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How did the 2022 global mpox outbreak happen? A travel-associated case 6 months earlier may provide important clues

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Approximately 6 months before an unprecedented global mpox outbreak was first identified in the United Kingdom, an adult man was diagnosed with mpox in Maryland, USA [1]. At the time of the investigation, the case was only the eighth monkeypox virus (MPXV) infection diagnosed in a non-African country during the preceding 3 years, all of which were associated with recent travel to Nigeria [2]. One of these 8 imported cases occurred in Texas, USA four months earlier; that case exhibited features clinically consistent with those classically reported in Africa (i.e., large and diffuse lesions, high fever and prodromal symptoms, umbilicated lesions in the same stage of development on specific anatomic surfaces) [3]. In contrast, the Maryland case was milder in severity and had signs that, at the time, were considered unusual for mpox. Several aspects of the Maryland case are noteworthy and in retrospect may offer clues to the origins of the 2022 global mpox outbreak, as well as explain how mpox might have spread undetected before emerging as a global outbreak.

1. The case

During November 2021, a Maryland resident returned to the United States after a month-long trip to Nigeria [1]. Shortly before departing Nigeria, the patient developed severe anal pain, followed 3 days later by a few painful pustules that were scattered across his face and progressed to involve his torso, arms, and inner thigh (Fig. 1). Within 24 hours of returning home, the patient presented to two urgent care facilities and an emergency room for burning and itching anal pain that he valued as a 10 out of 10 in severity; he reported no fever or other prodromal symptoms (e.g., fever, chills, malaise, lymphadenopathy) which were considered typical for mpox [4]. On physical examination, clinicians observed a tender, non-bleeding, thrombosed external hemorrhoid and several small (2–4 mm) pustules scattered on some skin surfaces and in varying stages of development on the same anatomic site; some of the skin lesions were umbilicated. Emergency room physicians suspected mpox because of the patient's recent travel to Nigeria. However, molluscum contagiosum virus or varicella zoster virus (VZV) were higher on the admitting clinicians' differential list, particularly because there were few lesions compared to what was classically associated with mpox at that time; in addition, symptoms improved within 24 hours of initiation of intravenous acyclovir, the treatment for presumptive disseminated VZV.

One day after discharge, hospital laboratory tests showed a negative serologic specimen for VZV, but a punch biopsy from an abdominal lesion revealed intracytoplasmic inclusion bodies, consistent with orthopoxvirus infection. Two days after hospital discharge (i.e., 6 days after arrival back in the United States), newly obtained lesion swabs yielded orthopoxvirus DNA at the Maryland Department of Health laboratory and were later confirmed by CDC's laboratory to be Clade II (formerly West African clade) MPXV.

2. The investigation

The patient had numerous potential contacts: he was symptomatic before boarding international flights; had taken ride share trips with multiple drivers; had been in contact with EMS; and visited three separate healthcare facilities (Table 1). The ride share drivers and treating healthcare personnel resided in three U.S. jurisdictions (Maryland, Washington, D.C., and Virginia) necessitating extensive public health coordination to identify potential contacts, determine the level of mpox risk based on a previously developed tool, and monitor the patient for 21 days (the incubation period for mpox) from last exposure [3]. No monitored contacts received vaccine post-exposure prophylaxis. The patient lived alone and self-isolated in his apartment for 2 weeks until all lesions resolved, the scabs had fallen off, and a fresh layer of intact skin formed. While sexual contact was not known to be a primary risk factor for mpox transmission at the time of this investigation, no close or intimate contact was reported by the patient, perhaps explaining the lack of transmission to monitored contacts.

During routine sequencing of mpox viral genomes, CDC found that the Maryland MPXV genome was distinct from previously sequenced travel-associated mpox cases. This MPXV genome displayed a high similarity to, and shared many unique mutations with, what was later

