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Global Immunization: Victories and Challenges

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Forty years ago this April, Dr. Thomas Francis stepped to the podium in Rackham Hall at the University of Michigan. He announced to a packed auditorium and to the world that field tests of the new Salk polio vaccine had demonstrated it to be highly protective. This was headline news throughout much of the world. It is hard to identify another single event in recent medical history that so riveted the attention of press and public alike.

There were good reasons for this. During the decade preceding the 1955 announcement, the number of paralytic cases in the United States had increased more than tenfold. Most other infectious diseases were diminishing in number; polio cases were increasing, and medicine and public health stood by helplessly.

The discovery in 1949 by Enders, Robbins and Weller that poliovirus could be grown in large quantities in tissue culture had opened the way for a vaccine to be produced. In less than five years, Salk and his colleagues had a vaccine ready for large-scale field trials. The trials, launched in 1954, involved nearly two million children in the United States, Canada

and Finland--the largest number ever to participate in such a trial.[1] Within weeks of the polio vaccine being declared effective and safe, it was licensed and large scale vaccination efforts begun.

The Francis announcement of 40 years ago heralded the dawn of a new era in the development and use of vaccines. Only two vaccines were then in moderately widespread use --the venerable smallpox and BCG vaccines-- both of highly variable quality depending on where the vaccine was produced. Far less use was made of the few other vaccines available-- rabies, diphtheria, tetanus, yellow fever--some because of questionable efficacy, and some because of adverse reactions.

The use of the new tissue culture techniques were to make possible a wide spectrum of new and improved vaccines. Many of these could be produced on a scale and with an economy never before possible. This served to encourage global cooperative efforts to extend the benefits of immunization to children throughout the world. This has been critical to recent progress in improving child survival because, as Dean Jamison will elaborate later, immunization has been shown to be by far the most cost-beneficial of all medical procedures

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[1]As an interesting footnote, and once a closely guarded secret, all vaccine was prepared in Canada at Connaught Laboratories and shipped in secret to the United States for bottling. Connaught had solved production problems that U.S. producers could not. The National Foundation for Infantile Paralysis felt that negative publicity might accompany use of a "foreign" product and so swore everyone to secrecy.

available.

The smallpox eradication program, launched by WHO as a global effort in 1967, succeeded in just over 10 years and at an average cost of less than $10 million per year in development assistance. In the course of that campaign, national health authorities discovered for themselves how readily an immunization program could be organized and how generally receptive people were to vaccination. Progress in eradicating smallpox provided the stimulus to expand vaccination efforts to include other vaccines. Thus the so-called WHO Expanded Program on Immunization (EPI) came into being in 1974.

EPI incorporated six antigens in addition to smallpox--diphtheria, tetanus, pertussis, poliomyelitis, measles and BCG. When it began in 1974, global immunization levels, except for BCG, were at less than 5%. By 1983, nine years later, they had risen to 20%, but progress was slow. Clearly, a greater commitment to the program was required by both national governments and donors. About this time, two organizations in particular stepped forward to play critical roles in transforming the effort. UNICEF embarked on a new Child Survival Initiative with childhood immunization as its core component, and Rotary International began a $100 million fund-raising drive for polio eradication--an effort ultimately destined to raise more than $300 million. With this support, as well as assistance from other donors, including USAID and Canadian CIDA, immunization levels throughout the

world began to climb rapidly. By 1990, coverage level of 80% had been reached in most countries, and those levels have since been sustained. Jim Grant, who played a key global role as promoter and cheerleader, once characterized the totality of the global EPI as the most extensive social development program ever launched--and so it is.

As EPI was expanded and strengthened, WHO staff in the Americas recorded an impressive, steady decrease in the number of polio cases. They believed that hemisphere-wide eradication of polio was possible, and in 1985 they proposed to the PAHO Directing Council an eradication program with a goal of "zero" cases by 1990. The member governments agreed. Several features of the program in the Americas laid the groundwork for a subsequent global effort. It placed special emphasis on the development of a surveillance network to report cases. This network began with approximately 500 hospitals providing reports sporadically. It now includes 20,000 health units reporting weekly. Each suspect case is investigated by a special epidemiologist, and specimens are processed promptly in one of a network of certified diagnostic laboratories.

