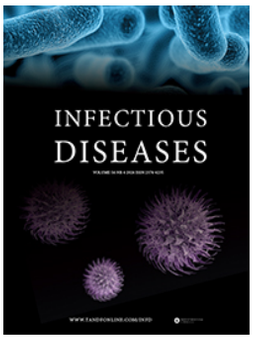

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The emergence of Alaskapox: exploring an unprecedented viral threat and implications for public health

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COMMENT

The emergence of Alaskapox: exploring an unprecedented viral threat and implications for public health

The number of zoonoses transmitted from animals to humans has nearly tripled in the past 40 years, complicit with human actions on the environment. By analysing the historical trends of five specific viral pathogens-filoviruses such as Ebola and Marburg, SARS coronavirus 1, Nipah virus, and the Machupo virus, through a database that included World Health Organisation (WHO) reported outbreaks since 1963 that caused the deaths of 50 or more people as well as historically significant events such as the 1918 and 1957 influenza pandemics, a total of 75 animal-to-human transmission events in 24 countries, with 17232 deaths, were detected. Of these, 15771 deaths were caused by filoviruses alone. Between 1963 and 2019, outbreaks increased by about 5% each year, with a 9% increase in deaths. Projecting these annual rates into the future, the number of transmission events is expected to be four times higher in 2050 and the number of deaths 12 times higher than in 2020 [1].

Emerging zoonoses are of greatest concern to humanity because they are appearing at a rate that is unprecedented in our human history and because they have a major impact on human health, social systems, and economic systems. In recent years, several outbreaks of Mpox have been recorded in different parts of the world. These outbreaks have caused concern among public health experts because of the contagious nature of the disease and its ability to spread rapidly among humans. In 2003, the United States experienced an outbreak of Mpox, which was a rather unusual occurrence and caused concern among public health experts. This outbreak was particularly significant because it was the first time Mpox had been documented so widely outside Africa. The outbreak was linked to the importation of infected animals, particularly exotic rodents from West Africa. These animals were subsequently sold as exotic pets in the United States, leading to transmission of the disease to humans. Symptoms reported during the 2003 Mpox outbreak in the United States were similar to those found in outbreaks in Africa, although they were generally less severe than Smallpox. Person-to-person transmission had been confirmed but was less common than transmission from infected animals to humans. U.S. health authorities responded to the outbreak by implementing active surveillance measures, contact tracing, isolation of confirmed cases, and infection control recommendations.

According to an Alaska Section of Epidemiology bulletin issued Feb. 9, 2024 [2], a new alert comes from Alaska, following the first known fatal case of an immunocompromised man on the Kenai Peninsula due to a newly discovered Orthopoxvirus (OPXV), namely Alaskapox virus (AKPV) [3]. It was first discovered in 2015 in a woman living near Fairbanks, with a total of seven cases reported through December 2023. AKPV has been identified as a pathogen that causes skin lesions in infected patients as showed here [4]. These lesions typically present as erythematous papules or nodules that progress to vesicles and pustules, often accompanied by surrounding edoema and erythema. In some cases, a central umbilication or scab may be observed, and they may occur singly or in clusters, distributed in various parts of the body, including the face, trunk, and extremities. In addition, patients may experience itching, or pain associated with the lesions. In some cases, AKPV-associated skin lesions may be accompanied by systemic symptoms, such as fever, general malaise, and regional lymphadenopathy. However, systemic manifestations are not always present, and the severity of symptoms may vary from mild to severe due to various factors, including the patient's age, immune status, and underlying health conditions. Immunocompromised individuals, such as those with HIV/AIDS or undergoing immunosuppressive therapy, may be at greater risk of developing severe AKPV disease due to their compromised immune function. Similarly, individuals with pre-existing skin conditions or wounds may be more susceptible to developing extensive skin lesions and complications from AKPV infection.

