Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, ***Watching Briefs*** *are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.*

Watching brief

Title	Emergence of novel orthopox virus in Alaska, USA
Authors	Danielle Hutchinson, Mohana Kunasekaren
Date of first report of the outbreak	29 July, 2015 (1)
Disease or outbreak	Alaskapox virus (AK2015) (1, 2)
Origin (*country, city, region*)	Alaska, USA
Suspected Source (specify food source, zoonotic or human origin or other)	Suspected zoonosis from small mammals, including squirrels, voles and shrews (1, 3). Tissue and blood samples collected from trapped animals in a field investigation in 2020 in the Fairbanks area were analysed and showed antibodies for the alaskapox virus (3). It is thought that the zoonosis may occur through contact with these mammals, or via domestic pets, for example cats (3).
Date of outbreak beginning	July 2015 (1)
Date outbreak declared over	N/A
Affected countries & regions	Alaska, USA (4)
Number of cases (specify at what date if ongoing)	4 cases as of 14th November 2021 (4)
Clinical features	Small lesion (singular) on extremity, with positive testing for generic *Orthopoxvirus* genus of *Poxviridae* family on PCR assay and sequencing confirming lineage AK2015 (1, 4, 5). Systemic features – fever, lymphadenopathy, muscle pain, fatigue (1, 4, 5).

<table>
<tr><td>Mode of transmission (dominant mode and other documented modes)</td><td>Other orthopox viruses are known to be transmitted by airborne, direct contact (including fomite transmission) or respiratory droplet spread (6). There is no evidence of human-to-human transmission for alaskapox virus. Follow-up of all close contacts was negative for signs and symptoms (1, 4, 5).

There was no travel history reported by any of the four cases. Common factors between the cases include residing in highly in highly vegetated areas surrounding Fairbanks, Alaska, and contact with small wild mammals or owning a cat (1, 4, 5). It is thought that zoonotic transmission may occur via contact with small wild mammals infected with the alaskapox virus as the primary host, or via pets (including cats) as an intermediate host (3).</td></tr>
<tr><td>Demographics of cases</td><td>All four confirmed cases lived in the Fairbanks area of Inland Alaska in low density, highly vegetated areas (1, 4, 5).

Table 1. Demographics and risk factors of confirmed Alaskapox cases
<table>
<tr><th></th><th>Sex</th><th>Age</th><th>Risk factors</th><th>Symptoms</th></tr>
<tr><td>July 2015 (1)</td><td>F</td><td>Middle aged</td><td>No travel, no pets, contact with small mammals in forested area (1)</td><td>Singular pox lesion on shoulder (confirmed AK2015 via PCR assay), fever, lymphadenopathy, muscle pain. Lesion resolved after 6 months (1)</td></tr>
<tr><td>August 2020 (5)</td><td>F</td><td>Adult</td><td>Outdoors (raspberry picking), 2 cats, no travel history (5)</td><td>Singular pox lesion on right shoulder (confirmed AK2015 via PCR assay), fatigue, fever, painful for 2 weeks, healed at 6 weeks</td></tr>
<tr><td>July 2021 (4)</td><td>F</td><td>Young child</td><td>Outdoors over summer, cat, no travel history (4)</td><td>Singular pox lesion on elbow (confirmed AK2015 via PCR assay), fever lymphadenopathy 4 days</td></tr>
<tr><td>Aug 2021 (4)</td><td>F</td><td>Middle aged</td><td>Outdoors (extensive gardening, cutting weeds), cat, no travel history (4)</td><td>Singular pox lesion on thigh (confirmed AK2015 via PCR assay), lymphadenopathy, joint pain (> 3 weeks)</td></tr>
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Case fatality rate	No deaths reported in this outbreak. CFR: 0% (n=0)
Complications	Symptoms 4 days – 6 months (Table 1). No data regarding potential long-term effects.
Available prevention	To prevent transmission from potential reservoir, it is recommended to avoid handling and feeding wildlife, working/playing in areas where there are wildlife faeces, and wash hands with soap and water after being in areas where wildlife has been sighted (7). As orthopoxvirus antibodies protect against infection from other orthopoxvirus species, it is likely that cross protection may occur from vaccinia-based smallpox vaccination (8).
Available treatment	Current advice specific for alaskapox virus is to cover the suspected lesion, avoid touching the lesion, and not share items that have touched the lesion (e.g. towels and bedclothes) with other people (4). While data is not available for the effectiveness of antiviral medication in the treatment of human orthopox cases, animal studies have shown that tecovirimat may be effective in treatment of orthopox disease (9). In July 2018, tecovirimat was approved for use in humans for treatment of smallpox related disease under an Investigational New Drug Application (IND), under the United States Federal Drug Administration's Animal Rule, where approval is based on established efficacy in animal studies (9, 10). Vaccinia Immune Globulin Intravenous can be used for complications following Vaccinia vaccine administration (8).
Comparison with past outbreaks	Alaskapox virus was first identified following the investigation of a single lesion on the shoulder of a woman from Fairbanks, Alaska, USA in July 2015 (1). The vesicle was swabbed and *Orthopoxvirus*-generic PCR assay testing was positive (1). Further sequencing confirmed a novel orthopoxvirus, AK2015, which was later named *Alaskapox virus* (*AKPV*) (2). There have been three further cases in the Fairbanks area, in 2020 and 2021, each presenting with a small lesion on an extremity, and positive testing for generic *Orthopoxvirus* genus of *Poxviridae* family on PCR assay and sequencing confirming lineage AK2015 (1, 4, 5). Symptoms common to each case were fever, lymphadenopathy, muscle pain and fatigue, lasting between four days and six months (1, 4, 5). All Orthopox viruses have DNA genomes that are highly similar, and infection with one may generate cross-protection with another (11). There is little known about the host, reservoir and transmission cycles (11). The orthopox viruses

