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MANAGEMENT OF RESERVE STOCKS OF VACCINE IN THE POST-SMALLPOX ERADICATION ERA[1]

Contents

Annexes

[1] Prepared by the Smallpox Eradication Unit, WHO/HQ, Geneva (December 1980).

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1. WHA Resolution on Reserve Stocks of Vaccine

The Thirty-third World Health Assembly declared that smallpox had been eradicated worldwide (Resolution WHA33.3) and endorsed the recommendations of the Global Commission for the Certification of Smallpox Eradication (Resolution WHA33.4). The Global Commission's report included the following statement and recommendations:

"Reserve stocks of vaccine

"Although human-to-human transmission of smallpox has been interrupted everywhere and the Global Commission believes that the likelihood of reintroduction of smallpox from laboratories or natural or animal reservoirs is negligible, it is prudent for WHO and national health authorities to be prepared for unforeseen circumstances. One measure that should be taken is to ensure that adequate reserves of potent freeze-dried vaccine are available. This vaccine should be stored at -20°C and its potency periodically checked. Seed lots of vaccinia virus for the further preparation of vaccine should be maintained, and stocks of bifurcated needles should be available.

"Recommendation (3). Sufficient freeze-dried smallpox vaccine to vaccinate 200 million people should be maintained by WHO in refrigerated depots in two countries, together with stocks of bifurcated needles.

"Recommendation (4). The stored vaccine should be periodically tested for potency.

"Recommendation (5). Seed lots of vaccinia virus suitable for the preparation of smallpox vaccine should be maintained in designated WHO collaborating centres."[1]

This current document has been prepared to guide certain Member States and laboratories or institutions which will be requested to implement these recommendations in collaboration with WHO.

2. Current Status of WHO Vaccine Reserve (December 1980)

Eighty-four countries have already stopped obligatory vaccination against smallpox and this number will increase. Only two countries still require smallpox vaccination certificates from travellers. Many countries have stopped production of smallpox vaccine or will do so in the near future. The WHO vaccine reserve must, therefore, be considered as the major source of vaccine if unexpected circumstances should occur, even though at least 30 countries are individually keeping a total of 102 million doses for their own reserves (Annex 1).

It is important that the vaccine being accumulated for WHO's reserve is properly preserved, maintains its quality, and is ready for use in an emergency.

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[1] Excerpt from recommendations on policy for the post-eradication era, The Global Eradication of Smallpox, History of International Public Health No. 4, WHO, 1980.

2.1 Quantity of WHO vaccine reserve

As of December 1980, the quantity of vaccine stored in Geneva is as follows:

Producer	Nominal doses	No. of batches
Belgium	2 019 500	17
Canada	3 553 000*	6
GDR	645 500	5
India	5 528 850	60
Iran	4 487 000	23
Netherlands	1 553 575	13
Sweden	996 000*	10
USA	4 963 900*	9
USSR	44 506 400	123
	68 253 725	266

*Jet injector vaccine

An additional 31 million doses have been pledged by the USSR and 6 million doses by India.[1] The vaccine is expected to arrive by the end of 1981. Thus the final size of the reserve will be 105 253 725 doses. Since the number of doses (15 to 25) contained in each ampoule is adequate to vaccinate, in the field, a minimum of 30 to 50 people when the bifurcated needle is used, the smallpox vaccine in the reserve will be sufficient to vaccinate more than 200 million people even allowing for the inevitable wastage of vaccine when it is actually used in the field.

Three million, seven hundred and twelve thousand bifurcated needles and three jet injectors are also being kept at WHO/HQ and 126 000 bifurcated needles and two jet injectors at the WHO Regional Office for South-East Asia in New Delhi.

The value of the WHO vaccine reserve of 100 million doses will equal US$ 2.6 million (1979 estimate, calculated at a rate of $26 per 1000 doses). It is estimated that the eventual annual cost of maintaining this vaccine reserve in Geneva will be US$ 20 000.

2.2 Storage facility

The vaccine is kept at two depots:

i. Société de Gares Frigorifiques
et Ports Francs de Genève
rue Blavignac 5
1227 Carouge
Switzerland

ii. WHO Regional Office for South-East Asia
World Health House
Indraprastha Estate
Mahatma Gandhi
New Delhi - 110002
India

The Geneva cold store is commercially operated. The construction of the New Delhi cold store was completed in October 1979, but it is not yet operational; it is now being tested for efficiency and dependability. It is planned to locate in New Delhi in 1981, 6 million doses of vaccine pledged by India and 19 million doses pledged by USSR.

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[1] Twelve million doses will be stored in the reserve in Geneva and 25 million doses in the reserve in New Delhi.

