First two cases of Monkeypox virus infection in travellers returned from UAE to India, July 2022

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**Case Report**

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Abstract
We report the first two confirmed cases of Monkeypox in foreign returnees from United Arab Emirates who presented with fever, myalgia, and vesicular lesions on the genital area with cervical lymphadenopathy. The oropharyngeal & nasopharyngeal swab, EDTA blood, serum, urine, lesion samples from multiple sites (lesion fluid, lesion roof and lesion base) were collected from both the cases on ninth post onset day of illness. The clinical specimens of both the cases were tested with real time PCR for Orthopoxvirus, Monkeypox virus (MPXV), West African clade specific MPXV. The specimens oropharyngeal & nasopharyngeal swab, urine, lesion samples from multiple sites (lesion fluid, lesion roof and lesion base) were tested positive for MPXV. The complete genome sequences obtained from skin lesions of case 1 and 2 showed similarity of 99.91 and 99.96% respectively with MPXV_USA_2022_FL001 West African clade. Phylogenetic analysis revealed that the two cases were infected with Monkeypox virus strain A.2 which belong to hMPXV-1A lineage of clade 3.

Introduction
The Monkeypox virus (MPXV), belongs to Orthopoxvirus genus and Poxviridae family which is endemic in Central and West Africa since 1970 and now has been reported from various non-endemic countries in 2022. On 23 July, the World Health Organization declared MPXV as a Public Health Emergency of International Concern (PHEIC) considering the global outbreaks in all the six regions in multiple countries. The cases found to occur mainly due to the imported infections from endemic countries and due to further community transmission.

The MPXV infection starts with a febrile illness with average incubation of 5–13 days with lymphadenopathy, myalgia, and headache, followed by deep-seated umbilicated vesicular/pustular rashes. The rash primarily starts from face (oral), genital or perianal region and then distributed in centrifugal manner to other parts of the body and progresses over time to scab. The primarily infection is of zoonotic origin through contact with infected animals. It is followed by secondary human-to-human transmission that occurs by direct contact with infected body fluids or lesions, via infectious fomites, or through respiratory droplets. The secondary transmission has been reported amongst close contacts through fomites (e.g., beddings, linens, clothes, etc.).

The West African and Central Africa (Congo Basin) are the two known clades of the MPXV, of which Congo Basin strain causes more severe illness, 0–11% mortality and increased transmissibility. The West African clade is found to be circulating in the current ongoing outbreaks of 2022 in non-endemic countries.

Here, we report the detection and genomic characterization of first two cases of MPXV infection with travel history from United Arab Emirates (UAE) to India during month of July 2022.

Clinical Presentation Of Cases
Case 1, a 35-year, male, resident of UAE had developed low-grade fever and myalgia on 5 July 2022. On the next day, he developed multiple vesicular rashes in the oral cavity and lips followed by single lesion on the genital organ [Figure-1A]. The lesions were umbilicated with the size 0.5 to 0.8 cm. Subsequently, the upper lip became edematous and then he developed umbilicated vesicular lesions in right infra-mammary, right tragus, right temple, and right deltoid region [Figure-1B]. He also had maculopapular rashes on both hands. With these complaints, he visited a medical facility on 9 and 11 July 2022. [Figure-1A]. Upon consultation, he revealed history of similar lesions amongst his friends and contact with suspected Monkeypox cases (denied sexual contact), a week prior to onset of symptoms. The clinician had advised the screening for MPXV and prescribed tablet Acyclovir.
However, he travelled from UAE to his hometown Kerala, India on 12 July 2022. On his return, he developed sore throat along with worsening of oral lesions for which he visited a hospital in Kerala. Considering his history of contact with suspected Monkeypox case and pustular lesions, he was referred to Government Medical College Thiruvananthapuram [GMCT][Figure-1A]. The patient had no known co-morbidities but gave history of self-limiting genital lesions eighteen months ago. During clinical evaluation, multiple cervical and inguinal lymph nodes were palpable, which raised a high suspicion of MPXV infection. The initial hematological and biochemical profile on the same day showed haemoglobin-14.1 gm%, leukocytosis [14,600/L], platelets-2,29,000/µL and random blood sugar level of 100 mg/dl. Serological investigations for Syphilis and HIV were non-reactive.

Case 2, a 31-year, male in Dubai, UAE had developed dysuria and genital swelling on July 8, 2022. On the next day, he developed fever with chills, myalgia, backache and headache. Subsequently, he developed multiple vesicular rashes on the genital organ and on both hands on July 10, 2022. [Figure-1A]. He travelled from Dubai to his hometown Kerala state, India on July 13, 2022. The lesions progressed and later spread to face, back, neck and forearm with cervical lymphadenopathy by July 15, 2022 [Figure-1C]. He visited government hospital locally and on the suspicion as Monkeypox case, he was isolated on July 16, 2022 He did not have any co-morbidity and denied any sexual or physical contact with suspected or confirmed MPXV case.

**Laboratory Analysis**

The oropharyngeal (OPS) & nasopharyngeal swab (NPS), EDTA blood, serum, urine, lesion samples from multiple sites (lesion fluid, lesion roof and lesion base) of both the cases were collected on ninth post onset day of illness i.e., July 13, 2022 and July 16, 2022 respectively. Further, they were referred to the World Health Organization Collaborating Centre for emerging and re-emerging diseases, ICMR-National Institute of Virology, Pune, India for the MPXV diagnosis.

