Monkeypox Research: Opportunities for central and west Africa

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A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo *

I. D. LADNYJ,1 P. ZIEGLER,2 & E. KIMA 3

This paper presents clinical and epidemiological information on a patient with smallpox-like disease, from whom a monkeypox-like virus was isolated. The patient was the first recognized human monkeypox case in medical history.

Discovery and Organization of Research

Table 9. Number of suspected monkeypox cases examined in peripheral health establishments, 1981–1986

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mongala</td>
<td>57</td>
<td>51</td>
<td>137</td>
<td>71</td>
<td>57</td>
<td>71</td>
<td>464</td>
</tr>
<tr>
<td>Sud-Ubangi</td>
<td>64</td>
<td>24</td>
<td>109</td>
<td>58</td>
<td>84</td>
<td>113</td>
<td>452</td>
</tr>
<tr>
<td>Sinkuru</td>
<td>22</td>
<td>44</td>
<td>72</td>
<td>49</td>
<td>97</td>
<td>80</td>
<td>364</td>
</tr>
<tr>
<td>Kwitu/Kwango</td>
<td>14</td>
<td>21</td>
<td>25</td>
<td>15</td>
<td>31</td>
<td>29</td>
<td>135</td>
</tr>
<tr>
<td>Total</td>
<td>157</td>
<td>140</td>
<td>363</td>
<td>192</td>
<td>269</td>
<td>293</td>
<td>1,415</td>
</tr>
</tbody>
</table>

Human Monkeys

Table 11. Numbers of specimens from Africa (lesion material and sera) examined by WHO collaborating centres in Atlanta and Moscow for evidence of poxvirus infection, 1980–1986

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting monkeypox</td>
<td>30</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>32</td>
</tr>
<tr>
<td>Cameroon</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Central African</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>146</td>
<td>75</td>
<td>105</td>
<td>–</td>
<td>328</td>
</tr>
<tr>
<td>Republic</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>Côte d'Ivoire</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>Nigeria</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>3,220</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>3,218</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>9,988</td>
</tr>
<tr>
<td>Zaire</td>
<td>1,964</td>
<td>4,244</td>
<td>475</td>
<td>1,058</td>
<td>882</td>
<td>656</td>
<td>705</td>
<td>9,988</td>
</tr>
<tr>
<td>Total</td>
<td>2,000</td>
<td>13,592</td>
<td>481</td>
<td>1,212</td>
<td>957</td>
<td>761</td>
<td>707</td>
<td>19,710</td>
</tr>
</tbody>
</table>

Not reporting monkeypox

| Countries      | 2    | 2,077| –    | –    | –    | –    | –    | 2,214 |
| Congo          | 2    | 21   | 9    | 7    | 3    | 3    | –    | 37    |
| Other countries| 30   | 21   | 9    | 7    | 3    | 3    | –    | 73    |
| Total          | 32   | 2,228| 9    | 7    | 3    | 3    | –    | 2,284 |

Total: specimens

| Total: specimens | 2,032| 15,820| 490  | 1,219| 960  | 766  | 707  | 21,994|
| Total: countries | 14   | 11   | 7    | 7    | 4    | 5    | 2    | 46    |

*Includes part of 12,810 serum specimens tested in serologic surveys in Congo, Côte d'Ivoire, Sierra Leone and Zaire.
Human monkeypox: secondary attack rates

Z. Ježek, B. Grabe, M. V. Szczeniowski, K. M. Paluku & M. Mutombo


L'inefficacité de la propagation de personne à personne, même dans des conditions d'exposition maximale, confirme l'hypothèse selon laquelle le virus de l'orthopoxvirose simienne est mal adapté à une transmission interhumaine continue et que ce mode de transmission ne constitue pas un problème de santé important.


Yvan J.F. Hutin,* R. Joel Williams,* Philippe Malfait,† Richard Pebody,† Vladamir N. Loparev,* Susan L. Ropp,* Mariangeli Rodriguez,* Janice C Knight,* Florimont K. Tshioko,‡ Ali S Khan,* Mark V. Szczeniowski,‡ and Joseph J. Esposito*

*Centers for Disease Control and Prevention, Atlanta, Georgia, USA;
†European Programme for Intervention Epidemiology Training, Brussels, Belgium;
and ‡World Health Organization, Geneva, Switzerland
What we don’t know about human monkeypox

• What is the current burden of monkeypox infection in enzootic areas?
• Has the risk of monkeypox changed since the 1980s?
• What are the risk factors associated with monkeypox infection?
• How transmissible is monkeypox?
• Is there evidence of long term protective immunity to monkeypox from previous smallpox vaccination?
Active Surveillance Program in Sankuru Province, DRC: 2002-2011
Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo


per capita incidence increased by factor of 20 (95% CI, 14-29) between 1981-86 and 2005-07.
Average annual cumulative incidence of human monkeypox, by health zone and dominant ecological characteristic, Sankuru, DRC

*Proportion of the population vaccinated in 2006-7 and in 1981-6 based on vaccination scar surveys. Vaccination rate steadily declined from 41.0% in 1981 to 4% in 1985.

