1979 GC.WP/79.5

SUPPLEMENTARY INFORMATION TO THE REPORT ON SMALLPOX ERADICATION IN CHINA[1]

The information included in this report was provided by the government of China in response to queries made during the visit to China in July 1979 by Professor F. Fenner, Chairman, Global Commission for the Certification of Smallpox Eradication, and Dr J.G. Breman, Medical Officer, Smallpox Eradication Unit, WHO, Geneva.

1. Smallpox Vaccine Production

Institutions

The nine institutions involved in the production of smallpox vaccine are shown in table 1.

Seed strain utilized

The vaccinia virus strain used for the production of smallpox vaccine in China is the Temple of Heaven strain, which is a strain of smallpox virus that was isolated in 1926 from a smallpox patient. The virus was passaged three times on monkey skin, then five times alternately on rabbit skin and rabbit testes and three times on calf skin. The virus was then alternately passaged 1-4 times through calf skin and 1-2 times through rabbit skin to maintain its immunogenicity. The passage and control of the virus strain for production of vaccine are carried out by the Institute for the Control of Pharmaceutical and Biological Products (ICPBP) in collaboration with each Institute of Biological Products concerned. The stock of this viral strain is kept in lyophilized state by the ICPBP. Chick embryo cell culture is inoculated with the Temple of Heaven strain and the virus suspension obtained after less than three such passages is used for the preparation of cell culture vaccine

Preparation of vaccine

The vaccine is made by a routine method. Ether is used to eliminate contaminating bacteria in the pocks and to the glycerine vaccine, ~~Pronase B~~ Protease Peptone is added as a preservative. Pronase B is used for calf lymph vaccine and Pronase B, gelatin or cane sugar and milk for lyophilized vaccine.

For the cell culture vaccine, chick embryo cells are used as substrate. The method utilizing a large (15 000 ml) rolling bottle is employed for the virus multiplication in the cell culture. The diluent is composed of 2.5% Pronase B, 2% starch and 60% glycerine in water.

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[1] See documents WHO/SE/79.142 (Rev.1), WHO/SE/79.151, SME/79.10 and SME/79.11

TABLE 1

INSTITUTES FOR THE PRODUCTION AND CONTROL OF SMALLPOX VACCINES

Institute	Location/ Province	Administered by	Activities
Institute for the Control of Pharmaceutical and Biological Products (ICPBP)	Beijing	State	Vaccine quality control and research on virus strains
Beijing Serum and Vaccine Institute	Beijing	State	Production of cell culture vaccine supply for north China
Chengdu Serum and Vaccine Institute	Chengdu Sichnan	State	Production of cell culture vaccine supply for south-west China
Ranzhou Serum and Vaccine Institute	Ranzhou Gansu	State	Production of cell culture vaccine supply for north-west China
Wuhan Serum and Vaccine Institute	Wuhan Hupei	State	Production of calf lymph and cell culture vaccine (50% each) for south-central areas of China and lyophilized vaccine for bordering areas
Changchun Serum and Vaccine Institute	Changchun Kirin	State	Production of calf lymph (70-80%) and cell culture (20-30%) vaccine supply for north-east China
Jiangxi Serum and Vaccine Institute	Ji-an Jiangxi	Province	Production of calf lymph vaccine for east China
Guangdong Serum and Vaccine Institute	Canton Guangdong	Province	Production of calf lymph vaccine for Guangdong
Honan Serum and Vaccine Institute	Zhengzhou Honan	Province	Production of calf lymph vaccine for Honan Province

Quantities utilized

Since the vaccination policy was changed greatly in China during 1979, now requiring only primary vaccination (at an age over one year) and no compulsory revaccination, the quantity of vaccine used in 1979 was greatly reduced.

TABLE 2

QUANTITY OF LIQUID VACCINE IN DOSES ISSUED IN CHINA IN 1978 AND 1979

Production institute	1978	1979
Beijing	15 734 000	5 266 600
Wuhan	28 846 500	5 356 000
Changchun	13 000 000	7 050 000
Ranzhou	22 010 000	6 600 000
Chengdu	29 033 000	8 220 000
Guangdong	58 298 000	13 000 000
Total	166 921 500	45 492 600

The quantities of lyophilized vaccine issued from 1975 to 1979 are shown in table 3.

TABLE 3

QUANTITY OF LYOPHILIZED VACCINE ISSUED, CHINA, 1975-1979

Year	Doses
1975	1 647 850
1976	1 242 300
1977	1 289 950
1978	1 070 000
1979	1 103 850

Stability and potency testing

The results of stability testing of liquid cell culture vaccine are shown in table 4.

