Memoranda
Mémorandums

Memoranda are statements concerning the conclusions or recommendations of certain WHO scientific meetings; they are signed by the participants in the meeting.

Les Mémorandums exposent les conclusions et recommandations de certaines réunions scientifiques de l'OMS; ils sont signés par les participants à ces réunions.

Bulletin of the World Health Organization, 62 (5): 703 – 713 (1984)

The current status of human monkeypox: Memorandum from a WHO Meeting*

In spite of a recent increase in the number of reported cases, human monkeypox remains a rare sporadic zoonotic disease with limited capacity to spread betweeen humans. As such, the disease does not at present require specific public health measures. However, much of the population in the enzootic region, especially in the 5–14-year age group, still retains some immunity as a result of vaccination against smallpox. Continuation of surveillance activities on the same scale as at present until 1989 should provide a clear indication of the extent to which human monkeypox may be considered a public health problem, either generally or in particular localities. Such surveillance should also provide a definitive clinical and epidemiological picture of this newly discovered disease. Further research on its ecology and epidemiology will be facilitated by the development of a simple, specific and sensitive serological test for monkeypox virus-specific antibodies.

Human monkeypox is a zoonosis that occurs sporadically in the tropical rain forests of West and Central Africa. Monkeypox virus belongs to the genus *Orthopoxvirus*, and in humans may give rise to an extensive rash with significant associated mortality, particularly in children. In the laboratory the virus has a wide host range. Animals infected in nature include some species of non-human primates, but the reservoir hosts are unknown. Man is an incidental host and spread from person to person is estimated to occur in only about 15% of non-vaccinated close family contacts.

Human monkeypox is clinically similar to smallpox, except for the occurrence of lymphadenopathy (Fig. 1, opposite p. 706). The similarity between the two infections led the Global Commission for the Certification of Smallpox Eradication, in their final report in December 1979, to recommend that surveillance for human monkeypox should continue in West and Central Africa, so that more could be discovered about the clinical features, epidemiology and natural history of the disease. Although, with the eradication of smallpox, this newly discovered disease constitutes the most important orthopoxvirus infection of man, information now available shows that it does not present a public health problem.

Surveillance activities were stepped up in 1982, and a substantial increase was observed in the number of reported cases of human monkeypox in Zaire (37 cases in 1982 compared with 52 for the twelve years 1970–81). In view of this, it was decided to maintain special surveillance activities in Zaire throughout 1983; as a result, further new and substantial findings have come to hand.

GENERAL SITUATION

Almost all cases of human monkeypox detected occurred in tropical rain forest areas; the majority of rain forest in West and Central Africa is to be found in Zaire (Table 1, Fig. 2 and 3). This accounts for the large proportion of cases detected in Zaire and for the concentration of surveillance activities in this country.

* This Memorandum was drafted by the signatories listed on pages 712-713 on the occasion of a meeting of the Committee on Orthopoxvirus Infections, held in Geneva on 28-30 March 1984. A French translation of this article will appear in a later issue of the *Bulletin*. Requests for reprints should be addressed to Chief, Smallpox Eradication, World Health Organization, 1211 Geneva 27, Switzerland.

Table 1. Number of human monkeypox cases reported in West and Central Africa by country and year, 1970–84

Country	No. of cases															
	1970	71	72	73	74	75	76	77	78	79	80	81	82	83	84[a]	Total
Cameroon										2						2
Central African Republic															5	5
Ivory Coast		1										1				2
Liberia	4															4
Nigeria		2							1							3
Sierra Leone	1															1
Zaire	1		5	3	1	3	5	6	12	7	3	6	37	56	3	148
Total	6	3	5	3	1	3	5	6	13	9	3	7	37	56	8	165

[a] January and February only.

Surveillance in Zaire

After 1981, active hospital and village-based surveillance was greatly intensified in three regions of Zaire, with the participation of 150 health stations and four mobile surveillance teams (Fig. 4). In 1982 and 1983, 90% of all cases in Zaire were discovered in these three Regions (Table 2). The increase in the number of cases seen in 1982 and 1983 may not be due solely to increased surveillance, but also, in part, to an increase in the number of susceptible persons exposed, or to fluctuations in the prevalence of the virus in its animal hosts.

