Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo

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Studies on the burden of human monkeypox in the Democratic Republic of the Congo (DRC) were last conducted from 1981 to 1986. Since then, the population that is immunologically naïve to orthopoxviruses has increased significantly due to cessation of mass smallpox vaccination campaigns. To assess the current risk of infection, we analyzed human monkeypox incidence trends in a monkeypox-enzootic region. Active, population-based surveillance was conducted in nine health zones in central DRC. Epidemiologic data and biological samples were obtained from suspected cases. Cumulative incidence (per 10,000 population) and major determinants of infection were compared with data from active surveillance in similar regions from 1981 to 1986. Between November 2005 and November 2007, 760 laboratory-confirmed human monkeypox cases were identified in participating health zones. The average annual cumulative incidence across zones was 5.53 per 10,000 (2.18–14.42). Factors associated with increased risk of infection included: living in forested areas, male gender, age < 15, and no prior smallpox vaccination. Vaccinated persons had a 5.2-fold lower risk of monkeypox than unvaccinated persons (0.78 vs. 4.05 per 10,000). Comparison of active surveillance data in the same health zone from the 1980s (0.72 per 10,000) and 2006–07 (14.42 per 10,000) suggests a 20-fold increase in human monkeypox incidence. Thirty years after mass smallpox vaccination campaigns ceased, human monkeypox incidence has dramatically increased in rural DRC. Improved surveillance and epidemiological analysis is needed to better assess the public health burden and develop strategies for reducing the risk of wider spread of infection.

active surveillance | orthopoxvirus | zoonosis | eradication

Monkeypox virus is a zoonotic orthopoxvirus that causes a serious smallpox-like illness in humans (Fig. 1). Since the global eradication of smallpox in 1977, monkeypox has been considered to be the most important orthopoxvirus infection in humans (1, 2). Humans can acquire monkeypox infection through direct contact with infected animals or humans. Since its discovery in 1970, the majority of cases have been reported in the Democratic Republic of the Congo (DRC); however, reports of monkeypox have increased in neighboring Republic of the Congo and a cluster of cases were reported in Sudan for the first time in 2006 (Table S1) (2–7). In 2003, the first report of human monkeypox outside of the African continent occurred in the midwestern United States and was associated with imported African rodents (8). The true geographic range of human endemic disease has yet to be determined; however, it is likely to coincide with the natural range of the zoonotic reservoir species, for which squirrels and several other rodent species have been implicated as candidates (9–11).

At the end of the smallpox eradication campaign, the Global Commission for the Certification of Smallpox Eradication concluded that continued smallpox vaccination to prevent monkeypox was not justified, despite the cross-protective immunity vaccinia vaccination provided against human monkeypox infection. Smallpox vaccination was officially discontinued in DRC in 1980; however, recommendations were made to assess the public health significance of monkeypox in the absence of mass vaccination campaigns. In response, the World Health Organization (WHO) supported an active surveillance program for human monkeypox from 1981 to 1986 (12). This intensive surveillance accounted for 338 of the 404 recognized cases in Africa during this period (13). Epidemiologic data from this program was used to create a stochastic model for spread of monkeypox between humans, which indicated that monkeypox virus was highly unlikely to sustain itself in human populations and, therefore, did not constitute a major public health problem (14, 15). This modeling analysis used available information to predict the future of monkeypox dynamics when the population was completely unvaccinated, but did not include statistical uncertainties and could not account for changes in the ecological reservoir and subsequent epidemiology.

After the active surveillance program ended in 1986, there was a long period of imperfect and anecdotal reporting during which the burden and geographic range of human monkeypox infection remained unknown. To assess the current risk of human monkeypox infection in endemic regions, we initiated an active disease surveillance program in health zones where the virus was known to circulate. Here, we describe the results of this program from 2005 to 2007 and compare them to archival data from the WHO-supported surveillance program conducted in comparable regions from 1981 to 1986.

