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Technical Advisory Group on Human Monkeypox. Report of a WHO Meeting.

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World Health Organization
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Response

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I. Introduction

The WHO Technical Advisory Group Meeting on Human Monkeypox was convened by the Department of Communicable Diseases Surveillance and Response (CSR). Dr. Martinez (Director, CSR) opened the meeting by noting that large outbreaks of human monkeypox had been reported from the Democratic Republic of the Congo (DRC) since early 1996. The epidemiological and laboratory features of the outbreaks remain incompletely defined, and the Advisory Group was convened to review the available data, and advise the organization on the appropriate measures to be taken. In particular, the Advisory Group was charged with:

- 1) identification of areas for further research into the public health impact of human monkeypox, and development of appropriate disease control mechanisms
- 2) formulation of recommendations to be considered by the Ad Hoc Committee on Orthopoxvirus Infections, meeting 14-15 January 1999.

Dr. Joel Breman was elected chairman and Dr. Joseph Esposito was elected Rapporteur. The Technical Advisory Group participants are listed in Annex 1. For one session of the meeting, the Advisory Group divided into 2 sub-groups to discuss specific issues and formulate recommendations relating to: (1) epidemiology and control, and (2) laboratory and ecologic research.

II. Background

Although monkeypox was first identified in primates in 1959, it was not recognized as a cause of human disease until 1970.* Reports of human monkeypox from 1970 to 1986 revealed 404 cases, mainly in children under age 16, in 7 west and central African countries (DRC, Côte d'Ivoire, Sierra Leone, Cameroon, Central African Republic, Liberia, Nigeria). Of these, 338 cases were identified during WHO intensified surveillance from 1981-86 in DRC (1980 population ~ 28 million), mainly in Equateur and Bandundu Provinces, and to a lesser extent in Kasai Oriental Province. Virtually all reported cases were investigated actively by WHO teams working in DRC. Of the 338 cases, 67% were seen during the rash stage and later verified as monkeypox by virus isolation. Twenty-three percent were seen soon after disease onset and were verified clinically and by detection of orthopoxvirus (OPV) antibodies in serum. The remaining 10% were corroborated by careful examination of epidemiological and clinical data. Vaccination scars indicated that 13% of the 338 patients had been immunized against smallpox, most of these >10 years previously. Primary or co-primary infections resulting from animal-to-human contact accounted for 72% of the cases, with inter-human transmission responsible for 28%. Clustering of cases in households was rare, as were chains of inter-human transmission beyond 2 generations; only 11, 3 and 1 cases proceeded to the third, fourth, and fifth generations, respectively. The overall case-fatality ratio was 10%.

* Jezek Z and Fenner F. *Human monkeypox*. Monographs in Virology, vol. 17. Basle, Karger, 1988.

Local population immunity from smallpox vaccination (which protects against monkeypox with >85% efficacy) was relatively good, with estimated coverage of $\geq 60\%$ during the 1970s and early 1980s. The secondary attack rate (SAR) was 9% for unvaccinated residents of the same household, 7% for all unvaccinated contacts, and 1% for all vaccinated contacts. These are markedly lower than smallpox SARs of 20% to 70%. Limited ecological and anthropologic studies detected monkeypox virus in one diseased squirrel (*Funisciurus anerythrus*) captured in DRC. However, OPV antibodies were identified in several squirrel and monkey species, as well as in other wild-caught animals in the endemic areas, indicating that monkeypox virus may have a broad host-range.

In 1986, intensified surveillance was discontinued. From 1987 to 1992, 12 cases were reported and verified by laboratory tests: 1 from Cameroon, 5 from DRC, and 8 from Gabon, the latter being a previously unknown endemic country. These numbers suggest that without intensified surveillance, incidence may be dramatically under reported.

III. Recent studies in the DRC, 1996-1998

Field and laboratory investigations

Between February and August 1996, 71 cases of human monkeypox, including 6 deaths, were reported amongst a population of 15,698 in 13 villages in the Katakombé health zone, Kasai Oriental, Zaire by local investigators. Three WHO sponsored multi-agency short-term missions were undertaken in 1997-98 to investigate this outbreak and continuing reports of cases through July, 1998. Their aims were to determine the magnitude of the outbreak, the risk factors for infection, assess the sustainability of transmission, and implement the most appropriate disease control measures. Active door-to-door case search was conducted in villages where cases were reported. A case was defined as an individual having a history of vesicular, pustular, or crusty rash, not clinically diagnosed as chickenpox, since February 1996.