In the areas studied, vaccination against smallpox was officially discontinued in 1980 but sporadic vaccination was carried out in 1981. In 1982 and 1983, the vaccination scar rate in children under 4 years of age fell substantially (Table 3). As the numbers of unvaccinated children increase it might be expected that the proportion of monkeypox cases in children would also increase. So far, there is no evidence of a shift in the age distribution of cases but it is too early to reach a conclusion on this matter. The increase in the number of cases might also be a temporary phenomenon, reflecting some cyclical fluctuation in the transmission of the virus among animals. Surveillance must be continued for a longer period in order to determine the reasons underlying the apparent increase in incidence. Additional information on the prevalence of monkeypox infection in selected animal species might be helpful in this regard.

Although the number of cases studied is small, the rate of person-to-person transmission between susceptible family contacts appears not to have changed significantly from the 15% estimated for the period 1970–81 (Table 4).

It is recommended that surveillance on human monkeypox in Zaire be continued at least until 1989 to monitor any change in incidence and to seek the reasons for any such change.

Incidence outside Zaire

In 1981, there was one case of human monkeypox in Ivory Coast and in February 1984, 5 cases were discovered among Pygmies in the southernmost part of the Central African Republic. Although the disease is well recognized in Zaire, the occasional occurrence of cases of monkeypox in other countries in West and Central Africa has given rise to rumours that smallpox has not been eradicated. It is important to provide full information on sporadic occurrences of this zoonosis to all countries in West and Central Africa. Adequate briefing should be given to the health authorities of countries with areas of tropical rain forest, so that health personnel will be aware of the existence of human monkeypox. National health services should be encouraged to report any suspected case of monkeypox to WHO, and special investigations, including the collection of specimens for laboratory study, should be made to confirm or negate the diagnosis. Pertinent information should be added to the WHO data bank on human monkeypox.

