

## Borealpox Virus: a Comprehensive Review of its Emergence and Global Recommendations

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### Abstract:

The emergence of the Borealpox virus (BRPV), formerly known as the Alaskapox virus (AKPV), in 2015 poses an intriguing scientific challenge. Despite being first discovered in Alaska, BRPV is a potential global threat, and reports

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of instances have raised questions about how serious it can be; especially in those with impaired immune systems. The unique characteristics of BRPV have been clarified through genomic characterization, providing insight into its evolutionary lineage and transmission dynamics. A recent death linked to BRPV highlights the difficulties presented by newly developing infectious illnesses, particularly for individuals who are already at risk. The implications of BRPV for public health call for all-encompassing management approaches; such as creating efficient treatments and customized interventions for various clinical presentations. Research and surveillance initiatives are vital for comprehending ecological reservoirs and patterns of transmission. Additionally, biosafety regulations and immunization programs are critical for controlling outbreaks and reducing the worldwide effects of BRPV. Prioritizing vaccination drive approaches, implementing stringent infection control measures, and reinvigorating disease surveillance systems are imperative for preventing BRPV. In addition, enhancing the training of frontline healthcare professionals and implementing the One Health concept are crucial measures that foster robust cooperation and adaptability, while confronting new public health concerns. A comprehensive review of the emergence and consequences of the Borealpox virus is necessary to direct future investigations and global public health campaigns. By utilizing interdisciplinary approaches and promoting global collaboration, we may successfully alleviate the danger presented by BRPV and protect public health across borders.

**Keywords:** Alaskapox virus, AKPV, Borealpox virus, BRPV, emerging infectious diseases, Orthopoxvirus, public health

## Introduction

A novel pathogen, previously known as the Alaskapox virus (AKPV) and now called the Borealpox virus (BRPV), emerged in the wide state of Alaska amid its magnificent scenery and isolated settlements in 2015. BRPV is an orthopoxvirus linked to skin-lesioning Mpox and Smallpox viruses. Most patients experienced mild illnesses that resolve naturally within a couple of weeks<sup>1</sup>. When BRPV was discovered deep within this northern frontier, the medical community was surprised by its enigmatic origins and possible danger. The scientific community was alarmed by this new species of the Orthopoxvirus genus, which was first found in Fairbanks, Alaska<sup>2</sup>. The threat of BRPV is real, even with just seven occurrences reported by February 2024 in the Fairbanks North Star Borough and the Kenai Peninsula Borough—one, of which was fatal: linked to a weakened immune system. Its discovery story appears to be a compelling medical mystery: a woman presents with unexplained lesions that reveal the presence of an Orthopox

virus that science has not yet identified. This mysterious virus was revealed through genetic exploration, named Alaskapox virus in 2019, and now Borealpox virus: as of April 1, 2024, marking a turning point in our understanding of infectious diseases in regions far around the globe<sup>3</sup>.

Although red-backed voles and shrews are the primary carriers of the virus, household dogs and cats may also help transmit the infection, in addition to human cases having also been reported. Several skin lesions (pustules or pumps), muscle and joint pain, and swollen lymph nodes have been reported as symptoms of Borealpox syndrome. Immunocompromised individuals may be more susceptible to more serious illnesses<sup>4</sup>. Although there have not been any verified cases of human-to-human transmission, people with skin lesions are encouraged to take precautions, such as bandaging the affected regions. Over the years, the increasing number of cases has raised awareness of this illness. A fatal case outside of the Fairbanks region occurred in January 2024, despite

the virus's initial moderate symptoms. This event has raised concerns about the potential severity of the virus; especially in immunocompromised individuals<sup>5</sup>. Considering the evolving nature of viruses and their implications for public health, a review of the Borealpox virus is essential to direct future research efforts and lessen the possible impact of this new infectious disease<sup>6</sup>. Thus, this study aimed to comprehensively examine the emergence of the Borealpox virus and its implications for public health, so as to inform effective prevention, monitoring, diagnosis, and management strategies on a global scale.

