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Conference on Vaccines, Prevention and Public Health: A Vision for the Future
Session 10: Summation

D. A. Henderson

This has been an extraordinary conference. It clearly has exceeded all expectations of its organizers. The program has been rich and varied and the speakers have offered a remarkable overview of accomplishment and a vision of what might be. It seems to me that there never has been a more auspicious time for the future of vaccine research, development and application.

We salute PAHO and the countries of the Americas for their efforts, especially over the past 25 years of the Expanded Program on Immunization (EPI), in accomplishing a revolution in disease prevention through vaccination. Special recognition is in order for the leadership provided by PAHO Directors Carlyle Macedo and Sir George Alleyne and especially for Dr. Ciro de Quadros and his staff. Over this brief time, we have witnessed the disappearance of polio from the Americas using an imaginative strategy which now serves as the template for the global eradication program. We have seen measles cases decrease to the point where fully nine weeks have elapsed since the last known case of measles in the Western Hemisphere. Neonatal tetanus cases are now found in less than one percent of all districts in Latin America. Diphtheria and pertussis have become rare if not endangered diseases.

New vaccines have been steadily introduced into immunization programs – vaccines for rubella and hepatitis B and hermophilus influenza. An effective yellow fever vaccination program has been mounted. A Revolving Fund for the purchase of vaccines was inaugurated in the Americas and this serves now as a model for other areas of the world. Most impressive are the annual national planning meetings that include national and international staff along with PAHO experts and which set specific goals and identify present and future needs –

another model which needs to be emulated elsewhere in the world. These are remarkable accomplishments that are not yet widely known or fully appreciated.

This meeting, as Dr. de Quadros has pointed out, occurs just 32 years after the first international conference on vaccines. It was held in this same room, in December 1970. It proved to be an historical turning point. Let me highlight a few points of special interest to give perspective to present events.

The intent of the1970 conference was to review the status of available vaccines and their application and to develop recommendations for their use both in the industrialized and developing countries. The meeting had been made possible by a generous contribution from Merck. The secretariat consisted of Charles Cockburn and myself, from WHO/Geneva and Conrado Ristori and Mauricio Martins de Silva from PAHO. During the course of the Conference, two committees met to draw up recommendations for routine vaccination programs that seemed most generally appropriate for the industrialized countries and a design for immunization programs for the developing countries. The latter were eventually to materialize some four years later in the form of the EPI. Such was its birth.

At the time of the conference, vaccination programs were not of high priority in most developing countries. As we were discovering in the course of the smallpox eradication campaign, only small numbers of children were being vaccinated against any diseases other than smallpox. Smallpox vaccination was offered in most countries because of the severity of the disease but, as we discovered, less than 10% of the vaccine then in use met accepted international standards. Moreover, vaccination was primarily available only in urban centers; programs extending throughout the whole of a country were uncommon.

Other vaccines were seldom used in the developing countries. BCG programs were supported in a number of countries by UNICEF. Measles vaccination had

recently begun in countries of Western and Central Africa with assistance from USAID and CDC; DPT was being provided to less than 5% of children in the developing world. Yellow fever vaccine was periodically provided in some African countries when epidemics threatened.

The conference subcommittee for the developing countries recommended programs that provided six antigens -- smallpox, BCG, DPT, measles, and typhoid. There was no mention of polio vaccine. You may wonder why. Polio was not then considered to be a significant problem in the developing world. Not until 1972, when the first lameness surveys were conducted did our understanding change. The lameness surveys, as you may recall, consisted of screening all children at school entry to ascertain what proportion had the characteristic flaccid paralysis of recovered polio cases. Such surveys were able to be performed rapidly and to cover a large population of children. First in Indonesia and later in Africa, it was demonstrated that paralytic polio was surprisingly more prevalent than any had appreciated. By 1974, when EPI started, polio vaccine was substituted for typhoid fever vaccine in EPI programs.

Two notable problems were highlighted at the 1970 Conference. First was the comparative dearth of vaccine research and development and, the second was the lack of both interest and resources for vaccination programs in both industrialized and developing countries. The principal concerns were: how to obtain affordable vaccines in quantity; how to secure the interest and commitment of governments and potential donors; how to mount effective national programs. Three decades later, many of those concerns remain but many solutions have been found. Dramatic changes have occurred and in no region of the world more than in the Americas.

