# Monkeypox Research : Opportunities for central and west africa

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*Bull. Org. mond. Santé*
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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.*




*Fig. 17.* Poster publicizing the reward of 500 zaires payable to persons reporting the discovery of a confirmed case of human monkeypox, as used in Zaire, 1981–1986 (courtesy of the World Health Organization).



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

| Subregion | 1981 | 1982 | 1983 | 1984 | 1985 | 1986 | Total |
|---|---|---|---|---|---|---|---|
| Mongala | 57 | 51 | 157 | 71 | 57 | 71 | 464 |
| Sud-Ubangi | 64 | 24 | 109 | 58 | 84 | 113 | 452 |
| Sankuru | 22 | 44 | 72 | 49 | 97 | 80 | 364 |
| Kwilu/Kwango | 14 | 21 | 25 | 15 | 31 | 29 | 135 |
| Total | 157 | 140 | 363 | 192 | 269 | 293 | 1,415 |



*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

| Countries | 1980 | 1981 | 1982 | 1983 | 1984 | 1985 | 1985 | Total |
|---|---|---|---|---|---|---|---|---|
| Reporting monkeypox | | | | | | | | |
| Cameroon | 30 | – | 2 | – | – | – | – | 32 |
| Central African Republic | – | – | 2 | 146 | 75 | 105 | – | 328 |
| Côte d'Ivoire | 2 | 6,129[a] | – | 1 | – | – | – | 6,132 |
| Nigeria | – | 1 | 2 | 7 | – | – | | 10 |
| Sierra Leone | – | 3,218[a] | – | – | – | – | 2 | 3,220 |
| Zaire | 1,968[a] | 4,244[a] | 475 | 1,058 | 882 | 656 | 705 | 9,988 |
| Total | 2,000 | 13,592 | 481 | 1,212 | 957 | 761 | 707 | 19,710 |
| Not reporting monkeypox | | | | | | | | |
| Congo | 2 | 2,207[a] | – | – | – | 2 | – | 2,211 |
| Other countries | 30 | 21 | 9 | 7 | 3 | 3 | – | 73 |
| Total | 32 | 2,228 | 9 | 7 | 3 | 5 | – | 2,284 |
| Total: specimens | 2,032 | 15,820 | 490 | 1,219 | 960 | 766 | 707 | 21,994 |
| Total: countries | 14 | 11 | 7 | 7 | 4 | 5 | 2 | |

[a]Includes part of 12,810 serum specimens tested in serologic surveys in Congo, Côte d'Ivoire, Sierra Leone and Zaire.

*Bulletin of the World Health Organization*, **66** (4): 465–470 (1988)


# Human monkeypox: secondary attack rates

Z. JEŽEK,[1] B. GRAB,[1] M. V. SZCZENIOWSKI,[2] K. M.PALUKU,[2] & M. MUTOMBO[2]

secondaires. De plus, il n'y a eu aucun signe d'augmentation du taux d'atteinte secondaire entre les périodes 1970–1980 et 1981–1986.

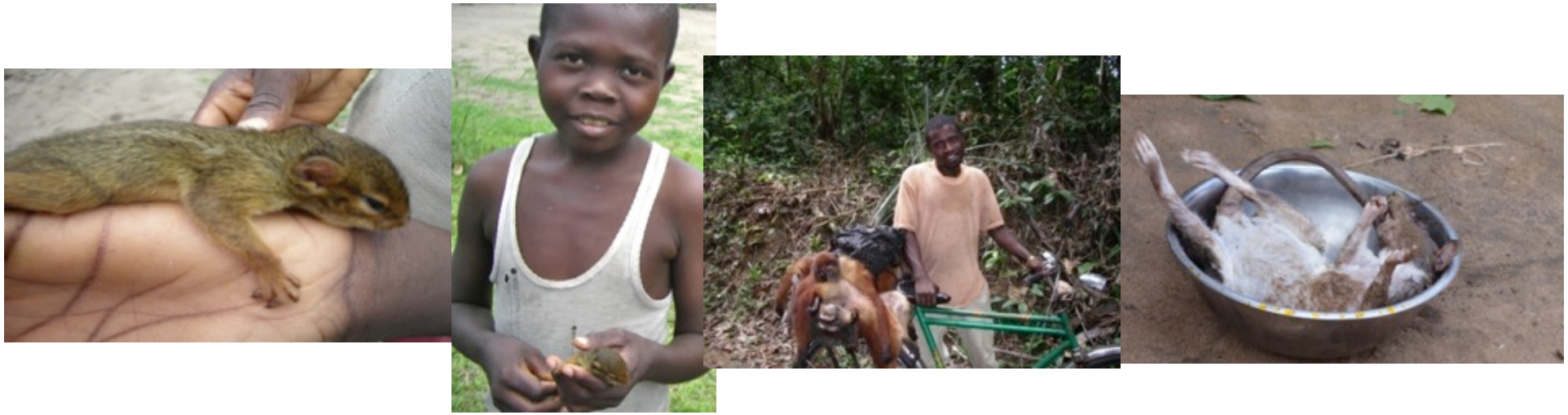
L'inefficacité de la propagation de personne à personne, même dans des conditions d'exposition maximale, confirme l'hypothèse selon laquelle le virus de l'orthopoxvirose simienne est mal adapté à une transmission interhumaine continue et que ce mode de transmission ne constitue pas un problème de santé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

## Outbreak of Human Monkeypox, Democratic Republic of Congo, 1996–1997

**Yvan J.F. Hutin,* R. Joel Williams,* Philippe Malfait,† Richard Pebody,† Vladamir N. Loparev,* Susan L. Ropp,* Mariangelli 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

