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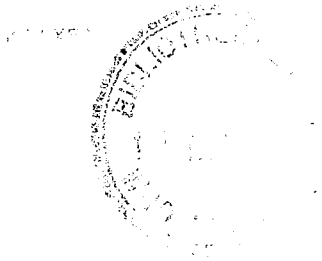

VACCINE PRODUCTION, STORAGE AND HANDLING

by

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Our principal weapon in the fight against smallpox is the vaccine. Unless the vaccine is potent at the time of administration, outbreaks cannot be contained and a programme of systematic vaccination is a meaningless exercise. Of first importance, therefore, in an eradication programme, is to assure at all times, that the vaccine is fully potent at the time of administration.

In introducing this subject for discussion, I should like to discuss and review with you those aspects of the production, storage and handling of vaccine which, I believe, are of particular interest and concern to you as programme supervisors. Certain of the more highly technical and research components of this subject, we may explore in the discussion period should you so desire.

When the global eradication programme began, we found that not more than 10% to 20% of all vaccine in use in endemic areas met WHO standards. In fact, in 1967, many specimens of vaccine which were tested, were found to contain no live vaccinia virus whatsoever. Unfortunately, some of this vaccine came from highly reputable national laboratories. The ability of these laboratories to test vaccine was no better than their ability to produce vaccine.

Four years ago, a number of endemic countries used liquid vaccine rather than freeze-dried vaccine. Liquid vaccine is less expensive and government officials considered this to be an important saving. Yet we know that even in temperate areas where refrigeration facilities are plentiful, much of the liquid vaccine is not potent at the time of application. I know this has been true in my own country. The vaccine is simply too unstable for routine use either in the field or in hospitals or in health centres. While liquid vaccine itself may be comparatively inexpensive, overall, it is very costly indeed to vaccinate large numbers of persons with nothing but glycerine and dead virus.

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Finally, at the beginning of this programme, we found that few paid any attention to vaccine storage and shipment. Regularly, we found large stocks of vaccine which had been stored for long periods in the hot sun and in unrefrigerated storage rooms. In health centres, we found substantial stocks of vaccine which had been kept for a year or more in physicians' desks and storage cupboards. Most of the vaccine, when tested, was found to be impotent. Literally, millions of doses of vaccine had to be destroyed.

In the development of the global eradication programme, the provision of ample supplies of freeze-dried vaccine of assured potency was obviously a first priority objective. Proper storage and distribution of this vaccine was equally important.

Assistance in the form of equipment, supplies and consultation was provided to vaccine production laboratories by both WHO and UNICEF. A meeting of experts in smallpox vaccine production was convened and a manual on vaccine production was prepared. Finally, arrangements were made with two laboratories, in Canada and the Netherlands, to serve as WHO Reference Centres for vaccine testing.

Now, four years later, the situation in respect to the vaccine has been completely altered. Almost all vaccine in use in endemic areas meets WHO standards. Increasing numbers of lots of vaccine are being tested (Fig. 1) and an increasing proportion is found to be satisfactory. Provisions for storage and shipment of vaccine have improved considerably as national authorities have appreciated the need for this.

However, we must not be complacent. The vaccine, in effect, represents the ammunition for our army of vaccinators and surveillance teams. If the ammunition is faulty the team can do very little. We must remain constantly alert to ensure that the vaccine continues to be satisfactory.

Let us briefly review pertinent aspects of this problem:

1. Production of freeze-dried vaccine

Use of freeze-dried vaccine in this programme is an absolute necessity. On countless occasions, I have been assured by producers of liquid vaccine that their vaccine is of good quality and that health staff are well-trained to preserve it properly. Repeatedly, we have demonstrated that this is not so. Freeze-dried vaccine is tested to assure that it maintains its potency when left at 37°C for 28 days. Liquid vaccine loses its potency in one to three days unless kept at deep-freeze temperature. We have yet to encounter a health staff anywhere so well trained that it has, in fact, been able consistently to preserve liquid vaccine properly. In brief, there is no excuse, no justification today for the use of liquid vaccine unless one is willing to accept take rates of anywhere from 0 to perhaps 50% in primary vaccinees.

