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Global Priorities in Vaccination

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Points To Recall:

- *Biomedical research now promises a cornucopia of new and improved vaccines that would be of great benefit to countries throughout the world.*
- *Whether these vaccines will be widely applied where they are most needed depends on our ability to fashion a public-private sector system to produce and distribute them in large volume and at affordable prices.*
- *The final step, vaccine administration, poses other but more soluble problems that are most readily addressed when health care providers accord immunization the high priority it warrants.*

At this conference, 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, the agenda, full as it has been, could not provide an exhaustive inventory. The point, however, is that the potential for immunization has been transformed in the last decade, 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 (IOM)[1] and in the National Institute of Health's *Jordan Report.*[2] These lists have been based primarily 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.

I have shared in the optimism and the excitement attendant upon the transformation of this field, which some have come to label *vaccinology.* However, what has become apparent lately is that there is another critical dimension to be considered in determining global priorities, one that has been studiously ignored until very recently. It is now the critical limiting factor. Although 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 affordable prices. These needs were clearly pointed out on the occasion of the launching of the Children's Vaccine Initiative (CVI) in 1990. However, even then, few appreciated the true magnitude of the difficulty we would encounter in providing needed, affordable vaccines of acceptable quality and the quandaries in devising appropriate strategies. A brief recapitulation of events may offer some perspective.

When the World Health Organization (WHO) Expanded Program in Immunization (EPI) was launched nearly 20 years ago, it called for the routine administration of five vaccines—oral polio, measles, diphtheria-tetanus-pertussis, bacille Calmette-Guérin, and smallpox. Only smallpox vaccine was then being produced in quantity in developing countries. It was closely monitored for potency and purity by WHO international collaborating centers. For nonproducing countries that required vaccine, donations were sought and obtained, the principal supplier being the Soviet Union. This global scheme for vaccine production and quality control did not arise by chance. Rather, it was the product of 6 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 the United Nations International Children's Emergency Fund (UNICEF) on request of the developing countries. Some countries produced some vaccine for their own use (primarily DTP), 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 the vaccines essentially at the incremental costs required for producing modest additional amounts in already-well-established facilities. For example, the price for purchasing three doses each of DTP and polio vaccines as well as one dose each of measles and BCG vaccines was initially less than 40 cents. Ten years ago, UNICEF purchased fewer than 150 million doses of all the vaccines combined[3]; in 1992, 850 million doses were purchased and the quantity will soon exceed 1 billion doses. To meet this demand, some manufacturers of some vaccines have had to expand their production facilities, and vaccine prices have risen to between 60 and 70 cents per dose. Still, this figure is far less than for comparable vaccines purchased under US federal contracts—now $40 for the same package of vaccines noted above. Even so, this US 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 insofar as new vaccines might be contemplated for developing countries.

Even as the CVI was being launched, serious stresses and problems began to occur in the 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 astonishment, it was

discovered that tetanus toxoid is being produced in about 40 countries, DTP in 30 countries, and BCG vaccines in 20 others.[4] In fact, nearly two thirds of all DTP 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 them would meet acceptable international standards.

The accomplishment of the EPI in establishing vaccine delivery systems reaching 80% of children in the developing countries is certainly laudable. However, the administration of subpotent or nonpotent vaccine accomplishes little in disease prevention. Such has indeed proved to be the case in the limited studies undertaken recently in areas where locally produced vaccines are being used.

Thus, the single highest priority now for the global program is not a research agenda but 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 5-year effort.

Lower on the agenda are questions of greater interest to practicing physicians: 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, and there are 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 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, even if provided in bulk, such vaccine would require purchase with convertible currencies. Donors now indicate that they are not willing to provide sums of this magnitude on a long-term basis, and many developing countries are not prepared to devote limited convertible currencies to this purpose. The only apparent solution is to develop production and/or packaging facilities in at least the larger developing countries.

Difficult questions have arisen as to the nature of such facilities. Is it mandatory that they meet all or most US or British standards for good manufacturing practice? These standards 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 that it 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, sho ld 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 constitute 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 IOM to undertake a comprehensive strategy review. This IOM report[5] was published recently.

The IOM Committee on the CVI 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."[5] The committee asserts 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."[5] The operative word is *development*, not basic research. Accordingly, the committee proposed the creation of a new entity, the 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 that would make them easier to distribute and administer;
4) Development of simple, low-cost vaccine-manufacturing technologies;
5) Exploration of vaccine technologies that are nonproprietary and, therefore, of less interest to commercial manufacturers; and
6) Adaptation and introduction of currently available vaccines to developing countries.