2.3 Storage temperature

Both depots are designed to maintain a temperature of -20°C or lower; fluctuations in temperature should be minimized. The temperature suitable for long-term storage was decided by the Global Commission based on the results of tests in five laboratories (Annex 2). In both depots the alarm system and standby generators with automatic switching capability should be periodically tested so that in the event of a power cut the system will function as designed. The results of such checking should be submitted to WHO/HQ. A contingency plan should be developed to cope with any other mechanical failures or long-lasting power cuts. Storage temperatures will be monitored by an automatic temperature recording system and the results will be submitted regularly to WHO.

2.4 Labelling of cartons containing vaccine batches

Cases or cartons of vaccine in storage bear the following information printed either in English or French on the cases or cartons: batch number; name of producer; number of cartons per batch; number of vials; number of doses per vial; total number of doses. The location of the vaccine in the store has been so arranged that sampling of vaccine from selected boxes can easily be done. WHO will maintain a full record of the vaccine reserve employing special forms as shown in Annex 3A and 3B.

3. Sampling and Dispatch of Vaccines for Testing

3.1 Vaccine samples and reconstituting fluid collected periodically from the reserve stocks will be tested regularly.

3.2 One batch will be assigned for testing from each ten or fewer supplied by any given producer. Five containers from each of the assigned batches will be taken every three years, each container from a different carton, unless there are fewer than five cartons per batch. Where there are more than five cartons per batch, the containers will be drawn at random from the cartons.

3.3 At each sampling period, in addition to samples of the assigned batches, samples of five containers per batch will be taken at random from the vaccine of those producers whose product is being sampled for regular assay. In subsequent sampling periods, samples taken at random will be drawn from batches not previously tested to ensure that all batches will be tested at some time. The number of batches sampled - at least one and not more than five - will be related to the total number of batches of vaccine from that producer. The aim of these random tests is to increase the assurance of stability of potency offered by the series of assay results on the assigned batches of vaccine.

3.4 The containers of vaccine for testing will be sent, with appropriate packing precautions and using a cold box, to WHO/HQ, where they will be forwarded to the only laboratory engaged in testing - WHO Collaborating Centre, Rijks Instituut voor de Volksgezondheid (RIV), Bilthoven, Netherlands - where those samples not intended for immediate testing will be stored at -4°C until the appropriate date.

3.5 The sampling of the reserve stocks in Geneva and New Delhi will be arranged once every three months.

3.6 Some batches of vaccine are in vials sealed by butyl rubber stoppers. Despite the known good qualities of butyl rubber in inhibiting gas exchanges between interior and exterior of sealed containers, it may be wise to test the potency of these batches more frequently after 10 years' storage in the long-term reserve. Depending on stability of potency, decisions about frequency of testing will be made after 10 years, and subsequently as indicated by the trend of test results.

4. Testing

4.1 Bacteriological tests and heat stability tests are unnecessary and will not be done for all samples, but only for selected samples as part of the laboratory's special study on heat stability.

4.2 Potency of vaccines will be tested by the pock-count technique which is reliable when performed by a skilled person who exercises the skill regularly. To ensure this regular exercise, the sampling of batches for testing will be phased (see 3.5 above) so as to enable the laboratory to arrange testing at regular, reasonably frequent intervals.

4.3 To ensure that the tests and their application are adequately controlled, each group of tests on any test day will include the assay of a reference vaccine. To ensure an adequate supply of reference vaccine beyond the foreseeable future, RIV's batch number 6713/18 should be used in its entirety (2000 ampoules). This special batch has served as an excellent working reference vaccine in this laboratory for the last 10 years during which time RIV, as WHO Collaborating Centre for Smallpox Vaccine, has tested samples from various producers for safekeeping, ampoules of this batch will be distributed to the following institutions:

(1) Centers for Disease Control, Atlanta, USA
(2) Research Institute of Virus Preparations, Moscow, USSR
(3) Laboratoire national de la Santé, Paris, France
(4) National Institute of Health, Tokyo, Japan.

Each institution will be asked to store its portion of the batch in more than one deep-freeze cabinet operating at a temperature no higher than $-20^{\circ}C$ in order to obviate the loss of the whole batch through failure of a single deep-freeze cabinet or even of all the deep-freeze cabinets in a single centre. Should RIV require replenishment of its stock of local reference vaccine, it will request return of stock from some or all of the other institutions.

5. Interpretation of Test Results and Subsequent Action

5.1 When potency assay results are read, if the reference vaccine gives the expected titre, then the results of the test assays will be read directly and recorded accordingly. Should the apparent titre of the reference vaccine be low, the assays must be repeated until satisfactory testing is ensured.