	known to cause disease in humans are variola, vaccinia, cowpox and monkeypox (11). Variola (the causative agent of smallpox) virus is a species of *Orthopoxvirus*, exclusive to humans with no known animal reservoir (6). Variola major caused significant mortality worldwide, with a CFR 20-50% in unvaccinated populations (6). Global eradication was declared by the World Health Organization in 1979, achieved via management of contacts, isolation and mass vaccination (6). Cowpox virus has been reported since the 1700s and sporadic human cases continue to be reported, mostly in Europe and Asia (11). It is endemic in rodents in Western and Eastern Europe and has also been reported to effect domestic cats (11). Human cowpox cases tend to be self-limiting with minimal mortality (11). Monkeypox virus is a species of the genus *Orthopoxvirus,* with two distinct clades (6). The Congo Basin monkeypox clade demonstrates high rates of human-to-human transmission, with a case-fatality rate in unvaccinated children of up to 14% (6). The West African clade has low rates of human-to-human transmission and reports of mortality are few (6). Historically, monkeypox was reported in people with a history of contact with live animals and in children under 16 (6). However, sustained human-to-human transmission was recorded in the Democratic Republic of Congo in a hospital setting in 2003 and more recently in Nigeria, where large outbreaks in urban areas were recorded between 2017 and 2019 (6). Currently, Nigeria continues to report monkeypox cases, with 79 suspected cases from January to November 2021(12). This has impact on the spread of monkeypox internationally. In the United Kingdom in May and June 2021, two family members contracted monkeypox from the index case, a returned traveller from Nigeria (13). There have been two cases of travel-associated human monkeypox from Nigeria to the United States in 2021, the first on July 15 (14). There were 200 contacts identified and followed for 21 days, with no ongoing transmission of the virus (14). Most recently on 16 November 2021, a travel-associated case was reported in Maryland, from a traveller returned from Nigeria, and contacts continue to be monitored with as yet no further cases (14). The most prolific outbreak has been in the Democratic Republic of Congo, who reported 6,257 suspected cases in 2020, with 72 deaths (CFR 2.6) (12). In 2021, to the 7th November there have been 2,764 cases reported with 72 deaths (CFR 2.6%) (12). Evidence of monkeypox in small mammals including squirrels and rodents suggest this may be the potential animal reservoir (6). Vaccinia is an orthopoxvirus and is the most studied of all poxviruses. It is used as the smallpox vaccine and continues to be useful as a tool in medical research. It is the focus of renewed interest as a vector for recombinant

