Status of human monkeypox, epidemiology and research...comparisons with smallpox...considerations for emerging orthopoxviruses

Inger Damon M.D., Ph.D.
Chief, Poxvirus and Rabies Branch

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Timeline

- **First observed in captive primate colonies**
  - 8 outbreaks 1958-1968
  - isolated and characterized from primate tissues
  - 1 outbreak in exposed zoo animals (anteater and primates)
  - No transmission to humans

- **First human disease 1970**
  - surveillance activities of smallpox eradication program
  - W. Africa (rare cases, no secondary human to human transmission)
  - Zaire (DRC)

- **Active surveillance Zaire (DRC) 1981-1986 (338 cases)**
  - Majority cases virologically confirmed
  - Human to human transmission

- **Ongoing outbreaks reported from DRC 1996-present**
  - Largely retrospective analyses
  - Minority cases virologically confirmed, use orthopoxvirus serostatus determination
  - Over 500 cases reported

- **First human disease reported outside of Africa, in the U.S. 2003**

- **Enhanced surveillance DRC RoC**
Monkeypox: the virus

• **Species of Orthopoxvirus genus - Member of the Poxvirus family**
  - Other Orthopoxviruses that infect humans – zoonotic except variola
    • Cowpox, vaccinia, variola
    • Ectromelia (mousepox), taterapox (gerbilpox) not known to infect humans
  - Large (~200 kb) complex double stranded DNA virus, cytoplasmic life cycle, brick shaped morphology
  - 95% nucleotide identity amongst species
  - 93% conservation of AA of antigens on viral surface
    • Contributes to efficacy of smallpox (vaccinia) vaccine
    • Serologic tests largely orthopoxvirus generic
Human clinical disease
Zaire experience: 1981-1986

Incubation period 10-12 days (assx), then:
Fever
prodrome: headache
Rash (dev’t ave d2 post fever)
progression
  monomorphic
  pleomorphic
  (40% v, 21% uv)
  “ordinary”/discrete
Mucous membrane lesions
  76% unvaccinated
  47% vaccinated
Lymphadenopathy
  86% unvaccinated
  53% vaccinated
CFR
  9.8% unvaccinated
all deaths occurred in
unvaccinated children <8

Resembles discrete ordinary smallpox

Severities of illness:
# skin lesions, systemic sx
Severe disease:
  74% uv, 39% V

Jezek, Fenner Monographs in Virology 1988
Monkeypox Zaire 1981-1986: transmission

- 245 primary cases (presumed animal source)
- 93 secondary cases (presumed human to human)
  - Majority household contacts
- SAR 40/431 (9.3%) unvaccinated household contacts
- SAR 13/989 (1.3%) vaccinated household contacts

Case control studies to determine primary animal source of infection difficult: multiple contacts

Confirmed cases – animal contact 2 to 3 weeks prior to rash onset (hunting, trapping, skinning, cooking, playing with carcass, eating):
  - Non-human primates (50%)
  - Terrestrial rodents (20%)
  - Antelopes and gazelles (13%)
  - Tree squirrels (7%)
Monkeypox ecology: reservoir?

- **1980’s trapping studies**
  - Orthopoxvirus seroprevalence in African species
    - Funisciuris sp (rope squirrel),
    - Heliosciuris sp (sun squirrel),
    - Lemniscomys (rodent)
    - Lophuromys (rodent)
    - Thamnomys (rodent)
    - Oenomys (rodent)
    - Praomys (rodent)
    - Cercocebus sp (non human primate)
    - Cercopithicus sp (non human primate)
    - Colobus sp (non human primate)
    - Allenopithecus sp (non human primate)
  - Virus isolation
    - 1 Funisciuris species (rope squirrel) with skin lesions in Zaire, area with human disease
## Genus and species of wild-caught animals, Katako-Kombe district, Kasai Oriental, Zaire, February 97