5.2 Assay results will be reported to WHO/HQ as soon as they are available.

5.3 Vaccines which fail the test repeatedly, i.e. have a titre less than 1×10^{8} pfu/ml, will qualify for further consideration.

5.3.1 The series of three-yearly assay results of any failed batch and assay results of all other tested batches from the same producer will be studied by a panel of nominated experts (see Annex 4). The inclusion of all test results of vaccine from a single producer will allow the panel to determine whether the failure is an isolated incident or indicative of a trend in deterioration in that producer's vaccine. The panel will normally recommend withdrawal and destruction of any batch which has badly failed the potency test. The panel will, however, exercise its collective judgement on the fate of batches which fail marginally. More frequent tests of such batches may be recommended so that the rate of deterioration may be more precisely determined. Such additional information will permit the making of well-informed decisions. This expert panel will also advise on the disposition of any of the vaccine reserve which has been extensively exposed to unfavourable conditions such as may occur in a natural disaster.

6. Maintenance of Seed Lots of Vaccinia Virus

6.1 It is not practicable for health authorities to maintain for many years the capability for production of smallpox vaccine by traditional methods in the hope and expectation that it will never be needed.

6.2 Relatively rapid production of large amounts of smallpox vaccine in future is likely to be successful only by the application of cell-culture methods. The only cell-culture smallpox vaccine that has proved sufficiently efficacious is the material produced in cultures of rabbit kidney cells by RIV, which has agreed to:

i. maintain a stock of vaccine seed virus (1000 ampoules) in a stable form, suitable for rapid expansion at need;

ii. make available, at need, supplies of seed virus and practical information for production of the tissue culture smallpox vaccine to laboratories and institutions competent to produce and process large amounts of infectious material both safely and hygienically;

iii. distribute a portion of the seed virus to the following three laboratories for safe and suitable storage at a temperature of -20°C:

(1) Centers for Disease Control, Atlanta, USA
(2) Laboratoire national de la Santé, Paris, France
(3) National Institute of Health, Tokyo, Japan.

6.3 As a corollary, health authorities which have in the past relied upon traditionally prepared smallpox vaccine, should be encouraged to close smallpox vaccine production units and convert both plant and staff to the production of biologicals of proven efficacy that do not necessarily require the application of high technology methods.

7. Emergency Supply of Vaccine

7.1 The vaccine stock will be made available on request to any country which undertakes emergency containment measures when a diagnosis of smallpox has been confirmed by both epidemiological and laboratory investigations.

7.2 The vaccine will not be supplied by WHO in any circumstances other than those outlined above.

7.3 The distribution of the vaccine will be sanctioned by the Smallpox Eradication Unit (SME), WHO/HQ, and coordinated by this unit and the Supply Services Unit (SUP), WHO/HQ or by the WHO Regional Office for South-East Asia in New Delhi. The quickest means of delivery should be ensured.

8. Future Management of Reserve Stocks

Procedures for sampling and testing the reserve stock should be reviewed at 10 yearly intervals, taking into account previous test results.

The continuation of the vaccine reserve should also be reviewed at 10 yearly intervals, in conjunction with epidemiological evidence regarding the prevalence or likely prevalence of orthopoxvirus infections in man.

9. Miscellaneous

9.1 The vaccine is not insured against loss by fire, flood, or failure of temperature control. However, if for some reason the designated temperature cannot be maintained and the vaccine is endangered, action should be taken according to the procedures which have been worked out for the Geneva company to evacuate the vaccine expeditiously to another adequately functioning cold store in refrigerated vehicles.[1] Similar arrangements should be made in New Delhi.

9.2 An inventory of all the vaccine in cold storage will be made annually and submitted to WHO/HQ. This report will include the number of cartons in store. This procedure should serve as an adequate physical inventory of the vaccine, permitting the resolution of differences in the records, should they occur, as soon as they are disclosed.

9.3 During periodic inspections note will be made of deterioration of the cartons and their identification marks; if necessary, cartons will be replaced or relabelled. Special attention should be given to those vaccines which are known to be poorly packaged. Experience will indicate whether repacking is necessary and at what intervals. Repacking can be done by SUP at SME expense. Plastic labels and oil-based ink or paint should be used for the identification marks. In addition to the identification code or number written directly on the carton at a distance from the affixed label, an embossed label (preferably metal) should be wired firmly to each carton.

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[1] Personal communication, Dr I. Arita, 30 June 1976.