At our conference this year, there has been a veritable cornucopia of initiatives pertaining to vaccine research and development. The sheer number of potential new products and the opportunities now offered actually create a quite different

problem and that is one of prioritizing those to be pursued most actively and how best to do this.

Many additional resources have become available for program implementation. UNICEF has played a key role as have the bilateral agencies, the Rotary International Foundation and the development banks. Countries have begun to set aside funds from national budgets in order to mount and strengthen programs. A special impetus has been provided by the Gates Foundation, especially in the areas of research and development as well as in program implementation. That Foundation's very generous support of public health has been an encouragement to other donors and foundations to examine the comparative benefits of prevention contrasted to therapy.

The capacity to deliver vaccines has vastly expanded throughout the Americas and, no less, in other areas of the world. National Immunization Days were a creation of Brazilian and Cuban health authorities and this strategy spread rapidly across the Americas and to countries in Africa and Asia. It has proved to be a critical component of the polio eradication effort but effective with other vaccine programs as well.

During this meeting, two particular challenges have been posed which I believe deserve highlighting as problems worthy now of special attention. First is that of devising approaches that permit the targeted development of new vaccine preparations. The second is the problem of deciding regulatory measures that are appropriate to countries where disease risks warrant the development of vaccines and drugs to cope with diseases of the tropics and which potentially may be need to be produced under regulatory strictures that are best adapted to the country and the problem. There are no simple or obvious answers to address either of these problems. However, if they are not addressed, it is clear that future progress will be much more problematical..

As we have heard, laboratory scientists are now producing seemingly countless numbers of new discoveries and new ideas that offer enormous promise. What is not clear is how and by whom the most promising can be identified and supported in order to undertake the necessary developmental research to translate them into practical products for use in the field.

We have heard at this meeting how costly and time-consuming it is to take a promising product from the research bench thro the developmental stages to production, to animal and human testing and, finally, to licensure. It requires a substantial involvement and commitment on the part of the private sector wherein resides the skills and knowledge to undertake such steps in development. Companies, understandably, need reasonable assurance that if they make such an investment in a product, it will be able to be recouped through sales. Vaccines, however, have not proven to be especially remunerative, especially those that are particularly intended for use in developing countries. The fact that we have today so few manufacturers and that the number continues to diminish is alarming. This was highlighted for us specifically with regard to malaria. It pertains with equal force, to many other products. Thus, it is critical to identify, with care, priority areas, to establish clear time lines for development and to work out means by which commitments for final products can be made.

The second consideration is the question of what regulatory provisions are most appropriate for which products and in which countries. Ever safer and ever more carefully monitored products are desirable, certainly, but each increment in improvement in standards of manufacture, testing and documentation bears with it a cost. This was brought home to me this past year as the United States and other countries sought to purchase smallpox vaccine for the first time since 1975. It cost, at that time, between US$.50 and $1.50 per vial, each vial containing 100 doses. The cost of the vaccine is now more than 100 times greater. This far exceeds changes due to inflation. We are now told that to bring a new vaccine to market in Europe or the United States would require something between

$200,000,000 to more then $500,000,000. If no mechanisms can be found to diminish these expenses, there will almost certainly be a number of products of immense potential value, especially to those in the endemic regions of the developing world, that will not make their way to market. It seems to me that it is appropriate and timely to reconsider regulatory and licensing mechanisms with this concern in mind.

There is a special need, as well, to consider regulatory measures in the context of programs and priorities. The implications of regulatory measures can be profound as witness the turmoil and vaccine shortages that resulted from a recent decision to require that thiomersal be removed as a preservative from all vaccines. A problem, potentially as serious, occurred early in the course of the smallpox eradication program. It was scarcely averted. For some 18 months after the program began, we had been successfully using jet injectors throughout Latin America and West and Central Africa. The injector deposited the vaccine in the superficial skin layers by injection instead of by scarification with a needle. Studies showed that the depth of vaccine deposition was about the same with each. However, quite unexpectedly, regulatory authorities in the United States decided that the vaccine used for jet injection had to be classified as an injectable product and so had to be sterile. We learned this only days before the proposal was to be brought before a WHO biological products control committee.

The smallpox vaccine was then being grown on the flank of calves, as it had been for a hundred years. However much the skin was cleansed, bacteria were carried forward in the vaccine. . Tests monitored both numbers and the absence of pathogens. Making it a sterile product was impossible. Vaccine grown in eggs or tissue culture could have produced a sterile product but laboratories that had tried to do so were unsuccessful in producing a sufficiently stable product for use in the field.