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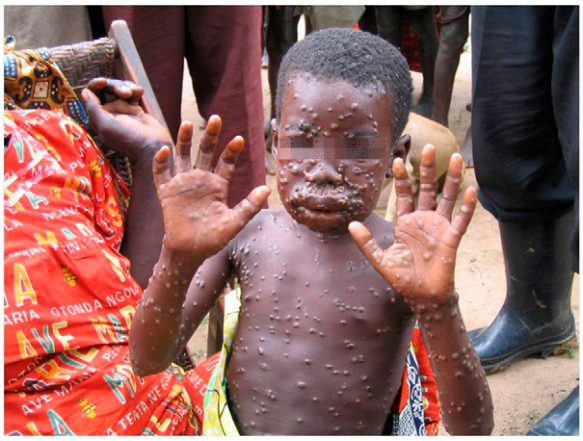

Fig. 1. Typical clinical presentation of human monkeypox in a 7-y-old female child, Sankuru District, Democratic Republic of Congo.

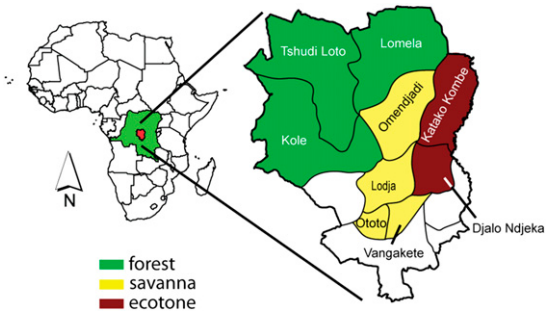

Fig. 2. Map of health zones with active surveillance for human monkeypox, designated by dominant ecological characteristics, Sankuru District, Democratic Republic of Congo: 2006–2007. Zones are shaded by dominant ecological characteristics: dark green, heavily forested zone; red, ecotone (forest–savannah mosaic); yellow, savannah.

Results

From November 2005 to November 2007, 760 cases of laboratory confirmed monkeypox were identified through active disease surveillance in the nine participating health zones (Table 1 and Fig. 2). We observed an overall annual crude incidence of 5.53 per 10,000, ranging from 2.18 to 14.42 per 10,000 population across health zones. Monkeypox occurred throughout the year with no detectable seasonality. Zones with the greatest forest cover (Kole, Lomela, and Tshudi Loto) consistently had the highest incidence compared with zones with a mixture of mosaic forests and savannah or those with predominantly savannah (Fig. 3 and Table S2).

The average age of cases was 11.9 y, ranging from 5 d to 70 y (median: 10 y). Almost all (92.1%) of the cases were born after mass smallpox vaccination campaigns officially ended in 1980. Only 3.8% (29/760) of monkeypox cases had evidence of previous smallpox vaccination compared with 26.4% of the overall population (Table 2). There were significantly more male (62.1%) than female cases (Fisher's exact test; $P < 0.001$), with significant gender differences for age groups 5–19 y old (Table 1).

In a single health zone (Kole) with comparable active disease surveillance activity in the 1980s and 2000s, the average annual incidence increased from 0.72 to 14.42 per 10,000, representing a 20-fold increase in incidence of human monkeypox over the 20-y period (Table 3 and Fig. 4). We also compared health zones with the most intense surveillance in the 1980s (Kole in the Sankuru District and Bumba health zone in the neighboring Equateur province) to zones with similarly intense efforts, comparable population demographics, and ecological characteristics (Kole, Tshudi Loto, and Lomela health zones) in 2006 and 2007. For these zones, the average annual incidence increased from 0.48 per 10,000 to 11.25 per 10,000 population, indicating the same trend (Table S3).

Based on our active surveillance program, we observed that the risk of human monkeypox is inversely associated with smallpox vaccination. In individuals who were born before cessation of official vaccination campaigns in 1980, vaccinated persons had a 5.21-fold lower risk of monkeypox as compared with unvaccinated persons (0.78 vs. 4.05 per 10,000). In this group, vaccine efficacy was estimated to be 80.7% (95% CI: 68.2–88.4%). In individuals who were born after 1980, the apparent benefit of vaccination is smaller, probably attributable to questionable viability of the relic vaccine doses administered during this period (16).

