

Update Le point

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Smallpox and its post-eradication surveillance*

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Dedicated to the Tenth Anniversary of worldwide freedom from smallpox

Since May 1980 when the Thirty-third World Health Assembly declared the global eradication of smallpox, WHO has been developing a comprehensive system of surveillance aimed at maintaining the world permanently free from this disease. By 1984 all countries had ceased smallpox vaccination of the general public and had withdrawn the requirement for smallpox vaccination certificates from international travellers. A number of countries have also discontinued vaccination of military personnel. Up until now WHO has maintained a stock of smallpox vaccine sufficient to vaccinate 300 million persons, but considering that 10 years have elapsed since the last endemic case of smallpox, maintenance of this reserve is no longer indicated. WHO continues to monitor rumours and coordinate the investigation of suspected cases, all of which turned out to be misdiagnosed chickenpox or some other skin disease, or errors in recording or reporting. Variola virus is now kept in only two WHO Collaborating Centres which possess high-security containment laboratories. Since the variola virus gene pool has been cloned in bacterial plasmids which provide sufficient material to solve future research and diagnostic problems, there is no need to retain stocks of viable variola virus any longer. The results of a special programme for the surveillance of human monkeypox have confirmed that the disease does not pose any significant health problem. In addition to testing human and animal specimens, WHO collaborating laboratories have made progress in the analysis of the DNA of orthopoxviruses and in the development of reliable serological tests.

The world's last outbreak of smallpox was in Somalia in October 1977. Subsequently, with the declaration of the global eradication of smallpox by the Thirty-third World Health

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Assembly" in May 1980, steps were taken to ensure world confidence in the fact of smallpox eradication so that the benefits of this achievement, especially termination of vaccination against smallpox, could soon be realized.

WHO therefore developed a system for post-eradication smallpox surveillance based on nineteen recommendations formulated by the Global Commission for the Certification of Smallpox Eradication (1). The goal of this surveillance, which was initiated by WHO in 1980 in accordance with these recommendations, was to maintain the world permanently free from smallpox. In 1981, a Committee on Orthopoxvirus Infections was appointed by the Director-General to advise the Organization on the implementation of the recommendations of the Global Commission. The Committee met in 1982, 1983, 1984 and 1986.

POST-SMALLPOX-ERADICATION ACTIVITIES

Vaccination policy

Routine vaccination of the public had ceased in several countries of North America, Europe and the Western Pacific even before the detection of the last smallpox case in Somalia in October 1977 (Fig. 1). Even so, 133 countries were still continuing routine vaccination programmes. With the declaration of the global eradication of smallpox in May 1980, the representatives of WHO's Member States endorsed the recommendation that routine vaccination against smallpox was no longer justified and should be discontinued in

" Resolution WHA33.3.

