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Enhanced surveillance of monkeypox in Bas-Uélé, Democratic Republic of Congo: the limitations of symptom-based case definitions

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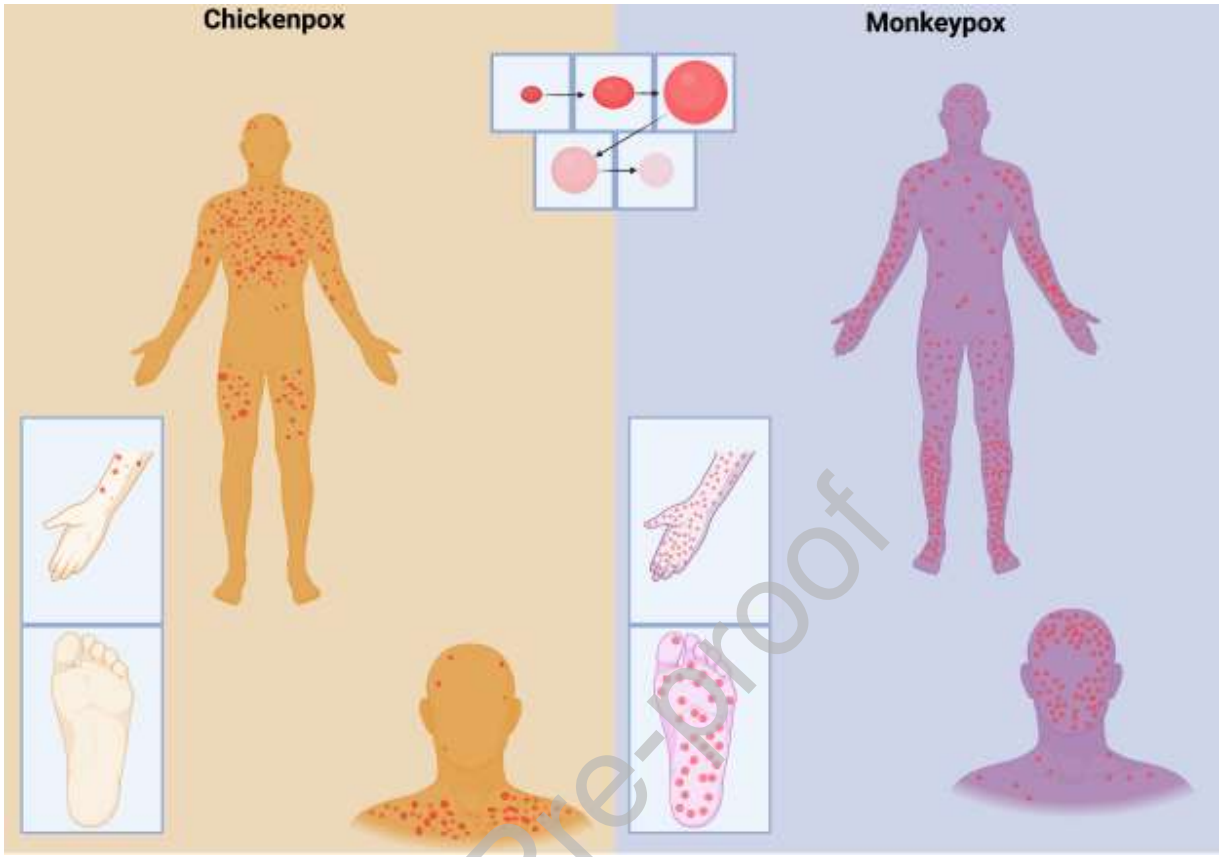
Graphical abstract



Abstract

Background: Following an outbreak of cases of vesicular-pustular rash with fever evocative of human monkeypox in Bas-Uélé province, Democratic Republic of Congo, surveillance was strengthened.

Methods: Households with at least one active generalized vesicular-pustular rash case were visited, and contact and clinical history information was collected from all household members. Whenever possible, skin lesion were screened by PCR for the monkeypox virus, followed by the varicella-zoster virus when negative for the former.

