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Alaskapox mystery solved by a one health approach

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On February 9, 2024 the US State of Alaska Epidemiology Bulletin reported the first death of a patient with Alaskapox virus infection[1]. This patient was only the seventh reported person with this Orthopoxvirus. Since the initial patient in 2015, all six previous Alaskapox patients lived in the Fairbanks region. All six were immunocompetent, had skin lesions, and none required hospitalization[2].

In contrast, this seventh patient with Alaskapox was an elderly immunocompromised man who lived several hundred miles south of Fairbanks in the Kenai peninsula of Alaska. He required hospitalization before his death in January 2024 with renal and pulmonary failure[1].

Dr. Julia Rogers, an epidemiologist with the US Centers for Disease Control and Prevention (CDC) who is assigned to the Alaska Department of Health was quoted as saying: "We were able to sequence the virus from this patient's case, and it did show that there was a distinction between this case and the clusters of cases that we were able to sequence from Fairbanks"[3].

Importantly, this most recent case is the first time that the Alaskapox virus has been found outside of the Fairbanks area, and also the first time a genetically distinct version of the virus has been found.

After the first patient in 2015 the origin of the infection due to this novel Old World orthopoxvirus was not determined. One hypothesis was that the virus was imported to Alaska by a traveler who had been in central

Asia; however, no supportive evidence was found[4]. Another hypothesis was that the virus was endemic in one or more animal species in the Fairbanks area of Alaska. To investigate this hypothesis a One Health approach was taken. The significance and value of the One Health concept is that it always takes an integrated approach that includes data from the health perspectives of humans, animals, and their environments.

Details of the initial investigation of the 2015 patient using the One Health approach included testing animals, the environment, and human contacts. Specifically, this initial patient in 2015 reported that wild animals including shrews, voles, and squirrels were abundant in the forest environment where she lived and they were regularly observed around her home[4].

Consequently, 31 small-mammal samples were collected from 12 individual animals belonging to 2 species i.e., the northern red-backed vole (*Myodes rutilus*, n = 9 animals) and the common shrew (*Sorex cinereus*, n = 3 animals). All 12 animals tested negative for orthopoxviruses by PCR[4]. However, these numbers were too small to rule out these animals species as being infected with Alaskapox virus. In addition, 23 environmental samples were collected from in and near the patient's home and all tested negative for orthopoxviruses by PCR[4].

In addition, as part of the One Health approach to the investigation of this 2015 patient, her family and friends were tested and none found to be positive. Of note, however, the "patient's older child was positive for anti-Orthopoxvirus IgM, but because this value was low and the corresponding anti-Orthopoxvirus IgG result was negative, the result was interpreted as equivocal"[4]. Unfortunately, no follow-up testing could be performed to see if the IgG seroconverted to positive. If it had, then person-to-person transmission would be one possible explanation.

This author went to Alaska in July 2020 and talked with state public health officials, a veterinarian involved in this investigation of the patient from 2015, and US CDC officials. The reason for going to Alaska was to help catalyze the discovery of the origin of this virus, how it infected the one patient five years earlier, and who else might be infected.

After a 2nd patient near Fairbanks was diagnosed in August 2020, and then two more patients in 2021, a much more extensive search for an animal source of the virus was initiated. This testing resulted in viable Alaskapox virus being isolated from two species: the northern red-backed vole and a shrew. In addition, 20/385 (5%) animals across these two species were positive for Alaskapox virus by PCR. These results were reported in an abstract at a CDC conference in 2023 by Newell *et al.*[5].

Thus, a One Health approach did eventually solve the question of the origin of the human infections with the novel Alaskapox virus. Moreover, now in 2024 the One Health approach should be applied to further testing of voles, shrews and any other potentially infected species across Alaska, and beyond in any parts of Canada and Russia where they exist. In addition, serosurveys in humans could be undertaken. Clinically, studies to assess whether antiviral drugs, vaccinia immune globulin (VIG) and vaccines that are effective against smallpox and mpox are also of benefit against Alaskapox.

Moreover, a "look back" investigation should occur to test animals, such as these species of voles and shrews, in Museum collections in Alaska, and northern parts of Canada, Russia, and China. An antibody test for the virus will allow for such retrospective, "look back", testing in both preserved animal and human blood samples. Confirmatory identification for this specific virus can be done by virus testing such as PCR

and genetic sequencing.

It can be anticipated that more genetically distinct versions of the virus will be found in geographically distant areas, such as was found in the most recent patient in Kenai peninsula of southeastern Alaska in contrast to the Fairbanks area. From this single patient it cannot be inferred that the Kenai peninsula strain is more virulent given that the patient who died was immunocompromised due to chemotherapy for cancer. In addition, it must be confirmed that he did not have any other infections along with the Alaskapox virus, e.g., the bacteria *Bartonella henselae* that causes cat scratch disease, given that he was reported to be scratched by a cat on several occasions[1].

Decades ago distinct differences in severity were recognized between smallpox variola major and variola minor, and between mpox clades in the Congo Basin and West Africa. Whether such genetic diversity and differences in clinical virulence will someday be found with this Alaskapox Orthopoxvirus requires international One Health surveillance and collaboration. Much more important information about this virus will come in the months and years ahead.

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