TABLE 4

STABILITY OF LIQUID CELL CULTURE VACCINE

Temperature	Duration of storage (months)	Number of pocks/ml CAM [a]	Number of plaques/ml HAd [b]
4° C	0	1.7×10^8	8.1×10^7
	3	1.1×10^8	1.0×10^6
	6	2.9×10^8	8.1×10^7
	9	1.7×10^7	8.9×10^7
	12	8.7×10^7	1.0×10^8
15-17° C	1	2.1×10^8	6.8×10^7
	2	1.2×10^8	4.4×10^7
	3	6.5×10^8	5.0×10^7
37° C	7	4.3×10^7	1.0×10^7
	14	9.3×10^6	1.3×10^6
	21	3.5×10^5	1.0×10^5

[a] chorioallantoic membrane

[b] haemadsorption

After storage at 15-17° C for three months, the titres are still above that required for the standard preparations; however at 37° C the vaccine is not as stable.

Table 5 shows a comparison of vaccine potency testing by various methods.

TABLE 5

COMPARISON OF VIRUS CONCENTRATION
TITRATED ON CAM AND TISSUE CULTURE (HAEMADSORPTION)

Batch No.	Vaccine	CAM	HAd
736	Calf lymph	5.6×10^7	6.7×10^7
726	Calf lymph	3.0×10^7	4.7×10^7
7211	Calf lymph	9.2×10^7	6.3×10^7
9083	Calf lymph	6.2×10^7	5.3×10^7
747	Tissue culture	2.3×10^7	3.5×10^7
7410	Tissue culture	2.0×10^7	2.5×10^7
7414	Tissue culture	2.5×10^7	3.1×10^7
73049	Tissue culture	7.2×10^7	6.5×10^7
73060	Tissue culture	6.0×10^7	5.5×10^7
Mean titre		4.89×10^7	4.9×10^7

Since 1974 the requirement for the titre of the vaccine was changed to 1×10^7 plaque/ml HAd in order to minimize adverse reactions following vaccination. The relationship between the titre and take rate of the vaccine was studied, as shown in table 6.

TABLE 6

CORRELATION BETWEEN VIRUS CONCENTRATION (HAd) AND PRIMARY VACCINATION "TAKE" RATES

Batch No.	Virus concentration (HAd)	Total number	Take rate (%)
7133-1	6.8×10^7	56	100
7133-2	3.5×10^7	52	100
7133-3	1.7×10^7	54	98.4
694-1	9.4×10^6	70	98.5
694-2	5.6×10^6	96	92.7
694-3	3.7×10^6	63	88.8
008	9.0×10^5	-	60
004	2.3×10^5	-	40

Vaccination complications

A study was conducted in 1974 in three subregions in Hopei Province to compare complications after use of the two types of vaccine. A total of about two million vaccinations, including 230 000 primary vaccinations and 1 860 000 revaccinations, were investigated.

There were 20 adverse reactions, as shown in table 7.

In order to compare the immunogenicity of the calf lymph vaccine and the cell culture vaccines, each was used for primary vaccination of one group of children. Two, three and six years later, both groups were revaccinated with the vaccine other than that used initially. The types of skin reaction after revaccination were recorded. No difference was found between all these groups, indicating that the immunogenicity of the two types of vaccine is similar (table 8).

The titres of the serum neutralization test six years after primary vaccination showed no difference between these two vaccines (table 9).

The Temple of Heaven strain of vaccinia virus used for the preparation of vaccines has good immunogenicity but causes relatively strong adverse reactions after vaccination. To reduce these reactions, a strain of vaccinia virus, K9, with weaker reaction after vaccination, was isolated by the method of plaque-purification. The rate of occurrence of high fever after vaccination with the K9 strain was found to be much lower than with the Temple of Heaven strain, while the efficacy of both vaccines as measured by the skin reaction after revaccination is about the same (tables 10 and 11).

TABLE 7

COMPLICATION RATES AFTER VACCINATION (1974)

Complication	Calf lymph vaccine						Cell culture vaccine					
	Primary vaccination (N=126 058)		Revaccination (N=923 969)		Subtotal		Primary vaccination (N=111 641)		Revaccination (N=134 724)		Subtotal	
	No. of cases	Rate /10^5	No. of cases	Rate /10^5	No. of cases	Rate /10^5	No. of cases	Rate /10^5	No. of cases	Rate /10^5	No. of cases	Rate /10^5
Multiple vesicular eruptions	4	3.17	3	0.32	7	0.66	3	2.68	0	0	3	0.28
Purpura	3	2.37	0	0	3	0.28	3	2.68	0	0	3	0.28
Generalized vaccinia	0	0	0	0	0	0	0	0	2	0.21	2	0.19
Vaccinia necrosum	1	0.79	0	0	1	0.09	0	0	0	0	0	0
Post-vaccinal encephalitis	0	0	0	0	0	0	1	0.89	0	0	1	0.09
Total	8	6.34	3	0.32	11	1.04	7	7.27	2	0.21	9	0.86