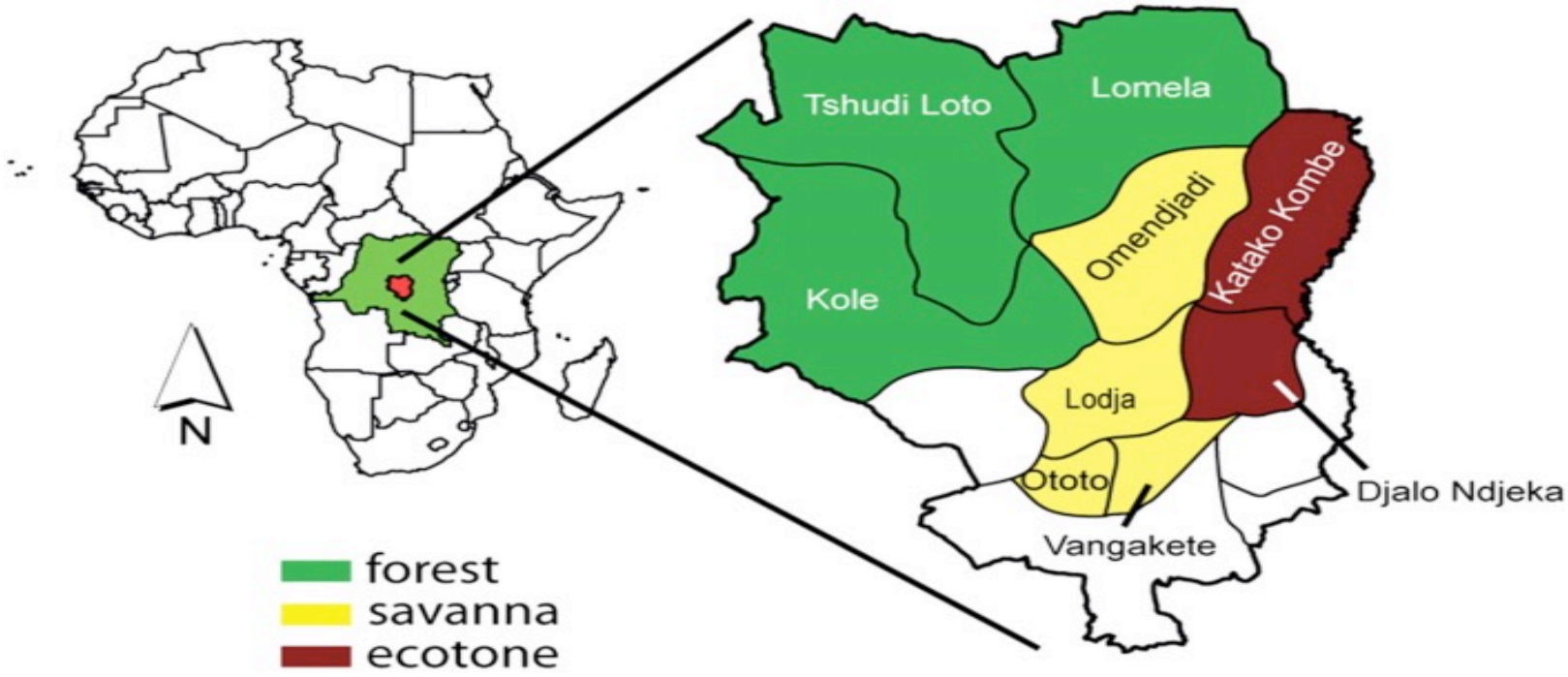
# What we don’t know about human monkeypox



- 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

**Map of health zones with active surveillance for human monkeypox, designated by dominant ecological characteristics, Sankuru District, Democratic Republic of Congo: 2006–2007.**

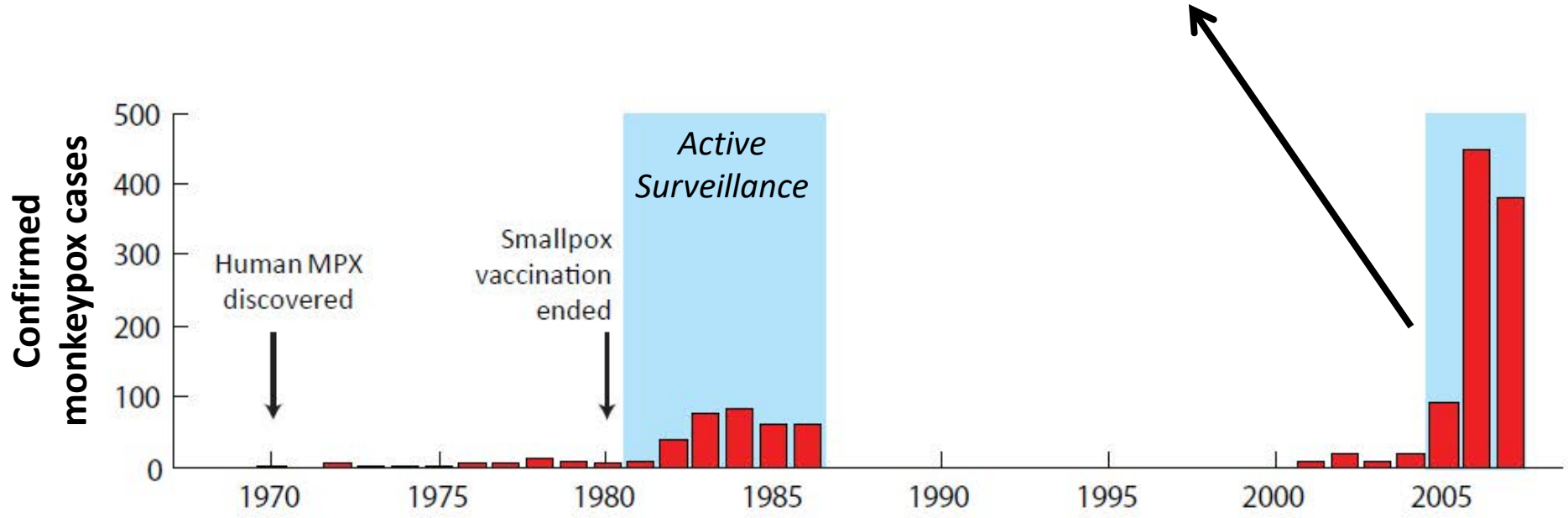



Rimoin A W et al. PNAS 2010;107:16262-16267

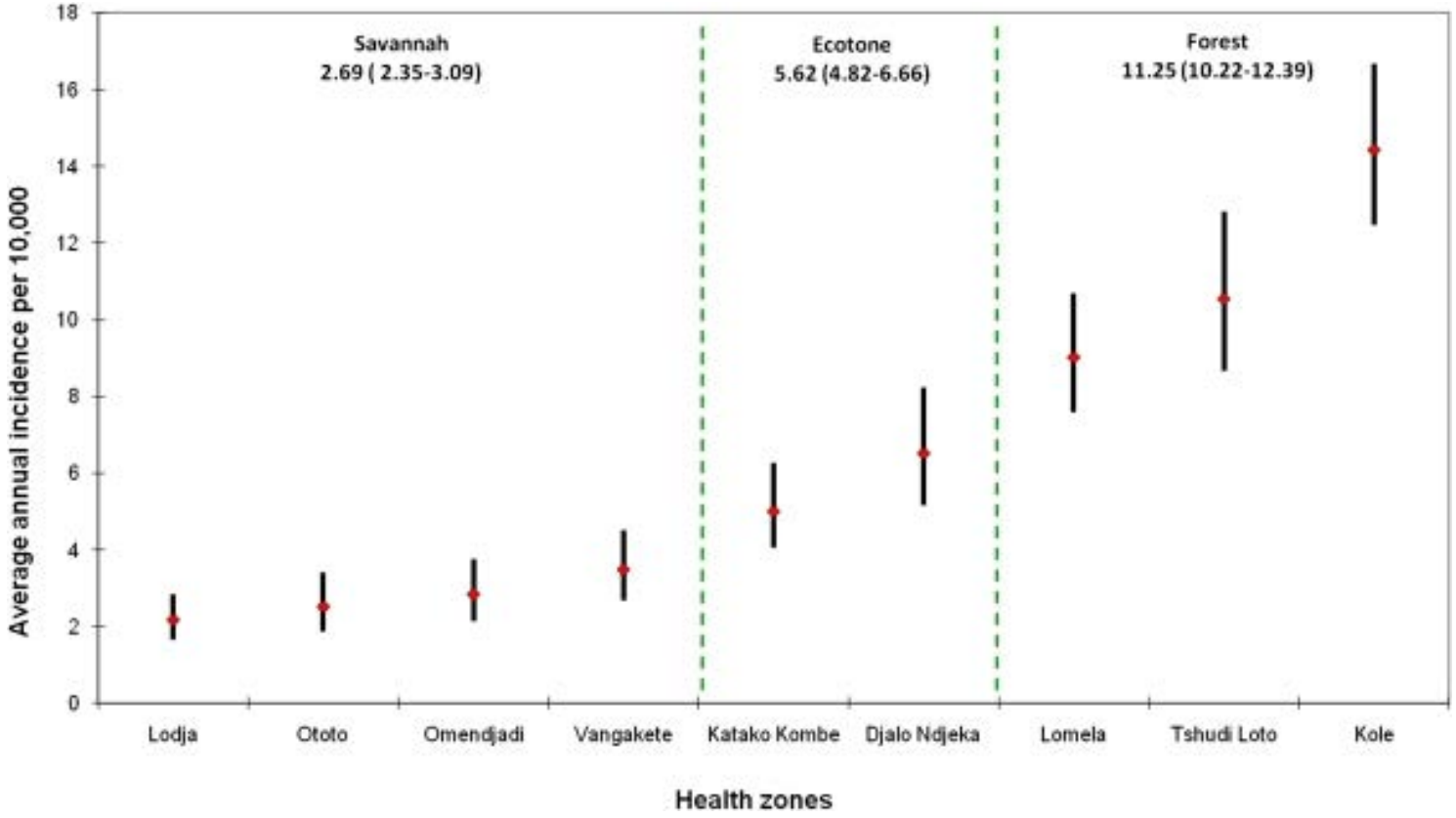
# Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo