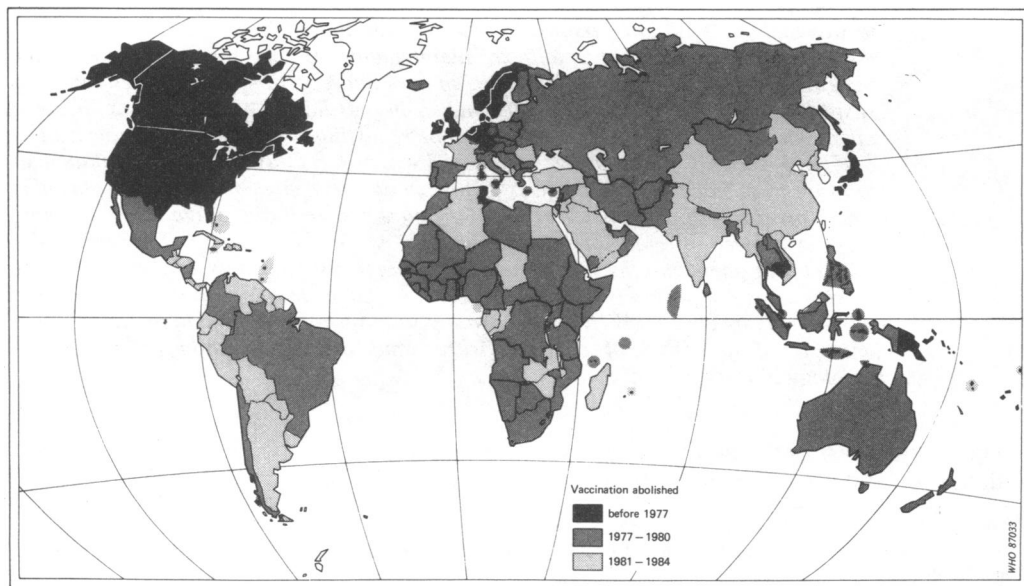


Fig. 1. Countries that abolished or reported the suspension of routine smallpox vaccination in the period before 1977, 1977-80, and 1981-84.

Table 1. Number of Member States of WHO continuing routine smallpox vaccination, by year and WHO Region, 1977-86

WHO Region	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986
Africa	43	43	32	11	1	1	0	0	0	0
Americas	27	25	25	22	0	0	0	0	0	0
South-East Asia	11	11	10	4	1	1	0	0	0	0
Europe	23	21	18	6	3	2	2	2	0	0
Eastern Mediterranean	21	16	12	6	2	1	0	0	0	0
Western Pacific	8	7	6	3	0	0	0	0	0	0
No. of Member States continuing vaccination	133	123	103	52	7	5	2	2	0	0
Total number of Member States	150	151	152	156	157	158	161	165	166	166
Per cent continuing to vaccinate	89	81	68	33	4.5	3.2	1.2	1.2	0	0

every country. By the end of 1980, only 52 of the 156 Member States of WHO were still continuing vaccination programmes and by the end of 1983, only Albania and France remained, both of which stopped all routine vaccination in 1984 (Table 1).

Routine vaccination, however, did not always cease immediately because appropriate instructions were not always effectively communicated to the periphery within countries. Sometimes, smallpox vaccine continued to be made available on request or the vaccine was misused, e.g., for treating herpes infections, warts, etc., which resulted in some severe complications (2-4). Through the *Weekly epidemiological record* and by direct communication with governments, WHO continually advised against vaccination and the use of smallpox vaccine therapeutically because of the risk of complications. In 1983 the Organization contacted governments and vaccine-producers and urged them not to distribute the vaccine. Nevertheless, military personnel have continued to be vaccinated in some countries which resulted in accidental vaccinal infection of civilians (5-7). In 1983, the Committee on Orthopoxvirus Infections recommended that military personnel who had been vaccinated should be confined to their bases and prevented from contacting unvaccinated persons for a period of two weeks following vaccination (8); finally, in 1986, the Committee recommended that smallpox vaccination of military personnel should be terminated (9).

International vaccination certificates for smallpox were still required by 23 of WHO's Member States in 1980. In May 1981, the Thirty-fourth World Health Assembly formally deleted smallpox from the International Health Regulations (10). Despite the cancellation of the requirement for smallpox vaccination certificates by health administrations, international travellers were still occasionally asked for such certificates at seaports or airports, or when applying for visas, or by travel agencies. WHO cooperated with national health authorities to correct the situation after reports of such incidents and assisted with the correction of information in tourist guides. By 1986 the number of such incidents had virtually ceased.

Smallpox vaccination is now only indicated for a small number of persons at special risk: (i) investigators who handle variola and monkeypox viruses in laboratories and persons entering such laboratories; (ii) laboratory workers exposed to other orthopoxviruses infectious to man (cowpox and vaccinia viruses); and (iii) staff of surveillance teams studying the epidemiological and ecological characteristics of monkeypox virus in Africa.

Reserve stock of smallpox vaccine

The WHO reserve stock of smallpox vaccine was established in 1980. The existence of such a stock made it much easier for Member States to decide to discontinue both smallpox vaccination and vaccine production. It was widely publicized that vaccine from this stock could be made available to any country needing to undertake emergency containment measures, should the diagnosis of smallpox be confirmed both clinically and by laboratory tests. In the event of an emergency, the vaccine and diluent, bifurcated needles, needle containers, instruction leaflets, and recognition cards could be dispatched to any country in the world within 24 hours.