#### **First case presentation and genetic characterization of the Borealpox virus**

On July 29, 2015, a middle-aged Alaskan woman went to an urgent care facility and reported having a spider bite on her right shoulder. Before seeing a doctor, she had been experiencing malaise, fever, exhaustion, and enlarged lymph nodes for five days. Her medical history indicated hypothyroidism, while there had been no recent travel beyond the nation's borders, no contact with sick people, and no history of skin infections. During an inspection, a doctor found that her right shoulder had two smaller nearby vesicles and a small ulcer that was red, warm, and sensitive<sup>2,7</sup>. A straight line of redness ran from her upper chest to her shoulder and back, suggesting that she had a viral infection. After being removed from a vesicle, a swab sample was submitted to the Alaska State Public Health Virology Laboratory for additional examination and diagnostic testing. MRC5, HEP-2, and RMK cell lines were cultured from swab samples on August 3. By August 10, cytopathic effects were visible in all three tissue cultures. The California Department of Public Health conducted polymerase chain reaction (PCR) tests for varicella-zoster virus and direct fluorescent antibodies for herpes simplex virus, which produced negative results<sup>7,8</sup>. An isolate from the MRC5 cell line was then sent to the Alaskan State Public

Health Laboratory on August 17. A general orthopoxvirus PCR test produced positive results, whereas, testing for non-Variola- and Variola-specific orthopoxvirus PCRs produced negative results. The initial swab sample and three cell culture isolates—one from each cell line—were sent to the Centers for Disease Control and Prevention's Poxvirus Laboratory by August 24. Positive results were obtained on August 27 from an orthopoxvirus-generic PCR assay performed on all four submitted samples<sup>7</sup>.

To distinguish a unique genetic branch within the Orthopoxvirus genus, this study examined a concatenated sequence alignment consisting of 28,037 base pairs<sup>9</sup>. AK2015\_poxvirus demonstrated a robust phylogenetic structure, with the Variola and Taterapox viruses recognized as sister taxa. It was placed as the sister of a monophyletic group that included all Old World Orthopoxviruses and was classified under the Orthopoxvirus genus. The genetic divergence between isolates within the North American clade was between 12.3% and 12.6%, while that between isolates from different Old World Orthopoxvirus species varied from 6.1% to 7.3%. Serological testing revealed no signs of recent exposure, even though adult contacts had received smallpox vaccinations. The patient's work history included sporadic employment in Alaska's petroleum sector and a brief stint with her partner working on Azerbaijani oil-drilling platforms<sup>4,10</sup>. Samples swabbed from objects that might be fomites did not contain any DNA from orthopoxvirus. Orthopoxviruses were not detected in environmental samples taken from the house or the surrounding area. The patient's active lesion was consistently warm and sensitive, and orthopoxviruses were not detected in small mammal samples taken from the region<sup>7</sup>. The genome of the BRPV isolate, which spans 210,797 bp and features 2.4 kb inverted terminal repeats (ITRs), is distinct from that of the New World and Old World Orthopoxviruses. Its A+T content is 67.2%, which falls between the New World and most Old World OPXVs. Despite its shorter ITR, its structure

aligns with typical OPXV patterns<sup>11</sup>. The BRPV is a unique branch between Old World and New World OPXVs, as it shares greater genetic similarity with the former. The central region of the genome, rich in conserved genes, reflects its closer relationship to Old World OPXVs. Gene annotation revealed 206 predicted genes in the BRPV genome, with substantial similarity to known OPXV proteins. However, several BRPV proteins exhibit novelty or greater similarity to New World or unclassified OPXVs. The hemagglutinin protein of BRPV contains a unique insertion, suggesting potential functional divergence<sup>12</sup>.

### The first fatal case

The demise of an Alaskan man from BRPV demonstrates some of the challenges presented by newly emerging infectious diseases, especially in those with a compromised immune system. The man spotted a sensitive red papule in his right armpit in mid-September 2023 while receiving cancer treatment on the Kenai Peninsula. After six weeks, he visited several healthcare facilities. The nature of the infection remained unknown despite medical intervention, including antibiotic therapy and rigorous diagnostic testing, until the Centers for Disease Control and Prevention (CDC) tested him when he was hospitalized in Anchorage. Subsequently, they discovered that he had Borealpox<sup>13</sup>. This is the first known hospitalization and death attributed to the virus, likely due to the compromised immune status of the patient. Dr. Joe McLaughlin, a state epidemiologist, emphasizes the importance of understanding the virus's transmission dynamics, prevalence in animal populations, and potential preventive measures<sup>14</sup>. The man's clinical course, marked by initial improvement followed by worsening symptoms and complications, highlights the challenges of managing severe viral infections; especially in individuals with underlying health conditions. Despite aggressive treatment, the man's condition deteriorated, leading to his death. Despite advances in antiviral treatments; such as

TPOXX, the lack of effective interventions against Borealpox underscores the urgent need for further research and development efforts<sup>4,15</sup>.

