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Human monkeypox: secondary attack rates

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Data on human monkeypox collected in Zaire during the six years 1981–86 were analysed to assess the extent of interhuman transmission of monkeypox virus. Among the 2278 persons who had close contact with 245 monkeypox patients infected from an animal source, 93 fell ill and were presumed to have been infected from the known human source: 69 of these were spread in the first generation, 19 in the second generation, and the remaining five cases in the third and fourth generation.

The secondary attack rates were correlated with the age, sex, place of residence, and vaccination status of the contacts. There was an overall 3% probability of becoming ill following infection from a known human source. The affected household was the main focal point for interhuman transmission of monkeypox virus. The highest attack rate (11.7%) occurred among unvaccinated household contacts in the age group 0–4 years. However, the majority of susceptible persons who had been close to patients in the confined space of poorly ventilated huts failed to develop illness. There was no evidence of an increase in the secondary attack rate between 1970–80 and 1981–86.

The inefficient spread from person to person, even in conditions of maximum exposure, supports the concept that monkeypox virus is poorly adapted for sustained transmission between humans and that such transmission does not pose a significant health problem.

Human monkeypox, which is clinically similar to smallpox, is a rare and sporadic illness occurring in the tropical rain forest areas of central and western Africa. Monkeypox patients have presented either singly or in small clusters in small villages located in forest areas, where the inhabitants usually have multiple contacts with a variety of wild animals. It is a classical zoonosis, the majority of human infections being attributable to contact with affected animals. There is, however, increasing evidence for interhuman transmission of the monkeypox virus (*1, 2, 4, 5*). Aspects of the human disease that require clarification include the ecology of the virus in wildlife, the mode of virus transmission from wildlife to humans, and the extent of person-to-person transmission.

One way to assess the extent of interhuman transmission is to determine the secondary attack rate, i.e., the proportion of individuals who, after exposure to a case infected from an animal source, become ill within the accepted incubation period, in relation to the total number of exposed contacts. This paper describes a study conducted in Zaire on the extent of interhuman transmission of monkeypox virus, based on investigations of 338 monkeypox patients reported during the years 1981–86, and follow-up of 3686 of their close contacts.

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MATERIALS AND METHODS

In 1981, active surveillance was intensified in five specific areas of Zaire covered by dense tropical forest, with the participation of some 150 health establishments and four mobile surveillance teams (*15*).

Field investigation

Several visits were made by the field surveillance teams, each composed of one experienced physician with one or two nurses and health inspectors, to localities where one or more monkeypox patients had been reported on the first visit. The local inhabitants were checked for clinical signs and symptoms of current or recent vesiculo-pustular disease and for the presence of vaccination scars. Persons who showed signs of skin lesions were carefully examined and clinico-epidemiological diagnoses were subsequently verified by laboratory testing of skin specimens or serum, or both. Household members and other close contacts of the identified patients were registered, interviewed and examined. Subsequent follow-up visits to the affected locality were made every 7–10 days to determine whether any additional cases had occurred, to examine contacts who had been absent during the earlier visit, and to collect further specimens. Through such field investigation, careful consideration was given to the possible source of infection for the affected individual(s).

Considerable importance was also placed on confirming clinico-epidemiological diagnoses by lab-

oratory tests which were carried out by the WHO Collaborating Centers for Disease Control in Atlanta, USA, and at the Research Institute for Viral Preparations in Moscow, USSR. Vesicular and pustular fluids and scabs were examined by electron microscopy and cultured on chicken embryo chorioallantoic membrane and in tissue culture. Sera were examined by the haemagglutination inhibition test, the fluorescent antibody test, ELISA, radioimmunoassay (RIA), and the RIA adsorption test. Sera were also tested for antibody to varicella-zoster virus by a fluorescent antibody test and ELISA.

Definitions and evaluation

The first case occurring in a focus, presumably infected from an animal source, is considered to be the *primary case*. A subsequent case among the close contacts, but whose onset of illness occurred within the first week after onset of rash in the primary case, is regarded as a *co-primary case*, attributable to the same non-human source of infection. Both primary and co-primary cases are also referred to as *index cases*. A patient having onset of rash between one and three weeks after exposure to an index case is considered to be a *secondary case*, which may have arisen by person-to-person transmission. Based on the date and sequence of illness, secondary cases are further classified by generation according to their rank in the presumed chain of transmission.