Discussion

Our data suggest that 30 y after the eradication of smallpox, the incidence of human monkeypox has dramatically increased in the DRC. Previous studies indicate that three main factors determine the burden of monkeypox virus in humans in enzootic regions: (*i*) vaccination against smallpox, (*ii*) exposure to animal reservoir species, and (*iii*) human-to-human transmission (17). Below, we discuss each of these factors and their potential contribution to the observed increased incidence in greater depth. We also provide an assessment of future research and surveillance needs based on the limitations of our study.

During the active surveillance program of 1981–86, previous smallpox vaccination provided 85% protection against human monkeypox (14). Since vaccination ceased in 1980, herd immunity to poxviruses has significantly decreased: In 1981, 84.7% of the population in our study region were vaccinated (based on vacci-

Table 1. Average annual incidence of human monkeypox by age group and gender in health zones with active disease surveillance, Sankuru District, Democratic Republic of the Congo: 2006–2007

	Females			Males			Total population		
Age group	MPX* cases	Incidence†	95% CI‡	MPX cases	Incidence†	95% CI‡	MPX cases	Incidence†	95% CI‡
0–4	78	7.95	6.37–9.92	107	9.69	8.02–11.71	185	8.87	7.68–10.24
5–9	59	5.08	3.94–6.55	108	8.98	7.44–10.84	167	7.06	6.07–8.22
10–14	63	6.28	4.91–8.04	122	12.51	10.48–14.93	185	9.35	8.10–10.80
15–19	27	4.48	3.08–6.51	69	9.04	7.14–11.44	96	7.03	5.75–8.58
20–24	24	3.38	2.27–5.03	30	5.23	3.66–7.47	54	4.21	3.23–5.49
25–29	22	4.40	2.90–6.65	13	3.81	2.22–6.51	35	4.16	2.99–5.78
30+	15	0.74	0.45–1.21	23	1.29	0.86–1.93	38	0.99	0.72–1.36
Total	288	4.12	3.67–4.62	472	6.99	6.39–7.65	760	5.53	5.15–5.94

*MPX cases, number of laboratory confirmed monkeypox cases.
†Average annual cumulative incidence calculated as number of cases divided by population at risk per 10,000 population.
‡CI, confidence interval.

Table 2. Average annual incidence of human monkeypox by age group and vaccination status, in health zones with active disease surveillance, Sankuru District, Democratic Republic of the Congo: 2006–2007

	Unvaccinated*			Vaccinated			Unvaccinated vs. vaccinated		
Age group	MPX[†] cases	Incidence[‡]	95% CI[§]	MPX cases	Incidence[‡]	95% CI[§]	Incidence ratio[¶]	95% CI[§]	*P* values
>0–4	185	8.87	7.68–10.24	—	—	—	—	—	—
5–9	167	7.06	6.07–8.22	—	—	—	—	—	—
10–14	185	9.35	8.10–10.80	—	—	—	—	—	—
15–19	96	7.03	5.75–8.58	—	—	—	—	—	—
20–24	52	4.16	3.18–5.46	2[‖]	5.91	0.72–21.50	0.70	0.17–2.89	0.627
25–29	29	4.58	3.19–6.58	6	2.87	1.06–6.29	1.59	0.66–3.84	0.298
30+	17	6.35	3.97–10.17	21	0.59	0.39–0.91	10.77	5.68–20.41	<0.001
Total	731	7.35	6.84–7.90	29	0.76	0.53–1.10	9.64	6.65–13.97	<0.001
b. > 1980	695	7.36	6.83–7.92	3	4.50	0.93–13.16	1.63	0.52–5.07	0.307
b. ≤ 1980	36	4.05	2.92–5.60	26	0.78	0.53–1.14	5.21	3.14–8.62	<0.001

**b. > 1980*, individuals born after 1980 (after official cessation of mass smallpox vaccination program); *b. ≤ 1980*, individuals born before cessation of mass smallpox vaccination program; Smallpox vaccination was administered sporadically from 1981 to 1984 after mass vaccination program had officially ceased and vaccine quality was questionable (16).

[†]MPX cases, number of laboratory confirmed monkeypox cases.

[‡]Average annual cumulative incidence calculated as number of cases divided by population at risk per 10,000 population.