### Public health implications

The emergence and pathogenesis of the Borealpox virus have significant consequences for public health, requiring a thorough grasp of the disease's clinical signs, transmission dynamics, and preventative measures. Similar to orthopoxviruses, the BRPV has an incubation period of five to twenty-one days<sup>16</sup>. During this time, the virus replicates at the injection site and then spreads by viremia to the lymph nodes and other organ systems. Similar to orthopoxvirus cases, the clinical manifestation of BRPV infection frequently consists of flu-like symptoms; such as fever, headache, malaise, and rash<sup>17</sup>. However, the unique features of BRPV highlight the necessity of specialized surveillance and management strategies<sup>18</sup>. A BRPV rash can appear anywhere on the body, although it usually starts on the face and moves to the trunk and limbs first. The lesions that appear vary in size and shape. Encephalitis, skin infections, and ophthalmic and pneumonitis disorders are among the complications that can occur, especially in susceptible groups, including young children, pregnant women and people with underlying immune weaknesses<sup>19</sup>. The lack of FDA-approved treatments for BRPV highlights the significance of supportive care and symptom management, which involves the administration of antibiotics to treat secondary bacterial infections, antipyretics, and extra oxygen<sup>20</sup>. The effectiveness of tecovirimat in treating BRPV remains uncertain, despite its potential to treat smallpox by blocking viral replication. This underscores the critical need for additional studies and clinical trials<sup>21</sup>. For severe cases of BRPV, monoclonal antibodies might provide a treatment option; nevertheless, safety profiles and production processes raise questions that should be carefully considered. Furthermore, research on the efficacy

of vaccinations and antibody-based treatments in reducing BRPV infections is warranted; especially in high-risk groups and environments where zoonotic transmission is probable<sup>22</sup>.

Similar to monkeypox, BRPV has zoonotic transmission patterns. Although the natural reservoir host is still unknown, rodents, red-backed voles, and shrews have been reported as carriers. This makes it difficult to break the chain of transmission and emphasizes the value of research and surveillance initiatives to determine the virus's ecological habitat<sup>23</sup>. The BRPV necessitates the development of comprehensive management strategies to address its impact on individuals. Various clinical manifestations of BRPV infections require tailored interventions, including supportive care: such as respiratory support, hydration, fever management and wound care<sup>24</sup>. Currently, there are no approved treatments specifically targeting BRPV infection. However, state health authorities can request antiviral medications from the Strategic National Stockpile to manage outbreaks in consultation with the CDC. These medications, including tecovirimat, cidofovir, VIGIV and brincidofovir, have all shown promise in preclinical studies against orthopoxviruses: including BRPV<sup>25</sup>. However, caution is needed regarding their use, dosing, and potential adverse effects. The availability of these medications through established protocols facilitates their deployment during outbreaks, providing healthcare providers with additional tools to mitigate the severity of BRPV-associated illnesses.

Further research and surveillance efforts are needed to understand the optimal management strategies for BRPV infections, and to enhance preparedness for future outbreaks<sup>26</sup>. Furthermore, no reports have been made on how BRPV has adapted to spread from person to person. The correlation between immunocompromised states, such as HIV infection, and BRPV infection, underscores the complex interaction between viral pathogens and host variables in determining the course

of disease<sup>27</sup>. The potential emergence of BRPV variations that could be more transmissible to people highlights the necessity of specialized preventive and control measures; such as focused vaccination programs and improved biosafety protocols. Furthermore, in an era of developing biotechnologies and global interconnections, the implications of BRPV for biosafety and biosecurity cannot be overstated. The potential for widespread transmission of BRPV in several geographic areas prompts worries about intentional abuse by unscrupulous people, which could endanger national security. The ease of access to contemporary biotechniques for manipulating viruses highlights the need for strong biosecurity measures and surveillance systems to reduce the possibility of bioterrorism utilizing BRPV<sup>28</sup>.

### Recommendations

Comprehensive measures are required to minimize transmission and contain breakouts to combat the BRPV internationally. Avoiding close, unprotected contact with people who have monkeypox-like rash symptoms and maintaining a safe distance from animals and animal products that may be contaminated are recommended<sup>29</sup>. When providing patient care or gathering diagnostic samples, infected patients should be kept apart, always wash their hands, and wear personal protective equipment (PPE). To reduce transmission, medical facilities must follow infection control protocols, which include taking routine precautions and managing waste properly<sup>30</sup>. Single-person rooms should be used to isolate patients with Borealpox infections, and airborne isolation rooms should be used for high-risk procedures. When entering patient rooms, medical staff should wear proper PPE. Hospital-grade disinfectants should be used for cleaning and disinfection. Patients that do not need to be hospitalized in a domestic environment should stay home alone and refrain from interacting with family members and pets. Patients and household members should wear PPE if close contact is needed, and visitors

