

CLEMENTS-MANN LECTURE– APRIL 22, 2013 April 19

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My thanks to the NFID, to Gregg and to Bruce, for the honor of presenting the Mary Lou Clements-Mann lecture. This year, we celebrate the world's 35th year without smallpox – a pestilence which throughout history had been unrivaled in its destructive force. Despite this, the decision in 1966 of the World Health Assembly to mount a serious eradication effort passed with a margin of only 2 votes. Many doubted that it was logistically feasible; others argued that eradication of any disease was impossible. Three previous eradication campaigns had failed; malaria eradication, the largest and most costly was then in its 11th year and was proving to be far more difficult than any had imagined. Its demise was only a matter of time. Confidence in WHO, in public health expertise, and in the concept of eradication had been shaken.

The smallpox program had been launched in 1967 with a 10 year time target which called for the last case to occur by the end of December 1976. Health staff from some 72 different countries were to take part in the program. A considerable number who provided key leadership were under the age of 40. They proved to be unusually creative, dedicated, willing to endure long weeks in difficult field conditions. As WHO Director General Mahler said: "They did not know that the task was impossible". And the target was missed -- but by only 9 months and 26 days. The potential for application of new ideas and the power of public health caused many to alter their own career directions and, for this, the field of infectious disease prevention profited enormously. Mary Lou Clements was one whose life and career were shaped by that program. Her inspiration and contributions in the field of vaccines are celebrated with this lecture.

For me, Mary Lou was a colleague, a friend, a leader and a creator. Our first meeting was early in 1975. She had just joined WHO and was en route to the Eradication Program in India. She came highly recommended by faculty of the London School of Tropical Medicine where she had just received her Diploma in Tropical Medicine; this was subsequent to 3 years of internal medicine residency.

The 1974-75 smallpox year proved ultimately, to be the critical one for the program. Only 4 countries remained endemic – India, Pakistan, Bangladesh, and Ethiopia. India was, far and away, the most formidable. Major epidemics were raging across northern India. In 1974, 188,000 cases had been

reported—perhaps 800,000 had actually occurred; 130,000 local staff were engaged in search and containment. We were desperate for more senior staff. The time was critical – full activity had to be sustained despite unbearable summer temperatures, primitive accommodations and dawn to dusk work. Some questioned the feasibility of a woman being able to provide leadership at this time in a country with an all male hierarchy. ML was unfazed. Her energy, friendly good humor, and ready willingness to work long hours under impossibly difficult conditions were inspirational. On August 15, 1975 Prime Minister Indira Gandhi announced that three months had passed without a known case. Certification would require 2 more years. ML continued throughout this period and subsequently arrived in Baltimore just in time to enroll as an MPH student. Her primary interests in immunization and infectious disease prevention continued as she worked with Mike Levine at Maryland for 6 years before returning to Hopkins in 1985 as Director of a new Hopkins University Center of Immunization Research. She compiled a remarkable record of accomplishment as she built an internationally distinguished program.

Applicable lessons from the program

I was asked specifically, to take up two subjects in this lecture: 1) lessons from the smallpox program and 2) prospects for the eradication of other diseases. Many illustrative lessons derived from the smallpox program. Much has been written about the importance of continuing research and dialogue between the field and the laboratory; the need for understanding, involvement and support from village worker level to highest authorities; the potential for contributions, especially by enthusiastic, young staff; a focus on management and quality control; and the critical need for sustained support by international agencies and other donors.

But let me take up the question of two specific components that I believe were pivotal. One was the surveillance-containment strategy, an epidemiological approach to disease control and elimination, and the second, the provision of a reliable and stable single dose vaccine. The potential applicability of each merits serious consideration in weighing various infectious disease eradication initiatives.

Surveillance – containment

To understand the anatomy of the smallpox eradication program, there is need to understand some elements of its history.

SLIDE 2 A token WHO smallpox eradication effort first began in 1959 at the instigation of the Soviet Union and the approval of the World Health Assembly. However, few resources were provided, voluntary donations were scant – its headquarters staff consisted of one medical officer.