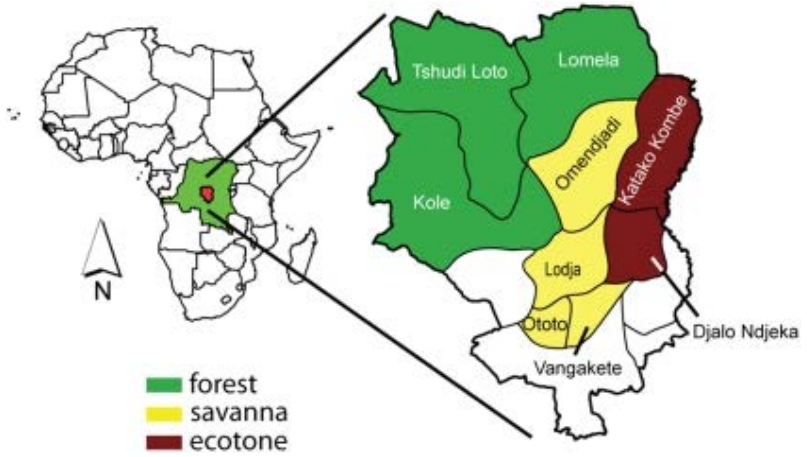
Anne W. Rimoin[a,b,1], Prime M. Mulembakani[c], Sara C. Johnston[d], James O. Lloyd Smith[b,e], Neville K. Kisalu[f], Timothee L. Kinkela[c], Seth Blumberg[b,e], Henri A. Thomassen[g], Brian L. Pike[h], Joseph N. Fair[h], Nathan D. Wolfe[h], Robert L. Shongo[i], Barney S. Graham[j], Pierre Formenty[k], Emile Okitolonda[c], Lisa E. Hensley[d], Hermann Meyer[l], Linda L. Wright[m], and Jean-Jacques Muyembe[n]

per capita incidence increased by factor of 20 (95% CI, 14-29) between 1981-86 and 2005-07.

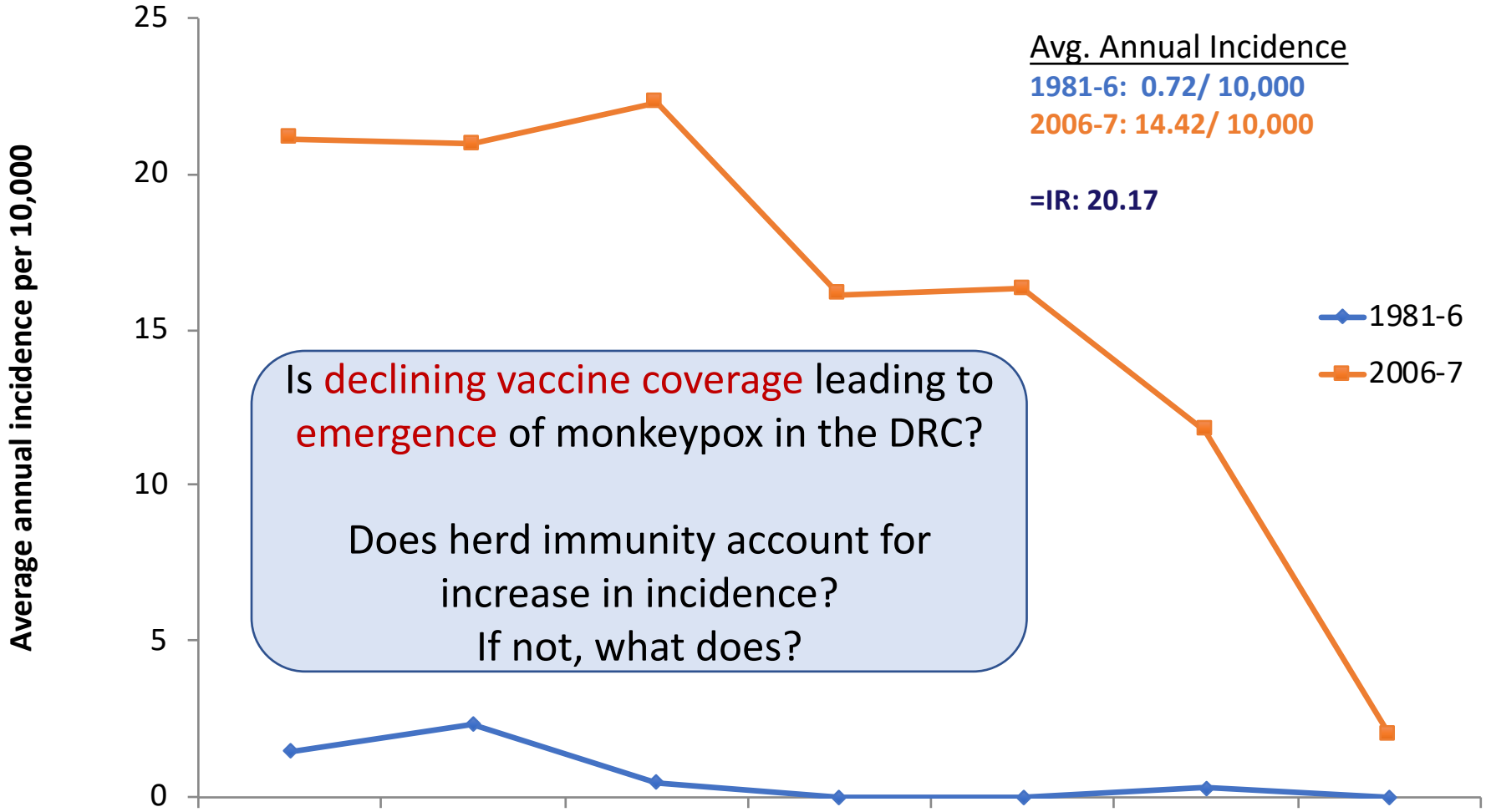


# Average annual cumulative incidence of human monkeypox, by health zone and dominant ecological characteristic, Sankuru, DRC



