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Camelpox: Target for eradication? ☆

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On June 28th, 2011, the United Nations Food and Agriculture Organization confirmed the eradication of rinderpest, a severe disease of cattle and related hoofed animals. Caused by a morbillivirus related to measles, rinderpest devastated European agriculture in the 18th century and produced massive outbreaks in Africa as recently as the 1980s. Its successful elimination followed a long effort that began more than 60 years ago and culminated in a global campaign of surveillance, quarantine and intensive vaccination (Roeder, 2011). In contrast to measles, which only affects humans, the eradication of rinderpest was made more challenging by the fact that the causative agent infected both domestic cattle and some wild bovine species (Horzinek, 2011; Morens et al., 2011). It is the second infectious disease to be eradicated, following the elimination of smallpox just over 30 years ago.

Success in extirpating one viral disease of animals raises the question of which others might be targets for eradication. In this issue of *Antiviral Research*, Sophie Durrafour and her colleagues point out that camelpox, a smallpox-like illness that occurs only in camels, could potentially be eliminated through an intensive vaccination program (Duraffour et al., in press). Although it has not been a recognized target for eradication efforts, and the toll of animal and human suffering from camelpox cannot compare to the mass die-offs and famine caused by rinderpest, the threat it poses to people whose well-being depends on the health of their camels makes the disease of considerable economic and public health importance. Like smallpox, camelpox meets the basic requirements to be a candidate for eradication: the disease affects a single host; its causative agent has no wildlife reservoir; and diagnostic tests and vaccines are available to diagnose the disease and block its transmission (Aylward et al., 2000; Moss and Strebel, 2011). As for other potentially eradicable diseases, a cost-benefit analysis could be performed to determine the priority of its elimination versus other health needs (Horst et al., 1999; Tambi et al., 1999).

Some background information will help explain what an effort to eradicate camelpox would involve. There are approximately 25 million camels in the world (http://faostat.fao.org). In north Africa and western Asia, the majority are dromedary (single-hump) camels (Fig. 1), while two-hump Bactrian camels are found in China, Mongolia and other areas of east Asia. For both species, camelpox is the most common infectious disease, potentially occuring wherever the existence of large herds and the movement of infected animals between herds makes the continuous circulation of virus possible (Fowler, 2010). Camelpox has not been seen in feral camels in Australia, in wild Bactrian camels in China and Mongola, or in New World camelids. Because it is most severe in young animals, outbreaks can be devastating for herds and the people who depend on them for meat, milk, hides and transport. Epizootics are most common in the rainy season (Wernery and Kaaden, 1995). The office Internationale des Epizooties (OIE, World Organization for Animal Health) lists camelpox as a reportable disease.

Like smallpox, camelpox is usually transmitted in airborne saliva droplets, but it can also spread through direct contact with skin lesions, and the virus can be transferred mechanically by ticks and other biting arthropods (Duraffour et al., in press). A 1–2-week incubation period is followed by fever and prostration and the development of a vesiculopustular rash. In some animals, lesions remain confined to the skin and mucous membranes of the nose and mouth, but in others they spread to cover much of the body (Fig. 1). In contrast to smallpox, in which pustules occur only on the skin and the squamous epithelium of the oropharynx, severely ill camels also develop proliferative poxviral lesions in the bronchi and lungs (Kinne et al., 1998). Because oral lesions severely impair the ability of young calves to feed, the case fatality rate may reach 25%. Animals that survive the disease are immune for life, and there is no chronic carrier state.

