CMED/EPI 526 – Spring 2009

Introduction

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CMED/EPI 526 – Spring 2008

Definitions: "Zoonosis" (pl. *zoonoses*, adj.*zoonotic*)

- "A disease that can be transmitted to man by vertebrate animals." (*Webster*)
- "An infection or infectious disease transmissible under natural conditions from vertebrate animals to man." (*JM Last, A Dictionary of Epidemiology*)
- "Diseases common to man and animals" (*Acha Szyfres)*

Types of Zoonotic Diseases

- Viruses
- Rickettsia
- Bacteria
- Protozoa
- Fungi
- Helminths
- Arthropods

Types of Zoonotic Diseases

- Zoonoses Transmitted by:
  - **Direct Contact**
  - **Alimentary (Foodborne and Waterborne) and**
  - **Aerogenic (Airborne) Routes**
- Zoonoses Transmitted by:
  - **Hematophagous Arthropods**
- Sapronoses (no vertebrate animal required)

Population Biology of Emerging and Re-Emerging Pathogens

Reference: MEJ Woolhouse. *Trends in Microbiology* 2002;10(10):S3-7

- *n* = 1415 human pathogens are known to date
- Causing 14 million human deaths per year globally
- *n* = 868 species (61% of total) of pathogens are zoonotic
- Most zoonotic agents are from ungulate (hooved mammals), carnivore, and/or rodent reservoirs of infection
- Zoonoses according to taxonomic class;

  > 95% of helminths, 38% of fungi, 84% of RNA viruses,

  > 36% of DNA viruses, 100% of rickettsia, 48% of bacteria

"Emerging" Definitions

- Emerging Pathogens = Increasing incidence in a new host population
- Re-Emerging Pathogens = Increasing incidence in an existing host population due to longer term underlying changes in epidemiology
- 75% emerging and re-emerging pathogens are zoonotic (↑vector-borne, ↓helminths)
- Subjective criteria often used in calling them "emerging"
- Possibility of reporting bias

Sources of Emergence

- From within the host population
- From the external environment
- From other host species

Reasons?

- Genetic changes in the pathogen
- Immunocompromised hosts
- Changes in host-pathogen ecology

➔ Host demography, movement, behavior, climate, land use changes, food production technology

Bushmeat Hunting, Deforestation, and Prediction of Zoonotic Disease

Nathan D. Wolfe,* Peter Daszak,† A. Marm Kilpatrick,† and Donald S. Burke*
*Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; and †Consortium for Conservation Medicine, New York, New York, USA

Three criteria predicting which microbes are most likely to emerge … Microbes that have a proven ability to :

1)Lead to human pandemics
2)Lead to panzootics in (nonhuman) animal populations
3)Mutate at high rates and recombine with other similar or dissimilar microbes.

➔ The high mutation rates of **RNA viruses** and their predominance within zoonotic emerging infectious diseases that are transmitted from human to human suggest that this group is a key candidate for future emergence

Emerging Infectious Disease Vol. 11, No. 12 December 2005

Public Health Strategies for Emerging Diseases

- Adequate diagnostic tools
- Well-designed surveillance systems
- Adequate infra-structure and human resources
- Effective local and global coordination
- Integration of medical and veterinary surveillance
- Shortage-market of properly trained professionals

Other UW Courses on Emerging Diseases

PABIO 201 - Newly Emerging Diseases in Public Health

EPI 520 - Epidemiology of Infectious Diseases

EPI 529 - Emerging Infections of International Public Health Importance

A Real-World Scenario...
Midwestern State Dept of Public Health

Patient #1: May 16

- 3 year-old girl hospitalized with cellulitis and fever
- Broad-spectrum antibiotics prescribed, (non-responsive)
- Bitten by newly acquired wild rodent pet
- Animal purchased on May 13 from a local swap meet
- Animal died on May 20, bacterial cultures found gram-negative bacillus
- Differential: Tularemia??? Plague???

Example skin lesions

Midwestern State, USA

Varicella?

HSV?

Cowpox?

Smallpox?

Vaccinia?

Patient #2: May 26

- Adult male meat-inspector
- Also worked as a wild and exotic animal distributor
- Bitten and scratched on May 18 by same rodent species
- Hospitalized on May 31
- Fever, chills, sweats, lymphadenopathy

Patient #2: June 3

- Public Health Dept. learned that Patient #2 sold two of these animals to the family of Patient #1
- Diagnostic tests: EM, PCR, DNA sequencing, VI, IHC

You are the Public Health Officer...

... What do you want to know ?

The pet…..

Species?

Origin?

Species?