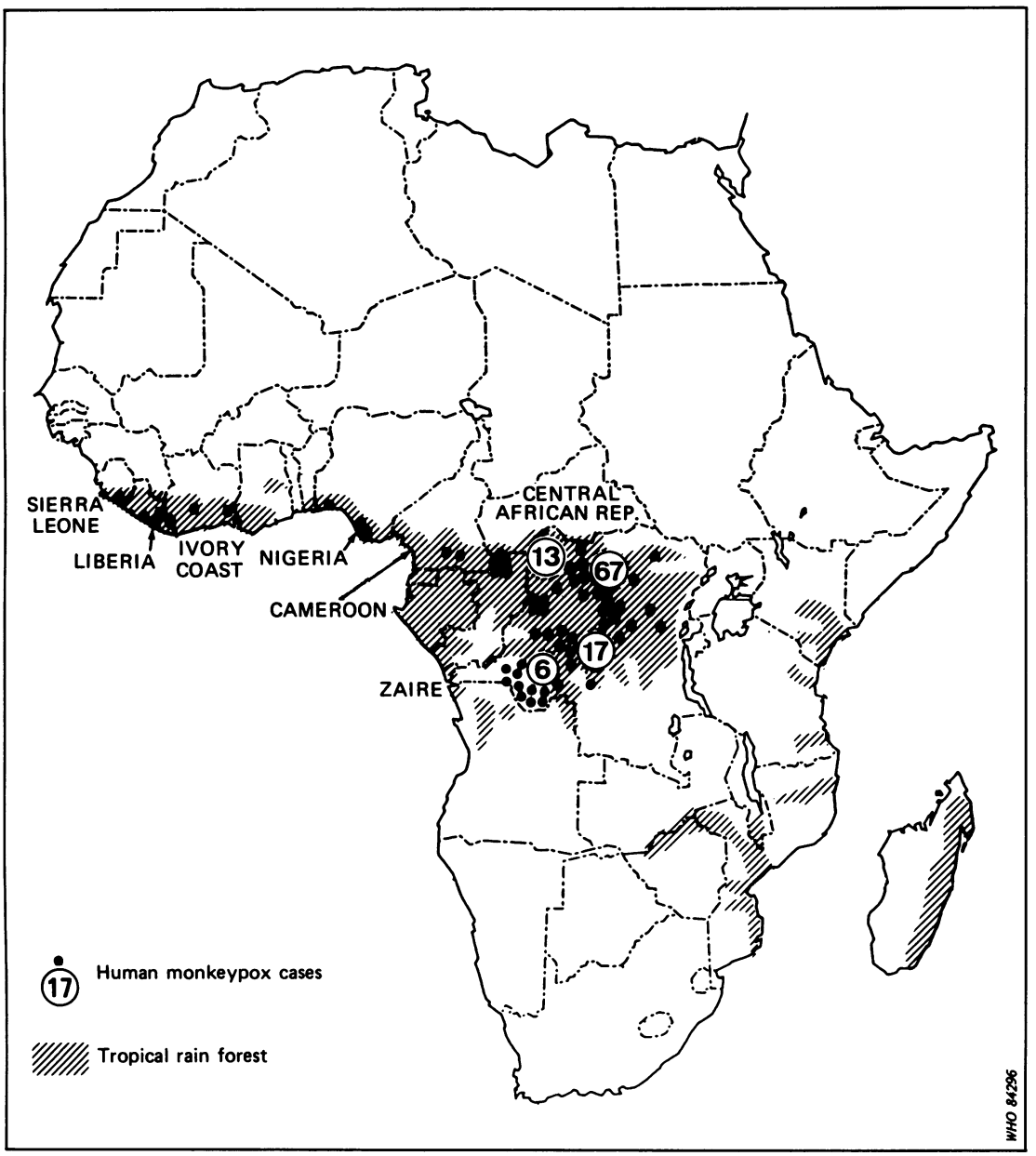


Fig. 2. Distribution of cases of human monkeypox reported in West and Central Africa between 1970 and 1 March 1984.

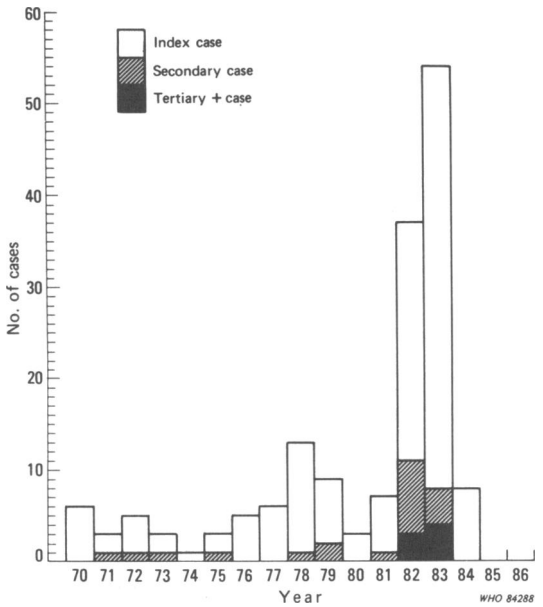


Fig. 3. Occurrence of cases of human monkeypox in West and Central Africa between 1970 and 1 March 1984.

DISEASE TRANSMISSION

Animal reservoirs and primary infection

The animal reservoir of monkeypox virus is as yet unknown, despite studies carried out by WHO collaborating centres and by special teams on several occasions between 1971 and 1979. The epidemiology does not fit that of an arthropod-borne disease. Serological investigation of specimens collected during the various surveys revealed that at least four species of monkey are infected in nature, and there is evidence of infection in chimpanzees. However, although sera containing antibodies to orthopoxviruses have been obtained from a wide range of animals, including squirrels, it is not yet possible to ascertain whether the positive reactions were due to an infection with monkeypox virus or another orthopoxvirus. Previously unrecognized orthopoxviruses have been isolated in other parts of Africa, e.g., from a gerbil in Benin and from horses in Kenya, and the existence of an orthopoxvirus, other than monkeypox, in rain forest areas cannot be excluded.

All patients with human monkeypox had had access to carcasses of animals of some kind within the presumed incubation period of about 14 days; however, so had other people living in the same villages. The majority of the animals concerned were apparently uninfected. These data provide no clue to the source of human monkeypox infection, and there is a need for case-control studies, to determine more precisely the kinds of animal with which cases have been in contact. Some evidence on this subject has already been collected. An infant in Zaire developed monkeypox 12 days after being abducted by a chimpanzee, an animal known to be susceptible to natural infection with monkeypox virus and to develop a generalized rash. The five cases discovered in Pygmies in the Central African Republic early in 1984 were infected at about the same time, and it was said that some days previously, they had eaten the meat of a monkey and a gazelle, both of which were sick with a pock-like disease. The Pygmies further said that pock disease was often encountered in monkeys and gazelles, and that meat from such sick animals was not given to children or pregnant women, since they might then contract a similar disease.

It is recommended that international cooperation be continued in support of the surveillance and research activities now centred in Zaire. A research centre, including a small laboratory unit, should be established in an appropriate place in Equateur Region, Zaire, to serve as a reference centre for surveillance activities. The centre would also act as a forward base for the collection and dispatch of specimens, provide some facilities for visiting scientists, and help to identify the animal hosts of the virus. Establishment of such a centre will be beneficial not only to Zaire but also to other countries of West and Central Africa where this zoonotic disease occurs.