Key results

The investigation team sent in February, 1997, identified 92 cases in 12 villages (total population 4 057) including Akungula, the original epicentre, which had the highest village specific attack rate (2.3%). The median age of cases was 10 years. Sex-specific attack rates were equal. Cases were clustered within affected households, with 45 cases occurring in 15 of 62 households in Akungula. The number of cases increased from February to August 1996, followed by a decrease until February 1997. 73% of case-patients reported contact with another case in the 7-21 days before rash onset, a higher proportion than during the 1980s. The first generation household secondary attack rate was 8.1% (95% CI 4 -12%), similar to the 9.3% SAR observed among unvaccinated persons in households during the 1980s.

Seven cases had active skin lesions at the time of the investigation; all were confirmed by MPV isolation and DNA identification. The remaining 85 cases were identified retrospectively from clinical history. Forty one of 82 inactive cases reported lymphadenopathy, a major feature of monkeypox, and all 79 inactive examined had scarring from a rash illness (median number = 52; range = 2 to 830; SD = 168). This picture of an essentially unchanged clinical presentation and similar transmissibility was supported by the genetic similarity of isolates with those collected during the 1970s and 1980s.

Serological confirmation of retrospectively isolated cases proved problematic: OPV antibodies were detected by plaque-reduction neutralization tests (NT) in only 41 (54%) of 76 inactive cases to provide serum, in 73% by Western blot (WB) and on 73% by haemagglutination-inhibition (HAI). This finding did not seem to be explicable by cross reactive antibodies from the non-MPX OPV vaccinia; only fourteen of 84 (17%) case-patients had a smallpox vaccination scar. There was some evidence to suggest co-circulation of varicella-zoster virus, as five of six active monkeypox cases living in one household also had serological evidence of recent varicella infection. Furthermore, 75% of 76 sera were VZV IgG seropositive. This raised the potential difficulties of determining from retrospective reports exactly which rash illness (chickenpox or MPX) was being described for the study period.

Civil unrest necessitated the premature evacuation of the investigation team from the field in February, 1997, but continuing reports of large numbers of cases were received over the following months. A second investigative team was sent to the area in October, 1997. Case searching was conducted over a much larger geographical area in villages where cases were reported. The case definition was changed to include possible chickenpox cases in the second mission. 419 additional suspect cases were identified resident in 54 Katakombé and 24 Lodja Health Zone villages (population of 0.55 million). The majority of cases were diagnosed retrospectively at the time of the investigation. Of the 395 retrospectively identified cases about 270 provided serum. Clinical features, age distribution, seasonal pattern (with an August peak) and household SAR were similar to that observed in the February mission. Primary cases (no history of contact with a human case and presumably infected from animal contact) were reported from throughout both health zones. A case-control study was performed to elucidate risk factors for disease acquisition.

Of the 20 active cases from both the February and October investigations in whom virological confirmation was made, monkeypox virus was detected in 13 patients, VZV in 5 patients, and dual infection in 2 patients. Combining serology results from both studies, approximately 255 (73%) of 350 sera were positive for OPV antibodies by at least one test, and about 50% by at least three tests. Of those cases with OPV antibodies, approximately 70% also had IgG antibodies to VZV. HIV co-infection did not seem to be a significant co-factor: only three of the case-sera tested showed HIV antibodies, of whom two also had OPV antibodies. The overall CFR for the February and October investigations was ~1%. The analysis suggests that monkeypox infection was probably responsible for the majority of the 511 cases reporting rash illness onset between February 1996 and October 1997, although VZV co-circulation was also responsible for a significant proportion.

In July, 1998, a follow-up team visited the area to collect control sera not obtained during the October 1997 investigation. Monkeypox transmission was continuing, and five active cases were detected and verified virologically. Local surveillance reported a total of 303 new, suspect cases in the nine months since the previous mission, although sera were only obtained from 19% of these. Of the 150 control sera collected nine months after the case sera, 11% were positive for OPV antibodies, and 33% for VZV IgG.

Conclusions

In conclusion, there has been an increased incidence of monkeypox infection from 1996-8 compared to the 1980s. However, there was no evidence of increased transmissibility. The household SAR was similar to historical findings and the sequence evidence currently available suggests that the virus is unchanged from earlier isolates. HIV was not a significant co-factor. Although in most respects the clinical features are unchanged from the period of intensive surveillance, the mortality was markedly lower, with a CFR of ~1%, compared to 9.8% between 1981-86. It is unclear if an epizootic of monkeypox was occurring in reservoir species in contact with humans. However, the increase incidence in the human population could be due to declining population immunity since the cessation of smallpox vaccination in DRC in 1982. This could have resulted in an increased incidence of primary cases as susceptible young people came in close contact with reservoir species, and also of a primary case leading to a larger number of secondary cases before the chain of transmission ceased. Hence, there was a higher proportion of secondary cases compared to the 1980s.