Almost all freeze-dried vaccine is provided in ampoules or vials containing 0.25 ml. Traditionally, this is referred to as a "25 dose" container although we know that with a container of this size, as many as 100 to 125 persons may be vaccinated with the bifurcated needle. Health officers have repeatedly asked if vaccine could be produced in perhaps 1, 5 or 10 "dose" containers for use in health

centres. This was carefully considered at the WHO Seminar on Vaccine Production. It was concluded that 0.20 or 0.25 ml containers are the smallest practicable amounts which can be dried and properly reconstituted. A number of different experimental approaches have since been tried to overcome this problem. None has proved effective - all have been very expensive to the extent that the cost of producing each container holding only 1 or 2 "doses" has been almost as great as producing one of the so-called 25 "dose" containers now used. The only practical way at present by which one may realize a saving in vaccine is to plan the vaccination programme so that more persons can be vaccinated in the course of a day. In many countries health centres plan special "vaccination days" and of course, the programme of vaccinators can be arranged so that they may perform 50 to 100 vaccinations per day.

2. Testing of vaccine

Regular testing of vaccine by a competent laboratory separate from the one producing the vaccine is a very important measure to assure that high standards are consistently maintained. One cannot be complacent about this, however. On three occasions now, we, as well as national programme staff, have been dismayed to find substandard vaccine being released by excellent laboratories who had maintained high standards for as long as 3 and 4 years. In each instance, the laboratory itself had become complacent and, having experienced problems in obtaining eggs for testing, began omitting certain of the test procedures. In each instance noted, corrective steps were able to be taken and the quality once again improved. Without independent testing, however, the problem might well have persisted for months or years - perhaps seriously jeopardizing an eradication programme.

WHO has made arrangements to permit the testing of two lots of vaccine every 3 months from all production laboratories in endemic countries. This amounts to 12 lots of vaccine each year. In particular cases where a laboratory is endeavouring to establish its production methodology or where eggs for testing are in short supply, provision may be made for testing of additional lots of vaccine.

It is also useful to check occasional samples of vaccine collected at health centres or from vaccinators in the field. If vaccine obtained at this level is of a proper standard, one may be further reassured regarding the quality of vaccine as actually administered.

The importance and value of regular vaccine testing cannot be over-emphasized.

3. Storage and handling

Freeze-dried vaccine, as you all know, is remarkably stable even when exposed to moderate heat. Indeed, it is perhaps one of the most stable vaccines available. However, we must not forget, that this stability is relative. Excessive heat for long periods can destroy the vaccine. To pass the WHO requirements for stability, each lot of vaccine must have more than 10^8 (100 000 000) virus particles per ml after being heated to 37°C for 4 weeks. Although some lots of vaccine may be satisfactory after even longer periods than this, many will not. As a practical matter then, it is advised that vaccine not be subjected to room temperature for a

total period of more than one month. Distribution of vaccine to sub-centres and to vaccinators must therefore be arranged to ensure that by the time the vaccine reaches the arm of the vaccinee, it will not have been out of refrigeration for a total time of more than 30 days. However, if by accident or error, a large amount of vaccine is kept at room temperature for longer periods, it should not be discarded. Samples should be submitted for testing as some lots of vaccine may still be suitable for use.

Some have felt that the test for stability should be set at 45°C as summer temperatures in some areas do exceed 45°C. However, careful review of the average or mean temperatures throughout endemic areas reveals that nowhere and in no month does the mean temperature exceed 37°C by more than one degree. The present tests are thus considered fully satisfactory.

After the vaccine is reconstituted it is like liquid or glycerinated vaccine and it deteriorates rapidly. Most vaccine falls below accepted standards after 18 to 24 hours although some lots may occasionally remain potent for a longer time. For this reason, it is advised that vaccine which is not used at the end of a day be discarded. It should be noted, however, that vaccine placed in direct sunlight will deteriorate faster than this - in fact, in a matter of a few hours. This must be carefully guarded against.

