Misdiagnosis between mpox and chickenpox: Evidence from laboratory surveillance in Portugal

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Background-Aim

- **Differential diagnosis plays a crucial role in distinguishing mpox, caused by the monkeypox virus (MPXV), from other clinically similar diseases, particularly in outbreak settings where the public health response depends on diagnostic accuracy.**
- **During the initial mpox outbreak in Portugal, clinical features such as fever and vesicular skin lesions overlapped significantly with those of chickenpox, caused by the varicella-zoster virus (VZV), thereby increasing the risk of misclassification in the absence of specific laboratory confirmation (Table 1).**
- **However, the 2022 mpox outbreak also presented with atypical features, such as genital lesions, fewer disseminated skin lesions, and limited systemic symptoms, which differed from classic chickenpox presentations.**
- **This study aimed to assess the extent of chickenpox cases misdiagnosed as mpox.**

Table 1: Key differences between mpox and chickenpox.

Characteristics	Mpox	Chickenpox
Causative agent	monkeypox virus (*Poxviridae* family)	varicella-zoster virus (*Herpesviridae* family)
Transmission	Direct contact with lesions or body fluids; Respiratory droplets in close contact; Contaminated materials (fomites)	Airborne via respiratory droplets; direct contact with vesicle fluid
Incubation period	6-13 days (range: 5-21 days)	10-21 days (usually 14-16 days)
Initial symptoms	Fever, headache, muscle aches, fatigue and lymphadenopathy (distinctive)	Fever, fatigue, loss of apetite, mild headache
Rash onset	1-4 days after fever onset	Usually within 24-28 hours of initial symptoms
Rash pattern	Lessions envolve synchronously: macules – papules – vesicles – pustules – crusts	Lesions appear in diferente stages simultaneously (pleomorphic)
Rash distribuition	Centrifugal: face, arms, legs, including palms and soles	Centripetal: trunk, face, scalp, rare on palms and soles
Lesion depth	Deep, firm, well-circumscribed	Superficial, fragile vesicles (“dew drop on a rose petal” appearance)

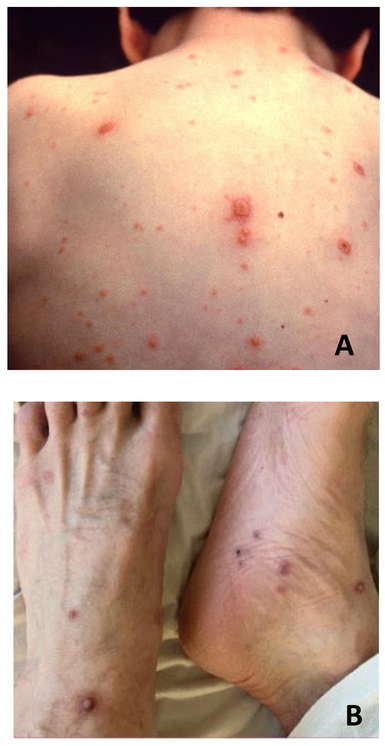

Figure 1: A) Chickenpox lesions on a patient's back; **B)** Mpox lesions on patient’s feet.

Methods

- **MPXV-negative lesion swabs collected between May and December 2022 from 484 patients aged 0 to 39 years were analyzed. Patients attending high-risk STI consultations were excluded to focus on a general population with skin lesions, avoiding bias from high-risk behaviors or underlying immunological or clinical conditions.**
- **DNA extraction from lesion swabs was performed using the MagMAX Viral/Pathogen Nucleic Acid Isolation kit in a King-Fisher Extractor (ThermoFisher), according to the manufacturer's recommendations.**
- **Real-time PCR for VZV DNA detection was carried out using the ARGENE® VZV R-GENE® assay (bioMérieux).**

Results

- **Of the samples analysed, 119 (24,6%) tested positive for VZV. This indicates that nearly one in four mpox-negative cases were, in fact, chickenpox.**
- **The majority of VZV-positive patients were male (76,5%), with a median age of 27 years, and 53,8% belonged to the 20–29 age group (Table 2).**
- **Positive cases were reported nationwide, with 55,5% concentrated in the Lisbon Metropolitan Area.**

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Table 2: Demographic data of the VZV positive cases, among the total MPXV negative cases from May 2022 to December 2022.