The immunization strategy consisted of two key elements. First were National Immunization Days, during which efforts were made to vaccinate all children under five years of age throughout a country. These special days were conducted twice each year, one to two months apart, during the low point in seasonal transmission, i.e., the coolest months of the

year. The second element of the strategy consisted of special house-to-house vaccination programs in high-risk areas. Specifically, these targeted the most densely crowded and poorest socioeconomic areas in cities. These high-risk areas, as defined by the program, included about 10% of a country's population.

The basis for this strategy was the recognition that poliovirus, like smallpox, may be widespread at the peak of its seasonal incidence but during the low point in transmission, it is able to continue spreading only among susceptible small children, mostly in a few densely crowded localities. Chains of transmission in rural and remote areas are interrupted spontaneously. Intensive vaccination, especially in the densely crowded lower socioeconomic areas serves to displace the wild virus.

The strategy in the Americas was dramatically successful, the last case occurring in August 1991. Eradication has now been certified by a distinguished independent International Commission.

A global polio eradication effort is now in progress. WHO's Western Pacific Region has taken a leading role, with a goal of eradication by the end of this year. China is a member of this Region and has now conducted four National Immunization Days, vaccinating more than 80 million children on each of these days. Polio transmission now appears to have been interrupted in China, Japan, Korea, the Philippines and Taiwan. Whether eradication can

be achieved by December in Laos, Cambodia and Vietnam remains to be seen, but I am confident that, in any event, the last cases should be seen in 1996.

Also, large areas in North Africa and many countries in the southern cone of Africa are no longer detecting cases. However, surveillance must be greatly strengthened before more can be said of the status of polio in these areas. Meanwhile, countries in both the middle East and southeast Asia are greatly accelerating their efforts.

Polio cases world-wide in 1994 numbered less than 10,000; 143 countries detected no cases whatsoever.

It is of significance that the polio eradication effort is being conducted as an intrinsic part of the broader program of immunization because the impetus of the polio campaign is serving to strengthen all immunization efforts. Moreover, it has succeeded as well in establishing surveillance systems now beginning to be used for measles and neonatal tetanus.

As we review the unprecedented progress in child survival itself over the past 30 years, it quickly becomes apparent that most of the progress can be accounted for by immunization alone. Specifically, there are three million fewer deaths each year due to diseases preventable with currently used antigens. Another two million children survive each year who would otherwise have died of smallpox. In brief, five million deaths are now being

averted every year. Smallpox-induced blindness no longer occurs, and the crippling paralysis caused by polio is rapidly disappearing. In just one generation the under five mortality rates for children have decreased by more than half in virtually every country throughout the world.

What might we expect over the next 30 years? Despite the progress we have made, the principal threats to child survival throughout the developing world remain the infectious diseases. Let us suppose that vaccines could be perfected and applied which would protect against malaria, tuberculosis, dengue, the more serious acute respiratory infections and diarrheas and, yes, AIDS. Through such immunization alone, mortality rates for children under five years could be reduced even more dramatically over the next 30 years than during the past generation.

Could such vaccines be developed? I believe that those who are most knowledgeable of vaccine research and development would be unanimous in asserting that they could. Several new vaccines that protect against important diarrheal and respiratory illnesses are virtually ready now for general use; a first-generation malaria vaccine has been shown to be effective; and a dengue vaccine is entering Phase Three trials. At this time, it would appear that a better tuberculosis vaccine and an AIDS vaccine are yet many years from realization. However, with the exponential growth of knowledge about how organisms cause infections

and how the body combats them, vaccine development has been transformed from often "trial and error" experimentation to a true science. Because of this, the question is not if, but when, suitable vaccines can be developed.