At the end of 1986 the stock amounted to 5 034 178 ampoules in 459 batches. Using bifurcated needles, this amount of vaccine would be sufficient to vaccinate about 300 million persons. For security purposes, the vaccine was stored in two independent locations in Switzerland—in Geneva and in Lausanne. Vaccine batches are regularly monitored for potency by the WHO Collaborating Centre for Smallpox Vaccine in Bilthoven, the Netherlands. Between 1981 and 1985 all but six batches of vaccine proved to have a satisfactory potency.

In 1985, 22 countries reported that they had their own national vaccine reserves amounting to over 100 million doses, of which some 82% were properly maintained and tested (Table 2). Many of these countries indicated that they intended to maintain the vaccine until the year 1990 although some had not yet established their policy on this matter.

At the time smallpox transmission was interrupted in 1977, WHO knew of 76 laboratories producing smallpox vaccine. This number had declined to 14 laboratories in 11 countries by 1984. Seed lots of vaccinia virus, suitable to establish vaccine production, were prepared by the WHO Collaborating Centre for Smallpox Vaccine in the Netherlands and distributed to laboratories in France, Japan and the USA and can be made available to any country through the Organization. In 1985, seed lots were being held in 17 laboratories in 13 countries where vaccine production had ceased, the Lister and Elstree strains of vaccinia virus being the most common (Table 3).

Taking into consideration the fact that nearly 10 years had elapsed since the last endemic case of smallpox, and that human monkeypox had not proved to be a significant health problem, the Committee on Orthopoxvirus Infections in March 1986 concluded that the maintenance of the global reserve of smallpox vaccine by WHO was no longer indicated (9).

Table 2. National stocks of smallpox vaccine, 1985

WHO Region	No. of countries	Number of doses ^a	
		Stored	Properly maintained ^b
Africa	1 (1) ^c	30 000 000	30 000 000
Americas	4 (4)	23 934 720	23 659 070
South-East Asia	2 (2)	13 976 100	—
Europe	9 (11)	19 145 500	17 845 500
Eastern Mediterranean	2 (2)	3 013 500	—
Western Pacific	4 (9)	12 395 500	12 395 500
Total	22 (29)	102 465 320	83 900 070

^a These represent minimum figures; 3 of the 22 countries that hold vaccine reserves have not indicated the number of doses held and are excluded from the totals shown.

^b Held at a temperature of less than 0 °C and periodically tested for potency.

^c Figures in parentheses are the number of institutions in the countries.

Table 3. Number of countries producing smallpox vaccine, 1977–85, and countries holding seed lots in 1985, by WHO Region

WHO Region	No. of countries producing vaccine									No. of countries holding seed lots in 1985 ^a
	1977	1978	1979	1980	1981	1982	1983	1984	1985	
Africa	5	5	3	1	0	0	0	0	0	1
Americas	14	14	10	3	1	1	1	1	1	3
South-East Asia	7	6	6	2	1	1	0	0	0	3
Europe	25	23	21	13	13	10	8	8	8	1
Eastern Mediterranean	7	7	6	2	2	1	1	0	0	2
Western Pacific	18	18	16	5	5	2	2	2	2	3
Total	76	73	62	26	22	15	12	11	11	13

^a Excluding those still producing vaccine.

Surveillance of suspected smallpox cases

Experience in many countries indicated that reports of suspected cases of smallpox could be expected to be received by WHO from various sources for several years, even after the declaration of smallpox eradication. The thorough and prompt investigation of such reports, supported by laboratory testing and subsequent disclosure of results, was regarded as a very important element in maintaining public confidence in the fact of eradication. In 1981, the Organization distributed guidelines for the management of suspected cases of smallpox,^b emphasizing that a suspected case of smallpox was a public health emergency and must be promptly investigated.

^b *Management of suspected cases of smallpox in the post-eradication period.* Unpublished WHO document. WHO/SE/80.157 Rev. 1.