Person-to-person transmission

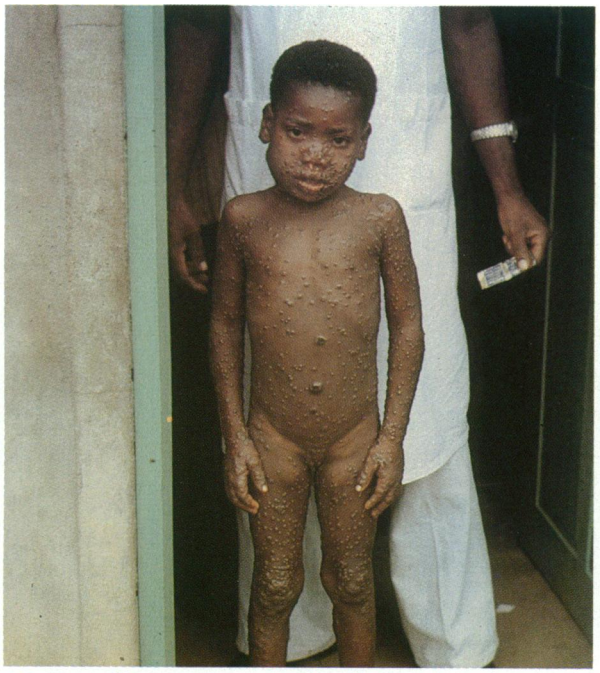
Human monkeypox is not easily transmitted from one person to another. Of 13 presumed transmission episodes among humans since 1982, transmission stopped at the secondary infection in 9 episodes, but may have proceeded to the third or fourth generation in four episodes (Fig. 5). The interval between onset of rash in subsequent generations varied between 7 and 23 days, which suggests that some of the episodes may have included co-primary infections or independent infections from animals. It is important to establish clearly the frequency of person-to-person transmission of human monkeypox, so that any future changes may be monitored.

It is recommended that, during surveillance activities, special attention be paid to the possibility of secondary and subsequent cases.

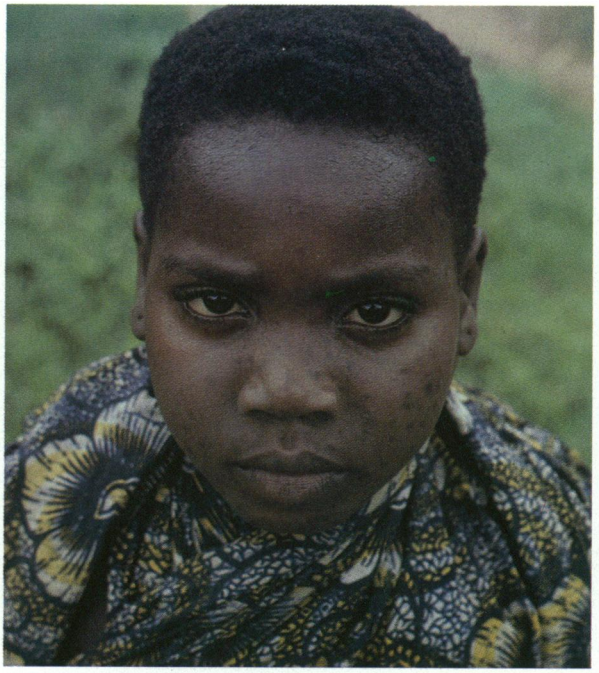
SEROLOGICAL DIAGNOSIS

The genus *Orthopoxvirus* includes nine known species, of which at least three (vaccinia, monkeypox,

