

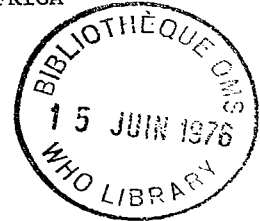


MONKEYPOX AND WHITE POXVIRUSES IN WEST AND CENTRAL AFRICA

INDEXED

by

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1. Introduction

Prospects for success in the global smallpox eradication programme are now highly encouraging. The last known case in Asia occurred in October 1975; the last case in Ethiopia, the only remaining endemic country, is expected to be detected and contained before December, 1976.

Smallpox eradication has been defined by the WHO Expert Committee (1972) as "The elimination of clinical illness caused by variola virus". The Committee added: "since there is no human carrier state of epidemiological importance and no recognized animal reservoir of the disease, the absence of clinically apparent cases in man may be assumed to signify the absence of naturally occurring smallpox". Evidence of the absence of an animal reservoir (Arita, 1968) has been strengthened over the last 10 years by the fact that greatly intensified epidemiological surveillance has not documented a single outbreak of smallpox in a smallpox-free area except when introduced by man infected in a known smallpox infected area.

During the past 10 years, however, there have been new findings. Monkeypox virus, previously thought to be restricted to monkey populations, has been recovered from 20 human cases of an exanthematous disease clinically indistinguishable from smallpox. During epidemiological investigation of these cases, all of which occurred in western and central Africa, four isolates resembling variola virus were obtained from specimens collected from monkeys and rodents captured in the area where the cases had occurred. These four strains, along with two strains isolated in Utrecht (Gispén, 1972) from kidneys of healthy monkeys, have been termed "whitepox viruses".

It seemed appropriate at this time to review these findings and to discuss their implications with regard to smallpox eradication.

2. Monkeypox

2.1 Monkeypox outbreaks in captive monkey colonies

Since 1958, when the first monkeypox outbreak in a captive monkey colony was reported (Magnus, 1959), nine additional outbreaks in laboratories have been recorded (four in Europe and five in the United States of America). (Arita, 1972). Six of the 10 outbreaks were confirmed by the isolation of monkeypox virus, an orthopox virus. At least four occurred among monkeys shipped from Malaysia. The significance of this is uncertain, however. Of 481 sera obtained from monkeys in Malaysia (Arita, 1972), none possessed poxvirus antibody. Thus, it is quite possible that susceptible Malaysian monkeys acquired infection from other simians or mammals some time during shipment to the laboratories.

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The last known outbreak of monkeypox occurred in a laboratory in Paris in 1968, the disease having occurred in one of two chimpanzees shipped from Sierra Leone where a human monkeypox case was detected in 1970 (Milhaud, 1969). Despite an increased alertness of laboratories to the possible occurrence of monkeypox, no outbreak has been reported since then. Furthermore, no naturally occurring monkeypox outbreaks have been documented in wild monkey populations.

2.2 Human monkeypox

Incidence

In 1970, the first human monkeypox case was discovered in a tropical rain forest area in Equator Province, Zaire (Ladnyi, 1972). In the same year, five cases were found in Liberia and Sierra Leone (Foster, 1972). From 1970 to December 1975, a total of 20 human cases were recorded in West and Central Africa (Map 1, Table 1).

Patients

Of the 20 patients with monkeypox virus infection, 13 were children under the age of five, two were between six and 15 years and the remaining five were adults. None of the cases, except case 6 (24 years old) and case 12 (30 years old) had been vaccinated before the presumed date of exposure. The clinical picture in most patients resembled smallpox and of 20 patients, four died (20%). Among the eight cases which occurred in Sierra Leone, Liberia, Ivory Coast and Nigeria, three were left with distinct facial pockmarks which could be observed after five years.

Laboratory diagnosis

In 13 cases, the diagnosis of monkeypox was confirmed by isolation of monkeypox virus, which is distinguishable from variola virus but belongs to the orthopox group (Magnus, 1959, Marennikova, 1971, Marennikova, 1972) in the remaining eight cases, the diagnosis was made epidemiologically, by detection of poxvirus by electron microscopic examination and/or by the presence of poxvirus antibody in the sera. Notably, in cases 7 and 8 (Nigeria) and 9 (Ivory Coast), sera taken five years after the onset of disease, showed specific monkeypox antibody (Gispen, 1976).