Any person who had face-to-face contact with an index case in the household or nearby area, at the workplace, school, hospital, etc. during the period of illness is regarded as a contact. A *household contact* is any person who regularly ate, slept and lived in the same hut or house as a patient with monkeypox. Contacts are further classified as *vaccinated* or *unvaccinated* according to the presence or absence of a vaccination scar.

Statistical significance was assessed by using the χ^2 test with Yates' correction for continuity.

RESULTS

Basic epidemiological features

A total of 338 monkeypox patients, 182 males and 156 females, were reported in Zaire during the period 1981–86. The disease affected all age groups, the youngest case being three months old and the oldest 69 years. However, most (86%) of the patients with monkeypox were children less than 10 years of age (Table 1); 43 out of the 338 patients (13%) had a visible vaccination scar(s), including five persons with a doubtful scar at a vaccination site but with a history of vaccination.

A total of 3686 persons were identified as having close, face-to-face contact with the reported cases of monkeypox. Their age distribution (Table 1) matched the age distribution of the general population; 2657 of them (72%) had a vaccination scar and the rest were regarded as unvaccinated. On average, there were 10.9 close contacts per monkeypox patient, with a range from 1 to 44. The relative frequency distribution of monkeypox cases according to the number of their close contacts is shown in Table 2.

Table 1. Age group and vaccination status of monkeypox patients and their contacts

Age group (years)	Monkeypox patients		Close contacts	
	Total number	With vaccination scar	Total number	With vaccination scar
0–4	175 (51.8)[a]	2 (1.1)	703 (19.1)	54 (7.7)
5–9	116 (34.3)	10 (8.6)	540 (14.7)	267 (49.4)
10–14	24 (7.1)	9 (37.5)	469 (12.7)	406 (86.6)
⩾15	23 (6.8)	22 (95.7)	1974 (53.6)	1930 (97.8)
Total	338 (100)	43 (12.7)	3686 (100)	2657 (72.1)

[a] Figures in parentheses are percentages.

Of the 338 reported human monkeypox cases, an animal source of infection was suspected in 245 patients (72.5%) and a human source in the remainder; 203 primary cases, each one appearing in a separate focus, were presumably infected from an animal source of infection. Forty-two patients, who developed the skin eruptions between a few hours and six days after the onset of the rash of the first case in the focus, were considered to be co-primary cases, presumably from the same non-human source of infection. In 93 patients the onset of rash occurred between one and three weeks after their exposure to a known human source, and the infection was attributed to person-to-person transmission of the causative

Table 2. Relative frequency distribution of monkeypox cases according to their number of close contacts

No. of contacts per case	No. of cases	Relative frequency
0–4	58	0.17
5–9	131	0.39
10–14	70	0.21
15–19	34	0.10
20–24	18	0.05
25–29	19	0.06
30–34	1	0.00
35–39	4	0.01
40–44	3	0.01
Total	338	1.00

Table 3. Number of monkeypox patients by year, source of infection, and sequence of person-to-person transmission, 1981–86

	No. of cases infected from:						
	Animal sources		Human source				
Year	Primary	Co-primary	First generation	Second generation	Third generation	Fourth generation	Total
1981	6	—	1	—	—	—	7
1982	22	2	13	3	—	—	40
1983	47	11	19	3	3	1	84
1984	52	10	18	6	—	—	86
1985	40	7	11	4	—	—	62
1986	36	12	7	3	1	—	59
Total	203	42	69	19	4	1	338

agent (secondary cases). Assuming an average rash-to-rash interval of 14 days, 69 of these secondary cases represented the first generation (infected by index cases), 19 patients belonged to the second generation, and the remaining five cases were due to third and fourth generation spread. The distribution of primary and co-primary cases, as well as presumed secondary cases, by their generation rank and year of occurrence during the six-year period of observation is shown in Table 3.