A decision to require that the vaccine be sterile would require a total restructuring of programs in at least 20 countries and possibly suspending most of them because vaccine for scarification was in short supply. Nevertheless, we were advised that the regulatory authorities were favorable to the idea. Fortunately, the WHO Director General understood the problem and insisted that the item be removed from the agenda.

The challenge for us in the years ahead is to appreciate that the discovery, development, application, and regulation of vaccines have to be viewed as integral processes with each element having important, sometimes critical, implications on the other components with decisions weighed accordingly.

What will another Conference look like 32 years from now? Who could possibly have predicted in 1970 how far we would have come in just one generation? It seems to me that the next 32 years promise to be even more productive provided that we address some of the more difficult areas I have noted.

I would like to conclude by, again, wishing PAHO a very happy 100th birthday. This has been a wonderful event for all participants and, in particular, for all of us who have been privileged to work with PAHO in any capacity. Thank you all for all you have done and are doing in building bridges throughout the Americas and to the rest of the world.

SUMMARY

remarks will be brief / no way to

Let me begin by saying ~~[illegible]~~ provide a overall summation that could possibly distill the essence of a very rich menu any more than one [illegible].

could distill the essence of a banquet in one or two spoonfuls

This has been an extraordinary conference - well organized; all-star list of speakers who have obviously come well-prepared. And at a time when progress in research + application of vaccines has never been more favorable or the future more auspicious.

One has to salute PAHO, the countries of the Americas with special leadership by Dr. Carlyle Macedo ~~and~~ Sir George Alleyne and Dr. Ciro de Quadros and his staff have pioneered an incredible revolution over the past 2K years -

~~[illegible]~~

~~which~~ It is breathtaking in scope and accomplishment - but still not widely grasped ~~[illegible]~~ or even known Polio / Measles / Tetanus / Diph / Pert.

→ rubella, hepatitis B and hemophilus infl., yellow fever. REVOLVING FUND NATL. PLANNING WITH DONORS.

~~[illegible]~~

~~[illegible] children [illegible] during this same period, an unprecedented decrease in infant mortality rates. Next~~

~~What~~ This meeting represents a fitting celebration over the 100th Birthday of an international organization whose stature is growing exponentially.

Our meeting ~~[illegible]~~, as Ciro pointed out, comes some 30 years after an Intl. Conference on Vaccines - held in this very room ~~[illegible]~~ ago in Dec. 1970.

I will say a bit about that [illegible] to provide ~~[illegible]~~ some historical perspective to appreciate from whence we have come.

Merck sponsored the meeting - the Secretariat consisted of Cockburn, DAH, Branco Cvjetanovic (WHO), Conrado Ristori and Mauricio Martins da Silva (PAHO)

At that meeting and Committees - drew up the design for immunization progs. for developing countries ⇒ "Expanded Program on Immunization"

VACCINES
3-yr. smallpox - most countries, but not rare, poor coverage.

BCG - a no. of countries - UNICEF ⇒

DPT - <5%

Measles - 18 countries of W + C Afr

Y. F.

Com vac. Smallpox BCG DPT Measles ~~+~~ Typhoid vaccine.

Polio and Yellow fever – were on the list for use in some countries where the problem was evident.
Indeed, it was not until we began lameness surveys in Indonesia and
later Africa was it appreciated that polio was a significant problem!
1970 conference – 2 major points
① Comparatively little said about research or development –
Actually not much being done.
② A very Real problem was that of stimulating interest in vaccinations in all
countries.

30 years later – These two problems have been well addressed
① Veritable cornucopia of vaccine discovery and research.
To is indeed poses a problem indeed in respect to priorities
② Vastly expanded capacity to deliver vaccines, to mount the necessary surveillance ‒ both reporting + lab to document progress. (Rotary, UNICEF, GAVI, bilat agencies, Banks)
(Note GATES)

From the meeting two areas emerged which it seemed to me now do
Two areas need special attention – Targeted development, regulatory structures
Enormous set of development with intriguing implications. Need more
① Could usefully strengthen mechanisms for targeted development –
Rabinovich spoke of this with re: malaria
Seems to me that focus and priority setting is needed in a number of other areas – , diarrheal dis. → resp. viruses (Resp. viruses)
Many initiatives but I don't sense there are many plans with strategically set time lines.
② It seems to me that the regulatory structures and vaccine production modalities deserve a very serious look. Ⓐ We've been told of the ↑ in costs to bring vaccine to market from ~$200+ ×10⁶ → $800 ×10⁶
Vaccine manufacturers becoming ever fewer in number
Need to be able to take research products and carry them thru to deliverable product

(Some suggest How do we produce BOCU?)