After 7 years and continuing complaints that more was not being done, the Assembly decided that Director General Candau should prepare a comprehensive 10 year eradication plan, including estimated costs. The report was to be discussed and voted on at the 1966 Assembly. If the report was rejected, smallpox eradication would be abandoned. Actually, such an outcome was not unwelcome to Candau. At the time, virtually all possible resources and efforts of WHO were consumed by a decade-old malaria eradication effort. It was failing. Candau had no confidence that smallpox eradication would fare better. He was reasonably confident, however, that the delegates would abandon the smallpox initiative when it was realized that substantially more financial resources would be needed and that each country would have to increase its financial contribution. As it turned out, the Assembly, after 3 days of debate, approved the plan but by a margin of only 2 votes.

SLIDE 3 Candau's report called for a two part program. First was a vaccination campaign intended to reach 80% vaccination immunity in the population. It called for use of the comparatively new freeze-dried vaccine and stipulated that it must meet international standards. Second –and to be undertaken at the same time-- was the establishment of a surveillance program. In brief, it called for obtaining a weekly report of smallpox cases from all health units and, in response, a "two or three day intensive mass program of vaccination in the immediate area".

Reporting of cases in the 1960s was considered to be so incomplete as to be worthless – so stated a 1964 Expert Committee. Later studies were to show that substantially less than 1% of cases were being reported. Epidemiological information was nil. In endemic areas, health authorities responded to more serious outbreaks utilizing such vaccine as they had – most of which was sub-standard. Where more organized efforts were undertaken, success was measured in terms of the number of vaccinations performed.

SLIDE 4 The concept of disease "surveillance and containment" was an important one. As you may recall, it was first introduced at CDC by Alex Langmuir after his arrival in 1949. It was first applied in coping with malaria and subsequently, with poliomyelitis beginning in 1955 when the Cutter

poliovaccine catastrophe occurred. Thereafter, surveillance was progressively expanded to include other infectious diseases, beginning with hepatitis and influenza. The principal elements were the systematic collection of reports of cases, epidemiological analyses, and reports to responsible health officials for action. My position during the 5 years preceding assignment to WHO had been as Director of Alex's Surveillance Section at CDC. In February 1966, I was asked to come to Geneva for a week to work with WHO staff in drafting the Director General's report to be presented that year to the World Health Assembly. That surveillance and containment was specified as a uniquely new and significant component was no accident.

Eastern Nigeria provided the first demonstration that the surveillance-containment strategy could be more efficacious than expected. Bill Foege with local Nigerian staff found that smallpox was much less contagious than many believed. Comparatively limited containment measures to contain reported outbreaks could dramatically hasten smallpox elimination over a large geographic area. This was confirmed about the same time in field studies in Pakistan by Tom Mack and a group from the University of Maryland. Supportive studies in India and Brazil followed soon after.

Surveillance data served to monitor progress in the program, to identify groups or areas at special risk, to focus efforts of the vaccination program, to redirect strategies. It demonstrated its value where ever it was used. However, traditional health authorities regularly resisted diverting even a few staff from mass vaccination to work in small containment teams.

Eventually, we adopted the slogan "Target Zero" hoping to shift attention to numbers of cases rather than numbers of vaccinations. For this, we even got some help from Snoopy with the help of Charley Schulz. SLIDE 5 To our surprise, a surprising number of countries became smallpox free even before a functional surveillance-containment program could be established. Whatever the case, the surveillance containment programs proved to be invaluable in certification activities to document that at least two years had elapsed without cases.

Smallpox vaccine

Many, including myself, have cited the efficacy of surveillance-containment as being a critical element in transforming control efforts into a feasible eradication campaign. Surveillance-containment did play an

important role. However, as I have reflected on the evolution of the program, I realize that, more important, was the provision of ample supplies of a fully antigenic, heat-stable vaccine. The vaccine, as you know, has a long history dating back more than 200 years. It was accepted as an effective preventative measure from the time of its discovery; its use steadily spread around the world. Effective, widespread use was limited, however, due to its loss of potency in ambient temperatures. In the 1950s, a solution to the problem was found -- the vital development that made eradication possible.