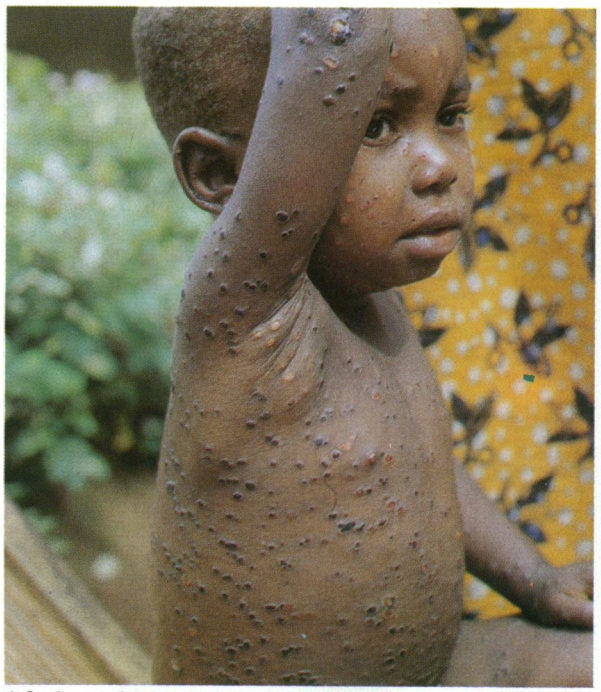
Fig. 1. Human monkeypox patients, Zaire



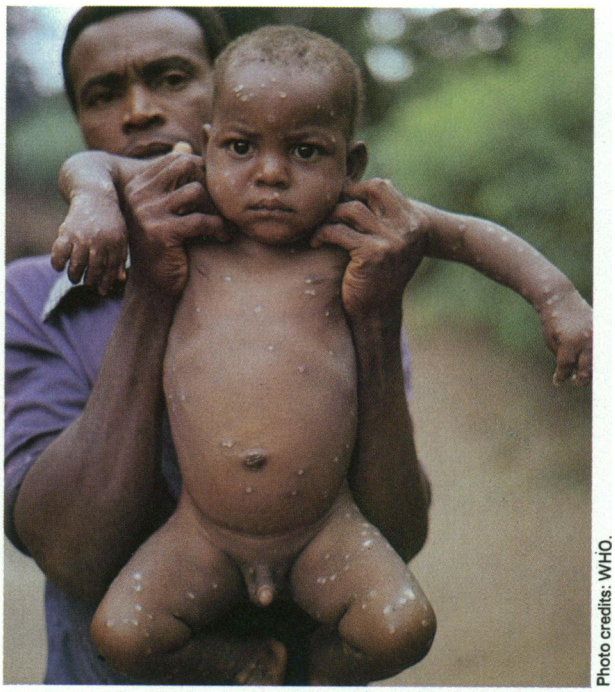
1.1. Case 25, age 7 years. Day 7 of rash in the acute stage. Note distinct bilateral inguinal lymphadenopathy. There is also submaxillar lymphadenopathy on the right side.



1.2. Case 25. 4½ years after illness. Note facial pockmarks. These disappear in 50% of patients after 5 years.



1.3 Case 81, age 3 years. Rash in scabbing stage, approximately day 12. Note lymphadenopathy in armpit.



1.4 Case 39, age 1 year. Day 24 of rash. Note depigmentation where scabs have come off. Even this mild case clearly shows more scarring on the extremities than on the trunk. Inguinal lymphadenopathy is still present.

Photo credits: WHO.

