UTILIZATION OF VACCINE IN THE GLOBAL ERADICATION OF SMALLPOX

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Immunization is potentially the most cost-effective procedure for disease control, its efficacy and practicability being governed by the characteristics of the antigen which is available. Vaccinia virus, although not ideal, is one of the best. It possesses a number of characteristics which, for the smallpox program, make it unusually suitable for developing countries - where trained personnel are few in number, where ambient temperatures are high and refrigeration is scarce and where funds, especially foreign currency, are limited.

Among the attributes of vaccinia virus, five were of particular importance. Had any one of these been lacking, the ultimate success of the program would have been seriously jeopardized. The attributes are as follows: (1) the vaccine was easy to administer; (2) it was comparatively simple to produce; (3) it was stable for long periods at ambient tropical temperatures; (4) it conferred remarkably durable immunity even after a single application; and (5) it was widely accepted, producing few recognized serious reactions.

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Ease of administration

A vaccine which can be readily administered to large numbers of persons with minimally trained staff and little equipment is especially advantageous in conducting a vaccination program in a developing country. Oral vaccine preparations are perhaps the easiest to administer but at present, few antigens can be administered successfully by this route. Most vaccines require percutaneous application but, other than for smallpox vaccine, they require the use of either needles and syringes or jet injectors.

Disposable needles and syringes would appear to be an obvious solution for large-scale vaccination campaigns, but even when purchased in bulk, their cost is prohibitive. If syringes and/or needles are reused after sterilization, the costs for supplies may be reduced but the logistics and effort required to do this are formidable.

Jet injectors offer an advantage where large numbers are vaccinated during the course of a day, but the injectors now available experience mechanical problems with distressing frequency and require skilled personnel to maintain and repair them. They are not usually practicable even when a few hundred persons can be vaccinated daily. During the global smallpox eradication program, jet injectors were used throughout western and central Africa and in Brazil, the first programs to be initiated. In these countries, it was possible to train or to provide sufficiently skilled personnel to repair and maintain the injectors over the three-to-five year period during which large numbers of vaccinations

were performed. To continue the programs for a longer period would have been problematical given the difficulties in sustaining distribution systems for spare parts and an interest on the part of donor countries in providing necessary replacement equipment and, in many instances, foreign technicians.

In 1968, the functional and elegantly simple bifurcated needle became the instrument of choice for multiple puncture vaccination (Henderson et al., 1972). The needle was developed by Dr. Benjamin Rubin of Wyeth Laboratories (Rubin, 1980), and the needle design was made available to WHO free of patent charges. We anticipated that the needles would be repeatedly sterilized and reused and so we altered their metallic content to make them more durable. They were produced by a German manufacturer at a cost of $5.00 per 1000. Field tests revealed that each needle was fully effective for 200 or more inoculations, whether sterilized by boiling or by heating over an open flame. Experience showed that village workers, with 15 to 30 minutes training, could satisfactorily reconstitute the vaccine and perform multiple puncture vaccinations. A vaccine vial containing 0.25 ml. of reconstituted vaccine, the smallest quantity of vaccine which was technically feasible to freeze-dry in a container, served to vaccinate approximately 100 persons. Such a vial of vaccine cost less than $1.00 to produce.

Multiple puncture vaccination, employing the bifurcated needle, was eventually used in all countries, displacing all other techniques and instruments. It remains, by far, the most practicable method for percutaneous inoculation.

Vaccine Supply and production

In an immunization program, personnel costs constitute the principal expenditure, the costs of vaccine usually representing only a fraction of the total. For a developing country, however, foreign currency cost rather than overall cost is the principal constraint. If vaccine cannot be produced locally, the principal foreign currency cost is for vaccine. Presently, in most immunization programs in developing countries, vaccines are donated or their costs are met largely by bilateral or multinational agencies. Provision of vaccines in this manner is not a satisfactory long-term solution, however, because it is difficult to sustain the interest of donors in continuing to make donations of substantial quantities of vaccine over long periods. Thus, local production of vaccine is preferred where the quantities of vaccine which are used warrant it.