# Average cumulative incidence of human MPX by age group in Kole Health Zone: 1981-6 vs. 2006-7.



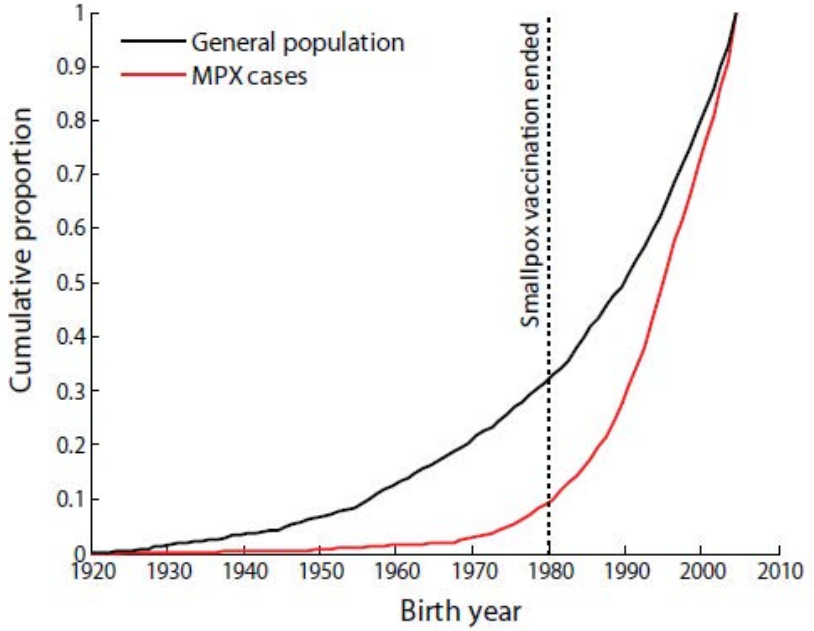

| Age group (years) | 0-4 | 5-9 | 10-14 | 15-19 | 20-24 | 25-29 | 30+ |
|---|---|---|---|---|---|---|---|
| **Population vaccinated* (%)** | | | | | | | |
| 2006-7 | 0 | 0 | 0 | 2 | 24 | 67 | 96 |
| 1981-6 | 16^ | 83 | 94 | 96 | 97 | 97 | 97 |

*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.

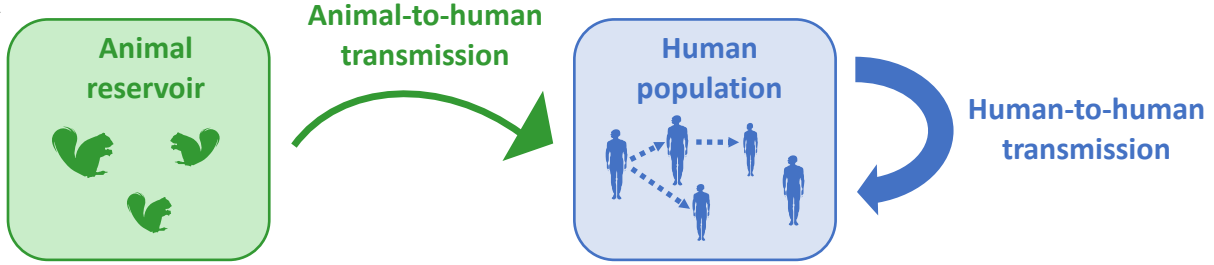



Analysis of data from 2005-2007 shows that smallpox vaccine gives 80.7% (70-89%) protection against clinical MPX infection.
→ **no significant decline over time**.

# 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?***

A

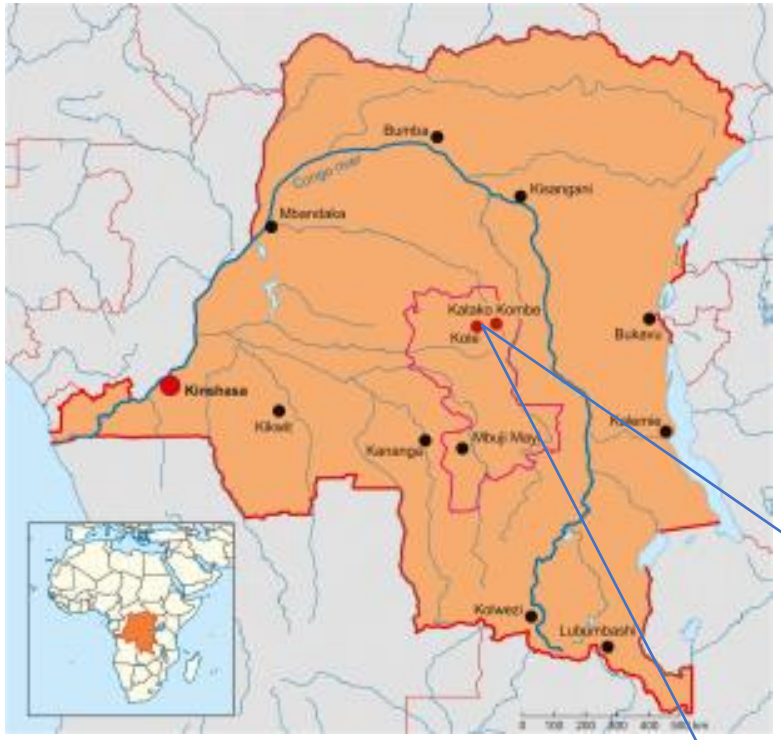



B

| Factor | Leads to increases in… | |
|---|---|---|
| | Animal-human transmission? | Human-human transmission? |
| Declining herd immunity (due to lower vaccine coverage or efficacy) | • | • |
| Increased MPX prevalence in reservoir | • | |
| Increased hunting of reservoir animals | • | |
| Declining immune status due to malnutrition or co-infections | • | • |
| Virus adaptation to humans | | • |
| Possibility of intergenerational transmission | | • |

