

Outbreaks of human monkeypox after cessation of smallpox vaccination

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The recent observation of a surge in human monkeypox in the Democratic Republic of the Congo (DRC) prompts the question of whether cessation of smallpox vaccination is driving the phenomenon, and if so, why is re-emergence not universal throughout the historic geographic range of the virus? Research addressing the virus's mechanisms for immune evasion and induction, as well as that directed at elucidating the genes involved in pathogenesis in different viral lineages (West African vs Congo Basin), provide insights to help explain why emergence appears to be geographically limited. Novel vaccines offer one solution to curtail the spread of this disease.

Monkeypox introduction

At the 64th gathering of the World Health Assembly in May 2011, a majority of delegates reaffirmed the view that the remaining stocks of variola virus, the causative agent of smallpox, should be destroyed. But consideration of precisely when that action should be taken was postponed for several years pending completion of crucial research addressing the development and assessment of tools for the treatment and control of the disease should it ever reoccur. This agenda of research includes the development and testing of vaccines and therapeutics, at the heart of which involves understanding the mechanisms that govern variola's virulence and its capability to evade host defenses. But how can these questions be addressed when naturally occurring disease has been eliminated and no satisfactory animal model exists?

In the absence of smallpox, human infections with monkeypox virus constitute the most significant communicable Orthopoxvirus-associated illnesses extant in the world today. Monkeypox is not a direct research-proxy or substitute for smallpox (monkeypox is a zoonosis that can affect a broad range of animal taxa, whereas smallpox was an exclusive disease of humans) but vaccines and therapies developed for smallpox may be useful for the prevention and treatment of monkeypox, and many of the cornerstones of pathogenesis and immunomodulation for both variola and monkeypox probably emanate from conserved homologous processes. Both variola and monkeypox viruses are considered threat agents that could be used

unlawfully for acts of bioterrorism. With monkeypox, there is the added question of its persistence in nature, and its potential for expansion in a world that is now more than 30 years without smallpox. A significant expansion of monkeypox in the world today could pose many of the same challenges as a resurgence of smallpox.

Monkeypox mainly affects people living in heavily forested areas of the Congo Basin, most notably in the Democratic Republic of the Congo (DRC), but it is evident that the virus still resides in regions of Africa from which cases of human monkeypox have not been reported for nearly 30 years. This was illustrated in 2003 when an outbreak of monkeypox in the USA, which resulted in 47 confirmed and probable cases, was traced to a shipment of live animals exported to the USA from West Africa [1]. Human infections with monkeypox virus have not been reported in West Africa since 1978. By contrast, recent epidemiologic studies suggest that monkeypox is currently exhibiting a robust emergence in the DRC [2–4] and sporadic occurrences of the disease in neighboring countries portends to its potential for spread [5–7], prompting the question of why monkeypox appears to be emerging in some environments and not in others.

During the past decade, several avenues of promising research, aimed at identifying the monkeypox virus's mechanisms for immune evasion and induction, the genes involved in pathogenesis in different viral lineages and the ecologic requirements of the virus, have yielded important insights into the factors that could be driving disease emergence. The concurrent development of novel vaccines and antigen delivery systems has provided potential avenues for control of monkeypox.

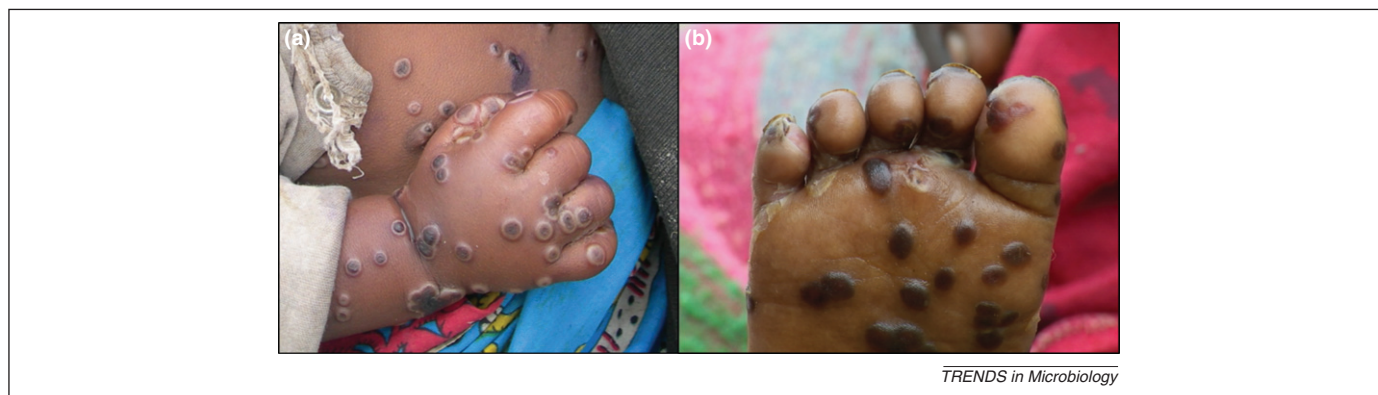
The emergence of monkeypox in the Congo Basin