Although camelpox has presumably existed for millenia, its causative agent was not isolated until the early 1970s, during the opening phase of the global smallpox eradication campaign (Sadykov, 1970; Roslyakov, 1972). At that time, the principal concern of poxvirus researchers was to ensure that variola virus did not have an unrecognized animal reservoir. Because the rashes of camelpox and smallpox closely resembled each other, and the two diseases were often found together in the same countries, it appeared that they might be caused by the same agent. In initial studies, Baxby showed that viruses from camels resembled variola in their cytopathic effect in Vero cells, their behavior in cross-neutralization tests and their lack of virulence for mice and rabbits, but they differed in that only variola virus produced a rash in rhesus macaques (Baxby, 1972). Further research showed that the camel viruses also differed from variola in their cytopathic effect in human cell lines and in the appearance of pocks on the chorioallantoic membrane

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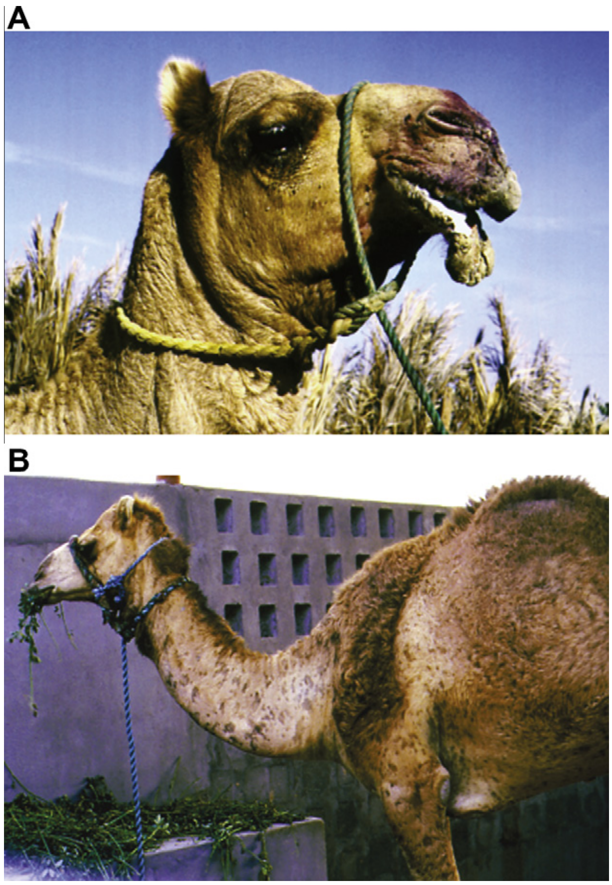

Fig. 1. Camelpox in dromedary camels in Bahrain. (A) Dense clusters of pustules on the lips and within the mouth. (B) Resolving generalized rash. From (Higgins et al., 1992), with permission.

of eggs (Bedson, 1972; Baxby, 1974; Marennikova et al., 1974). The injection of a large dose of variola virus failed to cause disease in camels, but a tiny amount of material from a sick camel produced a severe febrile illness with a vesiculopustular rash that spread to co-housed animals (Baxby et al., 1975). Camels that had been injected with variola virus were cross-protected against a later camelpox challenge, indicating that the agents were members of the same genus (Mahnel and Bartenbach, 1973). Whole-genome sequencing has since revealed that camelpox virus is variola's closest relative, suggesting that they share a common ancestor (Gubser and Smith, 2002).

By the end of the smallpox eradication campaign, it had become clear that camels were not a natural reservoir for variola virus. However, concern remained that, once the cessation of vaccination had removed the immune barrier to orthopoxvirus infection, camelpox might "jump" to humans and occupy the ecological niche vacated by smallpox. An investigation of the susceptibility of humans to camelpox was therefore undertaken in the early 1980s in Somalia, where the disease was present in many parts of the country. Jezek and his colleagues interviewed and examined some 500 camel herdsmen, all of whom had at one time or another been in contact with sick animals (Kriz, 1982; Jezek et al., 1983). Most had never been vaccinated against smallpox. Rashes were noted on a few of the herders, but samples from their lesions did not reveal an orthopoxvirus, and the men assured the investigators that camelpox was not transmissible. The possibility of human infection with camelpox virus was not conclusively demonstrated until 2010, when the agent was recovered from pustules on the hands of some Indian camel herders who had cared for sick animals (Bera et al., 2011). The lesions remained localized, and there was no person-to-person transmission. Interestingly, the self-limited nature of human infection with camelpox virus suggests that it could be used as a live smallpox vaccine, and historical records indicate that inoculation of material from camelpox crusts was employed for that purpose in Iran, long before Jenner developed his cowpox method (Tadjbahsh, 1994).