	vaccines (8, 15). As such, it can pose an infection risk to laboratory personnel, and multiple exposures and infections have been documented in laboratory workers (16). Sporadic disease following vaccination has been reported, also in contacts of vaccinees (8). In the previous cases of alaskapox identified in the Fairbanks area in Alaska, no specific sources of infection were identified and no history of travel outside the Fairbanks area four weeks prior to symptom onset was reported in these two patients. One common factor seemed that they were living in forested areas with population of small mammals which may be a likely source of infection (4).
Unusual features	The limited sequencing analysis conducted in 2015 suggested that the AK2015 virus was an orthopox virus that had not been previously described (1). Following this, genomic sequencing was completed and confirmed a novel orthopox virus that shared common ancestry with Old World Orthopox viruses, distinct from the New World orthopox viruses previously described in North America (2). It was named *Alaskapox virus* (*AKPV*) (2). Orthopoxvirus is a genus of the Chordopoxvirinae sub-family of the *Poxviridae* family of viruses (17). The genus contains two distinct clades of viruses, whose similar genomic sequences align with geographic origin in either the Old World (originating from Europe and Africa), or New World (North America) (2). Old World orthopoxviruses include those discussed above with potential to cause human infection, while New World orthopoxviruses, which include *raccoonpox virus, skunkpox virus and volepox* virus, do not have zoonotic potential (17). The divergence may be explained by differences in mammal hosts of the Old World and the New World (17).
Critical analysis	There is evidence of alaskapox virus infection of small mammals (mainly voles) in the Fairbank area (4). The forest area in which all four cases lived have large populations of these mammals. Tissue and blood samples collected from trapped animals in a field investigation in 2020 showed antibodies for the alaskapox virus in the blood of local squirrels, voles and shrews of the Fairbanks area (3). The sample size for this field study was not stated. In September 2021, 40 further traps were set in the Fairbanks area to analyse tissue of local animals for alaskapox virus, with results yet to be published (3). The true prevalence of alaskapox in humans is not known, and clinicians have been asked to increase their awareness of potential cases in order to better understand the distribution of the disease and potential severity (4). Since the eradication of smallpox and subsequent cessation of the global vaccination program, there is now an increasing human population with susceptibility to orthopox viruses (18). There have been increasing number and frequency of reports of outbreaks in both animals and humans (18). Patterns of

	viral evolution, combined with a susceptible human population in increasing contact with animals, require detailed surveillance and control of orthopox viruses with zoonotic potential (18). The ability of sera raised against one orthopoxvirus species to cross-neutralize another species is one of the fundamental reasons for cross-protection provided with vaccination (8). Vaccinia immunization is cross-protective against other orthopoxvirus infections, including variola (8). Preexposure vaccine efficacy is estimated to be as high as 100% for 1 to 3 years after vaccination (19). Complete protection against smallpox after vaccination is not lifelong, although data suggest that substantial protection may persist for up to 15 to 20 years (20). Experiences with monkeypox in the United States in 2003 suggest that immunity is not completely protective against systemic orthopoxvirus disease acquisition for more than 20 years after vaccination (21). Protection against death from the disease may persist even longer than protection against disease (20). Phylogenetic analysis of the novel alaskapox virus shows it is clustered with the Chordopoxvirinae sub-family (orthopoxviruses), however it has a very long branch on the pox virus tree and forms a distinct clade (2, 3). It does have higher sequence similarity to Old World orthopox viruses compared to New World, which has been an unexpected finding considering the location that the novel virus was isolated in (North America), where there are no Old World orthopox viruses endemic (2). The length of the branch on the phylogenetic tree suggests it may be an ancient lineage (3). It is possible that the protective benefits of the smallpox vaccine could extend against alaskapox virus due to the phylogenetic similarity with other Old World orthopox viruses, however the effect may be less than that seen in monkeypox, which is in the same clade as variola and therefore less divergent (2, 3).
Key questions	What is the prevalence of *Alaskapox* in humans in the Fairbank and wider geographical area in Alaska? What is the primary animal reservoir / host? What is the potential geographic spread of the host animal and therefore risk to humans? Could this spread and risk change seasonally due to animal movement or hibernation? What is the potential for human-to-human transmission of alaskapox virus? What preventative measures can be used?