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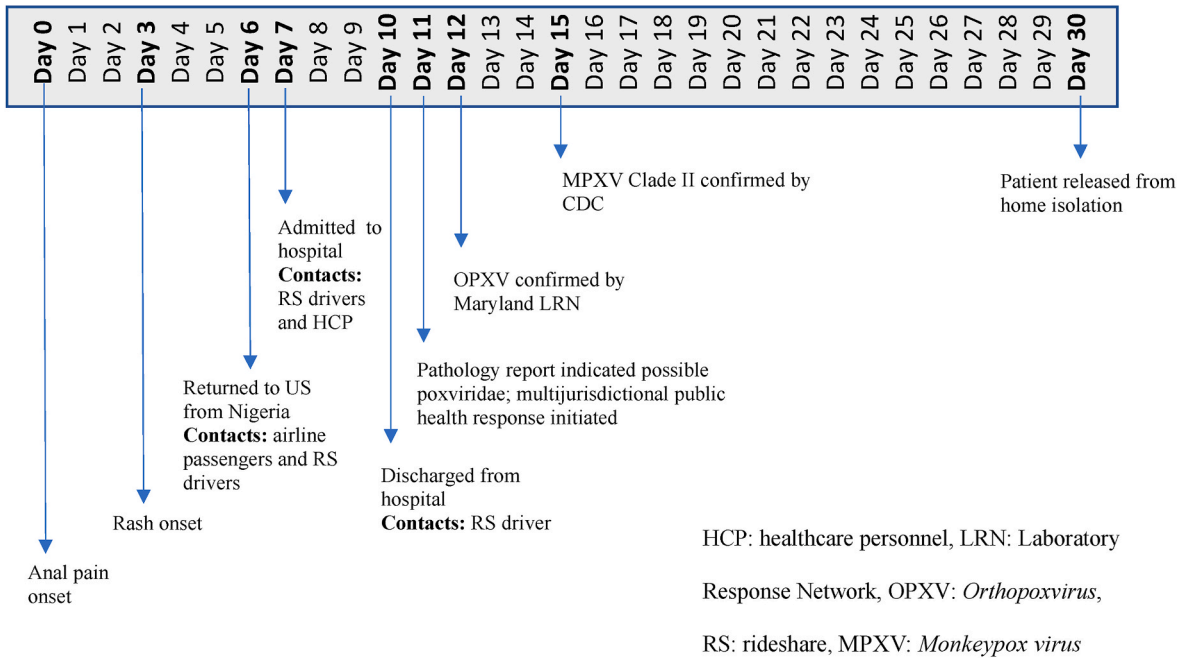

Fig. 1. Timing of illness progression and public health actions associated with a travel-associated case of mpox—Maryland, USA, November 2021.

Table 1
[a]Exposures[b] and risk classification of 66 contacts of a patient with mpox during travel to the United States to resolution of symptoms.

Contact category	Exposure type	Number	Risk classification
Airline passengers	Seated within 6 ft for flights ≥3 hours (i.e., within two seats) while passengers and patient wore masks	9	Intermediate
Healthcare personnel	Involved in patient care (e.g., examining a patient) while not wearing at least gown, gloves, eye protection and medical facemask for all contact episodes with the patient or patient's clothing, linens, healthcare equipment, crusts, or bodily fluids, or within 6 ft of the patient	6	Intermediate
	Involved in patient care while wearing at least gown, gloves, eye protection, and medical facemask or respirator for all direct and indirect contact episodes	37	Low or uncertain
	Within 6 ft of an aerosol-generating analytic instrument not contained in a BSC while specimens were loaded, run, and/or unloaded, or 1 h after unloading the specimens in the absence of appropriate personal protective equipment	6[c]	Low or uncertain
Ride share drivers	Within an enclosed space for <30 minutes while driver and patient wore masks, possible contact with contaminated surfaces	8	Low or uncertain

[a] Adapted from Rao AK, Schulte J, Chen TH et al. Monkeypox in a Traveler Returning from Nigeria - Dallas, Texas, July 2021. *MMWR Morb Mortal Wkly Rep* 2022; 71: 509–16.

[b] Exposures included sitting within 6 feet of the patient on an international flight, driving the patient in a rideshare vehicle, providing medical care to the patient, and not wearing appropriate personnel protective equipment (PPE) (i.e., an N95 or equivalent respirator) while within 6 ft of suspected aerosol-generating analytic instrument(s) that was not located in a biosafety cabinet while it was being loaded, unloaded, or operational.

[c] 4 of 6 laboratorians were unable to be reached for monitoring.

identified as the predominant circulating mpox genome (B.1) during the 2022 global outbreak, i.e., the Maryland virus shares a more recent ancestor with the outbreak variant than any other sequenced MPXV [5]. Notably, this patient's clinical signs, considered unusual at the time of his illness, were also more consistent with those later associated with the 2022 global mpox outbreak [6]. It is possible that the genetic changes associated with both the Maryland virus and the outbreak virus conferred similarly atypical clinical presentations.

The origin of the MPXV strain associated with the 2022 global outbreak remain unknown, however this case offers important clues. This 2021 case traveled to Nigeria and subsequently presented with clinical symptoms and an MPXV strain genetically more similar to those seen in the 2022 global mpox outbreak than in previous travel-associated mpox cases; the 2022 outbreak strain of MPXV was also likely circulating in Nigeria in 2021. While previous studies indicate that unrecognized widespread transmission prior to the 2022 global outbreak is unlikely [7], the possibility of multiple undetected sporadic cases similar to the case described in this report might have occurred. While this case did not result in any secondary transmission, likely due to isolation and lack of close, intimate contact while infectious, similar introduction events likely seeded the 2022 outbreak in multiple countries and facilitated the global spread of mpox.

This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.[1]

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Declaration of competing interest

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[1] See e.g., 45 C.F R. part 46.102(I)(2), 21 C.F R. part 56; 42 U S C. §241(d); 5 U S C. 552a; 44 U S C. §3501 et seq.

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[B] No conflict.

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