Demographic data	Positive cases number (%)
Gender	
Male	91 (76,5)
Female	28 (23,5)
Age group	
0-9	5 (4,2)
10-19	8 (6,7)
20-29	64 (53,8)
30-39	42 (35,3)
Portugal NUTS*	
North Region	31 (26,1)
Central Region	8 (6,7)
Lisbon Metropolitan Area	66 (55,5)
Alentejo Region	0
Algarve Region	11 (9,2)
Autonomous Region of Azores	0
Autonomous Region of Madeira	3 (2,5)
Total	**119**

* The Nomenclature of Territorial Units for Statistics (NUTS) is developed by Eurostat and is employed in both Portugal and the entire European Union for statistical purposes.

- **MPXV testing peaked in August, coinciding with heightened public and clinical awareness, whereas VZV detection peaked in June, aligning with the known seasonal pattern of chickenpox in Portugal (Table 3 and Figure 2).**
- **The monthly VZV positivity rate varied significantly, with the lowest observed in October (8.6%) and the highest in November and December (approximately 42%). These data suggest that a substantial number of mpox-suspected cases, particularly in the later months, were actually due to varicella.**

Table 3: Monthly distribution of analysed sample number and VZV PCR results in 2022.

Month/2022	Sample number	VZV Positive (%)	VZV Negative (%)
May/22	32	7 (21,9)	25 (78,1)
Jun/22	86	33 (38,4)	53 (61,6)
Jul/22	89	20 (22,5)	69 (77,5)
Aug/22	129	28(21,7)	101 (78,3)
Sep/22	73	11 (15,1)	62 (84,9)
Oct/22	35	3 (8,6)	32 (91,4)
Nov/22	19	8 (42,1)	11 (57,9)
Dec/22	21	9 (42,9)	9 (57,1)
Total	484	119	365

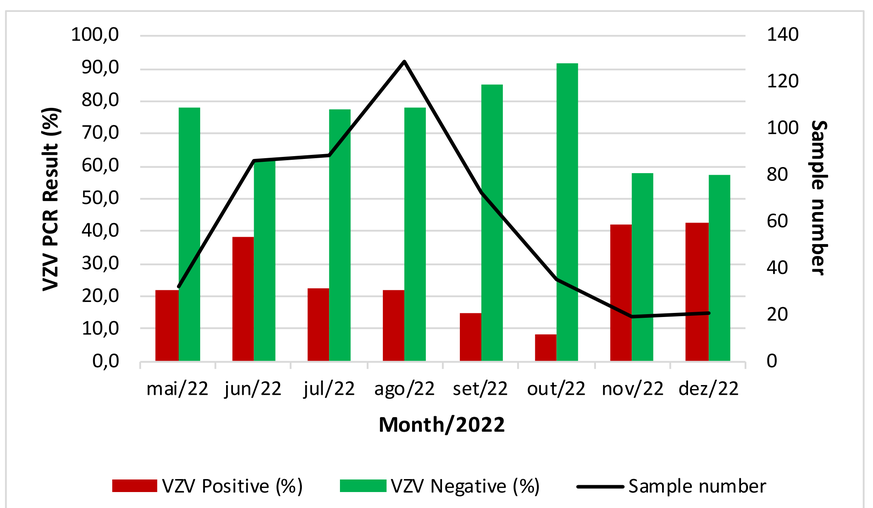

Figure 2: Monthly distribution of VZV PCR results among tested samples in 2022. The black line represents the total number of samples tested per month.

Conclusion

- **A considerable proportion of mpox-suspected cases were ultimately confirmed as chickenpox, underscoring the significant clinical overlap between the two diseases. The marked increase in VZV positivity toward the end of 2022 suggests that misdiagnosis remained frequent, even as clinical awareness of mpox improved.**
- **These findings demonstrate that clinical criteria alone are insufficient for accurate case classification during outbreaks involving diseases with overlapping presentations. Chickenpox represented a substantial proportion of mpox-negative suspected cases, reinforcing the persistent diagnostic challenge in distinguishing between emerging and endemic rash illnesses.**
- **This study highlights the critical role of integrated laboratory diagnostics in outbreak response, not only to improve case confirmation and guide appropriate clinical management, but also to prevent misreporting and misallocation of public health resources, especially when emerging and endemic pathogens co-circulate.**

References

7th CiiEM International Congress 2025
Caparica, 2-4 July 2025