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

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

This is a bold proposal that, at least in broad substance, I believe to be needed if we are to address meaningfully the nique 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.

The immediate goal of a special immunization initiative for the United States is to modify, expand, and motivate the existing infrastructure to assure that by 1996 we will be fully vaccinating 90% of all children by the age of 2 years. It has 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 imm nization-record system as a developmental step toward systems needed for health care reform;
4) Augmented support for basic and applied research pertaining to the immune system and immunization; and
5) Special support for the global polio-eradication campaign.

Over the next 2 years, financial support for immunization will be greatly expanded. Under recently passed deficit-reduction legislation, 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 health centers, and all Native American children. Additional vaccines may be added on the recommendation of the Secretary of Health and Human Services.

Appropriations for this program for fiscal year 1994 are more than $200 million above the 1993 budget. These added funds will be directed primarily toward the strengthening of state and local infrastructures, the development of vaccination registries, improvements in surveillance, and the expanded purchase of vaccines.

Meanwhile, the National Vaccine Program office, under Dr Tony Robbin's direction, is being reorganized and strengthened. We anticipate that its National Vaccine Advisory Committee will play a more prominent role in policy development and planning. A Program Operations subcommittee is already hard at work examining barriers to immunization and devising new solutions. A new Research subcommittee, with Dr Barry Bloom as chair, will deal with a number of important questions: 1) How best and when should new antigens be added for universal use? 2) How do we deal with m ltiantigen preparations in their development, in field testing, and in their application? 3) What policy guidance can be given with respect to new research initiatives? and 4) How do we solve vaccine production and supply problems in the United States with respect to our own needs as well as the needs internationally?

National data with respect to immunization coverage are important for monitoring progress and determining priorities. Until 1991, such data had not been collected since 1985. The data for 1991 have recently become available, and they are not encouraging. They were collected by the National Center for Health Statistics during the course of its National Health Interview Survey. The survey shows that for 2-year-old children, only 54% had received three or more doses of polio vaccine, 69% had received three or more doses of DTP, and 83% had received one or more doses of measles vaccine. Data for 1992 are now being analyzed on an expedited schedule, and provision is being made to obtain such data on a more current, quarterly basis in future years.

We intend also to obtain data on a state-by-state basis so that we can identify those states that are progressing satisfactorily toward meeting targets and those that may need additional help. This will be achieved by special telephone surveys beginning in 1994.

The ultimate test of an immunization program is, of course, its ability to prevent disease. This implies the need for prompt and complete reporting of cases of the vaccine-preventable diseases. It is apparent that each case that occurs represents, in some way, a failure in the system. By epidemiologic analysis of the failures, it should be possible to alter both strategy and tactics to minimize failures. Surveillance programs at national, state, and local levels now leave a great deal to be desired, but these will be greatly strengthened as part of the immunization initiative.

I believe the most critical problem, however, and the one that deserves the greatest attention, is to persuade health care providers that immunization must be accorded high priority. Immunization is, after all, by far the single most cost-effective intervention in our medical armamentarium. It is also the simplest of all medical procedures. One has to ask the obvious question: If we cannot routinely provide the simplest and most cost-effective of all medical procedures, what does it say about the efficacy and quality of other aspects of our medical care system? Immunization coverage, in brief, should represent a primary litmus test for performance in primary-care settings.

We asked two of the nation's largest and best-known health-maintenance organizations to assess their own performance in vaccinating young children. To their surprise and our collective chagrin, coverage for children enrolled in their programs was only 70%. They assured us this would quickly change but, curiously, neither had ever evaluated performance based on this very simple data analysis.

I am confident that if health care providers do accord routine immunization the priority it deserves, change can occur rapidly. I base that belief in part on the recent experience in Great Britain. Vaccination is not now nor has it ever been compulsory in Great Britain. Immunization levels previously hovered around 60%, a level, it was said, that could not be improved upon because of resistance and disinterest on the part of British parents. However, some 5 years ago, physicians

were offered a cash bonus if they succeeded in fully vaccinating 75% of the children on their patient lists. Immunization levels rose rapidly, and soon virtually all physicians were collecting the bonuses. A larger bonus was then offered for those reaching 90% of enrolled children. Immunization coverage again rose rapidly to the point where national coverage figures for fully immunized children are approaching 95%. Somehow or other, those "resistant" British parents were persuaded to change their views with respect to immunization, and, I hasten to add, without vaccination being made compulsory at any time. Is it possible that we might persuade American health care providers to take a similar interest in immunization? I hope so.