Table 4. International Rumour Register: number of suspected cases of smallpox reported to WHO headquarters, by WHO Region, 1980–86

WHO Region	Number of reports								Results of investigation			
	1980	1981	1982	1983	1984	1985	1986	Total	Chickenpox	Measles	Other skin disease	Erroneous/vague reports
Africa	9	11	5	5	6	5	6	47	18	7	8	14
Americas	3	6	0	4	5	0	1	19	11	1	3	4
South-East Asia	12	4	3	8	8	5	2	42	17	7	2	16
Europe	1	2	0	0	0	0	0	3	3	0	0	0
Eastern Mediterranean	4	3	2	1	2	0	0	12	2	1	2	7
Western Pacific	2	4	0	1	0	0	1	8	3	3	1	1
Total	31	30	10	19	21	10	10	131	54	19	16	42

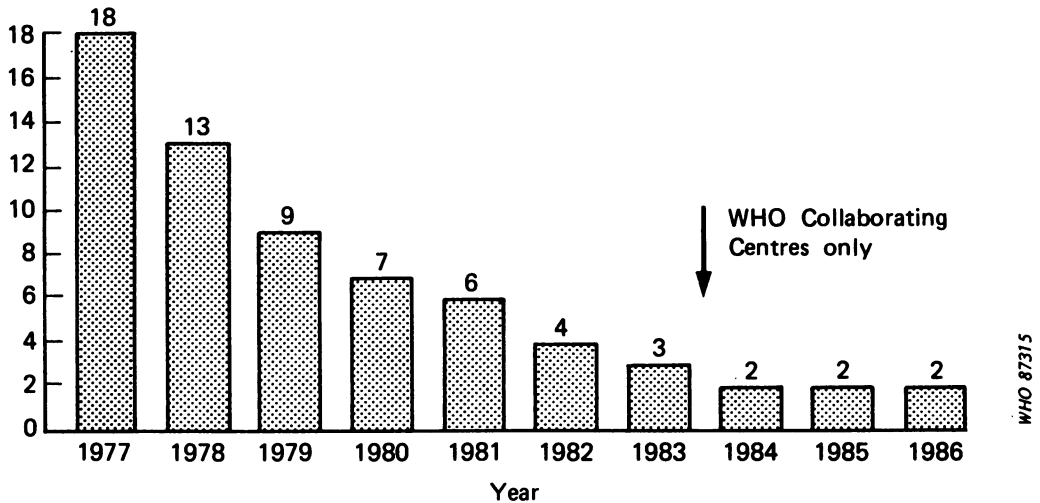


Fig. 2. Number of laboratories retaining variola virus, 1977–86.

Since 1980, WHO has coordinated the investigation of 131 rumours of smallpox which are recorded in an International Rumour Register. However, the majority of all rumours were promptly dealt with at country level; for example, between 1980 and 1985, 68 suspected cases of smallpox were examined in Bangladesh and 86 in India, of which only some appeared in the International Rumour Register. Most rumours reaching WHO originated with physicians, tourists, the general public or the media, rather than from the public health network. Laboratory diagnostic services were provided by the WHO Collaborating Centres at the Centers for Disease Control, Atlanta, USA, and the Research Institute for Viral Preparations, Moscow, USSR. All rumours have turned out to be diseases other than smallpox, the most common being chickenpox and other skin diseases, or else turned out to be unfounded rumours arising from recording errors or inaccurate or false reporting (Table 4). Monkeypox patients have been excluded from the rumour register and are listed separately. The results of investigations of such reports have been published periodically in the *Weekly epidemiological record*.

Retention of variola virus stocks

A laboratory-associated outbreak of smallpox in Birmingham, England, in 1978, provided strong reinforcement to WHO's efforts to limit the number of laboratories retaining variola virus stocks. In 1979, the Global Commission recommended that no more than four laboratories should hold and handle variola virus, and by 1980 the number had fallen from 76 in 1976 to 7 (Fig. 2). Since 1984, stocks of variola virus have been retained in only two WHO Collaborating Centres, in the Centers for Disease Control, Atlanta, USA, and the Research Institute for Viral Preparations, Moscow, USSR. Both are equipped with high-security, maximum-containment laboratories. Since 1978, WHO has sent teams of experts to periodically inspect all laboratories retaining variola virus and to verify that biosafety precautions met the WHO standards (Table 5). The virus is no longer cultured in these two laboratories, and in March 1986, the Committee on Orthopoxvirus Infections considered that there was no longer any need even to retain stocks of variola virus because

Table 5. WHO inspection visits to laboratories holding stocks of variola virus, 1978–86