[§]CI, confidence interval.

[¶]Incidence ratio: ratio comparing incidence in unvaccinated to vaccinated cases.

[‖]These two cases occurred in individuals who were born in 1983 and 1984 and had vaccination scars.

nation scar surveys), whereas today only 24.5% of the local population have evidence of past vaccination (4, 13). The impact of declining vaccination coverage on rising incidence is reflected in the age patterns of incidence, where much smaller increases in infection are observed for population groups with significant levels of prior smallpox vaccination (Fig. 4). More than 90% of cases identified in our surveillance program were born after mass smallpox vaccination campaigns officially ceased, and less than 4% of infected individuals had evidence of previous smallpox vaccination. Furthermore, our data suggest that vaccine-induced immunity is long lasting because individuals who were vaccinated against smallpox over 25 y ago still appear to be at significantly reduced risk of monkeypox. Long lasting cross-protective immunity from previous smallpox vaccination has been reported by Hammarlund et al. (18) based on the US monkeypox outbreak in 2003.

Contact with animal reservoir species is an important driver of monkeypox virus infection. The significant anthropogenic and demographic changes that have occurred in the DRC since the 1980s may have increased exposure of local populations to reservoir species harboring monkeypox virus, thus increasing the chances of animal-to-human infection. Monkeypox continues to occur almost exclusively in rural villages located in or near the tropical rainforest.

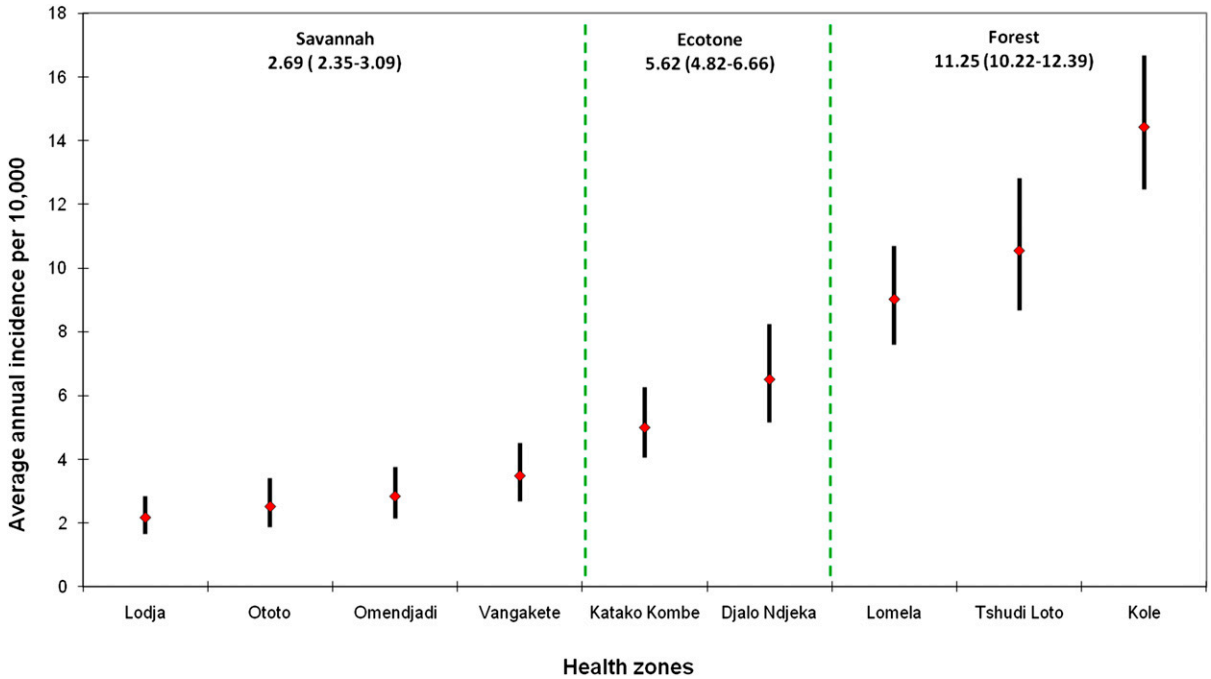

Fig. 3. Average annual cumulative incidence of human monkeypox, by health zone and dominant ecological characteristic, Sankuru District, Democratic Republic of Congo: 2006–2007. Cumulative incidence and 95% CIs are shown for each major geographical area. Ecotone is a transitional zone of mosaic forests interspersed with stretches of savannah between savannah and forest regions.