Human infections with monkeypox virus result in a disease that closely resembles discrete, ordinary smallpox [8]. This fact may have obscured appreciation of the disease's existence until 1970 when the first human infections with monkeypox virus were confirmed. Prior to that time, the virus had only been observed in the context of disease outbreaks among captive primates [9]; it is easily conceivable that naturally occurring human cases could have been attributed to smallpox. The first documented instances of monkeypox came to light during the intensification phase of the smallpox eradication programs in West and Central Africa, when rigorous laboratory investigations of lingering cases of suspected smallpox were routinely pursued [10].

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TRENDS in Microbiology

Figure 1. Monkeypox lesions on (a) the hand and (b) the feet of children in Equateur Province, Democratic Republic of the Congo (DRC). Photo credit: Saturnin R. Ibata, International Conservation and Education Fund.

As with smallpox, the first signs and symptoms of monkeypox, fever, headache and prostration, typically begin 8 to 12 days after exposure to the virus. Also, as with smallpox, this period of febrile prodrome is followed by the development of a highly characteristic pustular rash that can cover the entire body, including the palms of the hands and soles of the feet (Figure 1). This latter feature, along with the defined period of febrile prodrome and slow evolution of rash (over 8–14 days), helps to distinguish monkeypox from chickenpox, the extant disease with which it is most often confused [11].

Shortly after cessation of routine vaccination for smallpox, studies performed among cohorts of people exposed to monkeypox in a household setting demonstrated that smallpox vaccination (anywhere from 3 to 19 years prior) was 85% effective in preventing disease [12]. At that time, detailed epidemiologic studies in the DRC suggested that monkeypox was a rare disease with population annual incidence rates as high as 0.63 per 10 000 persons in one disease-endemic region [13] (Table 1). More recent estimates, derived using comparable surveillance methodologies, are suggestive of a steep rise in overall incidence during the intervening period to roughly 5.53 per 10 000 [4]. Now, as before, the highest age-specific incidences and the greatest numbers of cases occur among people <15

years of age, however a trend toward increasing incidence among persons aged 15–30 years (a relatively high proportion of whom would have benefited from vaccination during smallpox vaccination era, but not since) is evident. This shift points to the cessation of vaccination as one factor that could be contributing to an increasing disease burden in the DRC, but fails to account for why the disease has apparently failed to emerge in other areas formerly permissive for occurrence (e.g. West Africa).

Isolated outbreaks of human monkeypox have been reported in recent years from Sudan and Republic of the Congo [5–7], both of which share a border with DRC. Whether these events represent expected flare-ups caused by viruses circulating naturally within these countries or are spillover events attributable to the expanding virus population in the DRC remains to be seen. Virus isolates from both of these outbreaks are genetically most similar to other monkeypox isolates from the Congo Basin [14], but the similarity might be anticipated owing to geographic proximity alone.

Algorithm-based modeling exercises using point-occurrence data for human monkeypox to predict an overall ecologic niche for the virus suggest that the geographic area affected by monkeypox in the Republic of Congo does possess a suite of ecologic characteristics suitable for

Table 1. Human monkeypox cases reported from 1970 to 2005

Country	Year	Number of cases	Deaths	Refs
Congo Basin				
DRC	1970–present	Cases not fully enumerated ^a	Deaths not fully enumerated ^a	[3,4,13,27]
Cameroon	1979/1989	3	0	[68,69]
Central African Republic	1983	6	0	[70]
Gabon	1987	2	2	[71]
Republic of the Congo	2003	11	1	[7]
West Africa				
Liberia	1970	4	0	[72]
Sierra Leone	1970	1	0	[72]
Nigeria	1971/1978	3	0	[69,72]
Cote d'Ivoire	1971/1981	2	0	[69,72,73]
Other				
United States (ex. Ghana ^b)	2003	47	0	[24]
Sudan	2005	10	0	[6]

^a760 cases reported in the Sankuru District of the DRC during 2006–2007 [4]. A 4% mortality rate was reported during an outbreak in the Katako-Kombe Health Zone of the DRC in 2001 [2].

^bThe source of the monkeypox outbreak in the USA was traced to a shipment of animals from Ghana.

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