Given that countries in almost all parts of the world have now developed programs for vaccine administration that reach 80% or more children, what could thwart the optimistic potential we foresee? I would identify three major problems, each posing a formidable challenge: 1) vaccine supply; 2) vaccine quality; and 3) support for research. All are interrelated and potentially soluble. However, neither the solutions nor the necessary commitments to find the solutions are yet apparent.

The first critical challenge relates to the problem of producing inexpensively, adequate quantities of assured high quality vaccine. This is a far more difficult problem than it might appear on the surface. Although current EPI vaccines are inexpensive and in plentiful supply, we must recognize that all are now simultaneously in widespread use in the industrialized countries. The revenues from sales in the industrialized world have largely paid for development costs, as well as much of the capital investment needed to manufacture these vaccines. Prices for the developing country market thus are established at little more than the incremental costs of producing additional amounts of vaccine. Thus, the total cost for all EPI vaccines for one child is less than US 50 cents. But where do we find comparable levels of

support for the many important vaccines that have only a limited market in the industrialized world? Development and construction of production facilities cost money. What can be done to develop and produce such vaccines when costs cannot be recovered by sales in the industrialized world.

The second critical issue is vaccine quality assurance even for vaccines now in use. Vaccines purchased through UNICEF are not at issue. UNICEF-purchased vaccines must meet international standards. However, for example, more than two-thirds of the DPT vaccine is produced in national laboratories. Only a few of these have fully satisfactory quality controls. WHO has recently begun an international effort to assure that quality control standards are in place in all laboratories, but with limited funds and personnel, progress is slow.

The third critical challenge relates to the need for research support. Recent advances in immunology and biomedicine have opened up all manner of new and exciting avenues leading toward the development of protective vaccines. The question now is not whether there are productive directions for research but, rather, which of many options to pursue. But translating basic concepts into useful products requires substantial resources. The private sector has made and is making such investments for vaccines which can be expected to be profitable. However, as I noted, many of the vaccines of greatest potential interest in the

developing world have limited markets, at most, outside of their own countries and resources there are not sufficient to pay large amounts for purchase. Unfortunately, few national or international assistance agencies view research as an intrinsic part of their agendas and most national authorities are not prepared to support medical research which does not benefit their own citizens. This is a serious problem.

I am optimistic, however, that as an international community, we will eventually come to fully understand and support these needs, if not in the interests of furthering child survival, perhaps in the interests of assuring mankind's survival. What do I mean? Over the past five years, we have come to appreciate the now-existing and growing challenge posed by new and emerging infections in an increasingly well-travelled and heavily-populated world. Early detection and identification are the first lines of defense and here the surveillance systems and laboratory networks developing within the context of EPI can be of real value. Viruses are of special concern. Witness current problems with Ebola and Hanta viruses. Given the generally disappointing experience with antiviral agents, we now recognize that serious challenges by viral agents will require timely development and production of new vaccines as well as the rapid detection and characterization of the agent. This implies the need for an expanded research and development infrastructure, especially in tropical areas, and a range of

activities that broadly overlap our needs in immunization.

If we are to respond responsibly to the very real microbial threats we face, substantial additional resources will have to be made available--at a time when budgets everywhere are constrained. I submit, however, that if we have our priorities properly ordered, we will discover that resources are not really an issue. In our own country, one major budget which is being sustained, not cut, is that of the Department of Defense. This, of course, is to deal with threats posed by man against man. Those threats are real. How does this compare with threats posed by microbes against man? Recently, an estimate was offered that wars during this century had been responsible for the deaths of fully 100 million persons--a figure meant to impress. However, this number is certainly well less than half the number killed by smallpox alone this century before its eradication in 1977. And that was but one disease acting in a partially vaccinated world. What might a similar agent do in a totally unprotected population? I am convinced that we need to get serious in dealing now with microbes and vaccines. Resources are not a problem. It is our priorities which are.