# 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**

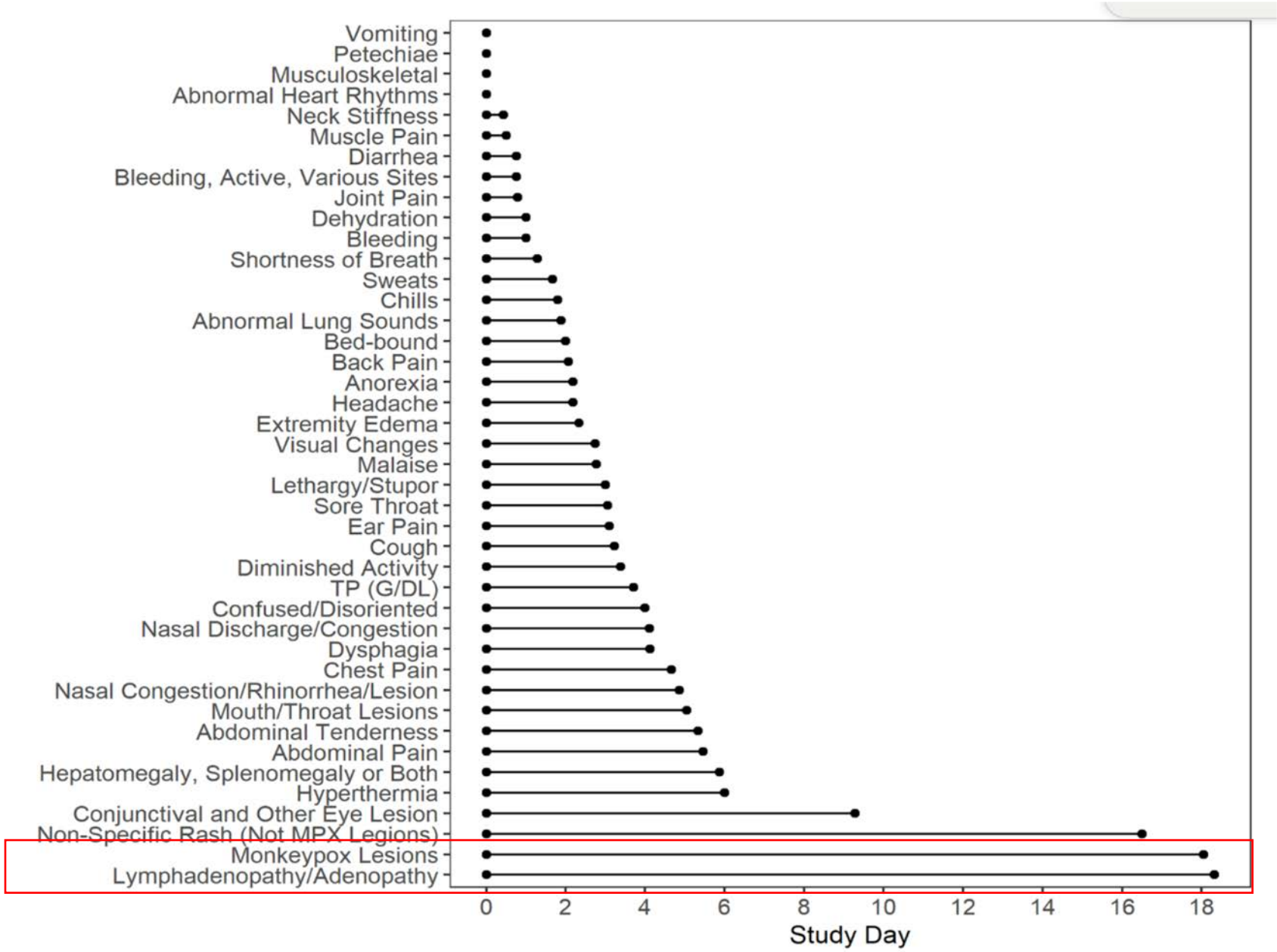
**Clinical symptoms**

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

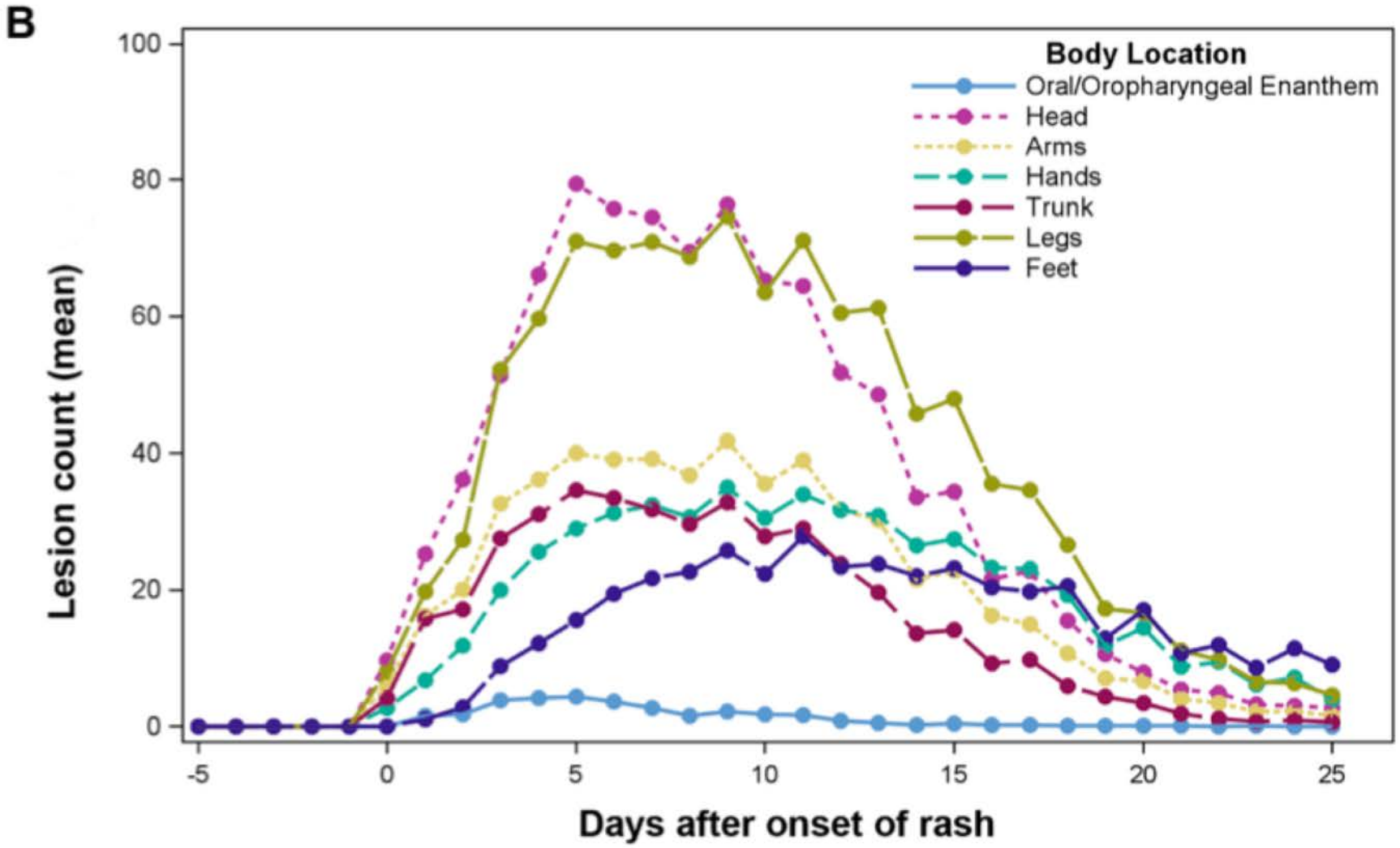
**Physical examination findings or signs**