A very brief history. Smallpox vaccine, as you will recall, was our first vaccine and the stimulus for Pasteur and others to develop other vaccines. It was in 1796 that Edward Jenner took pustular material from a cowpox lesion on the hand of milkmaid Sarah Nelms and scratched it into the arm of 8 year old Jimmy Phipps. Six weeks later, he inoculated Phipps with smallpox virus. He was protected. The cowpox virus or some variant of it was called vaccinia. He showed that pustular material from a vaccination pustule could be transferred to others who, in turn, would be protected. For the next seven decades, protection was effected primarily by arm-to-arm transfer of the virus. Unfortunately, syphilis and hepatitis B as well were occasionally transmitted with the virus.

SLIDE 6 LIQUID VACCINE In the 1860s, scientists demonstrated that it was possible to grow the vaccinia virus on the flank of a calf and distribute it in containers. The vaccine virus was viable for only a matter of days at ambient temperatures. But smallpox was such a major problem that production centers were set-up in many cities, including some in developing countries-- the manufacturing facilities consisting of little more than a stable and a cow. In many areas, the vaccine was put in capillary tubes; in some, the cows were walked from house to house by the vaccinator. Such remained the practice until methods for drying the vaccine pulp came into use during the 20th century.

SLIDE 7 MAP 1900 world-wide except Sweden and Australia

SLIDE 8 MAP 1958 Europe, North Africa despite use of a liquid vaccine

SLIDE 9 LESLIE COLLIER -- A stable vaccine 6 months @45°C.

SLIDE 10 Vaccine crisis

We were concerned about vaccine quality but laboratories in Canada and the Netherlands volunteered to test samples of vaccine. As we soon discovered, most of the vaccine was grossly unsatisfactory; half the lots were of low potency; some contained no detectable virus at all; and many had large numbers of

bacteria. Russian, U.S. and French vaccines were satisfactory but, otherwise, not more than 10% of the vaccine in used in endemic countries met acceptable standards.

It took 3 years before sufficient vaccine for all programs became available. This was achieved as quickly as it was because of the use of a remarkable new device for vaccination called the bifurcated needle.

SLIDE 11 BIFurcated needle From the time of the first vaccinations, vaccine had been inoculated by scratching or pressing vaccine through a drop of vaccine on the skin. In contrast, the bifurcated needle was dipped into the vaccine suspension; a very small amount was held by capillarity between the two prongs; 15 rapid punctures within a small area guaranteed a successful take. A 0.25 ml. vial of vaccine was required for 25 vaccinations using conventional methods. Use of the needle effectively quadrupled our vaccine supply and eased a serious shortage.

SLIDE 12 MAP 1958 BEFORE THE GLOBAL PROGRAM REPEAT

SLIDE 13 MAP 1970

Latin America, Thailand, Malaysia CDC CENTRAL/ WEST AFRICA 10 of 18 already smallpox free

SLIDE 14 MAP 1972 West Africa is Free; so is East Africa except Zaire: No surveillance-containment

SLIDE 15 ALI MAALIN –October 26 1977

CUT SLIDES

Prospects for the Eradication of Other Diseases

As we look to the future and the prospects for eradication of other diseases, it is difficult for me to forget the hostile climate toward the concept of eradication which prevailed during the late 1960s and 1970s. As the Assembly debated undertaking smallpox eradication in 1966, the massive malaria eradication campaign begun 11 years before was clearly collapsing; 2 billion dollars had been expended. There were more than 600 WHO malaria posts and 27% of all funds at WHO's disposal were devoted to malaria. Three 3 years later, with continuing problems emerging, UNICEF and USAID withdrew all support. Confidence in WHO and international programs was at a low ebb. This was reflected in a lack of interest in 1966 in undertaking another WHO eradication program. This explains why smallpox eradication was approved with a margin of only two votes

The success of the smallpox eradication program came as a stunning surprise. It came at a time when Rene Dubos and others asserted that it was untenable to believe that a single organism could be extracted from the complex ecological world in which it had evolved.