Transmission

The 20 cases occurred in 15 different villages. Eleven cases occurred as single case outbreaks. Cases 2, 3 and 4 occurred in village B, Liberia, within two days of each other, suggesting that the cases had been exposed to a course of infection at almost the same time. Cases 7 and 8 occurred in the same family in village E, Nigeria. Case 8, the mother of case 7, developed a mild rash nine days after her child's rash began, suggesting that human-to-human transmission may have occurred. Cases 11 and 12 occurred in village H, Zaire, on the same day, implying common source exposure. Cases 15 and 16 occurred in village K, Zaire, with an interval of 12 days. Case 15 is the sister of case 16, which again suggests that man-to-man transmission may have occurred.

Thus, on only two occasions is it believed that monkeypox may have been transmitted from man to man. Notably, in the Nigeria outbreak, there were 12 unvaccinated family members in contact with the patient but only one, case 8, was infected. Review of all known outbreaks to date reveals that only 2 of 30 susceptible household contacts (6.6%) developed disease, a transmission rate far lower than the 35% rate observed in smallpox outbreaks (Foster, 1973; Foegel, 1975).

Source of infection

In each locality (coded A through O, Table 1) and in the surrounding area, extensive epidemiological investigations have been carried out to seek the source of infection of human monkeypox cases. These investigations have failed to detect any smallpox or monkeypox cases before or after the occurrence of the index cases, except for the secondary household cases 7 and 15 as described before. Particular attention has been paid to the history of contact with monkeys. Monkeys are abundant in the areas surrounding all the localities. Cases 7, 10, 11, 14, 17 and 20 had close contact with monkeys before developing illness. Each had either eaten monkey meat, prepared monkeys for cooking or played with the carcasses or with live monkeys. However, suspected source material has not so far been obtainable for laboratory investigation.

All the localities where cases occurred are situated in tropical rain forest, except for locality M. Locality M is a town with a population of 40 000. Case 18 occurred in the centre of this town. There was no history of the patient having travelled outside the town before illness. On three occasions, 1, 6 and 12 months after this outbreak, special searches were conducted in primary schools to detect children with facial pockmarks. A total of 94 children with facial scarring resulting from a disease suffered during the previous three years were found, including case number 18. All showed vaccination scars, except case number 18 and one other. Clinical and epidemiological investigations indicated that the facial scarring had been produced by chickenpox (Zanotto, personal communication).

In 1975, a special survey was conducted in Sierra Leone, Liberia, Ivory Coast and Nigeria almost five years after smallpox cases occurred in these countries in order to detect any additional monkeypox cases. The survey teams searched for cases among persons living in the villages where the cases had occurred and in the surrounding 10-30 villages (Ladnyi & Netter, personal communications). These studies failed to detect any additional cases despite a vaccination coverage in the villages varying from 40 to 70%. Sufficient susceptibles thus were present to develop monkeypox if exposed to infection.

3. Search for an animal reservoir of monkeypox

Epidemiological investigations of human monkeypox cases have failed to trace the source. As noted, a serological survey of 481 monkeys in Malaysia revealed none with poxvirus antibody. Additionally, 1614 monkey sera obtained from various African and Asian sources were tested (Survey No. 1). Again, none was found with significant poxvirus antibody titres (Arita, 1972).

However, serological surveys conducted in areas of West and Central Africa where human monkeypox cases had been detected, revealed the presence of haemagglutinin inhibiting and neutralizing antibodies in a number of animals (Surveys 3-11). Since it is not possible at present to determine which orthopoxvirus infection might have induced antibody production and since there are many different naturally occurring poxviruses in mammals, the significance of these observations is unknown. Notably, in two sera from Survey 7, Gispen has reported the presence of specific monkeypox antibody as measured by his immunofluorescence technique (Gispen, 1976). Both sera were collected from adult female Cercopithecus aethiops monkeys in the north west part of Ivory Coast, West Africa, in 1973. (Breman, personal communication). Further studies are in progress.

Efforts to isolate monkeypox virus from specimens collected in these surveys were unsuccessful. However, in Surveys 3, 8 and 10 conducted in Zaire, the Research Institute of Virus Preparations, Moscow, recovered four variola-like poxvirus isolates. The isolates cannot be distinguished from variola virus employing currently available laboratory tests. All produce small, whitish pocks on the chorioallantois of chick embryos similar to variola virus. For purposes of reference, they have been termed "whitepox" viruses. A "whitepox" virus strain, inoculated experimentally, caused generalized rash in Cercopithecus aethiops monkeys (Nakano, personal communication). Despite the large number of specimens collected in surveys four and five in Liberia and Nigeria, no isolate was obtained.