TABLE 8

SKIN REACTIONS FOLLOWING REVACCINATION WITH CALF LYMPH AND TISSUE CULTURE VACCINE

Years (after primary vaccination)	Primary vaccination with	Revaccination with	Number	Primary reactions		Accelerated reactions		Immediate reactions	
				No.	%	No.	%	No.	%
2 [a]	Calf lymph	Calf lymph	100	7	7.00	46	46.00	47	47.00
		TC vaccine	102	5	4.90	43	42.16	54	52.94
	TC vaccine	Calf lymph	99	8	8.08	41	41.41	50	50.50
		TC vaccine	93	8	8.60	37	39.78	48	51.61
3 [b]	Calf lymph	Calf lymph	101	6	5.94	50	49.50	45	44.55
		TC vaccine	98	5	5.10	35	35.71	58	59.18
	TC vaccine	Calf lymph	108	7	6.48	41	37.96	60	55.56
		TC vaccine	99	3	3.03	33	33.33	63	63.64
6 [c]	Calf lymph	Calf lymph	118	4	3.39	57	48.30	57	48.30
		TC vaccine	118	9	7.63	63	53.39	46	38.98
	TC vaccine	Calf lymph	122	7	5.74	72	59.02	43	35.25
		TC vaccine	124	9	7.26	69	55.64	46	37.10

[a] $X^2 = 0.49$ $P > 0.05$ [b] $X^2 = 3.69$ $P > 0.05$ [c] $X^2 = 1.72$ $P > 0.05$

TABLE 9

COMPARISON OF SERUM NEUTRALIZATION TITRES OF TWO VACCINES
6 YEARS AFTER PRIMARY VACCINATION

Virus used for neutralization testing	Serum from different groups	Number	Antibody titre, in % of neutralization					
			50	50-	60-	70-	80-	90-
Cell culture vaccinia virus	Cell culture	131	32 (24.4%)	19 (14.5%)	22 (16.8%)	26 (19.8%)	24 (18.3%)	8 (6.1%)
	Calf lymph	111	27 (24.3%)	11 (9.9%)	22 (19.8%)	25 (23.5%)	20 (18.0%)	6 (5.4%)
Calf lymph vaccinia virus	Cell culture	98	37	24 (24.5%)	11 (11.2%)	19 (19.2%)	6 (6.1%)	1 (1.0%)
	Calf lymph	97	31 (32.0%)	23 (23.7%)	17 (17.5%)	18 (19.6%)	8 (8.2%)	0

TABLE 10

RATES OF HIGH FEVER AS A COMPLICATION OF VACCINATION WITH TWO KINDS OF VACCINE

Vaccine used	Place	Year	Virus strains of vaccines	Number	Rate of high fever (%)
Cell culture vaccine	Zhengzhou Honan	1971	K9 S TH S	195 189	2.1 7.9
	Jinhua Chejiang	1972	K9 S TH S	79 76	10.33 17.8
Calf lymph vaccine	Shanoguan Guangdong	1973	K9 S TH S	141 144	8.08 22.22
	Zhanjiang Guangdong	1974	K9 S TH S	120 115	6.12 7.92
	Beijing	1977	K9 S TH S	117 118	1.71 5.98

TABLE 11

REVACCINATION REACTION AFTER PRIMARY VACCINATION WITH TWO KINDS OF VACCINE

Interval between primary and revaccination (years)	Vaccinia virus strain used	Number	Primary reaction		Accelerated reaction		Immediate reaction	
			No.	%	No.	%	No.	%
2	K9 S TH S	113 291	4 20	3.5 6.9	22 77	19.5 26.5	87 194	77.0 70.0
4	K9 S TH S	125 281	0 13	0 4.6	45 91	36.0 32.4	80 177	64.0 63.0
6	K9 S TH S	91 212	7 17	7.7 8.0	39 83	42.9 39.1	45 112	49.4 52.83