A total of 2278 persons were identified as having had close, face-to-face contact with the 245 patients (203 primary and 42 co-primary cases) who had very probably been infected from an animal source. Only these figures are used as denominators for the calculation of subsequent secondary attack rates. Vaccination scars were identified on 1555 contacts (68%), the others being regarded as unvaccinated; 1420 (62%) of these contacts lived in the same household as a primary or co-primary case and the others lived separately but had face-to-face contact with a monkeypox patient during the illness (Table 4).

Secondary attack rates

As there were 69 secondary cases (first generation only), the observed crude secondary attack rate among contacts of the primary and co-primary cases was 0.03 (69/2278); that is, an overall 3% probability of becoming infected from a human source. Secondary attack rates were, however, strongly related to two variables: vaccination status and place of residence of the exposed persons. Table 4 shows that the attack rate among unvaccinated persons (7.47%) was significantly different from that among those who had been vaccinated in the past (0.96%) ($\chi^2=68.9$; $P<0.001$). The overall risk of attack for contacts living in the same residence as the monkeypox case

Table 4. Secondary attack rates among close contacts of primary and co-primary cases, according to the contacts' vaccination status[a] and place of residence

	Unvaccinated contacts			Vaccinated contacts		
Contact's residence	No. of contacts	No. of cases[b]	Attack rate (%)	No. of contacts	No. of cases[b]	Attack rate (%)
Affected village:	661	51	7.71	1373	14	1.01
Affected house	431	40	9.28	989	13	1.31
Neighbouring houses	196	9	4.59	319	1	0.31
Other houses	34	2	5.88	66	0	0.00
Other localities	62	3	4.84	181	1	0.55
Total	723	54	7.47	1555	15	0.96

[a] Vaccinated contacts were persons with a vaccination scar; those without such a scar were considered to be unvaccinated.

[b] Secondary cases/first generation only.

Table 5. Secondary attack rates in household contacts, by age group and vaccination status[a]

Age group (years)	Unvaccinated contacts			Vaccinated contacts			Total (all contacts)		
	No. of contacts	No. of cases[b]	Attack rate (%)	No. of contacts	No. of cases[b]	Attack rate (%)	No. of contacts	No. of cases[b]	Attack rate (%)
0–4	197	12	11.68	15	0	0.00	212	23	10.85
5–9	157	14	8.92	114	2	1.75	271	16	5.90
10–14	42	3	7.14	145	1	0.69	187	4	2.14
⩾15	35	0	0.00	715	10	1.40	750	10	1.33
All ages	431	40	9.28	989	13	1.31	1420	53	3.73

[a] Vaccinated contacts were persons with a vaccination scar; those without such a scar were considered to be unvaccinated.
[b] Secondary cases/first generation only.

(3.73%) was twice as high as the risk for those living outside the affected house (1.86%) ($\chi^2=5.73$; $P<0.05$).

The highest attack rate of 9.3% was found among unvaccinated contacts living in the same household as a monkeypox patient (Table 4); their attack rate was seven times higher than the corresponding rate for vaccinated household members (1.3%) ($\chi^2=50.8$; $P<0.001$). The secondary attack rate among exposed unvaccinated contacts residing in the same village as the primary case, or even in the neighbouring houses, did not differ from the rates found among exposed susceptibles residing in other localities (Table 4).

Among the unvaccinated household contacts the observed specific attack rates appear to be age-dependent, being highest in the 0–4-year age group (11.7%) and decreasing with age in older children (Table 5). There were no secondary cases among unvaccinated adults but the number of observations is too small to allow any conclusion. No such age-dependent relationship was observed in the attack rates among vaccinated household contacts.

Table 6 shows the secondary attack rates among male and female contacts residing with the monkeypox cases or residing outside the affected huts. The rates were consistently higher among females than males, but the differences did not reach the 5% probability level of significance.

Although the number of detected monkeypox patients increased substantially during the years of intensive surveillance, 1981–86 (a total of 48 cases were reported in Zaire in the period 1970–80 and 338 cases in the period 1981–86), the secondary attack rates for household contacts during both periods were similar (Table 7).