In September 1980, only 3 months after the declaration of smallpox eradication, a meeting was convened at the Fogarty Center with the theme: "What next do we eradicate?" Measles, tuberculosis, urban rabies, poverty, hunger, and others were suggested. Frank Fenner and I provided the opening presentation. It was difficult not to join in the wave of ebullient optimism that was palpable at the meeting. Target zero – the global eradication of man's most devastating pestilence had been achieved in just 10 years and at a total cost in international assistance of less than \$100 million (\$300 million in today's dollars); a disease that was infecting 10 million people each year and killing 20 million was no more; WHO had demonstrated its worth in bringing the nations of the world together in common cause; more than 700 international staff had experienced an appreciation of how much could be achieved with how little, given dedication, imagination and persistence. What next, indeed!

For those of us who had struggled personally with the array of challenges that had to be overcome, we recognized that smallpox eradication had been far easier than it would be for any other entity. We had been combatting a disease that was greatly feared by all, that was well-known and recognized by villagers, that had no sub-clinical cases to silently spread infection; and that could be prevented by a single inoculation. Moreover, it was not very contagious -- one patient seldom infected more than 2 to 4 others. Our principal weapon was an extremely inexpensive vaccine, that protected for decades with a single, simple inoculation, a vaccine which could withstand 37° C. temperatures for at least a month and which produced a visible pustule if vaccination was successful..

Civil conflicts had presented serious problems and personal risk. Civil wars occurred in Nigeria, Pakistan, Zaire, Sudan, and Ethiopia. Floods and famines plus civil disorder regularly produced hundreds of thousands of refugees and consequent spread of smallpox. Several specific instances are still fresh in my mind when major, all but fatal problems were averted by fortuitous circumstances beyond our control. Smallpox eradication succeeded but just barely – and this despite the many positive attributes for eradication. Thus our statement: (SLIDE 17)

"...there is no other disease which possesses so many characteristics favorable to eradication or for which we now have available, effective, simple and inexpensive measures for prevention or treatment".

Eight years later, in 1988, at the Talloires Conference, a program for polio eradication was being ardently advocated. Reluctantly, I accepted to join in the proposal but only on condition that a vigorous research program be supported to develop a far more antigenic and heat-stable vaccine. That was agreed to by both WHO and UNICEF at that meeting. Nothing was subsequently done.

Meanwhile, as smallpox eradication was being certified, many former smallpox staff, both national and international, began or joined the WHO sponsored "Expanded Program of Immunization". This had been launched in 1974 during the course of the smallpox eradication program as we looked beyond the immediate horizons. The vaccines included, initially, measles and polio vaccines along with DTP (diphtheria, tetanus, pertussis) vaccine and BCG. Gradually, other vaccines have been selectively added. Hopefully, this lays to rest the regrettable belief that funds for public health programs can only be raised under the banner of eradication. Finally, a belated salute to: Leslie Collier as a scientist to be recognized for perfecting the methods needed to making a stable and potent vaccine available and to Alex Langmuir who was the creator of the concept of surveillance-containment.

"Eradication may well be public health's greatest rhetorical weapon in the battle against dread disease. Indeed, the ability to command funding, popular support, the attention of politicians and positive media coverage by talk of disease eradication is unparalleled

D. A. Henderson 4/20/2013

The Clements-Mann Lecture
Eradication of Disease through Vaccination
 35th Anniversary of the last case of smallpox

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April 22, 2013

Smallpox eradication – at birth

- 1959 USSR proposes global smallpox eradication
- 1960-1966
 Budget – \$160,000 per year (average)
 One medical officer in Geneva; 4 assigned to countries
- 1965 Director-General to prepare 10 year plan

Program strategy
 Director General's Report to the World Health Assembly – May, 1966

- **Vaccination**
 - Target: 80% of population
 - Vaccine
 Freeze-dried, stable for 30 days at 37° C.
 Quality control by WHO standards
- **Surveillance**
 - To begin at the same time as vaccination program
 - Weekly case reports from all health centers
 - Containment of outbreaks to the extent possible