AKPV has been isolated mainly in people who have had contact with small wild mammals in the Alaskan region. However, its precise origin and distribution among animal populations are still not fully understood. The fatal case of AKPV, which took several months to diagnose, is significant because it differs from previously reported mild infections associated with the virus. This case marks the first occurrence of AKPV outside the Fairbanks area. The increased severity of illness in this case is likely attributed to the individual's immunocompromised state, as suggested by health officials. Until December, AKPV infections had manifested predominantly as mild illnesses characterised by skin rashes and localised lymphadenopathy. Notably, affected individuals had healthy immune responses, making treatment unnecessary. This clinical profile highlights the atypical nature of the fatal case and underscores the importance of further investigation into the pathogenesis and clinical spectrum of AKPV infections, particularly in immunocompromised populations. Given the severity observed in the fatal case of AKPV, it's imperative to consider treatment options, particularly antiviral therapy. Antipoxviral drugs, such as tecovirimat, have demonstrated efficacy against other Orthopoxviruses (OPXVs) and may hold promise in the management of AKPV infections. Tecovirimat, also known by its brand name TPOXX, is a small molecule inhibitor of OPXV replication that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of human Smallpox disease [5]. Studies have shown that tecovirimat effectively inhibits replication of variola virus, the causative agent of Smallpox, both *in vitro* and in animal models. Its mechanism of action involves targeting the viral enzyme p37, which is essential for the formation of mature virions [6]. Although specific data on the efficacy of tecovirimat against AKPV are currently lacking, its broad-spectrum antiviral activity against OPXVs suggests that it may be a viable therapeutic option for severe cases of Alaskapox. Other antiviral agents, such as cidofovir and brincidofovir, have demonstrated activity against OPXVs and could be considered as potential therapeutic options for AKPV infections. Cidofovir, a nucleotide analog, inhibits viral DNA synthesis by acting on the viral DNA polymerase enzyme [7]. Brincidofovir, a lipid-conjugated derivative of cidofovir, has better oral bioavailability and could offer advantages in terms of dosing and administration [8]. These results indicate that there are several potential treatment options for AKPV, but further studies are needed to evaluate the efficacy of these treatments against AKPV and to determine their optimal role in the management of this emerging infection.

To contribute to a finer-scale understanding of the dynamics of the epidemic, our team has defined a data dictionary to collect individual-level information on patients, including age, gender, symptoms, to effectively extract unstructured information from Alaska Department of Health PDF bulletins and make it available for research purposes. Data are freely available at: https://github.com/fbranda/alaskapox. Currently, we are making manual updates to the archive, as attention to this virus arose only after the first death was reported and given the still unclear nature of the situation and the limited incidence of cases, no special effort was required in updating the data. However, considering the possibility of a potential worsening of the situation and the increase in case reports, we are already exploring solutions to automate the updating of data by evaluating the integration of automated scraping methods that would allow us to quickly access and update the repository using government sources. This would ensure more timely and reliable availability of data in case the situation evolves. In addition, we also considered the needs of the public interested only in easily accessing information about Alaskapox without the need to download or manipulate data files. With a simple click on this URL (https://tinyurl.com/alaskapox), users can explore and view all relevant information regarding Alaskapox, presented in an accessible and user-friendly format directly on the web page. This solution goes beyond simply downloading data for research purposes but makes data access more immediate and convenient for anyone wishing to learn about the topic, allowing users to obtain up-to-date information in real-time, without having to wait for repository data update processes.

For what the genetic make-up is concerned, it should be pointed that AKPV stands out within the OPXVs due to its notable genetic variation compared to other known strains, despite its ability to induce similar skin lesions in infected individuals [3]. Indeed, according to the phylogenetic reconstruction of OPXVs, genome of AKPV represents a unique genetic lineage within the family, displaying significant divergence from the closely related strains [9]. From an evolutionary point of view, AKPV appears to be basal to the clade composed by OPXVs of the old world suggesting an ancient origin. It is very intriguing because, despite its recent discovery, it could represent an ancient lineage that, as far as we know, has not given rise to descendants or has not

proliferated in terms of diffusion. Nevertheless, it deserves attention. Indeed, one of the greatest lessons from the SARS-CoV-2 pandemic is the importance of ongoing and uninterrupted surveillance efforts [10] to deepen our understanding of the virus's behaviour, transmission dynamics, spill-over risks, and, of course, public health consequences. Continuing investigation into the genetic composition of the AKPV and its interactions with various host species, including small mammals, holds the potential to yield valuable insights into its origins and potential reservoirs.

Disclosure statement

The authors declare that there is no conflict of interest.

Authors' contributions

Conception and design: F.B.; investigations: F.B., F.S., M.C.; validation: M.C.; supervision: M.C.; writing – original: F.B., C.R., F.S., M.C.; writing – revision: F.B., C.R., F.S., M.C.

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