4. Whitepox virus

All four whitepox viruses have been isolated from monkey or rodent specimens collected in Equator Province, Zaire, where eight human monkeypox cases have been detected. The ecological features of this area are briefly described by Ladnyi as follows: "The entire district consists of dense tropical rain forest. There is a rainy season from February to November but even during the 'dry' months of December and January, it usually rains 2-3 times a week" (Ladnyi, personal communication) and by Steniowski: "The fauna of the region is very varied: the species of monkey seen most frequently are chimpanzee, colobus, cercopithecus, mangabey and, in the north, baboons. Among the rodents, there are numerous species of squirrels and rats, and the porcupine" (Steniowski, personal communication).

The circumstances in which the viruses were isolated are summarized in Table 3. The strains are as follows:

Chimp 9: was isolated from the kidney of a chimpanzee which was captured and killed near locality A, Basankusu area, where the first human monkeypox case (No. 1) was detected (Marennikova, 1972). The investigation during which this chimpanzee specimen was collected was made four months after the case occurred. Serum was also collected from the same chimpanzee and showed a significant poxvirus antibody titre, indicating that the animal had experienced a poxvirus infection. However, from specimens collected from eight other monkeys, no poxvirus was isolated, although some of them showed positive poxvirus antibody titres.

MK-7-73: was isolated from the kidney of a 'sala' monkey captured during investigation in Ubangi area, Equator, where cases 15 and 16 had occurred. Again poxvirus antibody was detected in the serum of the same animal. Specimens from 11 other monkeys were tested with negative isolation results (Marennikova, personal communication).

RZ-10-74 and RZ-38-75: were isolated from the kidneys of two rodents (species Mastomys natalensis and Helioscorus Bufor brachim) captured in Bumba zone, Equator, during investigation of case 18 (Marennikova, personal communication). Notably, in Bumba zone, between 1972 and 1975, four human monkeypox cases (11, 12, 17 and 18) occurred within an area of 100 km radius. RZ-10-74 was isolated from a specimen collected one month after the human monkeypox case had occurred. This virus was repeatedly isolated from the original specimen, but no sera were available for serological confirmation. RZ-38-75 was isolated from a specimen collected eight months after the occurrence of case 18. The serum of the rodent from which RZ-38-75 was isolated showed poxvirus antibody. On these two occasions virus isolation tests on a total of 48 monkey specimens and 328 rodent specimens were negative. Studies of antibody titres in these sera are in progress.

5. Variola-like virus isolated from monkey kidney tissue culture in a laboratory: laboratory whitepox virus

In September 1964, during routine processing of Malaysian cynomolgus monkey kidney tissue cultures at the Rijks Instituut voor de Volksgezondheid, Utrecht, poxviruses were isolated on two occasions - on 23 and 30 September respectively (specimens 64-7275 and 64-7255) (Gispen, 1967). These two isolates were found to resemble variola virus and were so designated as "whitepox viruses". No similar strains have been isolated before or since.

Of uncertain relevance is the fact that on 21 December, three months after isolation of the two whitepox virus strains, anteaters, brought to the Rotterdam Zoo on 9 December, developed a vesicular disease. Monkeypox virus was isolated from these animals (Gispen, 1967). Investigation revealed that the animals, prior to the development of disease, had close contact with cynomolgus monkeys, most probably shipped from Malaysia. These anteaters were the source of a subsequent monkeypox outbreak in the Rotterdam Zoo, where 21 monkeys and apes of various species suffered from the disease and 11 died (Peters, 1966).

Of further interest is the fact that on 9 December 1964 and 4 May 1965 respectively, the laboratory in Utrecht again quite incidentally isolated poxviruses from tissue culture of

cynomolgus monkey kidney. However, this time the isolates resembled monkeypox virus (specimens 64-9411 and 65-3993). The isolation of this first monkeypox virus occurred on 9 December when the anteaters were first brought to the Rotterdam Zoo.

Evidence suggests a common focus for the monkeypox virus strains and the whitepox viruses detected in the Utrecht Laboratory as well as the monkeypox outbreak at the Rotterdam Zoo.