Results: PCR results were obtained for 77 suspect cases distributed in 138 households, of which 27.3% were positive for monkeypox, 58.4% for chickenpox, and 14.3% negative for both. Confirmed monkeypox cases presented more often with monomorphic skin lesions, on palms of hands, and on soles of feet. Integrating these three features into the case definition raised the

specificity to 85%, but would miss 50% of true monkeypox cases. A predictive model fit on patient demographics and symptoms had 97% specificity and 80% sensitivity, but only 80% and 33% in predicting out-of-sample cases.

Conclusion: Few discriminating features were identified and the performance of clinical case definitions was suboptimal. Rapid field diagnostics are needed to optimize worldwide early detection and surveillance of monkeypox.

Keywords: monkeypox; Democratic Republic of Congo; chickenpox, diagnostic, Orthopoxvirus

Background

Monkeypox virus (MPXV) is a DNA virus belonging to the Orthopoxvirus genus within the Poxviridae family, which also includes other human pathogenic viruses such as the vaccinia, cowpox and variola (smallpox)viruses. MPXV is currently the most prevalent human Orthopoxvirus and has been re-emerging since the eradication of smallpox in 1980. In humans, it causes a disease similar to smallpox, called monkeypox (Durski et al., 2018). Two clades of MPXV have been identified: the West African clade (MPXV-WA) occurring in forest areas situated west of Nigeria, and the Congo Basin clade (MPXV-CB) in Central Africa (Sklenovská and Van Ranst, 2018). After an incubation period of usually 7 to 14 days (range from 5 to 21 days), human monkeypox typically begins with systemic symptoms (i.e. fever, myalgia) followed by a rash, classically starting on the face before centrifugally spreading to other parts, including hands and feet in patients infected with the MPXV-CB clade. Yet the route of infection seems to influence clinical presentation, incubation period, severity and duration of the disease (Reynolds et al., 2006) and in particular as observed in recent monkeypox outbreaks outside Africa (Adler et al., 2022, Noe et al., 2022). The skin lesions generally appear all at the same

stage (monomorphic), evolving within 2 to 4 weeks from macules to papules, vesicles, pustules, crusts, and scabs. Complications (e.g. secondary bacterial skin infections, bronchopneumonia, keratitis, cecity) (Damon, 2011) are frequent and mortality may be up to 10% in children. People (primary cases) get infected through contact with infected animals during farming, hunting, or bushmeat preparation activities, and human-to-human transmission (secondary cases) also occurs by respiratory droplets or by close contact with infected lesions or bodily fluids (Diaz, 2021, Makhani et al., 2019, Petersen et al., 2019).

Human monkeypox was first described in 1970 in the Democratic Republic of the Congo (DRC) (Ladnyj et al., 1972). It is now found in more than half of the health zones of the country, reaching an incidence exceeding 5000 cases per year (Hoff et al., 2017). More than 35 epidemics have been reported in other African countries and in recent years cases have also been increasing in returning travelers (Erez et al., 2019, Hobson et al., 2021, Mauldin et al., 2020, Rao et al., 2022, Yong et al., 2020) culminating in 2022 in an unprecedented multi-country outbreak (WHO, 2022). Since 2002, monkeypox is a notifiable disease in DRC and part of the nationwide implemented Integrated Disease Surveillance and Response (IDSR) system (DRC, 2011, 2012). All suspected clinical cases (and deaths) that meet the clinical case definition have to be reported weekly by each health zone to the national level (Hoff et al., 2017). As shown in Table 1, two case definitions of “suspect monkeypox cases” are provided in the national IDSR guideline: one for use in health facilities by nurses/doctors and a second one much broader (“fever and cutaneous rash”) designed for surveillance by community health workers.

Due to the remoteness of the endemic areas confirmatory testing by PCR, only available in the national reference laboratory (“Institut National de Recherche Biomédicale”, INRB, Kinshasa), is rarely performed. As a result, the robustness of field surveillance based on clinical suspicion