<table>
<thead>
<tr>
<th>Population vaccinated* (%)</th>
<th>2006-7</th>
<th>1981-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0</td>
<td>16^</td>
</tr>
<tr>
<td>5-9</td>
<td>0</td>
<td>83</td>
</tr>
<tr>
<td>10-14</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>15-19</td>
<td>2</td>
<td>96</td>
</tr>
<tr>
<td>20-24</td>
<td>24</td>
<td>97</td>
</tr>
<tr>
<td>25-29</td>
<td>67</td>
<td>97</td>
</tr>
<tr>
<td>30+</td>
<td>96</td>
<td>97</td>
</tr>
</tbody>
</table>

Avg. Annual Incidence
1981-6: 0.72/10,000
2006-7: 14.42/10,000
=IR: 20.17

*Is declining vaccine coverage leading to emergence of monkeypox in the DRC?*

*Does herd immunity account for increase in incidence? If not, what does?*

*Proportion of the population vaccinated in 2006-7 and in 1981-6 based on vaccination scar surveys. ^ Vaccination rate steadily declined from 41.0% in 1981 to 4% in 1985.*
The role of smallpox vaccination

• 1980s data suggested that smallpox vaccination was 85% protective (95% CI: 74-92) against clinical monkeypox infection.

Age distribution of recent infections suggests that vaccination is still protective.

Analysis of data from 2005-2007 shows that smallpox vaccine gives 80.7% (70-89%) protection against clinical MPX infection. → no significant decline over time.
Key challenge: To disentangle contributions of zoonotic spillover versus human-to-human transmission.

How much of the observed increase is due to Primary vs. Secondary Transmission?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Leads to increases in...</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Animal-human transmission?</td>
</tr>
<tr>
<td>Declining herd immunity (due to lower vaccine coverage or efficacy)</td>
<td>•</td>
</tr>
<tr>
<td>Increased MPX prevalence in reservoir</td>
<td>•</td>
</tr>
<tr>
<td>Increased hunting of reservoir animals</td>
<td>•</td>
</tr>
<tr>
<td>Declining immune status due to malnutrition or co-infections</td>
<td>•</td>
</tr>
<tr>
<td>Virus adaptation to humans</td>
<td>•</td>
</tr>
<tr>
<td>Possibility of intergenerational transmission</td>
<td>•</td>
</tr>
</tbody>
</table>
Clinical Characterization of MPX (2007-2011)- Sankuru
Clinical characterization of human monkeypox infection: 2008 – 2011
Patients followed for 3 weeks post enrollment:

- Daily evolution of Clinical signs, symptoms and skin lesions
- Daily evolution of lab parameters:
  - Hematology
  - Blood biochemistry
  - Urine analysis
  - Viral load (throat swab, lesion and blood)
  - Cytokine profile
  - Lymphocyte profile

1. Clinical characterization of human monkeypox infections in
2. the Democratic Republic of the Congo
Clinical symptoms

- Rash (96.8%)
- Malaise (85.2%)
- Sore throat (78.2%),
- Lymphadenopathy (57.4%)
- Anorexia (50.0%)

Physical examination findings or signs

- Skin lesions (99.5%)
- Lymphadenopathy (adenopathy) (98.6%).
- MPXV mouth/throat lesions (28.7%)
- Abnormal lung sounds (10.6%)
- Hepatomegaly, splenomegaly or both (7.9%)
- Bleeding (2.3%)
The duration of clinical symptoms and signs: average 3 – 5 days
Change in total lesion count or lesion count by body location over time
The pattern of distribution of Monkeypox associated lymph node
Comparison of **Maximum lesion count** by location among illness severity categories