Over the next 5 years, it is our intent to foster the development of an effective immunization program of which we can all be proud and, in the course of so doing, to eliminate the principal vaccine-preventable diseases—polio, measles, diphtheria, tetanus, pertussis, rubella, and hemophilus B infections in children under 5 years of age. Meanwhile, we must press on with needed research to lay the foundation for the introduction of new and better vaccines throughout the world.

References

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Discussion

Dr Kapikian: Dr Anthony, you commented that one of the end points is disease prevention. How about disease modification?

Dr Anthony: Yes, those are in the regulations: amelioration, treatment, prevention. There may well be some vaccines that fall into that category, and the Center for Biologics also controls a number of therapeutic agents: cytokines, monoclonal antibodies, gene therapy, etc.

Dr Katz: I would like to defend the Centers for Disease Control and Prevention, and Dr Cochi is here as head of their polio-eradication

activity, so maybe he will comment. I don't think it is correct to say that the CDC does not study poliovirus isolates that reach it. The CDC poliovirus laboratory, headed by Dr Olen Kew, is very much into that. That's their main charge. They do genomic analysis and molecular sequencing on isolates. In all the alleged vaccine-associated cases we have ever reviewed, any virus that has reached the CDC has been carefully studied.

Dr Cochi: I think the main clarification is to indicate that any isolates from patients with paralytic illness are characterized at the CDC laboratory as to whether they are wild or vaccine-associated. For nonparalytic isolates (for example, from patients with aseptic meningitis), there is not the capacity to characterize those isolates on demand. But the CDC also serves a function, globally, of being a reference laboratory for an enormous amount of work on characterizing poliovirus isolates.

Dr Katz: Kew has developed a technique for looking at sewage, which has always been a concern. How can you find wild virus when all the children in the country are excreting vaccine virus into the sewage? He has some new technology by which he can pick 1 out of 1 million plaques and find that it is wild virus rather than vaccine virus. Is that correct?

Dr Cochi: That is correct. I want to add that a national enterovirus surveillance system has been in place for 15 or 20 years, with voluntary participation by laboratories around the country. Despite this, resources have not been available to characterize isolates from nonparalytic cases submitted by those laboratories. However, we have recently obtained sufficient funding to be able to characterize *all* polio isolates from that system as either vaccine-type or wild. That will be a much-needed supplement to our wild-poliovirus surveillance in the United States.

Dr Ogra: But as of now, you do not type all nonparalytic isolates?

Dr Katz: Correct.

Dr Henderson: The US surveillance system now compares unfavorably with that in Latin America, where all cases of acute flaccid paralysis in persons younger than 15 years are being reported. We find that between one and two such cases per 100,000 children occur annually. These are not cases of poliomyelitis, but the fact that they are reported provides added confidence that the surveillance system is functioning well. Program staff obtain two stool specimens from each of these cases and they are examined for poliovirus. More than 2,000 stool specimens a year from all parts of Latin America are being examined.

In contrast, in the United States, we have no system for reporting acute flaccid paralysis. We are not, as noted, characterizing all polioviruses that are isolated. We have no system for testing sewage samples to determine if the wild poliovirus continues to circulate. The point, Dr Katz, is that our surveillance system is not strong, but new resources will be devoted specifically to surveillance because the system is deficient.

Dr Ogra: What about the funds that are going to come through Medicaid for vaccine delivery? Is the mechanism in place, and how soon will this be operational?

Dr Henderson: Right now, we are providing money through direct appropriation. The CDC is buying vaccines for the states. This additional provision through Medicaid commenced on October 1, 1994, and we are now working with Medicaid to try to develop simpler systems that have fewer forms and that are far more straightforward than existing systems. It will be interesting to see whether we succeed. Bureaucracy always makes things very complicated.

Dr Oldstone: What have we learned, for example, with vaccines that we normally use but that may not work well under certain conditions and lead to harm? I am thinking about the use of the measles virus and doubling its dosage. What lessons have been learned in that approach in health care delivery? How are we going to address that type of issue in the future?

Dr Henderson: This is among the questions that the Institute of Medicine committee considered. It concluded that we have a number of unique problems with vaccines and that they differ from those posed by pharmaceutical products. The measles-vaccine problem is but one of them. As one looks at the vaccines that have been in use in the global program, one sees that none have been significantly improved over the past 30 years. All are acknowledged to be less than optimally satisfactory, but little has been done to improve them. We know, for example, that the technology is available for a far more stable polio vaccine. However, none of the manufacturers are motivated because of the development costs and the expense of relicensing. An improved product will not net more profit than the product that is already on the market.