has so far been difficult to evaluate. Several diseases with generalized skin eruption may mimic monkeypox, such as chickenpox, measles, molluscum contagiosum, or rickettsioses. The field differential diagnosis between monkeypox and chickenpox is particularly challenging (Jezek et al., 1988, Leung et al., 2019, MacNeil et al., 2009) and coinfections are frequent (Hughes et al., 2020). Recent attempts to design clinical case definitions with a higher specificity for surveillance or care purposes have not yet undergone external validation (Osadebe et al., 2017). Following alerts from several health zones of the Bas-Uélé province, northeastern DRC (Aketi, Buta, and Titule; Figure 1) of a sharp increase of suspect monkeypox cases a first exploratory mission was conducted in 2016 and confirmed an ongoing outbreak of febrile illness with skin eruption, suspect monkeypox. It also identified important challenges and gaps impacting the quality of the surveillance and outbreak data, including the non-systematic registration of cases and the scarcity of sampling kits in the field. An active surveillance component was added, and access to confirmatory testing was reinforced through the project entitled "Strengthening academic capacity to respond to Monkeypox epidemics: discrimination and origin of eruptive fevers in the Democratic Republic of Congo (DRC)" (Laudisoit, 2017).

Methods

Study design, setting and population

In the framework of the project, enhanced active surveillance and household investigation of suspect monkeypox cases were first initiated in three health zones (Aketi, Buta, Titule) of the Bas-Uélé province, and later focused on the axis going North from Aketi (Figure 1), where most cases had been initially detected. This region is located in the lowland tropical rainforest of the

Congo Basin, with a long rainy season from April to November, where the population lives mainly from subsistence farming, hunting, and small-scale livestock breeding.

The study population consisted of all suspect monkeypox cases as well as all members of their households, residing in locations accessible to trained study collaborators. For this study, a suspect monkeypox case was defined as “any person with an active generalized vesicular-pustular rash, i.e., presenting with five or more cutaneous lesions such as macules, papules, vesicles, pustules, or crusts, (Table 1)”, based on the DRC case definition for community surveillance (DRC, 2012). This study case definition was a bit stricter than that for community surveillance (a minimal number of lesions was required) but still aimed to largely capture any patients with active skin eruption that could be sampled for diagnostic evaluation.

Enhanced surveillance and household investigation

Households in which at least one case of febrile eruptive skin disease was reported by community health care workers (RECO) were visited by the study team. The household visits were done during three field sessions (08-21/09/2017, 19-29/03/2018, 27/10-9/11/2018) and during the interval periods by trained registered nurses from the study areas.

At the household level, after having obtained written informed consent for household inclusion from the household head, epidemiological and clinical data were collected (number of household members, gender and age of each member, health zone/area and village of residence, geographical coordinates, past episodes of fever with skin eruption and smallpox vaccination status of each household member). In addition, for each individual considered as a suspect monkeypox case, signs and symptoms (focused on monkeypox features such as fever prodrome, type/stage of rash, ocular lesions, cervical lymphadenopathy), and risk factors (contact with sick

person, animal contact, type of contact, time since contact) were collected using standardized questionnaires. In case of additional individual consent (or ascent by child plus consent of parent/tutor in case of children) and if sampling material was available, up to a maximum of 2 skin biopsies (crusts, pustules, or vesicle liquid) were collected following a strict standard operational procedure. One skin biopsy was stored „dry" at room temperature in individual vials as per DRC monkeypox case management and surveillance guidelines and sent to INRB in Kinshasa (DRC, 2012). The second biopsy was stored in ethanol (70%) as a back-up and stored at UNIKIS. Venous blood was not collected. Data on outcomes or onward human-to-human transmission were not available, as cases and their households were not followed up longitudinally after the initial visit. During each field visit, information obtained in one household could lead to further investigational visits in other households of the same village (snowball enrolment).

Laboratory procedures

Skin lesion samples were screened sequentially at the virology laboratory of INRB, Kinshasa, for Orthopoxviruses (OPXV) using an Orthopoxvirus-specific real-time in-house PCR assay (Osadebe et al., 2017) and -if the lesions tested negative for OXPV - a second real-time PCR assay targeting the varicella-zoster virus (VZV) was performed. OPXV positive samples were not tested further for VZV and were considered MPXV as virtually no other known human pathogenic Orthopoxvirus causes a similar smallpox-like rash in humans. Results were officially reported back from the reference laboratory (INRB) to the provincial central health bureau as positive, negative, or "neither MPXV nor VZV", after interpretation of cycle threshold values.