Black-tailed prairie dog

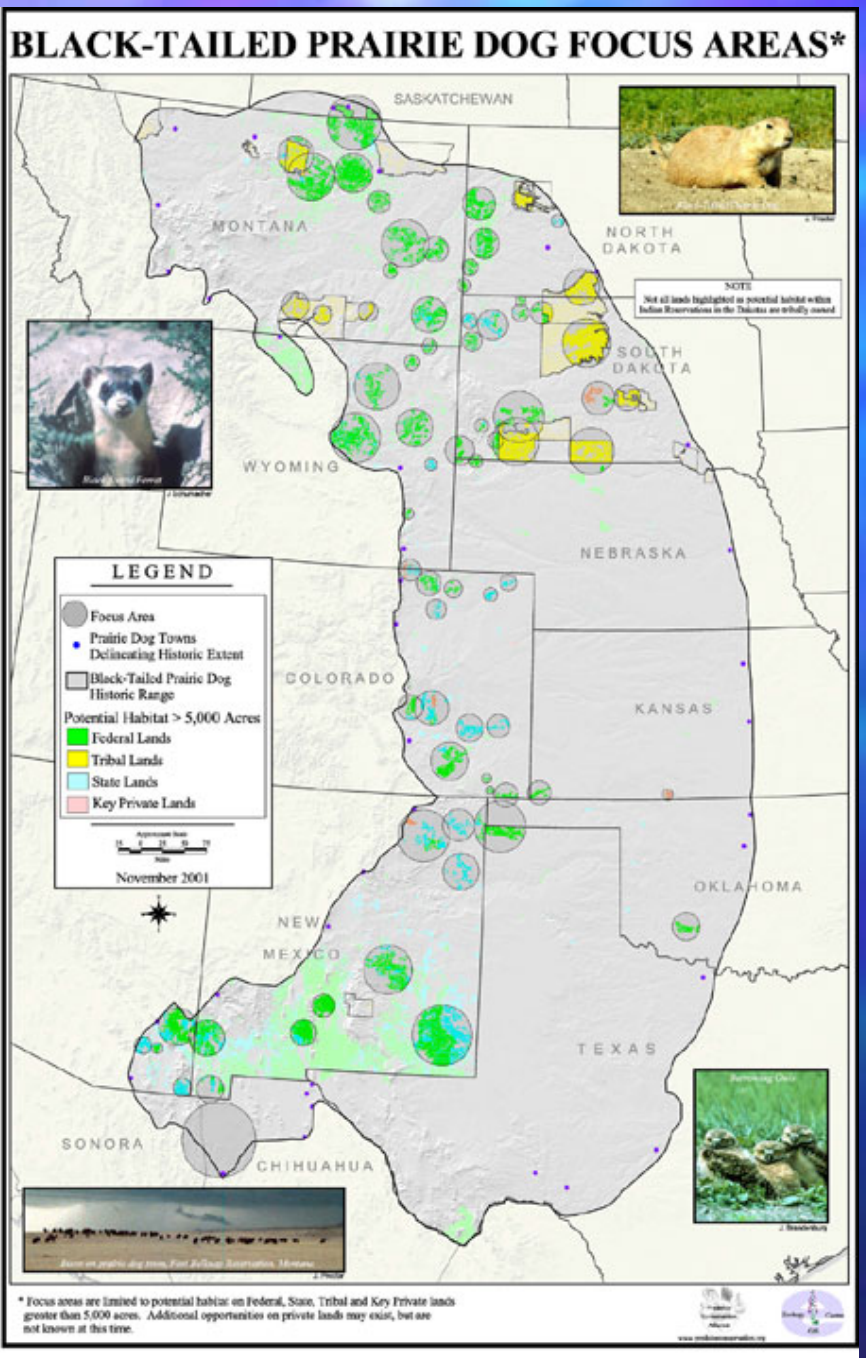
Cynomus ludovicianus

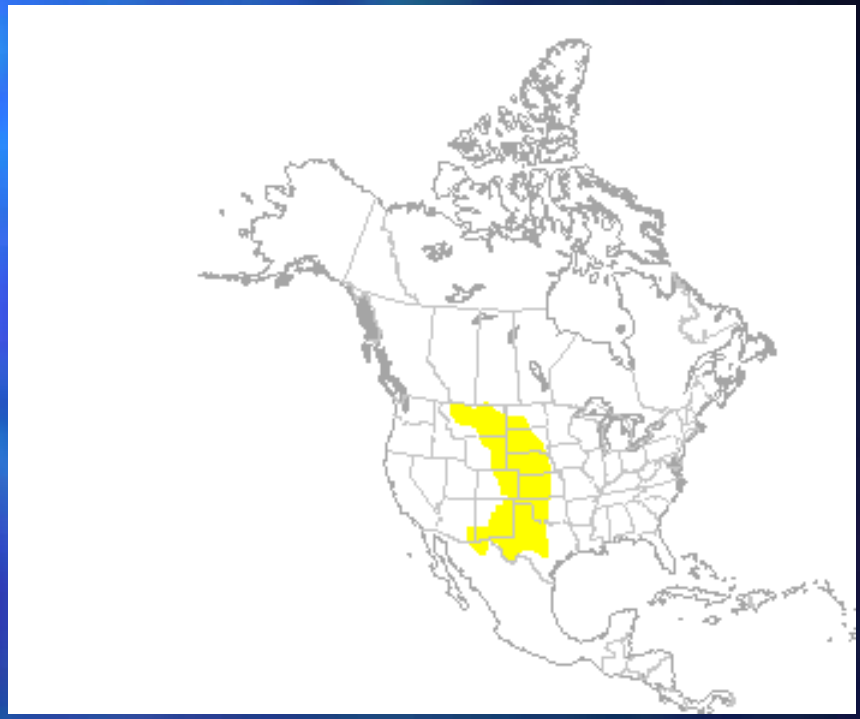
Origin?