There are other problems that are even more important. For example, one company developed a very promising measles vaccine of particular value to developing countries, but then shut down further development when it was determined that this product would compete with the manufacturer's existing product. How do we address this problem? What do we do about plague vaccine? The US Army tried to buy quantities of plague vaccine for use during the Gulf War but was turned down by every major manufacturer. This posed a most serious problem. But there are, in fact, a whole series of structural problems that need to be addressed.

As the IOM committee points out, solutions are unlikely to be forthcoming through the casual private-public sector relationships we have had. The basic question is, How do we draw on the best expertise of the private sector as well as our research enterprise to best respond to the challenges before us? It will not be easy. I have no certain blueprint in mind.

Dr Krugman: We all know that many, many parents are not aware of what happened back in the 1950s, '60s, and '70s, when we had major epidemics of polio and other diseases such as rubella, and of the fear at

that time. It seems to me that we have not successfully communicated the benefits of available vaccines, which have eliminated much anxiety and fear. I don't think we have done what the politicians in this country have done, and that is to use the appropriate news media to disseminate the information.

It can be done, and in a very articulate and dramatic way, and I think it should be done. Talk shows could be used for a purpose like this. Get persons who are articulate and who know about the past as well as the present, who know about the benefits, and who can convey the risk in a proper fashion, to get the information out to parents throughout this country. One program might reach 10 million to 15 million people, and this means should be available to the medical profession for educating parents.

Dr Henderson: Communication will be an important part of the national immunization initiative, and we intend to have an intensive publicity campaign. There is a great deal of interest and support. Organizations from McDonald's to Walt Disney to Rotary to Kiwanis to any number of volunteer organizations are prepared to participate. At the moment, we are designing a comprehensive national effort so that we can make the points you indicate.

But it is not only parents who have forgotten about the seriousness of the vaccine-preventable diseases. Health care providers also seem to have forgotten about polio and measles and rubella. For many, the attitude seems to be, "The child is going to get vaccinated at school entry anyway. Why be concerned about infant immunization?" In a CDC-funded study in Baltimore, in an area where more than 50% of children are on Medicaid, investigators found that of 550 children in their sample, only 2 children did not have a primary-care provider. The majority of children, in fact, were seeing the same primary-care provider over a period of at least 3 years. They estimated what the immunization coverage would have been if those children had been vaccinated appropriately whenever seen. It should have been 90%. In fact, the level was nearer 50%. I suspect that the experience in Baltimore could be replicated in many other places. We must convince health care providers that immunization is important, and they must give it priority, much as our British colleagues have so adequately done.

Dr Kapikian: What do you think about the future of the Children's Vaccine Initiative (CVI)? It came in with a bang a couple of years ago, and there were many recommendations. It sounded great, but it seems to have gone nowhere. Does it have a future, or is it going to be subsumed by other programs?

Dr Henderson: I think it has prospects. We have encountered serious difficulties because the World Health Organization program has not been well integrated or organized and, in consequence, has received far less than the needed support. We hope this will be resolved soon and that one individual, namely, Dr Ciro de Quadros, will head the entire operation. If this happens, the CVI would be given a new life and the potential for greater expression.

The philosophy of the CVI was based on the premise that many countries and many investigators are interested in solving a variety of problems. We hoped to bring together groups of people to think through the solutions to problems, to identify those who could make necessary contributions, and to have various individuals meet regularly to accelerate development. This is working quite well with respect to the development of a stable, oral polio vaccine. I'm not sure how well the tetanus and measles initiatives are going. However, I believe this is a promising approach and I am sure it will go much better when we have better WHO leadership.

Dr Katz: It is obvious that we can do better than we have done, and sometimes people feel that the "glass is half empty." Actually, we have done pretty well, despite an inadequate system and the many children who do not get immunized. Failure to immunize is not totally the fault of health care providers, though; lack of parental incentive, lack of education, and poverty are also to blame.

We obviously need funds for vaccine research and development, whether through the National Institutes of Health, the National Science Foundation, or other sources. Although I don't believe that a "one-shot" children's vaccine will be forthcoming in the next few years, I think we are moving in the right direction, toward both a national and an international commitment. We need pragmatic, political push behind what we do as scientists.