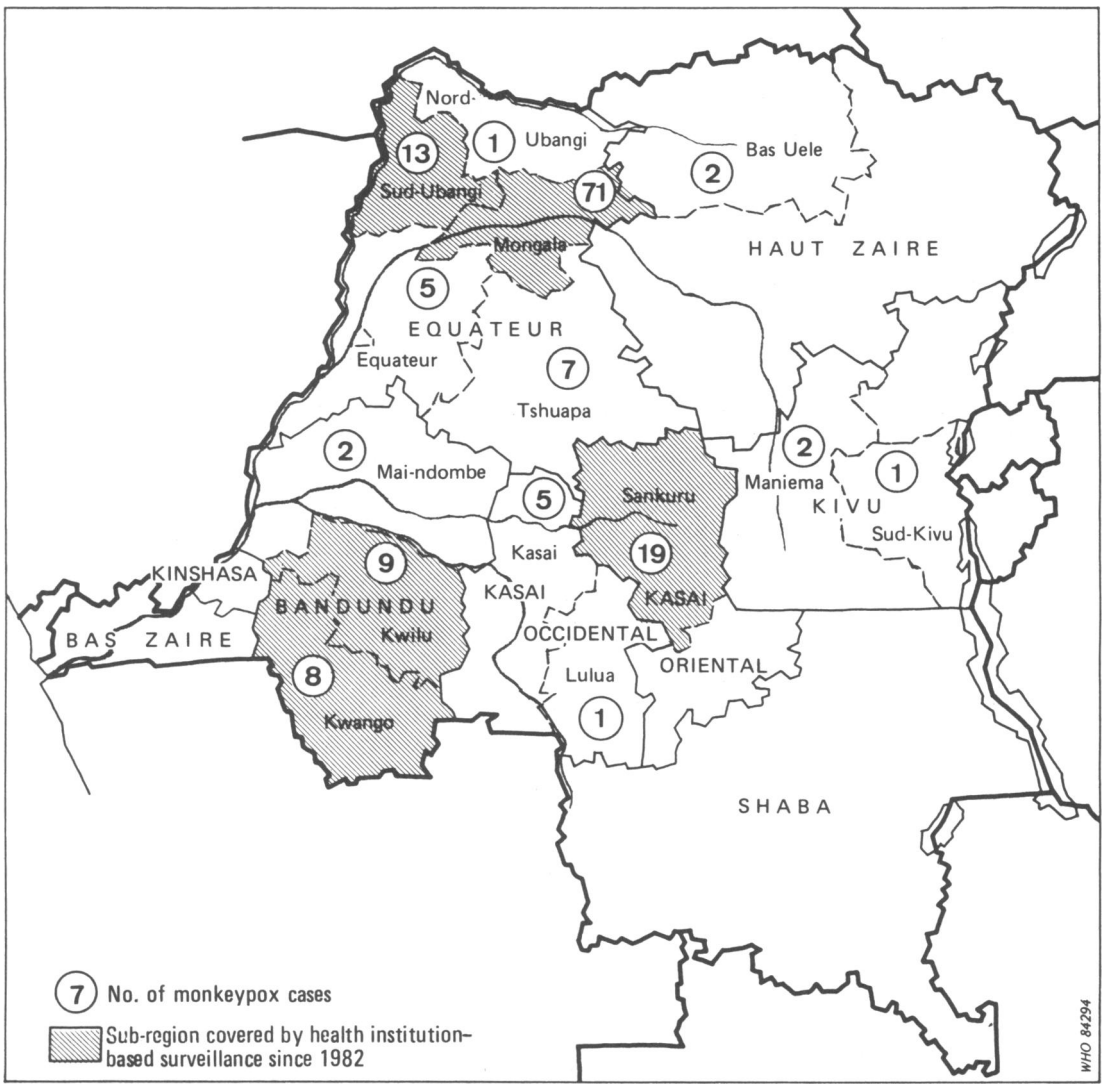


Fig. 4. Distribution of cases of human monkeypox in Zaire between 1970 and 1 March 1984.

Table 2. Number of human monkeypox cases in Zaire by region, 1970–84

Region	Population (million)	Year															Total
		1970	71	72	73	74	75	76	77	78	79	80	81	82	83	84[a]	
Bandundu[b]	3.6			1			1	1	1	2	1	1		8	3		19
Bas-Zaire	1.9																
Equateur[b]	3.0	1		3	3	1		3	3	4	5	1	5	20	47	3	99
Haut-Zaire	4.0													2			2
Kasai Occidental	2.2														6		6
Kasai Oriental[b]	1.8			1			2	1	1	5	1	1	1	6			19
Kinshasa	2.7																
Kivu	4.8								1	1				1			3
Shaba	3.8																
Total	27.8	1	0	5	3	1	3	5	6	12	7	3	6	37	56	3	148

[a] January and February only.
[b] Active surveillance of 5 million persons living in 5 subregions of Bandundu, Equateur and Kasai Oriental.

Table 3. Percentage of persons with a smallpox vaccination scar in villages where a human monkeypox case occurred and in surrounding villages, 1970–83

Year	Affected village				Surrounding area			
	No. of cases	Age group (years)			No. of localities	Age group (years)		
		0–4	5–14	⩾ 15		0–4	5–14	⩾ 15
1970	1	86.1	97.2	98.1	7	85.3	94.1	96.1
1971	–	–	–	–	–	–	–	–
1972	3	39.0	91.5	95.1	28	52.1	91.3	87.5
1973	2	61.9	95.0	94.2	8	60.0	94.4	93.1
1974	1	57.6	–	–	–	–	–	–
1975	1	55.6	80.8	85.7	7	5.7[a]	79.3	94.5
1976	4	44.6	83.5	87.7	52	40.0	83.2	88.7
1977	5	85.4	89.7	91.4	69	79.9	95.9	91.6
1978	8	74.6	92.8	93.9	103	61.6	93.3	92.8
1979	6	45.2	85.0	95.6	71	36.1	83.6	95.1
1980	3	43.7	87.4	92.9	15	41.2	94.9	92.5
1981	4	39.2	91.0	97.8	24	50.6	73.8	91.2
1982	19	33.2	81.6	94.2	179	26.3	86.9	93.4
1983	23	12.5	83.9	91.8	228	18.1	84.0	90.9

[a] Only 35 children aged 0–4 years were examined (2 with scar).

and taterapox) occur in West and Central Africa. All orthopoxviruses show extensive serological cross-reactivity in neutralization tests and other assays. For some years, methods have been available for presumptive species-specific diagnosis of monkeypox, variola and vaccinia, using sera pre-absorbed with viral suspensions. Such tests are not readily applicable to convalescent sera or sera from healthy animals or man taken during ecological or epidemiological surveys.