DISCUSSION

A systematic effort was made in Zaire between 1981 and 1986 to improve the detection, reporting and investigation of cases of human monkeypox. This improved surveillance and the prompt investigation of foci of infection showed that, although the majority of human attacks resulted from close contacts with affected animals, transmission of the monkeypox virus from person to person also occurred.

Attempts have been made to express quantitatively the risk of interhuman transmission of monkeypox virus and to measure the degree of spread of this pathogenic agent within a limited group of persons

Table 6. Secondary attack rates in male and female contacts, by vaccination status[a] and place of residence

Residence of contacts	Unvaccinated contacts			Vaccinated contacts			Total (all cases)		
	No. of contacts	No. of cases[b]	Attack rate (%)	No. of contacts	No. of cases[b]	Attack rate (%)	No. of contacts	No. of cases[b]	Attack rate (%)
Affected house:									
Males	209	18	8.61	471	4	0.85	680	22	3.24
Females	222	22	9.91	518	9	1.74	740	31	4.19
Other place:									
Males	142	5	3.52	269	1	0.37	411	6	1.46
Females	150	9	6.00	297	1	0.34	447	10	2.24

[a] Vaccinated contacts were persons with a vaccination scar; those without such a scar were considered to be unvaccinated.
[b] Secondary cases/first generation only.

Table 7. Secondary attack rates among household contacts, by time period and vaccination status[a]

Time period	Total contacts	Unvaccinated contacts		Vaccinated contacts	
		No. of contacts	No. of secondary cases[b]	No. of contacts	No. of secondary cases[b]
1970–80	190	25 (13.2)[c]	3 (12.0)[c]	165 (86.8)	2 (1.21)
1981–86	1420	431 (30.4)	40 (9.28)	989 (69.6)	13 (1.31)

[a] Vaccinated contacts were persons with a vaccination scar; those without such a scar were considered to be unvaccinated.
[b] Secondary cases/first generation only. [c] Figures in parentheses are percentages.

exposed to a human source of infection. The most widely used indicator is the secondary attack rate, i.e., the proportion of individuals exposed to a primary or co-primary case who became ill within the accepted incubation period. Initially introduced by C. V. Chapin (*16*) to measure the spread of infection within families, this rate has also been applied to any close aggregate of persons subjected to exposure to the causative agent through close contact with the source of infection. It provides directly a measure of the attack risk, which can be related not only to important personal characteristics (age, sex, vaccination status) but also to other circumstances (degree of contact, prophylactic measures, etc.). In human monkeypox, as in smallpox, the immune status of an exposed individual is a major determinant of the risk of infection; hence the observed secondary attack rates were strongly correlated with vaccination status.

The affected household appears to be the most important focal point for dissemination of monkeypox virus to susceptibles. This may be because most monkeypox patients, from the very onset of their symptoms such as fever, headache and feeling ill, usually rest in bed, so segregating themselves from the community but not from their household contacts. Families usually take care of even the severely ill in the family compound, and family members also provide much of the routine nursing for patients who have been hospitalized. Nevertheless, only 40 out of 431 unvaccinated persons, i.e., less than 10% of those who had been exposed to monkeypox patients in the confined space of relatively small and poorly ventilated huts, developed a subsequent illness (Table 7). Among household contacts, those who had direct physical contact with the infected person, by playing with the patient or sharing the same bed, and those who provided nursing care had an increased risk of subsequent attack, which emphasizes the importance of intimate contact in the spread of the disease.

There is still insufficient information to indicate precisely the mechanism of virus transmission from one person to another; both droplet-spread as well as direct physical contact are suspected. The absence of illness among neighbours who had no direct face-to-face contact with a monkeypox patient suggests that there is no (or only minimal) risk of airborne transmission.

The affected household is the most suitable unit for comparing differences in specific attack rates. Examination of the attack rates by age (Table 5) in unvaccinated household contacts shows that the rate was highest in the youngest age group (0–4-years old) and progressively decreased with age. This relationship with age seems to reflect close physical contact among very young siblings, which decreases with age. The higher attack rate among females (Table 6) reflects the close contact between monkeypox patients and female relatives who provide nursing care and is probably not due to a sex difference in susceptibility to the monkeypox virus.