Laboratory	1978	1979	1980	1981	1982	1983	1984	1985	1986
Centers for Disease Control, Atlanta, GA, USA	- ^a	+ ^a	-	+	+	-	+	+	-
U.S. Army Medical Research Institute for Infectious Diseases, Frederick, MD, USA	-	+	T ^b						
National Institute for Public Health, Bilthoven, Netherlands	-	+	-	T					
St Mary's Hospital Medical School, London, England	+ T								
Centre for Applied Microbiology and Research, Porton Down, England	-	-	+	+	T				
Department of Medical Microbiology, University of Birmingham, Birmingham, England	+ D ^b								
Research Institute for Viral Preparations, Moscow, USSR	-	+	+	-	-	+	-	-	+
National Institute of Virology, Sandringham, South Africa	+	+	-	+	-	+ D			

^a - = no visit; + = inspection visit.

^b T = stock transferred to WHO Collaborating Centre; D = stock destroyed.

of the existence of DNA from selected strains of both variola major and variola minor, cloned in *Escherichia coli* (9).

Surveillance of human monkeypox

Human monkeypox is clinically almost identical to smallpox and, in 1980, was designated the most important orthopoxvirus infection of man, requiring special surveillance in the post-smallpox-eradication era. Since 1980, the Organization has

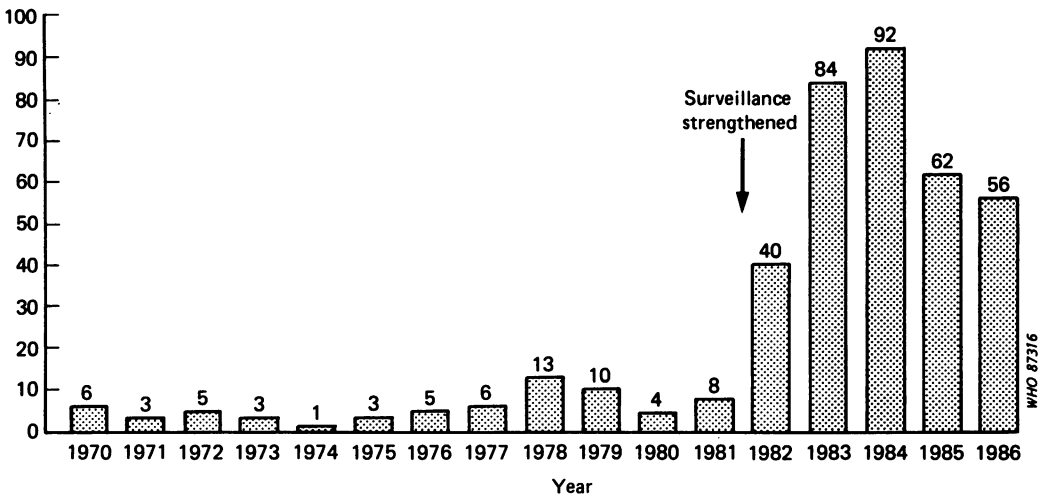


Fig. 3. Number of human monkeypox cases in western and central Africa, 1970–86.

strengthened its assistance to surveillance for human monkeypox and research on its epidemiology and ecology in selected endemic areas. These activities have been carried out mainly in Zaire, with a well-designed and well-supervised surveillance system based on peripheral health units and mobile surveillance teams.

The striking increase in the number of monkeypox cases reported in Zaire in the years 1982–84, compared with previous years (Fig. 3), was mainly due to this strengthened surveillance. In 1985 and 1986, the incidence declined despite an increasing number of susceptibles owing to the cessation of routine vaccination against smallpox. Human monkeypox remains an infrequent, sporadic zoonosis, 75% of the patients probably being infected from an animal source (11). There have been reports of presumed inter-human transmission but the majority stopped spontaneously after one generation. The average annual crude incidence rate observed in one of the most heavily affected areas was 6.3 per 100 000 inhabitants. No apparent change in the severity of the disease or in the secondary attack rate among close contacts has been noted in the 1980s, compared with the 1970s. The majority of primary cases contracting the disease from wild life failed to give rise to even one contact-infection (12).