Because camelpox virus resembles variola in its dependence on a single host, the disease could potentially be eliminated through a combination of surveillance, vaccination and quarantine. In the early 1990s, Higgins and colleagues demonstrated that an outbreak could be halted by immunizing animals with human smallpox vaccine (Higgins et al., 1992). However, because of concern that vaccinia virus could accidentally spread from recently inoculated camels to unvaccinated humans or to domestic or wild animals, researchers began to focus on developing attenuated camelpox virus vaccines that could only infect camels. Scientists in Dubai passaged a camelpox virus isolate some 80 times in a line of camel skin cells, and showed that the resulting virus (Ducapox®) was highly attenuated for young animals (Wernery and Zachariah, 1999). Another vaccine, now marketed as Orthovac®, was developed in Saudi Arabia through tissue culture passage, and proved safe and effective in field testing (Hafez et al., 1992). An attenuated vaccine was also developed in Mauritania (Nguyen et al., 1996) and a formalin-inactivated vaccine in Morocco (El Harrak and Loutfi, 2000). In contrast to products that require a "cold chain," the thermostability of these poxviral vaccines would facilitate their use in hot, dry regions where the disease occurs.

To eradicate camelpox, it would not be necessary to vaccinate all of the world's camels. Instead, veterinarians could employ the "ring vaccination" strategy that was so successful in the final phase of the smallpox campaign, in which intensive surveillance was used to detect cases of disease, followed by vaccination of all surrounding contacts and continued monitoring to ensure that no more cases occurred. For camelpox, such a strategy would have to include testing to differentiate it from a clinically similar disease, contagious ecthyma, caused by a parapoxvirus. Polymerase chain reaction (PCR) and other diagnostic assays have been evaluated in a number of countries (Balamurugan et al., 2009; Bera et al., 2011) and are delineated in the OIE's *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (OIE, 2009).

The diagnostic tests and vaccines needed for an eradication effort are available. Unfortunately, as with many public health problems, the challenge lies in bringing those tools to the affected animals. If camelpox only occurred in small, prosperous countries such as the United Arab Emirates, where the total camel population is less than 400,000, it could readily be eliminated. Instead, the disease is most prevalent in Somalia, Ethiopia and Sudan, three impoverished nations in the Horn of Africa with a long history of political instability and civil war, which are home to more than half the world's camels. Because of the logistical difficulties of reaching its nomadic inhabitants, Somalia was the last country in the world to be freed of smallpox. It now holds the largest number of camels of any country – some seven million animals – and camelpox presumably remains widely enzootic, as it was in the 1980s. Although the elimination of camelpox from that area will clearly be difficult, some encouragement may be taken from the fact that rinderpest was successfully eradicated from Somalia and its neighbors in the late 1990s (Roeder, 2011).

The idea of eradication has traditionally been associated with activities on a global scale, such as the current campaign to eliminate poliomyelitis, but such a massive effort would not be required for a disease like camelpox, which is confined to a specific region. For example, the program to eradicate Guinea worm (dracunculiasis), which appears to be approaching a successful conclusion, has been limited to those nations where the parasite is found (Hopkins et al., 2008). The fact that countries affected by camelpox include both wealthy nations, in which vaccines are in use, and some of the world's poorest countries, where most of the infected animals are located, suggests that a program of mutual cooperation would be the best path to eradication. Were the richer states to support a successful eradication campaign, they could recoup at least part of its cost by discontinuing their own programs of surveillance, diagnostic testing and vaccination. Researchers working toward the goal of "One Health" should consider which other diseases of humans or animals might succumb to a similar collaborative approach.

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