- 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%)

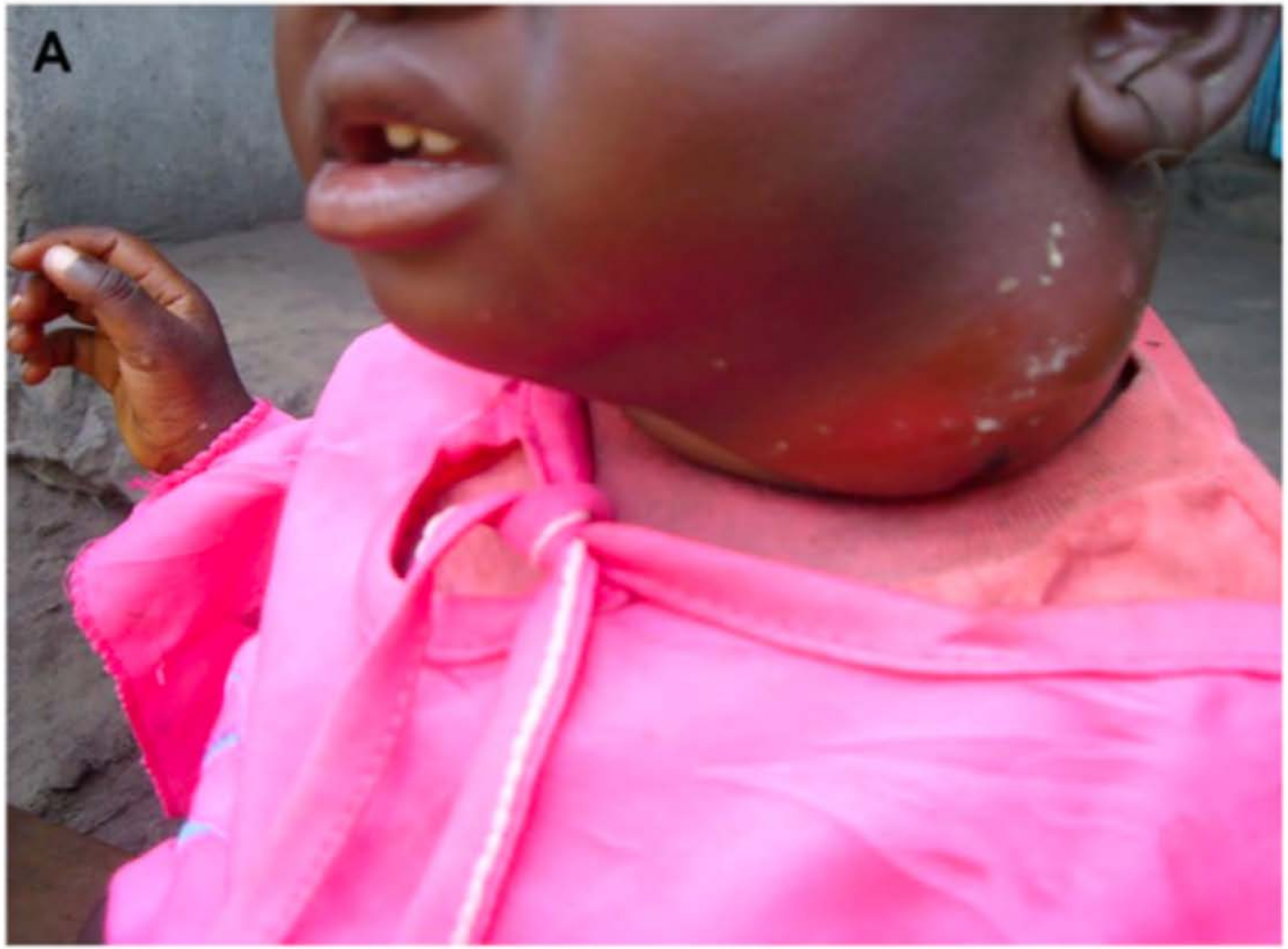
# The duration of clinical symptoms and signs : average 3 – 5 days