Any change in the monkeypox virus that could lead to increased transmissibility between humans would be a serious matter. However, as there was no increase in the secondary attack rate for household contacts from the period 1970–80 to the period 1981–86 (Table 7), there is no evidence for a change in the transmissibility of the virus. As in the case of other infectious diseases, the attack rate among close contacts of monkeypox patients is a reasonable measure of the contagiousness or transmissibility of the monkeypox virus. The potential for human-to-human transmission of this virus is considerably lower than that of variola virus; the 9.3% attack rate for monkeypox among unvaccinated household contacts contrasts with the rates for smallpox (range: from 37% to 88%) (*8, 10, 12, 14*), and is much lower than the rates for viral diseases that are maintained in nature by person-to-person spread (*3, 9, 11, 13*).

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RÉSUMÉ

ORTHOPOXVIROSE SIMIENNE DE L'HOMME: TAUX D'ATTEINTE SECONDAIRE

L'orthopoxvirose simienne de l'homme est une maladie rare et sporadique que l'on observe dans les forêts ombrophiles d'Afrique centrale et occidentale et qui ressemble cliniquement à la variole. C'est une zoonose classique, la majorité des infections humaines étant attribuables au contact avec des animaux malades. Toutefois, on a de plus en plus de preuves d'une transmission interhumaine de l'orthopoxvirus simien, dont l'importance peut être mesurée par le taux d'atteinte secondaire, c'est-à-dire la proportion des personnes en contact étroit avec un malade infecté par un animal qui contractent à leur tour la maladie pendant la période d'incubation reconnue.

Une étude a été menée au Zaïre en vue de déterminer l'ampleur de la transmission interhumaine de l'orthopoxvirus simien. Cette étude a porté sur 338 patients chez lesquels la maladie avait été diagnostiquée entre 1981 et 1986, ainsi que sur 3686 personnes ayant été en contact étroit avec eux, dont l'état de santé a été suivi. On a estimé que 245 patients avaient été infectés par une source animale (cas indicateurs) et 93 par une source humaine (cas secondaires). Parmi ces derniers, on a distingué 69 cas de première génération, 19 cas de deuxième génération et 5 cas de troisième ou quatrième génération. Au total, la probabilité de contracter la maladie à la suite d'un contact avec un malade a été évaluée à 3%.

Les taux d'atteinte secondaire présentaient une corrélation élevée avec l'état vaccinal des contacts et avec leur lieu de résidence, le domicile des malades constituant le principal foyer de transmission interhumaine du virus. Parmi les contacts vivant sous le même toit qu'un malade, le taux d'attaque a atteint 9,3% chez ceux qui n'étaient probablement pas vaccinés, alors qu'il n'a été que de 1,3% chez ceux qui présentaient une cicatrice de vaccination.

Le taux d'atteinte a été maximal chez les enfants de 0 à 4 ans, sans doute en raison du fait que les contacts physiques sont très étroits dans ce groupe d'âge et qu'il diminuent en général par la suite. On a observé une tendance plus prononcée à la transmission interhumaine entre sujets de sexe féminin. Cela est dû probablement aux contacts fréquents entre les enfants malades et les parentes qui les soignaient, plutôt qu'à une différence de sensibilité au virus liée au sexe. Il faut noter toutefois que la majorité des personnes sensibles et non vaccinées qui avaient été en contact étroit avec les malades dans des cases exiguës et mal aérées n'ont pas contracté la maladie. En aucun cas, la transmission ne s'est poursuivie au-delà de la quatrième génération de cas secondaires. De plus, il n'y a eu aucun signe d'augmentation du taux d'atteinte secondaire entre les périodes 1970–1980 et 1981–1986.

L'inefficacité de la propagation de personne à personne, même dans des conditions d'exposition maximale, confirme l'hypothèse selon laquelle le virus de l'orthopoxvirose simienne est mal adapté à une transmission interhumaine continue et que ce mode de transmission ne constitue pas un problème de santé important.

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