In order to estimate the prevalence of human monkeypox in central and western Africa, serological surveys were conducted in unvaccinated persons living in forest areas of the Congo, Côte d'Ivoire, Sierra Leone and Zaire. These surveys revealed that at least 0.7% of persons tested had monkeypox-specific antibodies.

Ecological studies of the animal host of monkeypox virus conducted in Zaire and the Central African Republic advanced rapidly in 1984–86 and indicate that squirrels are a significant reservoir of monkeypox virus in some areas (13). These animals are abundant among the oil-palms found in agricultural areas surrounding villages and separating them from the primary rain forest.

In March 1986, the Committee on Orthopoxvirus Infections felt that, with the low incidence rate of human monkeypox and growing confidence that the virus cannot sustain itself by inter-human transmission, human monkeypox does not pose a significant health problem and that further research could be considered within the broader context of overall research priorities in western and central Africa.

Laboratory investigations and research

WHO has been actively involved in the maintenance of suitable laboratory expertise and laboratory preparedness for unexpected problems that might arise in relation to smallpox or other poxvirus diseases of man. There have also been important unsolved virological and immunological problems related to orthopoxviruses that deserved further research.

Most of the laboratory diagnostic work has been carried out in the two WHO Collaborating Centres: the Centers for Disease Control, Atlanta, USA, and the Research Institute for Viral Preparations, Moscow, USSR. Between 1980 and 1986, these two centres tested about 22 000 specimens collected from suspected cases of smallpox and human monkeypox, persons infected by other poxvirus infections (tanapox, molluscum contagiosum, etc.), and clinically atypical cases of chickenpox, as well as from apparently healthy persons sampled in several sero-epidemiological surveys (Table 6). In addition to samples from humans, 2800 animal specimens collected during the search for the animal reservoir of monkeypox and tanapox viruses were examined.

Three main areas of research supported by WHO in the post-eradication era were the analysis of the DNA of variola and other orthopoxviruses, the development of a reliable and sensitive serological test specific for various species of orthopoxviruses, and ecological and epidemiological investigation of monkeypox virus. Laboratories in the USA, Japan and the USSR have produced monoclonal antibodies that are able to distinguish monkeypox virus

Table 6. Number of human specimens (lesion material and sera) examined for evidence of poxvirus infection by the WHO Collaborating Centres in Atlanta and Moscow, by WHO Region, 1980-86

WHO Region	1980	1981	1982	1983	1984	1985	1986	Total
Africa ^a	2000 (3) ^b	13 592 ^c (4)	481 (4)	1212 (4)	957 (2)	761 (2)	707 (2)	19 710 (6)
Africa ^d	32 (11)	2228 ^c (7)	9 (3)	7 (3)	3 (2)	5 (3)	0 (0)	2284 (18)
Americas	0 (0)	16 (1)	0 (0)	10 (1)	0 (0)	0 (0)	0 (0)	26 (2)
South-East Asia	1 (1)	0 (0)	13 (1)	3 (2)	0 (0)	0 (0)	0 (0)	17 (3)
Europe	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Eastern Mediterranean	10 (4)	36 (2)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	47 (5)
Western Pacific	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Total	2045 (21)	15 872 (14)	504 (9)	1232 (10)	960 (4)	766 (5)	707 (2)	22 086 (36)

^a Countries where monkeypox has been found (Cameroon, Central African Republic, Côte d'Ivoire, Liberia, Nigeria, Sierra Leone, Zaire).

^b Figures in parentheses indicate the number of countries that provided the specimens.

^c Includes 12 810 specimens collected in serological surveys in Côte d'Ivoire, Sierra Leone and Zaire.

^d Countries where monkeypox has not been found.

^e Includes 2114 specimens collected in a serological survey in the Congo.

from other known orthopoxviruses. A competitive antigen-binding inhibition assay using monoclonal antibodies for the immunodiagnosis of monkeypox virus has been developed recently in Japan.

Documentation of the smallpox eradication programme

As the eradication of smallpox is a unique event in the history of mankind, it was felt important to document the operational and scientific achievements of the programme, as well as the experiences and lessons, especially those that are applicable to other health programmes. The Organization published books describing the smallpox eradication programmes in Bangladesh (14), Ethiopia (15), India (16) and Somalia (17) and assisted in the preparation of a book dealing with the management aspects of the Indian smallpox eradication programme (18).