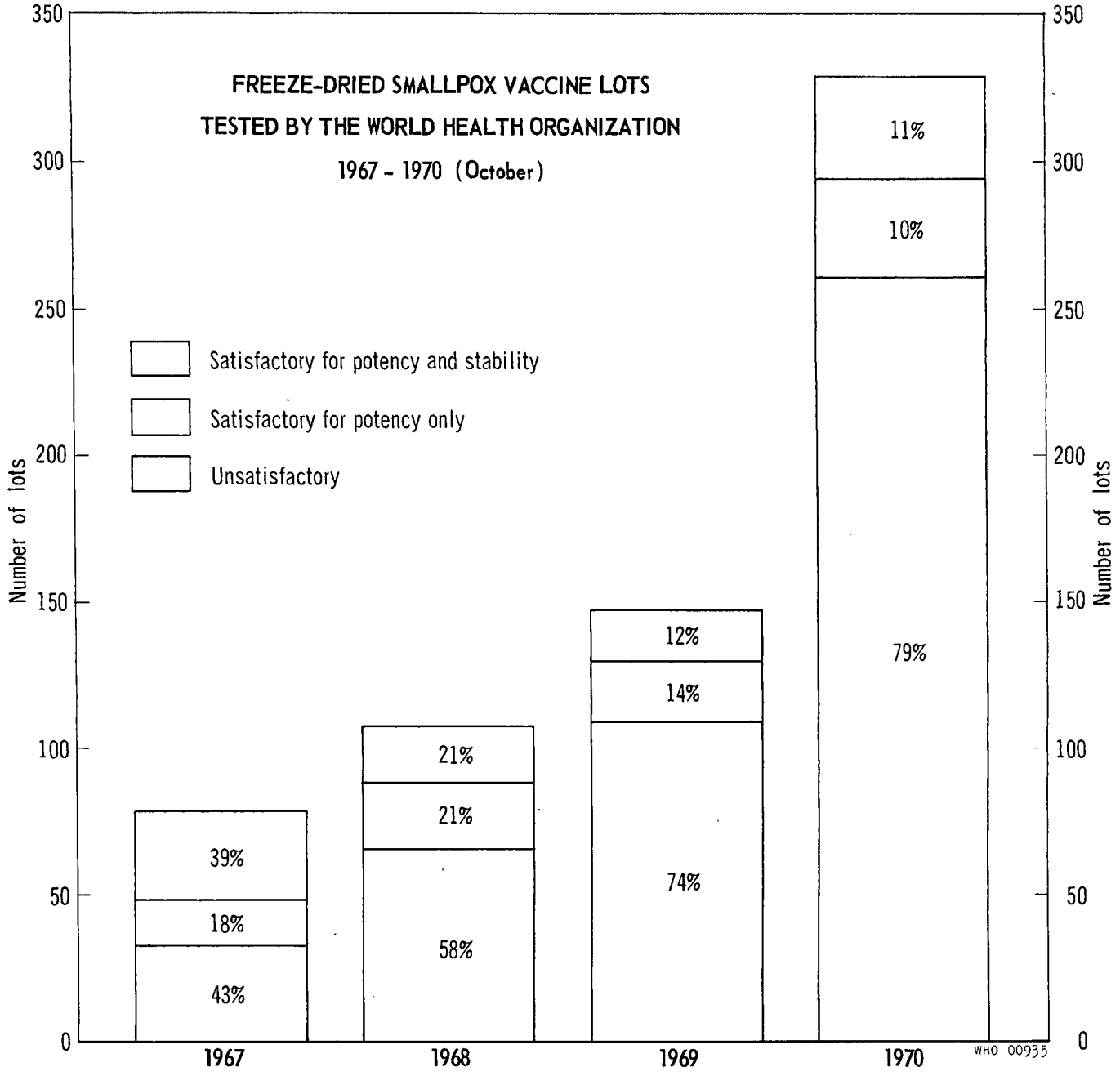
Summary

A very great deal could be discussed about vaccine production and its handling but, in these introductory remarks, I have tried to emphasize those points of interest and concern to programme administrators rather than points of concern for research workers.

Most important in any eradication programme is to assure that the vaccine in use is potent. If it is not, no programme, however successful administratively, is able to accomplish its objectives. Regular testing of vaccine is a necessity. As experience has shown, a laboratory which produces good vaccine for years may experience trouble at any time. It may not be recognized.

With good vaccine properly stored and distributed, the army of vaccinators and surveillance officers are assured of having live ammunition in the field. Without it, one has no programme.

FIGURE I


FREEZE-DRIED SMALLPOX VACCINE LOTS
TESTED BY THE WORLD HEALTH ORGANIZATION
1967 - 1970 (October)
Satisfactory for potency and stability
Satisfactory for potency only
Unsatisfactory
Number of lots
350
300
250
200
150
100
50
0
39%
18%
43%
21%
21%
58%
12%
14%
74%
11%
10%
79%
1967
1968
1969
1970
WHO 00935