Vaccines are a peculiar commodity – large volumes bought by govt, or because of govt. policies – not a ~~[illegible]~~ conventional market

Vaccines for biol. [threats] weapons – even more of a problem –
need to have production base, ability to move quickly to produce a vaccine we may not use. Need for intl. cooperation and

(B) ~~As~~ As one manu. rightly pointed out – careful thought [planning] needs to be given to ~~[illegible]~~ fact [that] regulation → cost.
Not much use to have a gold-plated vaccine no one can buy.

(D) Need to think thru what should, must, can be done – e.g. thimerosal. smallpox vaccine for jet injection. (implications of regulation)

Need to look at more of these problems on an international scale.

~~[illegible]~~
There are fundamental issues which will greatly influence ~~the~~ future progress

Conclude

~~[illegible]~~

~~One approach is what can be accomplished in unison.~~

~~We know there is so much more that we can do.~~

~~[illegible]~~

~~Health mortgages often are the first – to be followed by others by education, trade, [illegible] and others~~

Again wishing PAHO a happy birthday
our appreciation for the Org. having staged this meeting
and for its ~~[illegible]~~ tremendous contributions in building bridges of health and cooperation throughout the Americas

Pan American Health Organization

Vaccines and Immunization in the Americas: Milestones 1977-2002

1977
- PAHO Directing Council Resolution establishes the EPI in the Americas.
- Resolution also establishes the Revolving Fund for Vaccine Procurement

1978
- All countries appoint a National EPI Manager
- PAHO initiates training courses for EPI Managers

1979
- Pan American Sanitary Conference authorizes capitalization of the EPI Revolving Fund
- US$2.5 million worth of vaccines is purchased through the Revolving Fund
- First issue of EPI Newsletter is published

1980
- PAHO develops a methodology for multidisciplinary program evaluation/review, which generates annual plans of action at national level
- First multidisciplinary program evaluation/review conducted in Bolivia

1981
- PAHO Scientific Publication "Immunization and Primary Health: Problems and Solutions" defining a road-map for PAHO's Technical Cooperation on EPI
- First EPI Managers' Regional Meeting and First Cold Chain course held in Ecuador
- PAHO publishes the Position Paper on Immunization Delivery outlining the role of combining vertical and horizontal approaches on immunization programs

1984
*First region to develop and make use of *Days of Tranquility* to carry immunization campaigns in conflict areas, a concept that is now being widely used throughout the world

1985
- PAHO declares the goal of Polio eradication in the Western Hemisphere by the year 1990
- EPI Technical Advisory Group is appointed by PAHO Director
- Regional Inter-Agency Coordination Committee (ICC) is created by PAHO, with participation of USAID, UNICEF, IDB and Rotary International, with equivalent entities at country level
- Countries produce Five-Year Plans of Action (1986-1990) with identification of resources needed from both national as well as international sources
- US$ 110 million is mobilized from ICC Partners

1986
- Neonatal Tetanus control is accelerated

1987
- On PAHO's advice Cuba launches the first measles eradication campaign in the Region

1991
- Second cycle of Five-Year Plans of Action (1991-1995) is initiated
- Last case of indigenous polio is detected in Peru
- US$ 60 million is mobilized from ICC Partners

1994
- Americas is certified polio-free and Goal of Measles eradication is set by the PASC

1995
- Third cycle of Five-Year Plans of Action (1996-2000) is initiated
- Special Program for Vaccines and Immunization is established

1996
- Introduction of new vaccines is accelerated (MMR, HepB, Hib)
- US$ 32 million is mobilized from ICC Partners

1999
- Division of Vaccines and Immunization is established
- US$85 million worth of vaccines is purchased through the EPI Revolving Fund
- CDC and the World Bank join partnership, US$8 million dollars are mobilized

2001
* Over US$110 million in vaccine purchases through the EPI Revolving Fund
* Fourth cycle of Five-Year Plans of Action (2001-2005) is initiated

2002
- **By the end of August, eradication of endemic measles transmission in sight**
- Revolving Fund capitalization over US$20 million
- USUS7.6 million dollars are mobilized