<table>
<thead>
<tr>
<th>Body Location</th>
<th>Level 1 (N = 99)</th>
<th>Level 2 (N = 74)</th>
<th>Level 3 (N = 40)</th>
<th>Level 4 (Death) (N = 3)</th>
<th>Adjusted P value</th>
<th>Raw P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral/Oropharyngeal Lesions</td>
<td>0 (1.1)</td>
<td>2 (3.5)</td>
<td>7 (12.6)</td>
<td>29 (35.9)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Head</td>
<td>38 (47.7)</td>
<td>106 (122.3)</td>
<td>147 (153.5)</td>
<td>527 (546.0)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Arms</td>
<td>42 (65.4)</td>
<td>102 (105.1)</td>
<td>149 (200.9)</td>
<td>771 (896.0)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hands</td>
<td>19 (41.7)</td>
<td>38 (42.7)</td>
<td>75 (129.8)</td>
<td>222 (264.5)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Trunk</td>
<td>30 (45.7)</td>
<td>84 (91.9)</td>
<td>125 (190.5)</td>
<td>904 (924.2)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Legs</td>
<td>77 (128.7)</td>
<td>180 (208.0)</td>
<td>296 (438.3)</td>
<td>1284 (1431.2)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Feet</td>
<td>17 (65.6)</td>
<td>25 (35.9)</td>
<td>44 (67.1)</td>
<td>142 (133.1)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Total Body</strong></td>
<td>223 (352.7)</td>
<td>537 (567.5)</td>
<td>843 (1098.6)</td>
<td>3879 (4210.2)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Clinical laboratory findings
survivors (levels 1-3) vs. level 4 (death)

- Statistically significant differences in the alanine phosphatase (ALT) (90 vs 26 U/L; \( p = 0.0224 \), adjusted) and aspartate aminotransferase (AST) (415 vs 48 U/L; \( p = 0.0004 \), adjusted)

- For CBC (complete blood count) variables, no difference between survivors and fatal cases for any CBC variable. Neutrophil count show difference among the non-fatal categories

- The platelet count was \( 130 \times 10^3/\mu L \) in the fatal group vs \( 296 \times 10^3/\mu L \) among survivors (\( p = 0.0102 \), unadjusted)

- For urine, elevated protein among illness severity level 1, 59 mg/dL (SD 65.3), level 2 category 88 mg/dL (SD 87.3), vs level 3 category 114 mg/dL (SD 108.3); \( p = 0.0147 \), adjusted (data not shown)
Evolution of lesion for subject 135 who was enrolled as an asymptomatic subject and later developed disease.

Lesion Evolution in one fatal case (Subject 54)
Complications observed in monkeypox patients

- Keratitis in the left eye
- Staphyloma at the left eye 24 months after keratitis
- Caseification of eye lesions
- Secondary Dermatitis
- Œdema
Fetal Demise Due to Maternal Monkeypox Infection

Maternal and Fetal Outcomes Among Pregnant Women With Human Monkeypox Infection in the Democratic Republic of Congo

Placide K. Mbala,1 John W. Huggins,2 Therese Riu-Rivira3 Steve M. Ahuka,4 Prime Mulembakani,5 Anne W. Rimeoia,5 James W. Martin,6 and Jean-Jacques T. Muyembe7

4 spontaneous abortion among the 5 pregnant women enrolled in the study
DIAGNOSIS : Case definition

• **ALERT CASE**
Anyone with rashes with or without a history of fever

• **SUSPECTED CASE**
Any person, living or dead, presenting or having presented a high fever (≥ 38° C) with a sudden onset, and having been in contact with:
  • a suspected, probable or confirmed case of Monkeypox
  • a dead or sick animal
  • or living in the epidemic area

OR: anyone with sudden onset high fever and/or at least three of the following symptoms:
  • headache
  • Intense tiredness
  • Muscle aches
  • Back pain
  • vesiculo-pustular rash,
  • adenitis, pain in the throat, mouth ulcers, etc.
• PROBABLE CASE:

ANY case corresponding to the clinical case definition, who can no longer benefit from biological confirmation, with an epidemiological link with a confirmed or probable case.

• CONFIRMED CASE:

Any suspected case with a positive lab result.
Laboratory analysis

- PCR: for confirmation of the disease
- Sequencing: genomic variation, mutations, etc.
- Biochemistry: for supportive care and follow-up
- Hematology: for supportive care and follow-up
Opportunities

- Clinical trials of vaccines and drugs
- Well characterized clinical cohorts for Long-term sequelae and immunogenicity studies
- Improved diagnostics
- Monkeypox infection in key populations
  - Health Care workers
  - Hunters, Sanctuaries
  - Pregnant/breastfeeding women
- Co-infection (chickenpox, measles, HIV, rubella, etc.)
- Re-infection/Re-activation
- Transmissibility
- Genomic epidemiology of monkeypox
- Ecologic studies to determine host reservoir species
- Expanding active disease surveillance and serosurveys of humans and animals in geographically varied region
Partners

UCLA Fielding School of Public Health

NRB

Institut National de Recherche Biomédicale

University of North Carolina Chapel Hill

République Démocratique du Congo

Ministère de la Santé Publique

USAID | Predict

From the American People

Stanford University

IRD

Institut de Recherche pour le Développement

Metabiota

DTRA

OHSU

Oregon Health & Science University

NIH

National Institutes of Health

UCLA DRC

Health Research & Training Program