Despite the increased incidence of monkeypox, it was felt that the situation did not warrant the reintroduction of a smallpox vaccination programme, partially due to concerns about adverse events in a population with a potentially increasing HIV seroprevalence. Few active cases occurred during the investigations. Symptomatic treatment, isolation, and basic hygiene measures were advised to control transmission.

The surveillance and investigation activities provided valuable insights into human monkeypox in central DRC despite limitations by civil unrest, poor infrastructure and support, use of differing methodologies, co-circulation of chickenpox, and reliance on currently available serologic tests which are not adequately sensitive and specific. However, additional laboratory-based, epidemiological, and ecological prospective studies are needed to understand better the natural cycle of the virus and the true extent of the outbreak.

IV. Key Points and Conclusions from Working Papers and Discussion

A. Epidemiological surveillance

- The current surveillance system for monkeypox is inadequate in the DRC and elsewhere in Africa where human monkeypox may occur.
- There has been variability in investigation methodologies, and the protocols in the WHO Human Monkeypox Surveillance and Investigation Manual have not been used in the field consistently.
- Current data are incomplete on transmissibility because the suspected patient investigations have usually been delayed, and control patients have not been studied concurrently. Mathematical models developed from the findings of the WHO intensified surveillance programme 1981-86 indicated that human monkeypox could be transmitted for a maximum of 14 inter-human generations in a totally unvaccinated population under certain field conditions. Mathematical modelling of monkeypox transmission dynamics has not been performed recently.
- Due to delays in investigation, serological confirmation of suspected patients are being performed much more often than virological confirmation. The sensitivity, specificity and predictive values of the standard orthopoxvirus serological tests, and the newer tests, are not clearly defined.
- Monkeypox is a zoonosis, yet the reservoir(s) of human monkeypox remain uncertain, despite the isolate of monkeypox virus from one squirrel found in the wild. Orthopoxvirus antibodies have been detected in several animal species in the endemic area.
- Recent, short, investigations have not clarified satisfactorily the clinical, epidemiological or ecological features of the current monkeypox outbreak(s). It is possible that an epizootic is occurring, requiring more prolonged and sustained investigations.
- Major delays in receiving laboratory results and epidemiological analyses from collaborating laboratories have occurred because of administrative problems, and the lack of capacity to perform such tests and analyses in the DRC.
- Skilled staff and resources for performing satisfactory surveillance, investigations, and research are lacking in the DRC and other affected countries.

B. Control and prevention

- Antiviral therapy/research. There are several promising antiviral drugs under development which may offer therapeutic benefit for monkeypox patients. Cidofovir has demonstrated protection in challenge studies performed in animal models.
- Vaccination. Known complications from smallpox vaccine (vaccinia), which protects against monkeypox, and the possibility of an increase in prevalence of HIV/AIDS in monkeypox-endemic areas, are contraindications to smallpox vaccination at this time.

C. Information, health education, and training

- Health information for the local populations in monkeypox-endemic areas and training for medical and paramedical staff are needed.

D. Laboratory issues

- Laboratory diagnostic and research capabilities for monkeypox are weak in the DRC.
- With decreased interest in orthopoxvirus research in the past 20 years, capacity for diagnosis and research has declined greatly. Support for strengthening this capacity is needed now and in the future within the WHO Orthopoxvirus Collaborating Centres and allied laboratories. Reliable tests are needed for serological differentiation of orthopoxviruses, and research into the molecular virology and pathogenesis of monkeypox is required.
- In-country screening and analysis of epidemiological information and samples for laboratory testing could ease the burden on collaborating centres and save resources currently expended on specimen transport.
- The WHO specimen collection and shipment instructions need updating. The field samples coming to WHO-affiliated laboratories are often poorly identified and packaged.

V. Recommendations

A. Epidemiological surveillance

1. There should be reestablishment and strengthening of human monkeypox surveillance systems; these systems should detect suspected cases promptly, assure rapid notification to national and WHO authorities, and elicit timely and comprehensive investigations. While the focus should be in forested areas of the Kasai Oriental Province of DRC, surveillance in other areas of DRC and other African countries should also be re-established or strengthened through WHO.
2. An updating of the WHO Human Monkeypox Surveillance and Investigation Manual should be prepared promptly by experts in human monkeypox and diseases resembling monkeypox. A review panel should give special attention to case definitions for routine surveillance, investigative, and research purposes. Case definitions should consider clinical and laboratory criteria.
3. The transmissibility of human monkeypox needs to be determined with urgency. Monkeypox modelling, begun in the 1980s, should be re-explored using current techniques.
4. The sensitivity, specificity and predictive values of new orthopoxvirus serological assays need to be evaluated as part of prospective investigations; it would be desirable to use sera archived in past monkeypox studies (1970s-1980s) which performed virologic confirmation of cases. Clinical and epidemiological information should be correlated with virologic and serologic data.
5. Differentiation of monkeypox from other orthopoxviruses by serologic testing merits the highest priority.
6. HIV seroprevalence in rural and urban areas within the areas under surveillance and study needs to be determined. In particular, the occurrence and clinical picture of chickenpox (and monkeypox) in HIV-infected and uninfected children needs to be studied.
7. Ecologic and natural history studies of human monkeypox need review by an expert panel convened to develop a protocol, and advise on the feasibility of such studies.
8. A population-based study is advised as the best way to understand the clinical, epidemiologic, and ecologic characteristics of human monkeypox, and associated laboratory-testing issues. At a minimum, a well-defined