Table 3. Average annual incidence of human monkeypox by age group, Kole health zone, Sankuru District, Democratic Republic of the Congo: 1981–1986 vs. 2006–2007

	1981–1986			2006–2007			2006–2007 vs. 1981–1986		
Age group	MPX* cases	Incidence[†]	95% CI[‡]	MPX cases	Incidence[†]	95% CI[‡]	Incidence ratio[§]	95% CI[‡]	*P* values
0–4	14	1.48	0.88–2.48	40	21.12	15.52–28.75	14.32	7.79–26.31	<0.001
5–9	17	2.34	1.46–3.74	45	20.96	15.67–28.04	8.97	5.14–15.67	<0.001
10–14	3	0.47	0.10–1.37	40	22.28	16.36–30.32	47.39	14.66–153.18	<0.001
15–19	—	—	—	20	16.12	10.44–24.89	—	—	—
20–24	—	—	—	19	16.32	10.45–25.47	—	—	—
25–29	1	0.31	0.01–1.71	9	11.77	5.38–22.34	38.36	4.86–302.70	0.001
30+	—	—	—	7	2.01	0.81–4.15	—	—	—
Total	35	0.72	0.51–1.00	180	14.42	12.47–16.69	20.17	14.04–28.97	<0.001

*MPX cases, number of laboratory confirmed monkeypox cases.
[†]Average annual cumulative incidence calculated as number of cases divided by population at risk per 10,000 population.
[‡]CI, confidence interval.
[§]Incidence ratio: ratio comparing incidence in unvaccinated to vaccinated cases.

Degraded secondary forests and semideciduous forests with many oil-palm trees, two habitats associated with monkeypox risk, are often found near these villages (9–11). Continued clearing of forest from logging or to open new land for agriculture may favor an increase in human exposure to squirrels and other suspected reservoir species, providing increased opportunities for zoonotic transmission of monkeypox (10, 17). Additionally, recurrent civil war and collateral increase of poverty has forced residents to rely more extensively on locally available sources of protein, such as monkeys, squirrels, and other rodents for sustenance—all of which are potential sources of human infection. Indeed, the age, sex, and spatial distributions of cases (the highest incidence is in male children under the age of 20 living in forested regions) align with reported patterns of hunting behavior.

Besides the likely changes in the incidence of primary infection, there are also reasons to believe human-to-human transmission may have increased. Beyond its direct effect on individual susceptibility, declining vaccine coverage has the potential to cause additional nonlinear increases in human-human transmission. Entire households are now mostly or completely vaccine naïve, as compared with the 1980s, when only small children were susceptible. Thus, today there is an opportunity for intergenerational transmission within households, particularly between parents and children—a possibility that should be investigated via contact tracing studies and mathematical modeling analyses.

Several limitations in our study may have resulted in underreporting of the true incidence of human monkeypox in participating health zones. Given limited resources, it was not possible for our surveillance team to reach all reported cases because of