Surveillance-containment

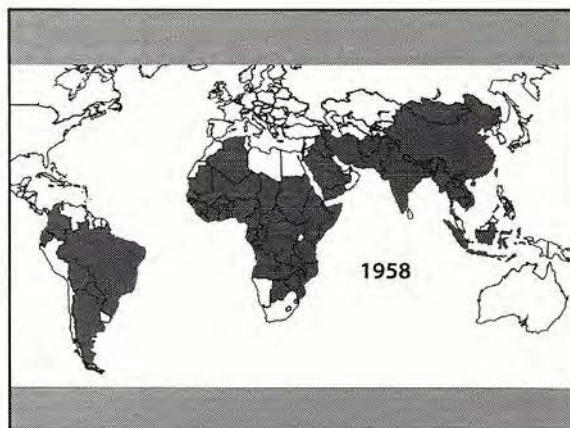
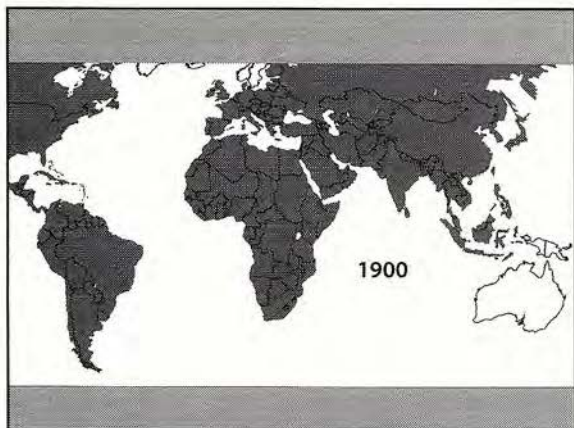
- **Concept of Surveillance** – Alex Langmuir, 1949
 Inspiration – Wm. Farr, U.K. Registrar General's Office
- **Application** – U.S. malaria, polio, measles, hepatitis
- **Application – Global program**
 - 1966 Bill Foege and CDC team in Eastern Nigeria
 - 1966-67 Tom Mack, et al in Pakistan
 - 1967 Rao in Madras, India
 - 1967 Morris in Brazil

Compromised



"Liquid" vaccine

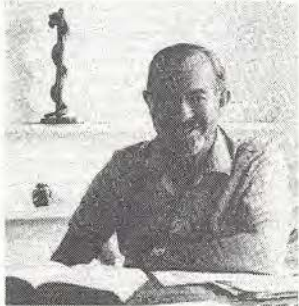
- **Vaccine pulp** – beginning material
 Calf, sheep, water buffalo
 Shaved, scarified, vaccine suspension applied
 Sacrificed at 5 to 7 days; lymph scraped off
- **Liquid vaccine**
 Put in capillary tubes and sealed
 Stability limited to a few days
 Universally used from 1860s until replaced by dried vaccine nearly a century later
- **Early dried vaccine – 1920-1970**
 Frame for its colonies or former colonies



Dr. Leslie Collier
Lister Institute, U.K.

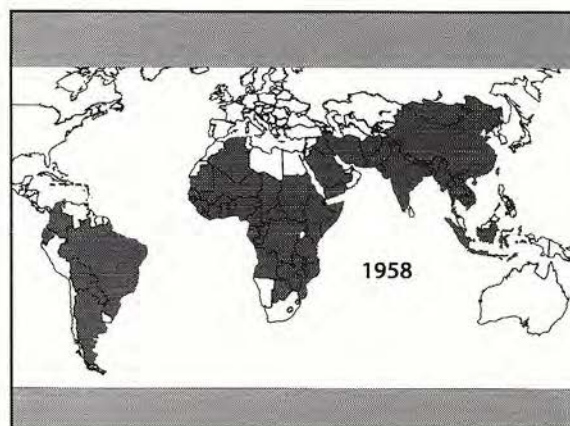
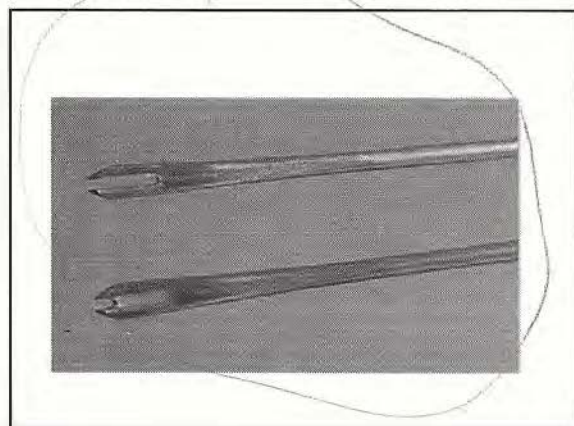
Developed a practical industrial method for freeze-drying vaccine and designed the industrial-grade equipment