References	1. Springer YP, Hsu CH, Werle ZR, Olson LE, Cooper MP, Castrodale LJ, et al. Novel orthopoxvirus infection in an Alaska resident. CID. 2017(64):1737–41. 2. Gigante CM, Gao J, Tang S, McCollum AM, Wilkins K, Reynolds MG, et al. Genome of Alaskapox Virus, a Novel Orthopoxvirus Isolated from Alaska. Viruses. 2019;11(8):708. 3. Rozell N. Scientists set traps north of Fairbanks to catch clues about mysterious Alaskapox virus: Anchorage Daily News; 2021 [updated 20 September 2021. Available from: https://www.adn.com/alaska-news/science/2021/09/18/setting-traps-north-of-fairbanks-to-catch-clues-on-the-mysterious-alaskapox-virus/. 4. Mooring E, Newell K, Werle Z. Additional Cases of Orthopoxvirus Infection in fairbanks-area Residents, 2021. State of Alaska Epidemiology Bulletin. 2021;13. 5. Mooring E, Olsen L, Werle Z. Second case of novel orthopoxvirus infection in a Fairbanks-area resident. State of Alaska Epidemiology Bulletin. 2020(11). 6. Doshi RH, Hoff NA, Rimoin AW. Smallpox and Other Poxvirus Diseases. Control of Communicable Diseases Manual. 7. CDC. Healthy Pets, Healthy People: CDC; 2021 [updated June 9, 2021. Available from: https://www.cdc.gov/healthypets/pets/wildlife.html. 8. Peterson BW, IK. D. Orthopoxviruses: vaccinia (smallpox vaccine), variola (smallpox), monkeypox, and cowpox. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8. Philadelphia: Elsevier; 2014. 9. CDC. Monkeypox - For Clinicians - Treatment: Centers for Disease Control and Prevention; 2021 [updated 17 July 2021. Available from: https://www.cdc.gov/poxvirus/monkeypox/clinicians/treatment.html. 10. Hoy SM. Tecovirimat: First Global Approval. Drugs. 2018;78:1377-82. 11. Silva NIO, de Oliveira JS, Kroon EG, Trindade GdS, Drumond BP. Here, There, and Everywhere: The Wide Host Range and Geographic Distribution of Zoonotic Orthopoxviruses. Viruses. 2020;13(1):43. 12. WHO ARO. Weekly Bulletin on Outbreaks and other Emergencies. Week 45: 1-7 November 2021.: World Health Organization; 2021 [updated 7 November 2021. Available from: https://apps.who.int/iris/bitstream/handle/10665/348305/OEW45-0107112021.pdf. 13. WHO ARO. Monkeypox - United Kingdom of Great Britain and Northern Ireland Online: World Health Organization.; 2021 [updated 8 July 2021. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/monkeypox---united-kingdom-of-great-britain-and-northern-ireland.

14. CDC. Monkeypox in the United States Online: Centers for Disease Control and Prevention; 2021 [updated 17 November 2021. Available from: https://www.cdc.gov/poxvirus/monkeypox/outbreak/us-outbreaks.html.
15. Verardi PH, Titong A, Hagen CJ. A vaccinia virus renaissance: new vaccine and immunotherapeutic uses after smallpox eradication. Hum Vaccin Immunother. 2012;8(7):961-70.
16. MacNeil A, Reynolds MG, Damon IK. Risks associated with vaccinia virus in the laboratory. Virology. 2009;385(1):1-4.
17. Emerson GL, Li Y, Frace MA, Olsen-Rasmussen MA, Khristova ML, Govil D, et al. The Phylogenetics and Ecology of the Orthopoxviruses Endemic to North America. PLoS ONE. 2009;4:e7666.
18. Shchelkunov SN. An increasing danger of zoonotic orthopoxvirus infections. PLoS Pathog. 2013;9(12):e1003756-e.
19. Meltzer MI. Risks and benefits of preexposure and postexposure smallpox vaccination. Emerg Infect Dis. 2003;9(11):1363-70.
20. Kunasekaran MP, Chen X, Costantino V, Chughtai AA, MacIntyre CR. Evidence for Residual Immunity to Smallpox After Vaccination and Implications for Re-emergence. Mil Med. 2019;184(11-12):e668-e79.
21. Karem KL, Reynolds M, Hughes C, Braden Z, Nigam P, Crotty S, et al. Monkeypox-induced immunity and failure of childhood smallpox vaccination to provide complete protection. Clin Vaccine Immunol. 2007;14(10):1318-27.