Great plains of N. America

“Pups” born April-July

BLACK-TAILED PRAIRIE DOG FOCUS AREAS*





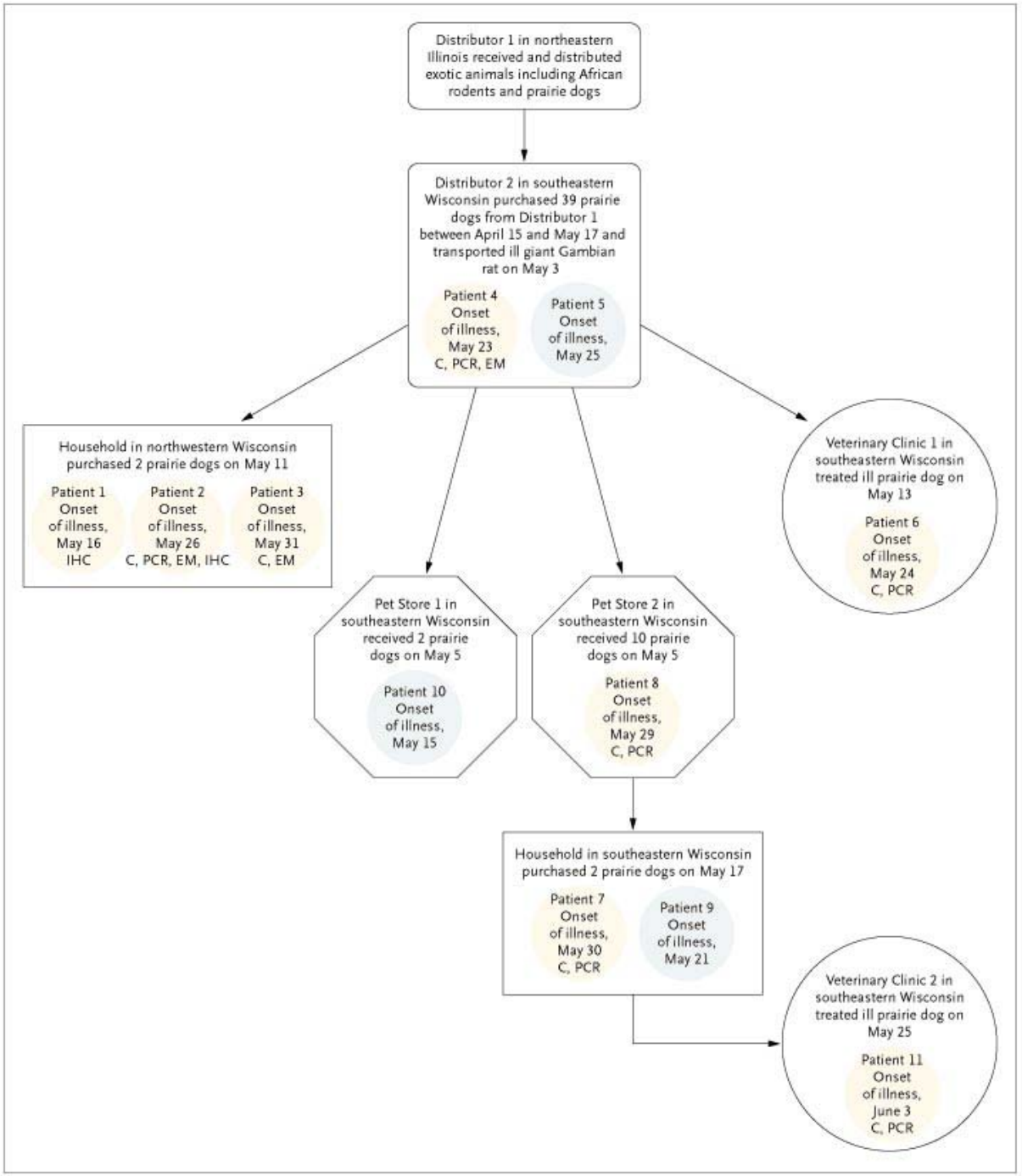
Trivia Question: Prairie dog towns may extend over 1000 acres, each divided into wards. Individual family groups live within wards, known as “coteries”.