The method of serological diagnosis of monkeypox currently used in most laboratories is an initial

Table 4. Human monkeypox secondary attack rates in unvaccinated household contacts, 1970–81 and 1982–83

Age group (years)	1970–81			1982–83		
	No. of cases	No. of contacts	Attack rate (%)	No. of cases	No. of contacts	Attack rate (%)
0–4	2	18	11.1	9	52	17.3
5–14	3	17	17.6	5	40	12.5
⩾ 15	1	5	20.0	2	10	20.0
Total	6	40	15.0	16	102	15.7

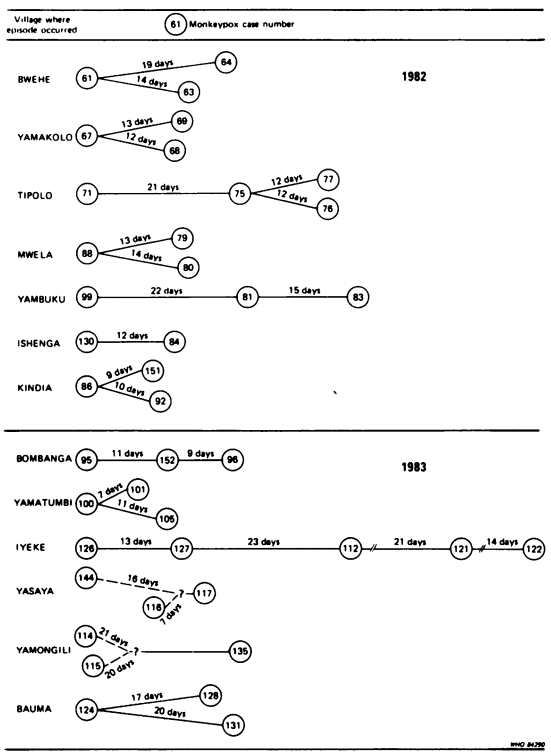


Fig. 5. Person-to-person transmission of monkeypox in Zaire in 1982 and 1983. The time interval between cases refers to the number of days between onset of rash in the two patients.

screening haemagglutination inhibition test, followed by absorption with vaccinia antigen, and a final enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA) for the remaining specific monkeypox antibody. Although this test is very insensitive, there is, at present, no reliable alternative.

The lack of an appropriate specific and sensitive serological test for monkeypox virus has somewhat reduced the value of two large-scale surveys of human monkeypox in Africa: an ecological survey in Zaire in 1979 and a serological survey to determine the prevalence of human infection in Congo, Ivory Coast, Sierra Leone and Zaire in 1981. Although orthopoxvirus-positive sera were found in both surveys, in many cases it was impossible to specify the virus species. To support the surveillance and field studies of human monkeypox, a sensitive and readily applicable test for monkeypox virus-specific antibodies is urgently required, for analysis of sera collected during ecological and epidemiological surveys. Such a test is also needed to help determine whether sporadic subclinical infection occurs. At the moment, it is not known how soon such a test may become available.

Laboratory investigations

Work is now being carried out in laboratories in various parts of the world with a view to developing a sensitive and specific serological test for antibodies to monkeypox virus.

Two laboratories in the USA have produced monoclonal antibodies that are able to distinguish monkeypox virus from other known orthopoxviruses. Collectively, these monoclones react with a wide variety of proteins from virus-infected cells as well as from purified virus. Attempts at competitive blocking of the monoclone with polyvalent sera and isolation of proteins on affinity columns have not so far been successful, but these efforts are still at an early stage.

DNA studies of variola and monkeypox viruses are being carried out in the United Kingdom and USA, and have been started in Japan. Endonuclease maps have been prepared for several strains of the viruses and for certain fragments of the genomes. A technique has been developed, that uses electron microscopy to compare segments of the DNA of

variola and monkeypox in homoduplex and heteroduplex form. This technique can locate the regions of the large DNA molecules where the two viruses differ significantly from each other. Preliminary results have localized one region of heterogeneity between the two viruses, which should be studied further. It is considered that extension of the heteroduplex investigation to cover the whole genome of at least two strains of each of the two viruses would be most useful.

Serum specimens from patients with tanapox come for the most part from people with a history of vaccination against smallpox; cross-reaction tests using tanapox and orthopox antigens are therefore difficult to interpret. The Centers for Disease Control in the USA are about to start laboratory studies of monospecific sera raised in laboratory animals against tanapox and monkeypox viruses.