Smallpox vaccine was able to be produced in many developing countries, but even with this effort, it was difficult to assure the continuing availibility of adequate quantities for the global eradication program (WHO, 1980). In most instances, donations were obtained only with difficulty and because laboratories in most industrialized countries had small capacities, contributions were proportionately small. Fortunately, during the early years of the program, two major contributors provided most of the vaccine which was needed. Approximately 140 million doses annually were provided by the Soviet Union through bilateral and multilateral contributions and 40 million doses were provided by the U.S.A. to countries in western and central Africa. The

balance of perhaps 20 to 30 million doses was initially provided through contributions of other industrialized countries and through production in developing countries.

Support was provided by WHO and UNICEF to laboratories in developing countries to produce their own vaccine. In these laboratories, vaccinia virus was harvested from the skin of calves or water buffalo and, after a comparatively simple series of steps to purify and concentrate it and to reduce the bacterial content, it was freeze-dried in vials or ampoules. Some laboratories were able to embark on large-scale production within a period of two years, although most required somewhat longer. By 1971, more than 250 million doses of vaccine were produced in the developing countries, most of which met accepted international standards as determined by independent assay in WHO collaborating laboratories (table 1) (Arita, 1973).

Experience showed that for most laboratories, a more complex production technology, such as one involving tissue cultures, would not have been possible. Indeed, not until the 1970s did any laboratory in any country succeed in producing a heat stable, freeze-dried vaccine employing vaccinia virus grown in tissue culture (Hekker et al. 1973). Nevertheless, early in the programme some concerned with biological standards proposed, as a matter of principle, to modify the international standards to require that vaccine for the jet injectors be bacteriologically sterile. The vaccine then in use had a very low bacterial count and was required to be free of pathogens but a sterile vaccine would have required production in tissue cultures. Fortunately, the

application of these standards were able to be forestalled; otherwise, vaccine for the jet injectors would not have been available. No known complications are known to have occurred, however, as a result of use of the non-sterile but pathogen-free preparations.

Vaccine stability

The logistics and problems involved in maintaining antigens at a proper temperature from the time of production until inoculation have been well documented by those concerned with the WHO Expanded Program on Immunization. The provision and maintenance of refrigerators and insulated boxes for transport are formidable problems for most developing countries. Many imaginative approaches and solutions have been devised in recent years, but despite highly commendable efforts and numerous training programs, maintenance of the "cold chain" has proved to be one of the Program's most vexing challenges. For the smallpox eradication program, however, the problem was much less difficult.

Commercially acceptable techniques for producing an exceptionally heat stable vaccine were elucidated by Collier at the Lister Institute in the 1950s (Collier, 1955). One of the criteria for an acceptable vaccine was that it exhibit a potency of $10^{8.0}$ pock forming units (pfu) when assayed on chick chorioallantoic membrane after incubation at 37°C for one month. This concentration of vaccinia virus was about 50 times greater than that required to obtain vaccine take rates of more than 95% in primary vaccines. Some laboratories, in fact, substantially exceeded

these standards, both in vaccine titer and stability. Some vaccines contained more than 10^9 pfu and retained titers of 10^8 pfu or greater for as long as 6 to 12 months at high ambient temperature.

Standard procedures in the smallpox eradication program called for the vaccine to be stored and shipped in such a manner that it was exposed to temperatures of greater than 4°C for no longer than one month. In most programs, this implied storage of the vaccine in conventional refrigerators or freezers only in the capital city and provincial or state capitals. In these cities and towns, working refrigerators as well as electricity and/or kerosene were more readily available. From these depots, the vaccine was distributed to health centers and field staff once each month, a comparatively simple logistical problem. Even so, there were a number of documented failures in the system and, unquestionably, many undocumented ones. Nevertheless, repeat titrations of improperly stored vaccine, when conducted, usually revealed an adequate level of potency, the margin for permissible error in handling being so great. No other vaccine available today approaches smallpox vaccine in its stability.