heavily-endemic population in Kasai Oriental Province should be designated for special emphasis surveillance.

9. National capability for serologic, and eventually virologic, diagnosis should be evaluated, established, and maintained.
10. Increased resources, training, administrative and logistical support will be needed to assure that a satisfactory surveillance system and diagnostic capacity is re-established.

B. Control and prevention:

1. Antiviral therapy/research

- Laboratory screening for antiviral drugs against monkeypox and other OPVs should be expanded.
- A preclinical trial and, where appropriate, a clinical trial in the field, of cidofovir, the first promising anti-orthopoxviral drug, is endorsed; attention to feasibility, clearance by institutional review boards in collaborating countries, and active collaboration of scientists in the monkeypox-endemic countries must occur.

2. Vaccination

- Currently available smallpox vaccines should not be used in monkeypox-endemic areas until the epidemiologic picture of monkeypox and the risks from vaccination are clarified.
- Determination of HIV-status of patients, their families and communities is needed for assessing the risk of using vaccinia in monkeypox-endemic areas with a substantial prevalence and incidence of HIV/AIDS.
- Evaluation of the possible usefulness of attenuated vaccinia strains for persons who are immune deficient or otherwise have contraindications to smallpox vaccination is advised.

3. Information, health education and training

- Health education for local populations should focus on rapid recognition and reporting to an informed health official.
- Local health care providers and regional authorities should receive information on differential diagnosis, specimen collection, case management, notification and investigation procedures, and collection/shipment materials.
- Scientific articles on the previous investigations and technical notes, for the medical-care and scientific communities, should be published and distributed widely, particularly within monkeypox-endemic countries.

- Increased training is needed for national and local staff in clinical, epidemiologic and laboratory features of monkeypox, and its control and prevention.

C. Laboratory issues

1. A central laboratory in highly affected countries (presently the DRC) capable of implementing orthopoxvirus/monkeypox modern diagnostic assays, for lesion material (PCR, antigen capture) and sera (ELISA, Western blot) should be established when feasible.
2. WHO Collaborating Centres (Atlanta, Koltsovo) and other laboratories (e.g. Public Health Laboratory Service, London; United States Army Research Institute for Infectious Diseases, Ft. Detrick; National Institute for Infectious Diseases II, Tokyo; WHO Collaborating Centre for Diagnostics Development and the Armed Forces Institute of Microbiology, Munich) involved in OPV research should continue developing and evaluating rapid, sensitive, and specific virologic and serologic diagnostic tests suitable for use in-country, both for central laboratories and field use; these should include filter paper blood and salivary antibody and antigen assays. Collaborative efforts should focus on evaluating available reagents for incorporation into assays (e.g. monoclonal antibodies against OPVs, particularly monkeypox).
3. The WHO document on “Collection, storage and shipping of specimens from humans for monkeypox and haemorrhagic viruses,” should be updated. A monkeypox and related VZV document that includes a one to two page summary pamphlet and illustrated instruction card for field use is needed. Such revision should conform with new WHO guidelines for sample taking and transportation, and be aimed at encouraging local workers to be compliant with these guidelines.
4. Support should be given to enhance education programmes and training of personnel involved in field studies to obtain accurate case histories to accompany well-organized clinical sample sets.
5. WHO Collaborating Centres in poxvirus research (Atlanta, Koltsovo) and other laboratories involved in OPV research (Munich, Fort Detrick, London, Tokyo) should continue molecular biologic studies. This research would include DNA sequencing and viral structure, function, and biologic studies of new and earlier monkeypox virus isolates.
6. The capacity for performing epidemiological investigations, collaborative laboratory research, and training of staff at the WHO Collaborating Centres in Atlanta and Koltsovo should be increased, and other research institutes encouraged to bring more interested investigators into this research arena. The WHO Collaborating Centre at Koltsovo has emphasized its commitment to offering its facilities and expertise for collaborative work in monkeypox research.
7. Increased support should be obtained to undertake the required laboratory studies.