Radioimmunoassay absorption (RIAA) tests have been carried out by the Centers for Disease Control, Atlanta, GA, USA, on sera from West Africa. Evidence of previous monkeypox infection was obtained in a few of these, but many gave equivocal results. A possible explanation for this has been provided by work carried out at the Research Institute for Viral Preparations, Moscow, USSR. Using cowpox or vaccinia virus to infect laboratory animals previously infected with the other virus, it was found that the serological response to the second virus varied with the inoculum and with the time interval between the two infections. Only in certain circumstances could the second infection be positively identified by serological tests. This may be an instructive model for the sera collected in Africa from suspected cases of monkeypox. It is the experience of the American and Russian laboratories that, when epidemiologically and clinically presumed monkeypox occurs in a previously vaccinated person, the serological diagnosis of monkeypox can often be made from the result of the fluorescent antibody test together with the RIA or ELISA titre, even though this might conflict with the RIAA result.

Suggestions for future work

The elucidation of the epidemiological patterns of monkeypox and the identification of the reservoir and/or intermediate hosts depend to a large extent on the development of a reliable and sensitive serological test specific for monkeypox antibodies. This will require the coordination of studies being carried out in the various interested laboratories throughout the world. Possible approaches that may be adopted in tackling this problem are as follows.

— Development of competitive blocking ELISA, with blocking by polyvalent sera from humans or animals of enzyme-labelled monkeypox-specific monoclonal antibodies providing evidence of monkeypox-specific antibody.

— Continuation of work to produce more monkeypox-specific monoclonal antibodies.

— Affinity column isolation of proteins by monoclonal antibodies and the exploration of whole or enzyme-digested proteins as possible sources of monkeypox-specific antigen usable in a serological test.

— The exploration of anti-idiotype antibodies as a source of synthetic antigen, which could be used as monkeypox-specific antigen for a serological test.

— The use of monkeypox-specific polyclonal sera to capture monkeypox-specific antigens potentially usable in an ELISA.

— Continuation of the search for monkeypox DNA segments that code for protein potentially usable as antigens in a monkeypox-specific ELISA.

It is specifically recognized that, for this development, intensive collaborative work will be required, both in the field and in the laboratory.

* * *

R. N. Basu, National Institute of Communicable Diseases, Delhi, India
P. Brès, Pasteur Institute, Paris, France
E. Coffi,[a] Institute of Hygiene, Abidjan, Ivory Coast
K. R. Dumbell, PHLS Centre for Applied Microbiology and Research, Porton Down, England
F. Fenner, The John Curtin School of Medical Research, Australian National University, Canberra City, Australia
W. Gerhard,[a] Wistar Institute of Anatomy and Biology, Philadelphia, PA, USA
M. Germain, Office de la Recherche Scientifique et Technique Outre-Mer (ORSTOM)/SSC, Bondy, France
P. Greenaway, PHLS Centre for Applied Microbiology and Research, Porton Down, England
D. A. Henderson, School of Hygiene and Public Health, John Hopkins University, Baltimore, MD, USA
Y. Ichihashi, Microbiology Department, Medical School, Niigata University, Niigata City, Japan
W. Joklik,[a] Department of Microbiology and Immunology, Duke University Medical Center, Durham, NC, USA
Kalisa Ruti, Expanded Programme on Immunization, Kinshasa, Zaire
T. Kitamura, Division of Poxviruses and Special Pathogens, National Institute of Health, Tokyo, Japan

[a] Unable to attend.

J. McCormick, Special Pathogens Branch, Centers for Disease Control, Atlanta, GA, USA
S. S. Merennikova, Moscow Research Institute for Viral Preparations, Moscow, USSR
T. Monath, Vector-borne Diseases Division, Centers for Disease Control, Fort Collins, CO, USA
J. Nakano, Division of Poxviruses and Special Pathogens, Centers for Disease Control, Atlanta, GA, USA
J. D. Williamson, Department of Virology, Wright-Fleming Institute of Microbiology, St Mary's Hospital Medical School, London, England

WHO Secretariat
(Headquarters: Geneva, Switzerland)

I. Arita, Smallpox Eradication
F. A. Assaad, Division of Communicable Diseases
B. Grab, Smallpox Eradication (*Adviser*)
Z. Jezek, Smallpox Eradication
L. Khodakevich, Smallpox Eradication
S. K. Litvinov, Assistant Director-General
V. Oviatt, WHO Special Programme on Safety Measures in Microbiology
J. Wickett, Smallpox Eradication (*Consultant*)