccines.

REORGANIZATION - National Immunization Program, National Vaccine Program Office, under Dr. Anthony Robbins.

National Vaccine Advisory Committee - To assume a more prominent role in policy development and planning.

Research Subcommittee - Barry Bloom

1. To examine state of play vis-a-vis vaccine development:

   - Determine how best and when to introduce new antigens;

- To assess the proposals for multi-antigen preparations and strategies needed to permit them to be incorporated in the vaccine program.

2. To provide broad policy guidance on research initiatives.

3. To explore problems and possible solutions for vaccine production/supply in the U.S.

Program operations subcommittee - primarily:

To identify barriers and to advise on solutions

Status of immunization in the U.S. today:

- 1991 - National Health Interview Survey
  - 80% measles
  - 69% DTP
  - 53% polio
- 1992 - Survey results will be out this month/Not a great record.
- Jan - more intensive surveys begin to provide us State data.

Surveillance - Strengthened and expanded - every vaccine preventable illness is a failure in the program.

- Polio surveillance a special problem - certification - one of the weakest programs in Americas.

- Begin to do concurrent evaluation of data and utilize these for program purposes.

What is the most critical problem? Priority to vaccination by health care providers:

Kaiser Permanente
Harvard Community Health Plan

- Most cost-effective medical procedure and the simplest.

- A litmus test for HmOs/group practices, etc. If one can't perform the simplest.

- British experience

What I've discussed primarily is the program operations side. Of what interest is this to you?

- We need to deliver an effective credible product; to demonstrate what can be done, largely with what is in hand; to establish a level of respect and confidence among policy makers and politicians so that they can perceive the future.

- Meanwhile, we need to and must press on with the needed research to lay the foundations for the next decade.

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