<table>
<thead>
<tr>
<th>Animal Species Processed</th>
<th>Number</th>
<th>Proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Cercopithecus ascanius</em></td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td><em>Cercopithecus neglectus</em></td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td><em>Cricetomys emini</em></td>
<td>19</td>
<td>29.7</td>
</tr>
<tr>
<td><em>Dendrohyrax arboreus</em></td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td><em>Funisciurus anerythrus</em></td>
<td>4</td>
<td>6.3</td>
</tr>
<tr>
<td><em>Funisciurus congicus</em></td>
<td>18</td>
<td>28.1</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>3</td>
<td>4.7</td>
</tr>
<tr>
<td>Domestic pig</td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td><em>Galogoides demidovii</em></td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td><em>Genetta rubiginosa</em></td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td><em>Heliosciurus rufobrachium</em></td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td><em>Lophoromys flavopunctatus</em></td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td><em>Mus minutoides</em></td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td><em>Perodicticus potto</em></td>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td><em>Petrodromus tetradactylus</em></td>
<td>4</td>
<td>6.3</td>
</tr>
<tr>
<td><em>Praomys spp</em></td>
<td>2</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>64</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
April 9th  Shipment from Ghana to Texas

Gambian giant pouched rats  *Cricetomys gambianus*

Dwarf dormice  *Graphiurus murinus*

Sun squirrels  *Heliosciurus sp.*

Striped mice  *Hybomys trivirgatus*

Brush-tail porcupine  *Atherurus africanus*

Rope squirrels  *Funisciurus sp.*
Initial Events U.S. 2003: Pt 1, 2, 3 WI; Pt 4 IL

ill prairie dog, prairie dog owners, exotic pet distributor

- No mortality
- Occupation: 17/47 confirmed/probable cases
  - Vet clinic and pet store workers; none in health care workers
- Human disease acquired from exposure to (ill) prairie dog
  - Household study: daily contact/handling significant risk for illness
- Airborne and contact transmission (Croft et. al. EID 2007)
  - Rapid confirmation
  - Lab diagnostics developed via smallpox preparedness
  - By August, 2003
  - 37 Confirmed Human Cases
    - Virologic, including PCR
  - 10 Probable Human Cases
    - Symptomatic (fever and pustular rash) with known exposure
    - IgM Serologically positive with known exposure, fever OR rash
  - Illness in US appeared less severe than expected
  - No mortality
  - Rare severe cases: encephalitis (JID 2004); pharyngeal edema (PID 2004)
  - No human to human transmission documented

[Image of prairie dog]
Investigations: US outbreak

• Remote smallpox vaccination protective [Hammerlund et al Nat Med 2005]

• Remote smallpox vaccination (>25 years previous) no mitigation of illness severity and/or not protective [Huhn et Al. JID 2005, Croft et. Al EID 2007, Karem et. Al. Clin Vaccine Immunol 2007]

• Route of infection associated with illness manifestations [Reynolds et. Al. JID 2006]
  – “Complex” invasive exposures associated with more rapid progression and disease severity

• Behaviors: Direct exposure (handling) or cleaning prairie dog cage associated with enhanced risk for infection [Reynolds et. Al. EID 2007]
  – Consistent with previous considerations in Africa: meat preparation, peridomestic pests

• Anti-OPXV-IgM marker for recent orthopoxvirus infection [Karem et. Al. J Clin Invest 2003]
  – OPXV “ naïve” or previously vaccinated persons
  – Titers to 1 year in ~60% of persons
Human case patient

June 2003

Impfondo, Republic of Congo

6 chains of human to human transmission inferred: household and hospital; 11 probable or confirmed cases tested at CDC; 1 death

Maximum parsimony analysis of complete genomes:

CLADOGRAM

Bootstrap value

Absolute genetic distances

*Likos et.al. JGV 2005*
2 clades: distinctive clinical presentation, epidemiology, and genomics

- Comparative epidemiology: U.S. outbreak 2003 (W African clade) and DRC investigations 1981-1986 (Congo Basin clade)
  - human disease was more transmissible and more severe among DRC than US case-patients
    - independent of patient age and vaccination status.

- Laboratory – convenience sample
  - Viral DNAemia more protracted in RoC case patients than in U.S. case patients

- Laboratory – C Basin clade virus more virulent in aerosol exposure non-human primates

- Identify a subset of host range or host response modifier proteins deleted or predicted to be non-functional in W African clade
  - Could differentially effect viral recognition and clearance
    - complement control protein
    - Ortholog of myxoma virulence factor
    - IL-1 binding protein
    - others

monkeypox virus - prairie dog model of human systemic monkeypox/orthopoxvirus infection

- **West African MPX**
  - LD50 intranasal $5.9 \times 10^3$
  - Intradermal (id, $4 \times 10^5$) or intranasal (in, $4 \times 10^5$)
  - Objective:
    - Viremia precedes rash
    - Generalized rash day 9/12 id, d12 in
      - id#=7-17 (ave 11.5)
      - in#=3-10 (ave 5.5)
    - 4/4 survive (id)
    - 4/4 survive (in)
    - Viral shedding to day 15-21