6. Discussion

More than five years have elapsed since the last smallpox patient was detected in West and Central Africa (June, 1970). Since that time, many suspect cases have been reported and investigated clinically and by laboratory study. None have been found to be smallpox although, as described, eight have proved to be caused by monkeypox virus. To determine if any possible hidden focus of smallpox may have persisted in West Africa, an intensive field survey was organized in 1975. Five million children in 12 000 primary schools, maternity child health centres and markets were seen by national and WHO survey teams looking for recent facial pockmarks. None of the children were found to have pockmarks resulting from a smallpox-like illness which occurred after 1970, although many pockmarks were found among older children who had smallpox prior to 1970. In addition, in the 8000 medical health units and markets in the countries, the teams specifically sought to learn of rumours of smallpox. All suspect smallpox cases reported to the teams turned out to be chickenpox or other vesicular disease. In Zaire, where the last smallpox case was reported in 1971, 16 smallpox surveillance teams visit 4000 health units throughout the country once every six months to search for and investigate smallpox suspects. During the last five years, more than 500 specimens have been collected by these teams and tested by WHO collaborating laboratories in Moscow and Atlanta. These surveillance activities in Zaire resulted in the discovery of 12 human monkeypox cases but no smallpox cases.

These observations together with the results of monkeypox surveys conducted five years after the outbreaks, provide increasingly convincing evidence that smallpox transmission in West and Central Africa has been interrupted and that the occurrence of human monkeypox is extremely infrequent. The fact that man-to-man transmission of monkeypox virus appears to have taken place on two occasions is probably more of academic than practical significance. Even if one assumes that both cases did occur as a result of human-to-human transmission the rate of transmission among susceptible household contacts is so low that it would seem unlikely that persistent human-to-human transmission could be established. Notably, in the Aba area of Nigeria, where cases 7 and 8 occurred and where 80% of preschool children had never been vaccinated (Netter, personal communication), monkeypox has not manifested itself in endemic form.

Although the animal reservoir of monkeypox virus is still unknown, it is assumed that such a reservoir does exist in West and Central Africa. For investigational purposes, Equator Province, Zaire, is of special interest since 8 of the 20 monkeypox cases were reported from this province. Whether the reservoir might be monkeys or rodents or perhaps other mammals is uncertain. Notably, laboratory studies show that the host range of monkeypox virus includes primates, rabbits, mice and anteaters (Peters, 1966; Marennikova, 1976, personal communication).

Whitepox virus is indistinguishable from variola virus by presently available laboratory tests but it is unknown as to whether it is capable of inducing human infection and, if so, whether it can be transmitted from human to human. A generalized rash was produced in Cercopithecus aethiops after subcutaneous or intraperitoneal introduction of high virus concentrations (10⁷ to 10⁸ pfu/ml) (Nakano, personal communication). These are unnatural routes of infection and thus no generalization can be made about what may be occurring in nature. Further, in Equator Province, where the presence of animal reservoirs of whitepox virus might be suspected, no smallpox-like disease except for human monkeypox has been detected during the last five year period of surveillance. Thus, whitepox virus and true variola virus may well behave differently in the human host.

A substantial national and international effort has been made to accomplish the eradication of smallpox and the goal is now in sight. It is certainly warranted to continue epidemiological surveillance and, meanwhile, to study further the laboratory characteristics of the orthopoxviruses.

ACKNOWLEDGEMENTS

The authors are most grateful to various workers from the ministries of health in Sierra Leone, Liberia, Ivory Coast, Nigeria and Zaire, who performed the epidemiological investigations of the human monkeypox outbreaks in these areas, to Dr F. Fenner, Centre for Resource and Environmental Studies, the Australian National University, Canberra, Australia, who reviewed the paper and made suggestions and to Miss C. I. Sands, Smallpox Eradication unit, WHO, who assisted in the series of drafts in preparation of this paper.

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TABLE 1. HUMAN MONKEYPOX CASES

Case No.	Locality	Province	Country	Age	Sex	Vacc. Scar	Date of Onset of Rash	Severity*	Death	Laboratory			
										EM Poxvirus	Monkeypox Isolate	Pox Antibody	Specific Monkeypox Antibody
1	A	Equatoria	Zaire	9 ms.	M	-	24.8.70.	2	-		+		
2	B	Grand Gedah	Liberia	4	F	-	12.9.70.	2	-	+	+	+	
3	B	Grand Gedah	Liberia	4	M	-	13.9.70.	1	-			+	
4	B	Grand Gedah	Liberia	6	F	-	13.9.70.	1	-			+	
5	C	Grand Gedah	Liberia	9	M		2.10.70.	2	-	+	+	+	
6	D	Aguebu	Sierra Leone	24	M	+	1.12.70.	2	-	+	+	+	
7	E	Aba	Nigeria	4	F	-	9.4.71.	3	-	+	+		+
8	E	Aba	Nigeria	24	F	-	18.4.71.	1	-				+
9	F	Aben Gourrou	Ivory Coast	5	M	-	18.10.71.	2	-			+	+
10	G	Kasai Oriental	Zaire	1	M	-	2.3.72.	2	-	+	+		
11	H	Equatoria	Zaire	3	M	-	27.7.72.	3	+	+	+		
12	H	Equatoria	Zaire	30	F	+	27.7.72.	1	-			+	
13	I	Equatoria	Zaire	7 ms.	F	-	16.9.72.	2	+	+			
14	J	Bandundu	Zaire	2	M	-	30.10.72.	2	+	+	+		
15	K	Equatoria	Zaire	3	F	-	10.1.73.	2	-	+	+	+	
16	K	Equatoria	Zaire	5	F	-	22.1.73.	2	-	+		+	
17	L	Equatoria	Zaire	7 ms.	M	-	6.5.73.	3	+	+	+		
18	M	Equatoria	Zaire	4	F	-	6.8.74.	2	-	+	+		
19	N	Bandundu	Zaire	40	F	-	4.1.75.	3	-		+	+	
20	O	Kasai Oriental	Zaire	23	F	-	9.3.75.	1	-	+	+	+	