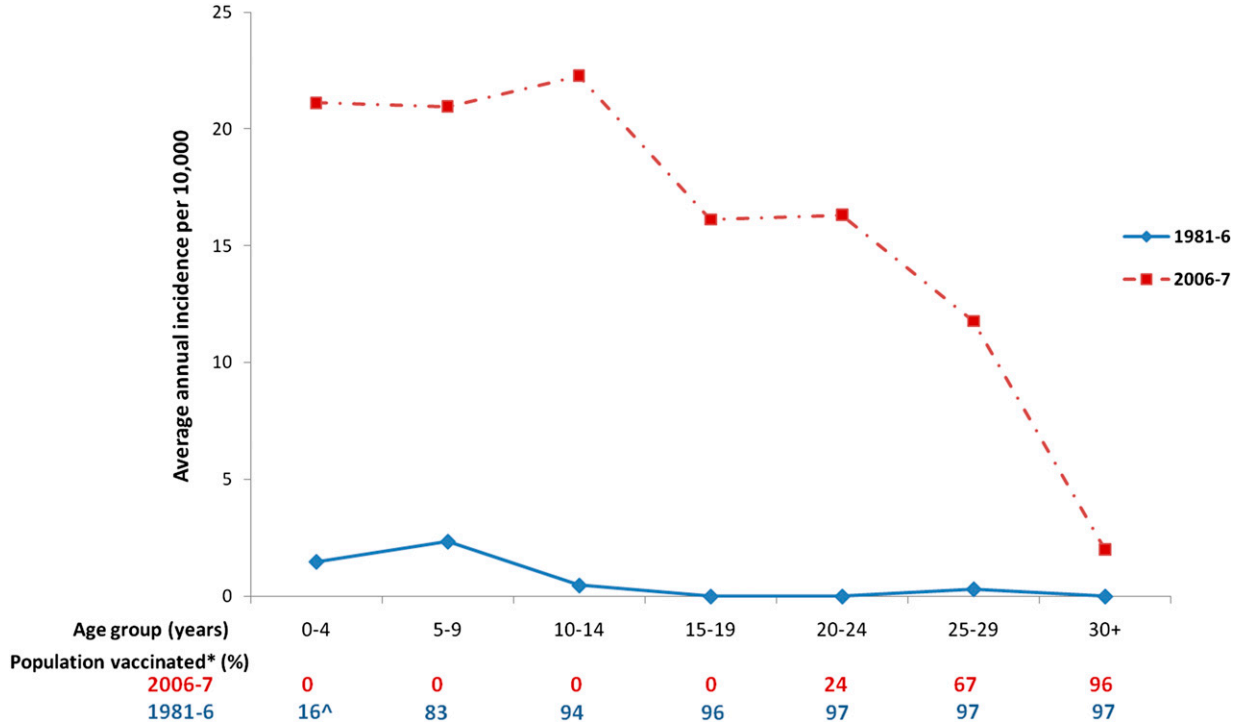

Fig. 4. Comparison of average annual cumulative incidence of human monkeypox by age group Kole Health Zone, Demographic Republic of Congo: 1981–86 vs. 2006–7. *, proportion of the population vaccinated in 2006–7 and in 1981–6 based on vaccination scar surveys in 1981–6 and in 2006. ^, vaccination rate steadily declined from 41.0% in 1981 to 4% in 1985 (13, 33).

their remote locations. In addition, the population has become more rural and isolated with inconsistent access to healthcare providers, thereby diminishing the chance for case reporting and identification. We also lacked the diagnostic capacity to analyze serum, so only acutely infected individuals with active lesions could be laboratory-confirmed and included in our study sample. Thus, we were unable to identify survivors of recent monkeypox virus infection or quantify the frequency of subclinical infection. We used similar case investigation methods and forms as the WHO-supported active surveillance program in the 1980s; however, their program had funding and manpower resources well beyond those available to our program (including a reward equivalent to $90 USD to any individual—including health care workers—who reported a monkeypox case) (13). Given these limitations, we consider the rise in incidence reported likely a conservative estimate of the true increase.

Even though monkeypox virus probably circulates in many parts of the DRC, financial constraints also limited our surveillance coverage. We chose the Sankuru District as the focus of our disease surveillance program for three reasons: (*i*) since 1996, the majority of reported monkeypox outbreaks were reported from these zones, (*ii*) it was a region of epidemiologic priority for WHO-supported active disease surveillance in the 1980s, thus enabling a direct comparison of data from the same geographic area, and (*iii*) the socioeconomic, demographic, and ecologic characteristics of the Sankuru are representative of other regions where monkeypox is also known to circulate. In the 1980s, 89% of all monkeypox cases were discovered in zones with active surveillance, and observed incidence in these zones was markedly lower during periods when they were not under special surveillance (13). We observe the same effect when examining the reporting patterns in 2006–2007, indicating that most cases are missed by passive surveillance systems. Active surveillance in regions where the virus is known to circulate is thus essential to gain quantitative insight into the true burden of monkeypox infection, its geographic range, and patterns of emergence.