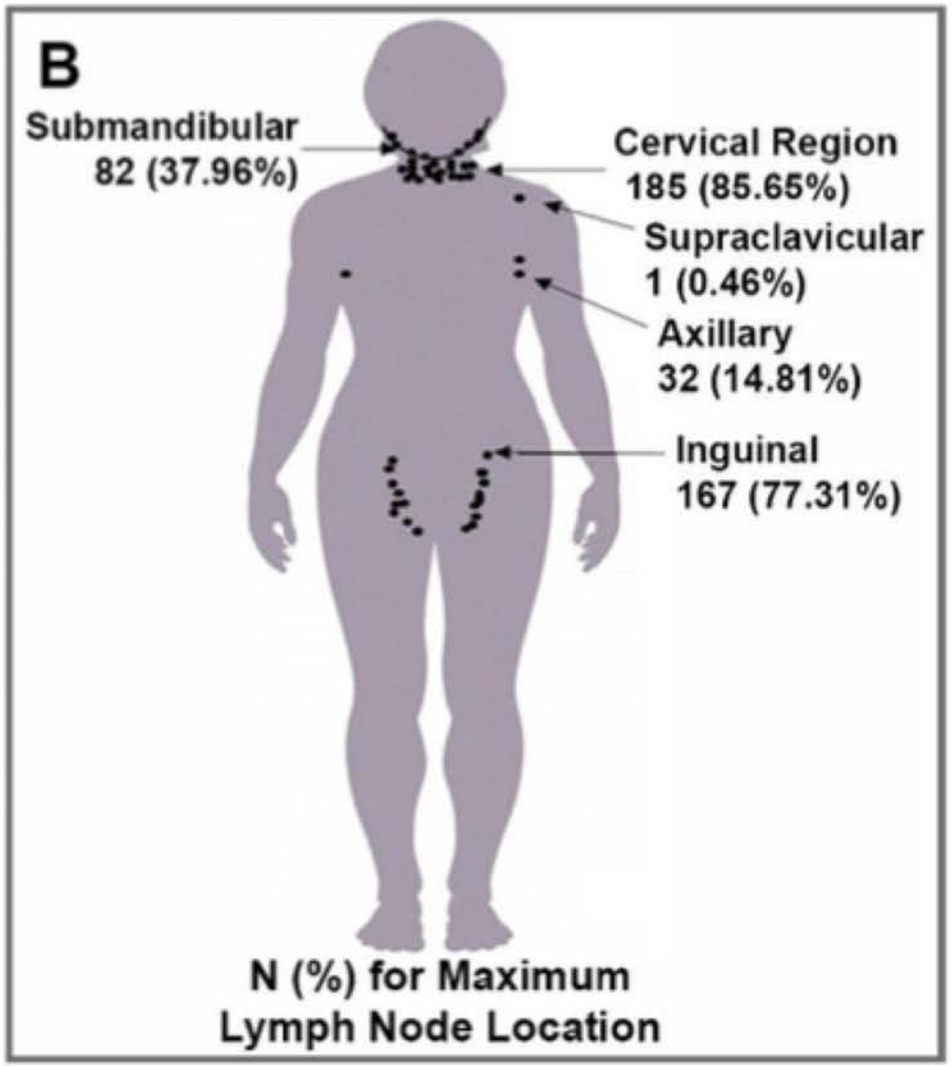


# Change in total lesion count or lesion count by body location over time



# The pattern of distribution of Monkeypox associated lymph node



# Comparison of Maximum lesion count by location among illness severity categories

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

# Clinical laboratory findings
## survivors (levels 1-3) vs. level 4 (death)

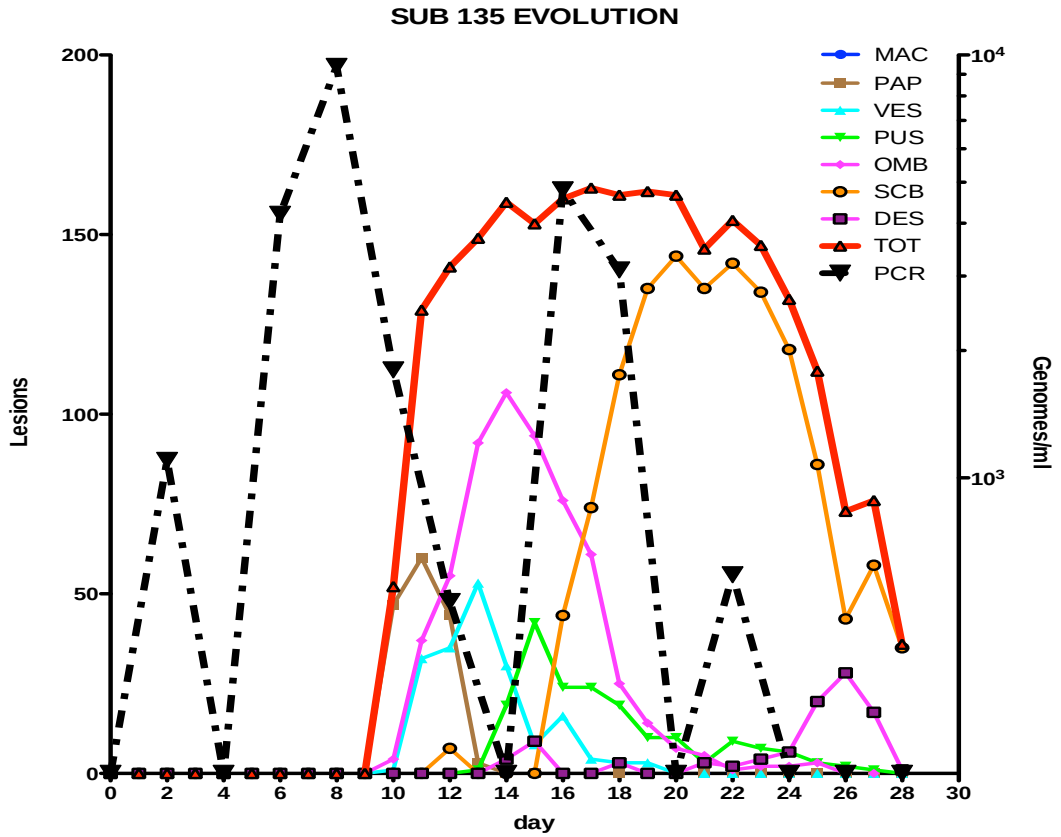
- Statistically significant differences in the **alanine phosphatase (ALT) (90 vs 26 U/L; p = 0.0224, adjusted)** and **aspartate aminotransferase (AST) (415 vs 48 U/L; p = 0.0004, adjusted)**

- 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**

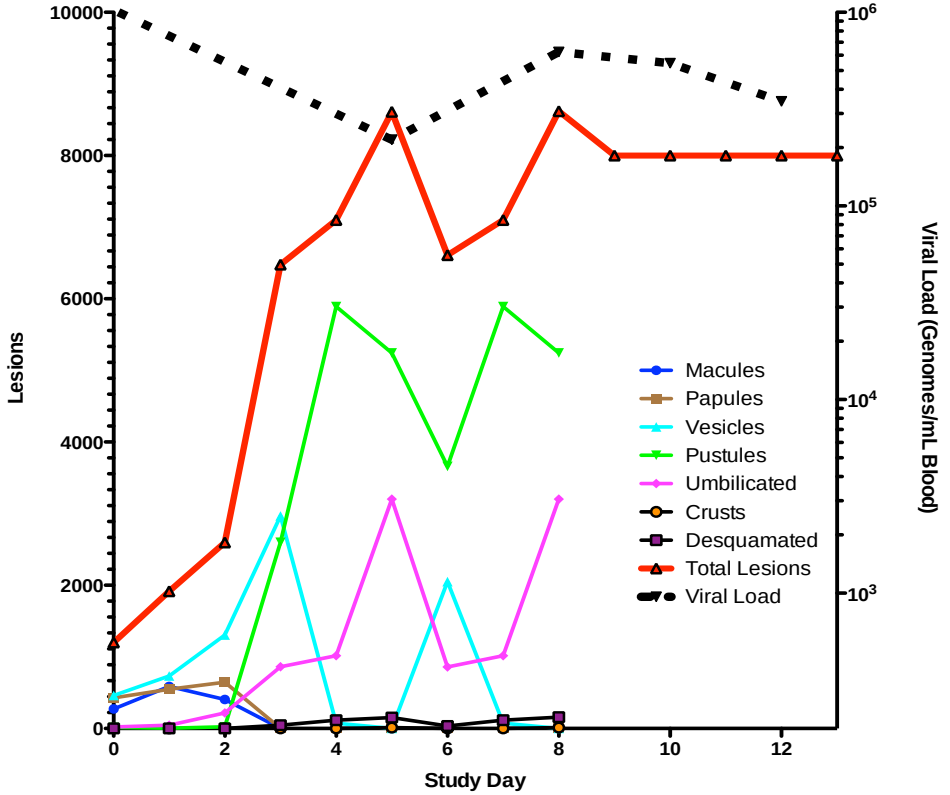
- The **platelet count was 130 x 10^3/µL in the fatal group vs 296 x 10^3/µL among survivors (p = 0.0102, unadjusted)**