2. Administrative Structure of Health Services

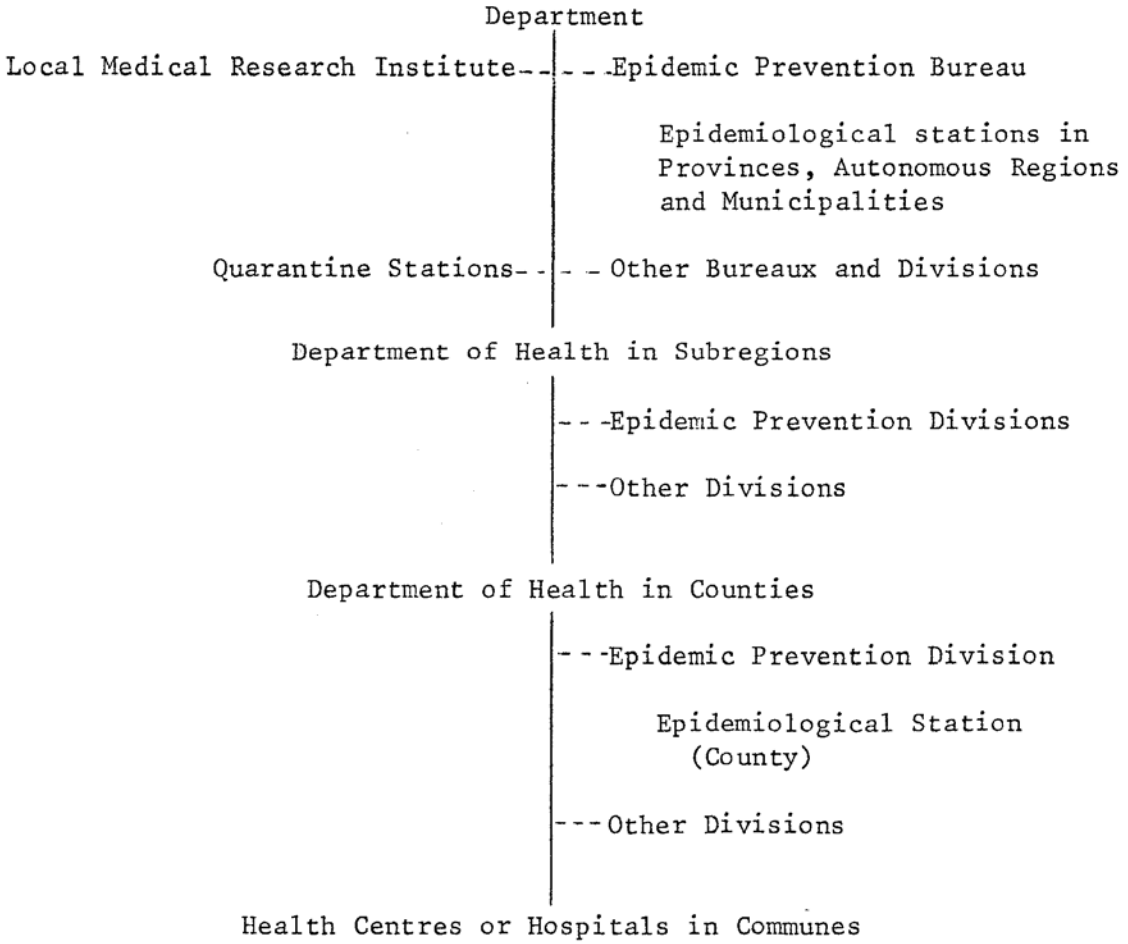
2.1 Departments of the Ministry of Health

- Maternity and Child Health
- Industrial Health
- Medical Sciences and Technology
- Medical Education
- Medical Practice
- Chinese Medicine
- Pharmacology
- Foreign Affairs
- Epidemic Prevention
- Health in Provinces, Autonomous Regions and Municipalities

2.2 Bureaux of the Department of Epidemic Prevention

- Epidemic Prevention
- Hygiene and Sanitation
- Biological Products

2.3 Structure of the Department of Health in the Provinces, Autonomous Regions and Municipalities



2.4 Medical Research Institutes under the Ministry of Health

These include, among others, the Institutes of:

- Research of Biological Products
- Control of Pharmaceutical and Biological Products; and
- Chinese Academy of Medical Sciences, including the institutes of:
  - Epidemiology and Microbiology
  - Virology
  - Parasitic Diseases
  - Hygiene and Sanitation, and other institutes.

3. Quarantine Services in South-west China

To prevent the spread of the quarantinable diseases, including smallpox, into or out of China, quarantine services and stations have been set up in the border areas in south-west China. They are situated in Fangcheng, Beihai, Pingxiang and Nanning in Guangxi Autonomous Region; Haikou and Zhanjiang in Guangdong Province; Kunming and Hekou in Yunnan Province; and in Zhangmu in Tibet. Their duty is to examine the health and hygienic condition of travellers and their baggage, as well as of aeroplanes, trains, trucks and other vehicles, and to carry out any necessary anti-epidemic measures.

At present, attempts are being made to improve the techniques and procedures of these quarantine services and stations, such as simplification of the quarantine procedures and utilization of telegraph or radio in the reporting system.

For those border areas where no quarantine station has been set up the Health Department of the Local People's Government requires its subordinate health centres or epidemiological stations to do the quarantine work, including the health inspection and examination of travellers.

The quarantine services reinforce their quarantine measures according to the monthly epidemiological and statistical data reported by the local health departments or stations in the border counties.

If there is any epidemic of a communicable disease occurring in a neighbouring country, the Health Department of the Local People's Government ensures the necessary organizational and technical measures to prevent the spread of the disease into Chinese territory.