The emergence of human monkeypox has potentially serious public health consequences for populations in the DRC but may also be a global health concern. The monkeypox outbreak in the United States in 2003 demonstrated that the virus is capable of spreading to new animal reservoirs outside central Africa. In this case, American prairie dogs were infected by rodents imported from Ghana and served as amplification vectors, ultimately transmitting disease to humans (19). American ground squirrels are also highly susceptible to the virus, suggesting that the host range of New World species may be large (20). If monkeypox were to become established in a wildlife reservoir outside Africa, the public health setback would be difficult to reverse. The possibility that rising incidence may reflect increased human-to-human transmission raises further health concerns and should be studied because greater circulation among humans opens the possibility of geographic spread by travelers, prompting analogies to the international spread of SARS or the pandemic influenza of 2009. However, the distinctive symptoms of human monkeypox would aid greatly in its containment. Increased prevalence in humans, particularly immunocompromised hosts, may also provide more opportunity for monkeypox virus to acquire mutations that increase its fitness in human hosts, possibly leading to increased transmissibility, virulence, and pathogenic potential (21).

A salient question arising from our surveillance data are how much animal-to-human ("primary") transmission versus human-to-human ("secondary") transmission contributes to the increasing incidence of human monkeypox. There has been long-standing concern that declining population immunity may allow human-to-human transmission to cross the threshold beyond which sustained spread of monkeypox is possible (14). Defining the factors underlying increased incidence, and their impact on primary versus secondary transmission, is thus a crucial direction for ongoing research. Further studies are needed to identify the type of animal and human exposures associated with human monkeypox infection and evaluate the respective roles of person-to-person and animal-to-person transmission. Additionally, a better understanding of the mortality and complications associated with monkeypox infection should be assessed. Continued active disease surveillance in endemic regions coupled with household and contact studies with long-term followup would address these important questions.

Although the eradication of smallpox was a tremendous public health achievement, the subsequent global cessation of vaccinia virus vaccination has had two major adverse consequences. First, the majority of the world's population is now vulnerable to a bioterror attack with variola virus; second, the people of central Africa who are in frequent contact with monkeypox-infected animals are no longer protected against infection. The United States and other high-income countries have taken steps to deal with the first problem, by stockpiling vaccine and investigating new antiviral therapies for use in the event of bioterrorism. However, no country has taken responsibility for dealing with the increased burden of monkeypox in impoverished rural African populations. Thirty years after the singular accomplishment of smallpox eradication, the increasing incidence of human monkeypox we observe in DRC should be closely monitored. Failure to pursue a more comprehensive assessment of epidemiology, risk, and possible control measures could have serious implications. Inaction ignores the preventable morbidity suffered by indigenous populations, in the worst case risking increased adaptation of monkeypox to humans and potentially resulting in a lost opportunity to combat this infection while its geographic range is still limited.

The burden of human monkeypox infection in endemic regions may be reduced through a multi-pronged approach, including (*i*) health education campaigns addressing handling of potential animal reservoir species to prevent animal-to-human transmission and (*ii*) barrier nursing practices and isolation of acutely infected patients to prevent human-to-human spread. Vaccination remains an alternative control strategy; however, the logistics of reinstating vaccinia vaccination as a part of routine immunization programs would be extremely difficult, given the poor health infrastructure that exists in endemic regions. Additionally, licensed Dryvax vaccine has many known adverse side effects and is contraindicated in immunocompromised individuals. Targeted vaccination in at-risk populations such as health care workers who treat monkeypox patients and individuals who are highly exposed to animal reservoir species in endemic regions could be considered with alternative vaccines such as modified vaccinia Ankara (a replication-defective vaccinia virus) or LC16M8 (an attenuated live vaccinia approach), which have the potential to circumvent problems associated with the current smallpox vaccine (22, 23).