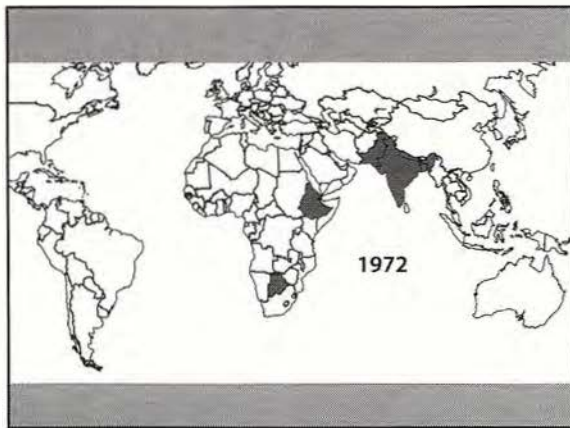
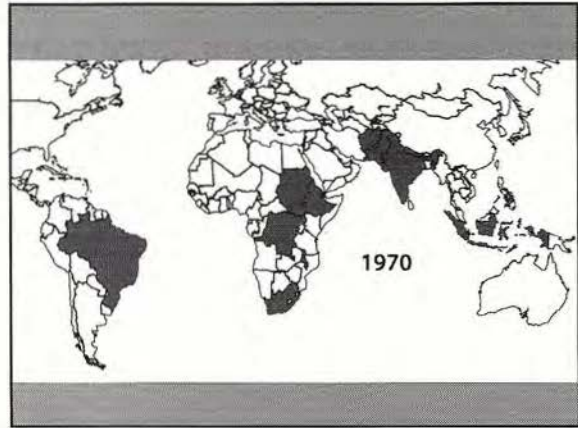
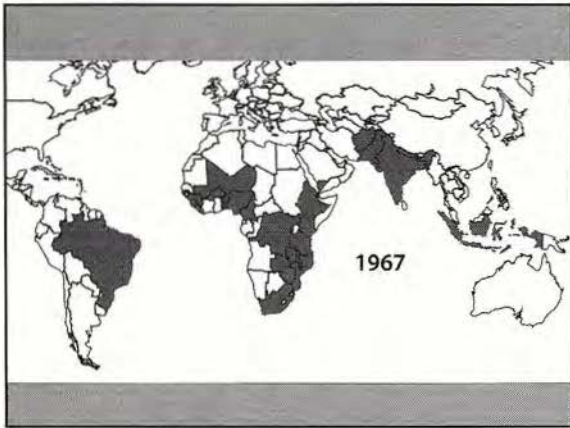
UNICEF furnished equipment WHO began vaccine testing and training in 1958.



The Freeze-dried vaccine crisis 1967

- Quantity needed per year -- ~ 350 million doses
U.S. and USSR -- committed to 75 million doses
Balance expected from 59 active national producers
- International testing labs -- Netherlands, Canada
Approximately 10% of vaccine in use met standards
- Production manual written -- 22 labs visited
By 1972, 41 labs producing potent and stable vaccine
- Bifurcated needle tested and distributed
Standard 25 dose vaccine vial vaccinates 100





What next to we eradicate?

- Henderson-Fenner keynote:
...there is no other disease which possesses so many characteristics favorable to eradication or for which we now have available, effective, simple and inexpensive measures for prevention or treatment.

1980 Meeting on Eradication at the Fogarty Center

Polio