A comprehensive reference work, *Smallpox and its eradication*, dealing with the scientific, operational and administrative aspects of the global eradication of smallpox, is now in preparation by WHO to mark the 10th anniversary of the occurrence of the last case of endemic smallpox. Numerous articles on smallpox and related orthopoxvirus infections have been published in WHO's periodicals and elsewhere, and documentation relating to the programme has been catalogued and retained for archival purposes in WHO headquarters in Geneva.

CONCLUSIONS

For many centuries the word "smallpox" brought terror to the civilized world because millions of people had died or been disfigured by this infection. The World Health Assembly's declaration of global eradication in May 1980 was therefore a historic landmark in man's conquest of disease. The nineteen recommendations for a post-eradication policy, effectively covering all important health aspects concerned with orthopoxviruses, which had been formulated by the Global Commission for the Certification of Smallpox Eradication and endorsed by the Thirty-third World Health Assembly, have now been implemented so that the world can be permanently free from smallpox.

REFERENCES

1. WORLD HEALTH ORGANIZATION. *The global eradication of smallpox. Final report of the Global Commission for the Certification of Smallpox Eradication*. Geneva, 1980.
 2. KERN, A. B. & SCHIFF, B. L. Smallpox vaccinations in the management of current herpes simplex: a controlled evaluation. *Journal of investigative dermatology*, **33**: 99–102 (1959).
 3. FREED, E. R. ET AL. Vaccinia necrosum and its relationship to impaired immunological responsiveness. *American journal of medicine*, **52**: 411–420 (1972).
 4. U.S. FOOD AND DRUG ADMINISTRATION. Inappropriate use of smallpox vaccine. *FDA drug bulletin*, **12**: 12 (1982).
 5. LABORATORY CENTRE FOR DISEASE CONTROL Vaccinia outbreak—Newfoundland. *Canada diseases weekly report*, **7**: 29–30 (1981).
 6. CENTERS FOR DISEASE CONTROL. Contact spread of vaccinia from a recently vaccinated marine—Louisiana. *Morbidity & mortality weekly report*, **33** (3): 37–38 (1984).
 7. CENTERS FOR DISEASE CONTROL. Contact spread of vaccinia from a National Guard vaccinee—Wisconsin. *Morbidity & mortality weekly report*, **34** (13): 182–183 (1985).
 8. Orthopoxvirus surveillance: post-smallpox eradication policy. *Weekly epidemiological record*, **58** (20); 149–154 (1983).
 9. Committee on Orthopoxvirus Infections: report of the fourth meeting. *Weekly epidemiological record*, **61** (38): 289–293 (1986).
 10. WORLD HEALTH ORGANIZATION. *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board, Volume II, 1973–1984*. Geneva, 1985.
 11. ARITA, I. ET AL. Human monkeypox: a newly emerged orthopoxvirus zoonosis in the tropical rainforest of Africa. *American journal of tropical medicine and hygiene*, **34**: 781–789 (1985).
 12. JEŽEK, Z. ET AL. Human monkeypox: a study of 2510 contacts of 214 patients. *Journal of infectious diseases*, **154**: 551–555 (1986).
 13. KHODAKEVICH, L. ET AL. Role of squirrels in sustaining monkeypox virus transmission. *Tropical and geographical medicine* (in press).
 14. JOARDER, A. K. ET AL. *The eradication of smallpox from Bangladesh* (WHO Regional Publications, South-East Asia Series No. 8). New Delhi, WHO Regional Office for South-East Asia, 1980.
 15. TEKESTE, Y. ET AL. *Smallpox eradication in Ethiopia*. Brazzaville, WHO Regional Office for Africa, 1984.
 16. BASU, R. N. ET AL. *The eradication of smallpox from India*. (History of International Public Health series, No. 2). New Delhi, WHO Regional Office for South-East Asia, 1979.
 17. JEŽEK, Z. ET AL. *Smallpox eradication in Somalia*. Alexandria, WHO Regional Office for the Eastern Mediterranean and Ministry of Health, Somali Democratic Republic, 1981.
 18. BRILLIANT, L. B. *The management of smallpox eradication in India: a case study and analysis*. Ann Arbor, University of Michigan Press, 1985.
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