Methods

Study Location and Population. We initiated an active human monkeypox disease surveillance program, providing technical training, equipment, material support, and supervision for intensified surveillance activities in nine contiguous health zones in the Sankuru district of the Kasai Oriental province in central DRC (Fig. 2). The combined population of the participating zones was estimated at 676,839 in 2006 with a population density of 14.28/km^2 (24). Most villages in this region are located in small clearings in the forest, surrounded by traditional agricultural fields. The local inhabitants are subsistence farmers and hunters and obtain virtually all protein from hunting wildlife, most commonly duikers, monkeys, and rodents (4, 11, 17, 25).

Case Investigation Methods. In each participating health zone, a monkeypox surveillance officer was trained in clinical case identification, investigation, and reporting. These officers were based at the zone hospitals and were provided with standard forms, specimen collection materials, and a motorcycle for transportation to conduct surveillance activities. Local health care workers and institutions were trained to identify suspected cases and instructed to notify the monkeypox surveillance officer if a suspected case occurred. For each suspected case, a physical examination was conducted; scabs, vesicle fluid, and blood samples were collected; and clinical and epidemiologic data were obtained. A standardized questionnaire was used to obtain information on patient demographics, exposure to potentially infected animals and humans,

and signs and symptoms of illness and factors that might affect susceptibility, including smallpox vaccination history. Ethical approval for this study was obtained from participating institutions, and informed consent was obtained from all participants. Because of logistic and budgetary constraints, we were unable to consistently conduct follow-up visits, thus information on mortality and secondary transmission could not be ascertained.

Definitions. A case of suspected human monkeypox was defined as an individual with a fever (>38 °C) accompanied by a vesicular-pustular rash. Suspected cases were classified as vaccinated or unvaccinated based on presence of a smallpox vaccination scar. Cases were defined as confirmed based on detection of monkeypox virus from scab or vesicular fluid by PCR. For the purpose of calculating annual incidence, surveillance years were defined as follows: Surveillance year 2006: November 23, 2005–November 30, 2006; Surveillance year 2007: December 1, 2006–November 30, 2007.

Laboratory Methods. PCR-based molecular assays were used for diagnosis of monkeypox and/or orthopoxvirus infection at the Bundeswehr Institute of Microbiology and the US Army Research Institute of Infectious Diseases. DNA was extracted from scab and vesicle fluid from suspected cases by using the MagNA Pure Compact System from Roche or the QIAamp 96 DNA blood kit from Qiagen. Orthopoxvirus verification was accomplished by using described techniques for PCR amplification of the fusion protein gene present in all orthopoxviruses, including monkeypox virus (26, 27). Orthopoxvirus-positive samples were confirmed with a second PCR assay that discriminates monkeypox-specific DNA signatures from those of other orthopoxviruses (28).

Data Sources. Original datasets of laboratory-confirmed monkeypox cases detected during the active surveillance program from 1981 to 1986 were provided by WHO Headquarters (15). Population size and age structure estimates for participating zones in the 1980s were derived from the 1984 DRC National Census data (29). Population estimates for participating health zones for 2006 and 2007 were obtained from the DRC Ministry of Health (24). Additionally, we conducted a house-to-house census of 12 representative villages in the Sankuru District in 2007 to verify reported village population estimates. We also used our census data to extrapolate age distribution, sex ratios, and smallpox vaccination rates (based on visual evidence of smallpox vaccination scars) for the entire study region.

Statistical Methods. Univariate analysis was performed for categorical variables by using χ^2 or Fisher's exact test, as appropriate. The SE of the age-adjusted incidence was calculated by using the exact binomial computation when cells had fewer than 10 observations; otherwise, the Wilson computation was used (30). Cumulative incidence was calculated as the number of cases divided by the estimated population per 10,000 persons. Vaccine efficacy was calculated as the difference between cumulative incidence in the unimmunized versus the immunized populations, divided by cumulative incidence in the unimmunized (31). We only included individuals who were born before official cessation of smallpox vaccination campaigns in 1980 in our vaccine efficacy estimate. Vaccination was carried out sporadically from 1981 to 1984; however, vaccine quality and administration was questionable (16), thus we excluded the few individuals vaccinated during this period in our analysis. All statistical analyses were conducted with STATA version 10 (32).

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