Durability of immunity

In 1967, conventional wisdom held that revaccination every three to five years was essential to sustain adequate levels of vaccinal immunity. However, this assumption was soon called into question by surveillance data which showed that 80% to 90% or more of cases occurred among those with no vaccination scar and no history of vaccination. The reason for

this was revealed in studies by Heiner and his colleagues (Heiner et al., 1971) who found that many who were partially protected by immunization experienced subclinical infections with a subsequent substantial increase in antibodies. In the endemic countries, therefore, immunity was a composite of responses to prior infection with both vaccinia and variola viruses. A single primary vaccination provided remarkably durable protection in such areas, sample surveys showing vaccine efficacy ratios of 80% or greater among those vaccinated 20 years or more previously. Unfortunately, similar data are not available from non-endemic areas.

Although successful vaccination prior to exposure was remarkably effective in preventing naturally acquired smallpox infection, it was far less effective in preventing vaccinia virus replication in the skin when revaccination was performed. In fact, most individuals to whom a high titred vaccinia virus was administered experienced a so-called "major reaction," i.e. erythema and induration at the vaccination site at the sixth and eighth day, even when as little as 6 to 12 months had elapsed since their previous vaccination.

Administration of vaccine and acceptance of vaccination

Vaccine was administered to all persons in the population irrespective of age, illness or other conditions. The only stated contraindication to vaccination was serious illness which appeared likely to result in death of the vaccinee within a few days and whose death might be attributed to smallpox vaccination. These policies differed from those

in industrialized countries where vaccination was not usually administered to those under 6 to 12 months of age, to pregnant women or to those with eczema. Vaccination from the time of birth was initiated on the basis of Rao's studies in Madras, India, which showed this practice to be efficacious and safe (Rao, 1972). Possible pregnancy was disregarded because of the unusually high risk of death from smallpox among pregnant women and the rarity of complications following vaccination. Eczema likewise was not considered a contraindication because of the widespread occurrence of skin infections in many developing countries and the difficulty which vaccinators, as well as trained clinicians, encountered in differential diagnosis of skin conditions.

Vaccination was generally well-received. Aside from the expected reaction of a lesion on the arm and a short-lived fever, few vaccine complications were observed. Resistance to vaccination was uncommon although sometimes occurring among those who objected for religious reasons and among some rural Asian populations who feared any incapacitation during the harvest or planting season. Infrequent but serious complications such as post-vaccinal encephalitis are well-documented in industrialized countries and undoubtedly occurred in developing countries as well. However, with encephalitic symptoms due to other diseases being so widely prevalent, the frequency of those due to vaccinia virus could not be documented and were rarely noted. That vaccination was so widely accepted, indeed sought by most, became evident when government authorities endeavored to stop vaccination following eradication. Popular demand caused many governments to continue the practice for a number of years even though it was no longer needed.

Summary

The availability of a protective antigen against smallpox with the characteristics of vaccinia virus was critical to the success of smallpox eradication. WHO staff and collaborating scientists in many laboratories expended considerable time and effort in assuring the adequacy of supply of smallpox vaccine and, through a variety of quality control measures, of its potency, stability and purity. To meet demand, however, required expanded production in the developing countries themselves. If international standards had required a sterile vaccine produced in tissue culture, such production would not have been possible. The vaccine itself had unique properties of stability, the best of any antigen available today, which greatly facilitated its use in the field and because vaccination left a permanent scar, assessment of vaccinal immunity in a community was comparatively easy. Finally, for a percutaneously administered antigen, the multiple puncture technique was by far the simplest and least expensive. If it were possible to utilize vaccinia virus as a carrier for other antigens, the difficulties intrinsic to providing adequate quantities of vaccine for developing countries and of conducting immunization programes would be greatly minimized.

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Table 1
Estimated Quantities of Freeze-dried Vaccine
Produced in Developing Countries - 1971

	Millions of doses
Argentina	12
Bangladesh	30
Brazil	45
Burma	15
Colombia	4
Ecuador	2
Guinea	5
India	80
Indonesia	30
Iran	15
Kenya	10
Peru	5
Thailand	15
	268
People's Republic of China	?
Mozambique	?