- 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.**

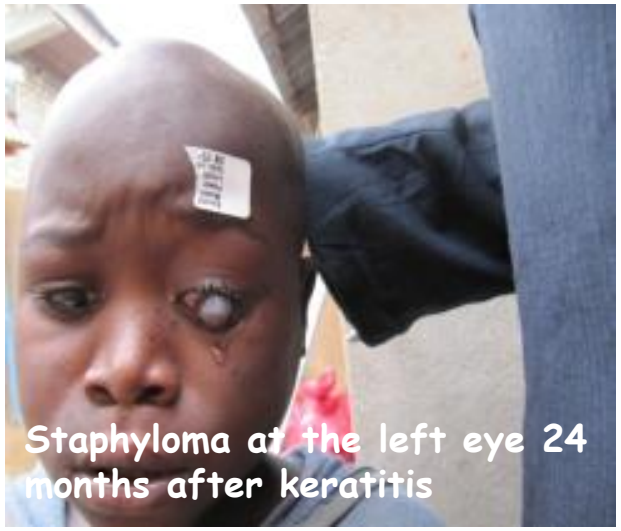


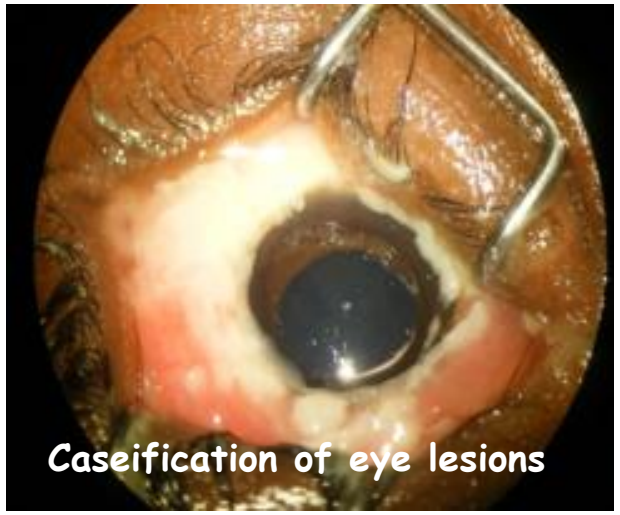

**Lesion Evolution in one fatal case (Subject 54)**



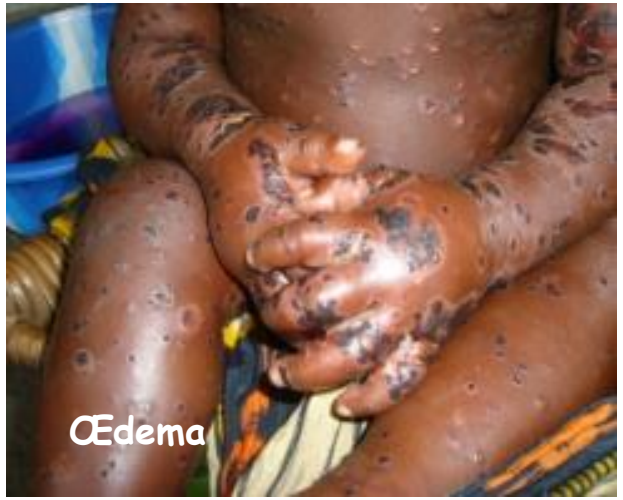
# Complications observed in monkeypox patients


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

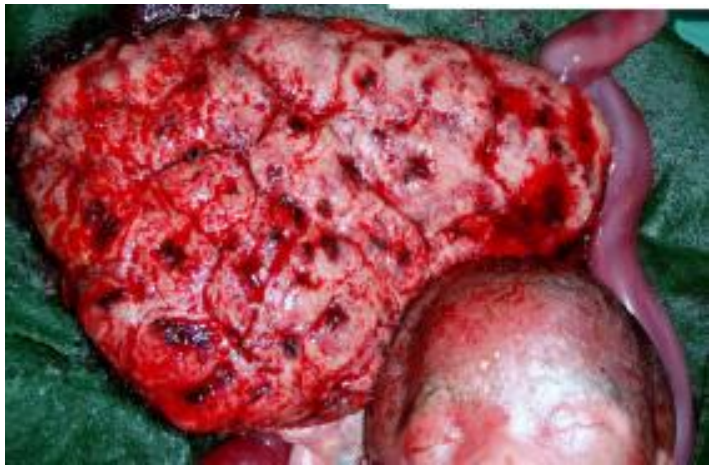
*The Journal of Infectious Diseases*

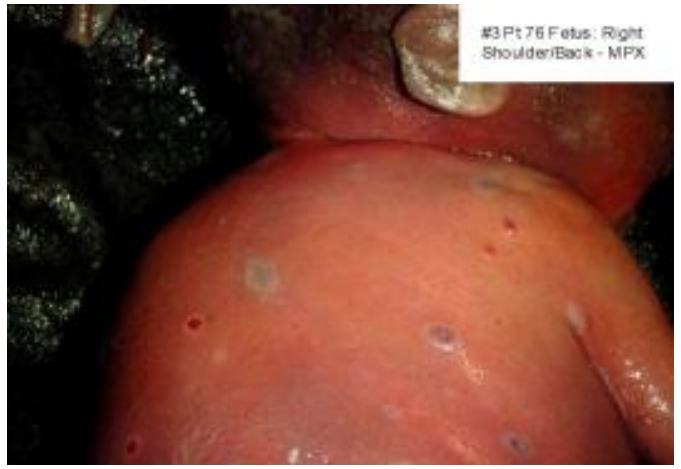
BRIEF REPORT

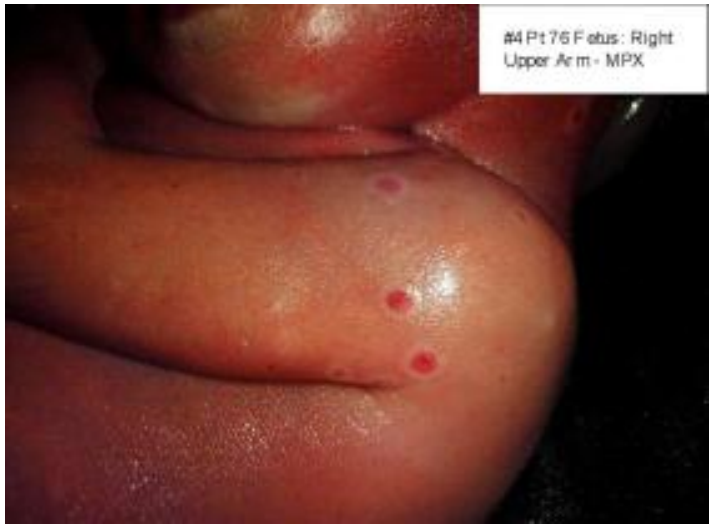
## Maternal and Fetal Outcomes Among Pregnant Women With Human Monkeypox Infection in the Democratic Republic of Congo

Placide K. Mbala,[1,2] John W. Huggins,[4] Therese Riu-Rovira,[3] Steve M. Ahuka,[1] Prime Mulembakani,[2] Anne W. Rimoin,[5] James W. Martin,[6] and Jean-Jacques T. Muyembe[1]

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 HEALT

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