- **Congo Basin MPX**
  - LD50 intranasal $1.3 \times 10^5$
  - Intradermal (id, $4 \times 10^5$) or intranasal (in, $4 \times 10^5$)
  - Objective:
    - Viremia precedes rash
    - Generalized rash day 9-12
      - id#=8-28 (ave 15)
      - in#=5-12 (ave 6.75)
    - ¾ survive (in)
    - 2/4 survive (id)
      - Deaths days 11-13
    - Viral shedding to day 18-21

# = lesions on face + Inner leg

Hutson et al JGV 2009; Hutson et al Virology 2010
Rash progression
Model system

• Evaluate therapeutics
  – ST-246 trial completed

• Evaluate vaccines
  – Also as post exposure prophylaxis

• Evaluate pathogenesis
  – Host response modifier predictions
Digital image from Sudan (late 2005), outside the recognized range of monkeypox

Need for education and training in recognition and diagnosis of systemic orthopoxvirus infections

- Enhanced surveillance
- Laboratory-based surveillance
- Community outreach
Surveillance

Tshuapa District, Equateur Province

- Area: ~1/2 size of France
- 12 health districts
- Est. population 1.5 million
- Reported cases MPX (MOH)
  - 2006: 266 (2.3% mort.)
  - 2007: 233 (4.9% mort.)
  - 2008 through Sept: 666 (5.1% mort.)
  - 2009* through April: 230 (5.2% mort.)

Drs. Robert Shongo, Marcel Balilo

Current estimated annual incidence

- Assume: 60 cases/month
- Assume: 50-70% accuracy clinical dx
- 2.4 - 3.6 /10,000 (~5% mort.)

Data sources
- National Institute for Biomedical Research (INRB)
- Dr. Jean J. Muyembe
- Dr. Elizabeth Pukuta
- Dr. Placide Mbala

National Program to Combat Monkeypox and Hemorrhagic FEVERs
- Dr. Robert Shongo, Marcel Balilo

(*) Ave. 65.5% failure in reporting of general health statistics noted for period Jan-April across health zones
Monkeypox Project

Resulting Videos:
Monkeypox - Testimony
Understanding Monkeypox

Country:
Republic of Congo

Summary:
INCEF has expanded its work on raising awareness of zoonotic diseases (diseases that pass from animals to humans and vice versa) through a collaboration with the Center for Disease Control in Atlanta Poxvirus and Rabies Branch.

Monkeypox is a rare viral disease that occurs mostly in central and western Africa. It is called "monkeypox" because it was first found in 1958 in laboratory monkeys. Blood tests of animals in Africa later found that other types of animals probably had monkeypox. Scientists also recovered the virus that causes monkeypox from an African squirrel. These types of squirrels might be the common host for the disease. Rats, mice, and rabbits can get monkeypox, too.

Monkeypox was reported in humans for the first time in 1970.

INCEF has produced two films for dissemination on a village by village basis addressing the cause and repercussions of the most recent outbreak in the Likouala Region of the Republic of Congo in 2003, and giving scientific explanation of the...
Diagnostics

• **Nucleic acid**
  – *Pan poxvirus* (Li et al. J Clin Micro 2010)

• **Seroologic**

• **Reference center vs. field use?**
Is the geographic distribution of monkeypox static?

- **Evidence against**
- **U.S. outbreak 2003** – *global commerce can introduce virus to non-African susceptible species*  

- **Sudan** [Damon, Chowdury, Roth NEJM 2006]
  - *Imported virus vs. unrecognized endemic virus*

- **Models of distribution based on human disease (Africa)**
- **Models of potential distribution of susceptible species**
Ecological Niche Modeling

**Geographic Space**
- occurrence points
- Native range prediction

**Ecological Space**
- Modeling Algorithm
- Environmental variables
- Model of niche in ecological dimensions
- Projection back onto geography

**Environmental variables**
- temperature
- precipitation
Predictions of possible human monkeypox disease prevalence using GARP models - 2

Ecological variables of importance: mean annual precipitation, flow direction, land cover

Levine et. al. PLOS 2007
Modelled distribution of one implicated species

Peterson et al 2006, Perry et al 2006
Although two phylogenetically distinct clades are apparent, they appear to occupy similar ecological niches.
Molecular clock (coalescent) analyses suggest variola, the causative agent of human smallpox, diverged from a zoonotic ancestral virus as early as 16,000 to 68,000 years ago.