should be forbidden. It is important to adhere to proper wound care and hygiene protocols, which include covering skin lesions, avoiding contact lenses, and not shaving the affected area. These suggestions highlight how crucial it is to adopt measures to prevent BRPV from spreading and safeguard public health throughout the world. Strict cleanliness standards are essential for halting the global spread of BRPV<sup>31</sup>. This entails cleaning commonly touched areas; such as worktops and light switches, carefully washing personal belongings, and refraining from sharing them. Prioritizing hand hygiene is advised for patients who may have come into contact with potentially contaminated objects or surfaces. This can be achieved by washing with soap and water or using hand rubs containing alcohol. In communal restrooms, surfaces should be cleaned and sanitized following each use. When cleaning homes where Borealpox is suspected or confirmed, the CDC offers temporary instructions emphasizing the need to continue infection control measures until lesions heal or public health officials decide to stop taking preventative measures<sup>26</sup>.

An integrated strategy that includes risk communication, surveillance, diagnostics, and community involvement is required to combat BRPV. Strong surveillance systems are essential for quickly identifying and tracking outbreaks, so that quick action may be taken to stop their spread. Timely case identification, facilitated by accurate diagnostics, supports efficient management and control initiatives<sup>32</sup>. Clear risk communication to the population, including accurate information dissemination regarding BRPV, preventive measures and accessible therapies, is equally crucial. By promoting cooperation, trust, and adherence to control measures, community engagement enables communities to take an active role in epidemic response efforts<sup>32,33</sup>. Vaccination strategies are essential for preventing and controlling the global threat posed by BRPV. While no current reports document the development of a vaccine for BRPV, its potential exists. As with most OPXVs, BRPV infection

elicits an immune response against two antigenically distinct variants: mature virions (MV) and extracellular enveloped virions (EV), leading to the expression and detection of any variants<sup>34</sup>. The MV form, composed of a core surrounded by a membrane, harbors over 80 proteins; including a central core containing around 20 proteins responsible for viral mRNA synthesis and modification<sup>34</sup>. These core proteins represent promising candidates for exploring BRPV vaccine development. Future research should focus on evaluating the immunogenic potential of these core proteins to determine their suitability as vaccine targets. Studies could assess their ability to stimulate a protective immune response against BRPV infection.

Existing knowledge and experience from vaccinia virus and other Orthopoxvirus vaccines can inform the design and development of a potential BRPV vaccine. Alternatively, with an estimated efficacy of at least 85%, smallpox vaccinations are expected to provide significant protection against Borealpox: notwithstanding the lack of data on vaccination efficacy specific to the current outbreak. The key instruments in this area are vaccines; such as ACAM2000 and Jynneos, which are authorized for both smallpox and monkeypox<sup>35</sup>. Preexposure prophylactic immunization is advised; especially for those considered at high risk. Vaccines can be obtained by contacting the CDC Emergency Operations Centre and the CDC Drug Service. To reduce the likelihood of sickness, vaccinations for post-exposure prophylaxis should ideally be given four days after the initial exposure<sup>36</sup>. The CDC's Strategic National Stockpile offers vaccines for post-exposure prevention, and the CDC Emergency Operations Centre offers advice on immunization use.

Additionally, booster doses may need to be given every three years; especially to individuals continuously at high risk of contracting Borealpox. Jynneos vaccination programs, which highlight the significance of finishing the two-dose schedule for maximum protection, are now in



progress. These extensive immunization programs are essential to the international response to lessen the effects of BRPV outbreaks and protect public health globally<sup>26</sup>. In anticipation of future epidemics of BRPV, it is critical to improve frontline healthcare workers' education and training in accurately and quickly diagnosing the virus as well as effectively caring for and treating BRPV patients<sup>37</sup>. Adopting the One Health approach holds great promise in tackling health and environmental challenges; however, slow development and limited adoption across borders, cultural norms, and economic institutions have made it difficult to apply widely. These challenges must be overcome to promote collaboration across different societal strata and disciplines of expertise to fully realize the One Health concept's benefits. By bridging these differences, we may strive toward a more resilient and sustainable future for all parties concerned<sup>38</sup>.

## Conclusion

In conclusion, the pathophysiology, dynamics of transmission, and origins of the Borealex virus, previously known as the Alaskapox virus, are all thoroughly examined in this review. This highlights the necessity of enhanced monitoring, diagnostic tools, and protective measures to lessen its effects on people and animals. This recent, deadly instance serves as a reminder of the difficulties associated with newly emerging infectious diseases; especially for those with a weakened immune system. The evaluation also emphasized the value of teamwork in addressing the complex issues posed by zoonotic infections; such as BRPV infections, particularly through implementing the One Health strategy. Encouraging global collaboration, education, and research can help protect public health and build a more resilient future.

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## Conflict of interest

The authors declare no conflicts of interest.

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