ANNEX 1

STATUS OF NATIONAL STOCKS OF SMALLPOX VACCINE ACCORDING TO INFORMATION RECEIVED BY THE SMALLPOX ERADICATION UNIT (1 DECEMBER 1980)

Region	Country	Doses of smallpox vaccine stocked
AFRO	Cameroon	4 000
	Congo	81 800
	Kenya	430 000
	Mauritius	20 000
	Mozambique	200 000
	Niger	200 000
	Zaire	434 000
Total		1 369 800
AMRO	Canada	1 000 000
	Colombia	6 600 000
	Peru	4 000 000
	USA	15 000 000
Total		26 600 000
EMRO	Egypt	30 000 000
	Iran	5 000 000
	Pakistan	3 500 000
	Syria	200 000
Total		38 700 000
EURO	Finland	10 000 000
	Germany, Fed. Rep.	9 000 000
	Hungary	3 000 000
	Netherlands	3 000 000
	Switzerland	4 500 000
	UK	?
	USSR	?
	Yugoslavia	200 000
Total		29 700 000
SEARO	Burma	1 339 875
	Indonesia	1 000 000
	Mongolia	100 000
	Thailand	500 000
Total		2 939 875
WPRO	Japan	1 913 000
	New Zealand	1 000 000
	Philippines	200 000
Total		3 113 000
Grand Total		102 422 675

SMALLPOX VACCINE POTENCY AFTER LONG-TERM STORAGE AT DIFFERENT TEMPERATURES

Institution	Batch No.	Date of preparation	Original virus content pfu/ml	Storage temperature	Results of latest retesting		
					Date	Storage period	Virus content pfu/ml
Connaught Laboratories Limited, Canada	1517-11	24.3.71	unknown	+4°C	28.8.79	8 years	$10^{8.03}$
	1517-12	24.3.71	"	+4°C from 1976	"	8 years	$10^{8.07}$
	1517-11	24.3.71	"	-20°C	"	3 years	$10^{8.05}$
	1517-12	24.3.71	"	-20°C	"	after 5 years at +4°C	$10^{8.17}$
Public Health Laboratory, Colindale, England	683A	1963	unknown	-15°C	1980	17 years	8.1
	700	"	$10^{8.3}$	"	1976	13 years	$10^{7.6}$
	701	"	$10^{8.0}$	"	"	13 years	$10^{7.9}$
	703	"	$10^{8.1}$	"	"	13 years	$10^{7.9}$
	705	"	$10^{8.3}$	"	"	13 years	$10^{8.1}$
	707	"	$10^{8.4}$	"	"	13 years	$10^{8.2}$
	709	"	$10^{8.5}$	"	"	13 years	$10^{8.2}$
Rijks Instituut voor de Volksgezondheid, Netherlands	total of 7 batches	1972-1973	unknown	+4°C	1976	3½-4½ years	satisfactory
Swiss Serum and Vaccine Institute, Bern, Switzerland	ZL 4695	19.4.66	1.10^8	-20°C	1976	10 years	$1.13.10^8$
	ZL 8885	8.9.70	$2.6.10^8$	"	"	6 years	$2.97.10^8$
	total 20	1966-1974		"	"	6-10 years	satisfactory
	ZL 10180	20.6.72	$2.4.10^8$	+4°C	1976	4 years	$1.84.10^8$
Wyeth Laboratories Incorporated, USA	177501	24.4.63	unknown	+5°C	4.1974	11 years	$10^{8.2}$
	181902	12.11.63	"	(till 1970)	4.1974	11 years	$10^{8.2}$
	185901	20.3.64	"	-20°C	4.1974	10 years	$10^{8.1}$
	206001	29.10.65	"	(from 1970)	4.1974	9 years	$10^{7.8}$
	total of 7 batches	1963-1965	"		4.1974	9-11 years	$10^{7.8}$-$10^{8.2}$

INVENTORY SUMMARY, SMALLPOX VACCINE, GENEVA

Country of Origin	
Gare Frigorifique Location No.	
Number of Pallets	
Number of Cartons	
Number of Doses	
Doses per Vial	

Batch Nos.	Carton Numbers	Total Cartons	Total Vials	Total Doses	Date Last Test

ANNEX 3A

VACCINE CONTROL RECORD

SOURCE:

Lot No.	Amount	Dose per vial	Location No.	Box Nos.	Date manufacture	Date rec'd.	RESULTS							
							Date tested	Initial	After 1 hr. at 100°C	Initial	after 4 weeks at 37°C	Bacterial count per ml.	Ref	Other/ Remarks

ANNEX 4

PROPOSED PANEL OF EXPERTS

Dr. A. C. Hekker	Rijks Instituut voor de Volksgezondheid, Postbus 1, Bilthoven, Netherlands.
Professor C. Kaplan	Department of Microbiology, University of Reading, London Road, Reading RG1 5AQ, England.
Dr S. S. Marennikova	Research Institute of Virus Preparations, 1 Dubrovskaya 15, Moscow 109088, USSR.

Note: The assistance of Chief, Biologicals, WHO/HQ, will also be requested.

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