Evaluation of clinical case definitions

After this study was designed and approved, another research group published the results of a large case series of confirmed monkeypox and chickenpox cases and evaluated the DRC health facility case definition (called case definition A in this manuscript) and an alternative one (case definition B, elaborated to better discriminate both conditions) (Table 1). In addition, based on a receiver operating characteristic model including a set of 12 signs and symptoms, other combinations were proposed, since the performance of both case definitions A and B was unsatisfactory (Osadebe et al., 2017). We used our dataset retrospectively to also evaluate the diagnostic accuracy of both case definitions (with some slight adaptations – Table 4) and other combinations, using the actual features that had been captured during our field study.

Statistical analysis

Descriptive statistics, using medians and interquartile ranges for continuous variables and percentages for categorical variables, were used to summarize the results of the household investigations. Comparisons were calculated by Pearson"s chi-squared or Fisher exact test for categorical variables and the Kruskal Wallis test for continuous variables. Differences were considered statistically significant if $p < 0.05$. Diagnostic value and performance of signs/symptoms and different case definitions were expressed in sensitivity, specificity, positive and negative predictive value (PPV and NPV), and positive and negative likelihood ratios (LR + and LR-), using standard formulas. All statistical analyses were performed using Stata 15.0 software (StataCorp LP, College Station, TX, USA).

Predictive model

We fit a model to predict PCR-confirmed cases using patient sex and age group, prior smallpox vaccination history, and presence of signs/symptoms. We generated interaction variables for every binary combination of variables, dropping interactions that were fully determined by other variables. We then fit a Bayesian logistic model to random training subset of 75% of PCR-confirmed cases, using a regularizing prior (Student‟s t) on variable coefficient to optimize for out-of-sample prediction. We calculated the posterior odds ratios associated with each variable and interaction, and measured out-of-sample performance on the remaining 25% of cases. Model-fitting was performed in R 4.2.0 (RcoreTeam, 2022) , using the Stan modeling framework (StanDevelopmentTeam, 2022) and brms package (Bürkner, 2017).

Data Availability Statement: De-identified data and R code for the predictive model are deposited on Zenodo at https://dx.doi.org/10.5281/zenodo.6574450 (Mande et al. 2022).

Results

Generalized skin eruption with fever evocative of human monkeypox was notified in 143 households, making a total of 948 people (median number of members/household: 6; interquartile range [IQR] 4-9) and reported by the RECO to the local health staff. These households were visited by the study teams between September 2017 and May 2019 (94 in the first year and 49 in the second year of the project). In a total of 106 households (106/143; 74.1%), representing 678 household members, the study team confirmed that at least one case responded to the study definition of suspected MPX. Overall, 138 patients (of whom 74 or, 54%, were aged <15 years) fulfilled the study definition of suspect monkeypox case (Table 2).

The cases resided in 32 villages distributed in 12 health areas within three health zones (Aketi, Buta, Titule). Eighty-nine households (89/106; 84.0%) had one suspect case, 10 had two, four had three, one had four, and within two families, all members (6 and 7, respectively) had an active generalized vesicular-pustular rash fitting the study definition at the time of the household visit. During site visits, among households with active cases of skin eruption, 23/100 (n=100, info missing for 6 households) also reported recent and distant past episodes of fever with generalized skin eruption in their households (distant, i.e., >3 months earlier for 13; recent, i.e., within the last 3 months for 10).

Complete PCR results were obtained for 77 out of the 138 active suspect monkeypox cases (55.8%). Twenty-one of 77 patients (27.3%) tested positive for MPXV, and 45, out of the 56 MPXV-negatives, were positive for VZV. The remaining 11 cases remained negative for both MPXV and VZV. One suspect monkeypox case, negative for MPXV, was not tested for VZV.

Next, we compared the socio-demographic, clinical characteristics, and risk factors between the 21 confirmed monkeypox cases, the 45 confirmed chickenpox cases, and the 11 cases reported as negative for both PCR assays (Table 3).

Sociodemographic characteristics (age, gender) were similar in the three groups. In terms of clinical signs and symptoms, rash characteristics were the only symptoms that differed significantly between monkeypox and chickenpox cases. Monkeypox confirmed cases more often presented with cutaneous lesions in the same stage of the skin eruption (monomorphic) (85.7% vs 40.0% for the chickenpox cases; p=0.001); and more often had lesions on hands palms (85.7% vs 33.3%; p<0.001) and feet soles (71.4% vs 17.8%; p<0.001) compared to chickenpox patients. Forty percent of both confirmed monkeypox and chickenpox patients presented with