*
 1 : mild
 2 : intermediate
 3 : severe

TABLE 2. WILD ANIMAL INVESTIGATION RELATED TO HUMAN MONKEYPOX OUTBREAKS

Survey No.	Testing Laboratory	Year of Specimen Collection	Place of Specimen Collection	No. of Specimens	Animals	Type of Specimens	Poxvirus Isolation	Circumstances for collection of specimens
1	Monkeypox Study Group	Collected in 1963-69, but tested in 1970-71	Japan	64	Monkeys	Serum	-	Random
			Philippines,)	378				
			Indonesia,)					
			Malaysia)	165				
			& Thailand)					
			India	703				
Chad,)								
Upper Volta,)	304							
Mali, Kenya,)								
Senegal)	Unknown							
	Total	1 614						
2	Monkeypox Study Group	1970	Malaysia	481	Monkeys	Serum	-	Random
3	Moscow	1970	Zaire	9	Monkeys	Serum and kidney	White poxvirus (chimp 9)	Case 1
4	Atlanta	1971	Liberia	371	Monkeys, rodents and other miscellaneous species	Serum and various tissues	No isolate	Cases 2-4
5	Atlanta	1971	Nigeria	68	Monkeys and rodents	Serum and various tissues	No isolate	Cases 7-8
6	Atlanta	1971-72	Ivory Coast*	102	Monkeys, rodents and other miscellaneous species	Serum	-	Case 9
7	Atlanta Utrecht	1973-74	Ivory Coast*	207	Monkeys	Serum	-	Case 9
8	Moscow	1973	Zaire	12	Monkeys	Serum and kidney	White poxvirus (MK-7-73)	Cases 15-16
9	Moscow	1973	Zaire	92	Monkeys and rodents	Serum and kidney	No isolate	Case 17
10	Moscow	1974	Zaire	378	Monkeys and rodents	Serum and kidney	White poxviruses (RZ-10-74, RZ-38-75)	Case 18
11	Moscow	1975	Zaire	67	Monkeys and rodents	Serum and kidney	No isolate	Case 19

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Moscow: S. S. Marennikova, Research Institute of Virus Preparations, Moscow, USSR.

Atlanta: J. Nakano, Viral Exanthems Branch, Center for Disease Control, Atlanta, Georgia, USA.

* Three sera provided by Dr. J. Breman, O.C.C.G.E., Bobo-Dioulasso, Upper Volta.

TABLE 3. WILD WHITE POXVIRUS ISOLATES FROM EQUATORIA PROVINCE, ZAIRE

Survey No.	White Poxvirus	Isolated from	Place of specimen collection	Date of human monkeypox onset	Date of specimen collection	Confirmation of isolation		
						Pox antibody in original animal		Repeat Test
						HAI	Neut.	
3	Chimp 9	Chimpanzee	near locality A Basankusu	August 1970 (case 1)	January 1971	1 280	>40	N.D.
8	MK-7-73	"Sala" monkey	near locality K Ubangi	January 1973 (cases 15-16)	February 1973	256	80	N.D.
10	RZ-10-74	Mastomys natalensis	near locality M Bumba Town	August 1974 (case 18)	September 1974	N.D.	N.D.	+
10	RZ-38-75	Helioscorus Buforbrachim	100 km north of loacality M, Bumba Town	August 1974 (case 18)	March 1975	-	80	N.D.
						-	20	

N.D. - Not done

LOCATION OF MONKEYPOX CASES - 1970-1975