The laboratory diagnosis on the clinical samples of both the cases (OPS, NPS, EDTA blood, serum, urine, lesion fluid, lesion roof and lesion base) was carried out using real time PCR for Orthopoxvirus, MPXV, West African clade specific MPXV. All the clinical samples of two cases were positive for MPXV, except the EDTA blood and serum of case 2. The clinical specimens of case 1 showed viral load (Copy number/ml) in the NPS (7.4×10^5/ml), OPS (3.4 ×10^6/ml), urine (3.4 ×10^6/ml), serum (1.8 ×10^6/ml), EDTA blood (6.8 ×10^4/ml), lesion roof (1.1 ×10^8/ml), lesion fluid (6.3 ×10^6/ml) and lesion base (2.3×10^8/ml). Similarly for the clinical specimens of case 2 had the viral DNA copy number/ml in NPS/OPS (5.9×10^7/ml), urine (3.4 ×106/ml), lesion roof (8.4 ×10^5/ml), lesion fluid (2.1 ×10^7/ml) and lesion base (5.5 ×10^8/ml).

Further, the skin lesions of both the cases were sequenced with next generation sequencing using Illumina platform. The complete MPXV genome was retrieved for both the cases and analyzed using CLC Genomic Workbench 22.0. The Maximum likelihood tree has been generated in IQ-TREE software with 1000 bootstrap replications. The sequence analysis of case 1 and case 2 revealed similarity of 99.91% and 99.96% respectively with Monkeypox virus isolate MPXV_USA_2022_FL001, complete genome [GenBank accession no. ON674051]. The retrieved sequences [GenBank accession no. EPI_ISL_13953611 and EPI_ISL_13953610] from the clinical specimens of confirmed Monkeypox cases in India belonged to the A.2 descendent lineage of hMPXV-1A lineage of clade 3 (West African clade) (Fig. 2). It has significant 34472 nucleotide mutation of allele T. (https://github.com/nextstrain/monkeypox/blob/master/config/clades.tsv).
The two close contacts [Mother and brother] of the case-1 showed symptoms of sore throat, were screened negative for the MPXV. Considering the surge in COVID-19, cases globally and in India, these cases were screened and brother of the case-patient was found positive for SARS-CoV-2. The three close contacts of case 2 were asymptomatic in observation period.

**Discussion**


The clinico-epidemiological history and laboratory analysis of two confirmed Monkeypox cases in India suggest travel-associated introduction of MPXV infection in the country. The genome of both the cases matched closely with the A.2 lineage of clade 3. Recently, Gigante et al., demonstrated highest similarity of two MPXV sequences from 2022 outbreak in USA (USA_2022_FL001 and USA_2022_VA001) with MPXV sequences from a 2021 (ON676707), a travel-associated case from Nigeria to Texas which belongs to lineage A.2. The current Monkeypox outbreak in USA represents the circulation of MPXV lineage A.2 from 2021 which has evolved from lineage A that caused the Nigeria outbreak in 2017–2018.\(^{14}\) The MPXV genome retrieved from confirmed Monkeypox cases with travel history from UAE to India also demonstrated the circulation of A.2 lineage in UAE. Unfortunately, no epidemiological data is available for the introduction of MPXV to UAE.

An increase in the number of Monkeypox cases with low mortality rate has been observed with B.1. Its estimated time of emergence in the European continent has been predicted to have occurred in as early as March 2022. The B.1 lineage has significant 77383 nucleotide mutation of allele A.\(^{15}\) However, there is no information available which can differentiate between the transmission pattern of A.2 and B.1 lineage.

Since the detection of Monkeypox cases in India, the containment measures have been taken by Department of Health Research, Ministry of Health and Family Welfare. This includes the isolation of case and contacts, quick screening of all the symptomatic contacts, strict adherence to the personal protective equipment and hand hygiene, hospital infection control practices and intense health education in the community. India has demonstrated quick and continuous vigilance and preparedness to detect the first two MPXV cases within a day of entry of the case in the country. This emphasized the alertness of the all stakeholders including airport authority and the clinicians to be alert for the patients who have rash like illness with international travel irrespective of age, gender or sexual orientation. The surveillance of suspected Monkeypox cases could be strengthened by screening the at-risk population such as men who have sex with men (MSM) and female sex workers (FSW) by National AIDS Control Organization, India. Besides this, adhering to the COVID-19 protocol during the air travel would be beneficial for reducing the transmission amongst the co-passengers and crews through respiratory droplets.

**Declarations**

**Ethical approval**

The study was approved by the Institutional Human Ethics Committee of ICMR-NIV, Pune, India under the project ‘Providing diagnostic support for referred samples of viral hemorrhagic fever and other unknown etiology and outbreak investigation’. The written informed consents were obtained from both the cases.
**Author Contributions**

PDY, RRS contributed to study design, data analysis, interpretation and writing and critical review. ARS, SK, AMS, AR, PVK, RB, SSSM, SM, DYP, AEG, RR, MS, AU, GNS, MR, SS, PJ, SMJ contributed to data collection, interpretation, writing and critical review. PDY, RRS, ARS, DYP, PA, NG, NV contributed to the critical review and finalization of the paper.

**Conflicts of Interest**

Authors do not have a conflict of interest among themselves.

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References


Figures
Figure 1

A) Graphical presentation depicting the time line of detection, travel history and laboratory diagnosis of first two cases of Monkeypox in India; Umbilicated characteristic MPXV pustular lesions on 9\textsuperscript{th} post onset day of illness of B) Case-I; C) Case-II

Figure 2

The phylogenetic tree was constructed using Maximum likelihood method. The reference sequences for the MPXV genome clades and lineages were downloaded from the NCBI website (Clade 1, Clade 2, Clade 3, Lineage A, A.1, A.2, A.1.1 and B.1). The MPXV genome sequences retrieved from two confirmed Monkeypox cases in India are marked in red color with GISAID accession ID (EPI_ISL_13953611 and EPI_ISL_13953610) in A.2 lineage along with sequences from USA.