Alt: as early as \(~1500\) years ago

Li et. al PNAS 2007
Distinct orthopoxvirus evolutionary lineages variola and monkeypox viruses

Chen et. Al. Virology 2005

138 kb core region (VAC COP C7L-A51R)
Parsimony analysis
1000 bootstraps
Can monkeypox occupy the niche left by variola eradication?

- Viruses with distinct evolutionary lineages
- Human to human transmission vs. CFR as “phenotypes” to consider
- Consider interhuman $R_0$
  - Variola “3-5”
  - Monkeypox <1 (Fine et.al. 1988) – contain sustain without repeated animal introductions
  - Changes since 1980 studies of monkeypox?
    - Increased “secondary” human cases observed in the 1990’s (WHO Technical Advisory Report 1999, Breman Emerging Infections v4, Nalca et. Al. CID, 2005)
    - Increased population of susceptibles (cessation routine smallpox vaccination in 1980)
    - Changes in the virus?
- Interhuman Transmission in RoC 2003 efficient
  - 6 generations uninterrupted H-H transmission
  - 4 generations (1980’s) longest previously documented
- Surveillance system differences?
- Genetic changes?
- Immunity?
- Behavioral changes?
“Serosurvey” 2006 – Likuola region
Republic of Congo

- High seroprevalence of anti-orthopoxvirus reactivity
  - 49.1% in population <25 (no prior vaccination)

- “recent” focus of monkeypox virus exposure in Gangania
  - rash not associated with +IgM – subclinical infections?
    - Route of exposure
    - Exposure dose
    - Species of animal source of exposure

- Alternative hypothesis – infection with other non-pathogenic orthopoxvirus(es)

Lederman E. et. Al. AJTMH 2007
A Silent Enzootic of an Orthopoxvirus in Ghana, West Africa: Evidence for Multi-Species Involvement in the Absence of Widespread Human Disease

Mary G. Reynolds,*† Darin S. Carroll,† Victoria A. Olson, Christine Hughes, Jack Galley, Anna Likos, Joel M. Montgomery, Richard Suu-Ire, Mubarak O. Kwasi, J. Jeffrey Root, Zach Braden, Jason Abel, Cody Clemmons, Russell Regnery, Kevin Karem, and Inger K. Damon

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No active human cases
Human (age < 20) OPXV IgG seroprevalence +++

Map courtesy of Rebecca Levine
Monkeypox: The Unanswered Animal Questions

- Where does the virus live in nature?
  - Reservoir?
  - Distribution?
  - Seasonality?
  - Importance of reservoir vs. intermediate hosts in transmission to humans?

- Rodents
  - Cricetomys, 2 species (gambianus, emini)

- Graphiurus, 14 species (parvus, olga, kelleni, murinus, microtis, lorraineus, christyi, surdus, crassicaudatus, platyops, rupicola, hueti, monardi, occularis)

- Funisciurus, 9 species (carruthersi, isabella, lemniscatus, congicus, bayonii, substrriatus, leucogenys, pyrrhopus, anerythrus)

- Heliosciurus, 5 species (ruwenzorii, gambianus, rufobrachium, mutabilis, undulatus)

- Non human primates
  - Cercocebus, Cercopithicus, Colobus, Allenopithecus spp
Summary thoughts

• monkeypox is a “living” model for evolution/emergence of human pathogenic orthopoxviruses (R.Regnery)

• monkeypox is an example of a zoonotic disease virus whose emergence/existence in the human population needs to be understood in the context of
  – The virus
    • Factors affecting transmission
    • Factors affecting pathogenicity
  – animal populations (examples: reservoir host(s), transmitting host(s))
  – Human populations
    • Acquired and genetic factors
  – the larger ecosystem
    • Behaviors which lead to human infection or disease
    • Barriers for virus survival
    • Other endemic orthopoxviruses?

• this knowledge will provide the “evidence” for (human) disease control and prevention efforts
  – Vaccination – use of less reactogenic vaccines?
  – Education
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JJ Muyumbe (INRB)
Elizabeth Pukuto (INRB)
Questions – contact Inger Damon idamon@cdc.gov

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.