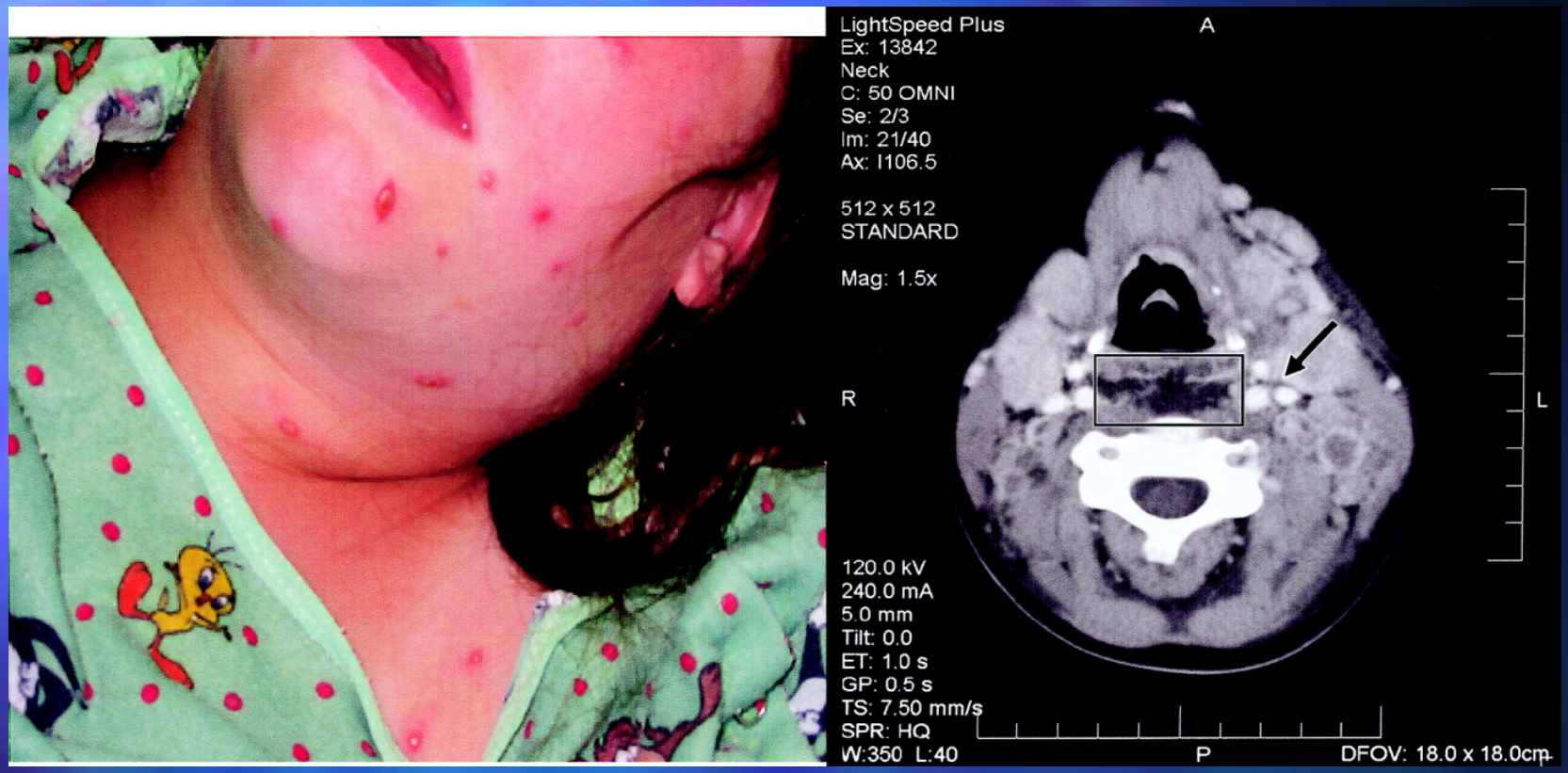
The outbreak continued!

- Trace-back and Trace-forward
- 9 more cases within 3 weeks
- Overall, 5 males, 6 females
- Age range 3-43 years (median=28)
- Patients #1 and #4 were bitten or scratched by an ill prairie dog
- What do you want to do now?

Notes:

- All linked to Distributor #1
- Veterinary staff
- Multiple cases within households
- Person-to-person?
- Animal deaths
- Poor records for trace-back!





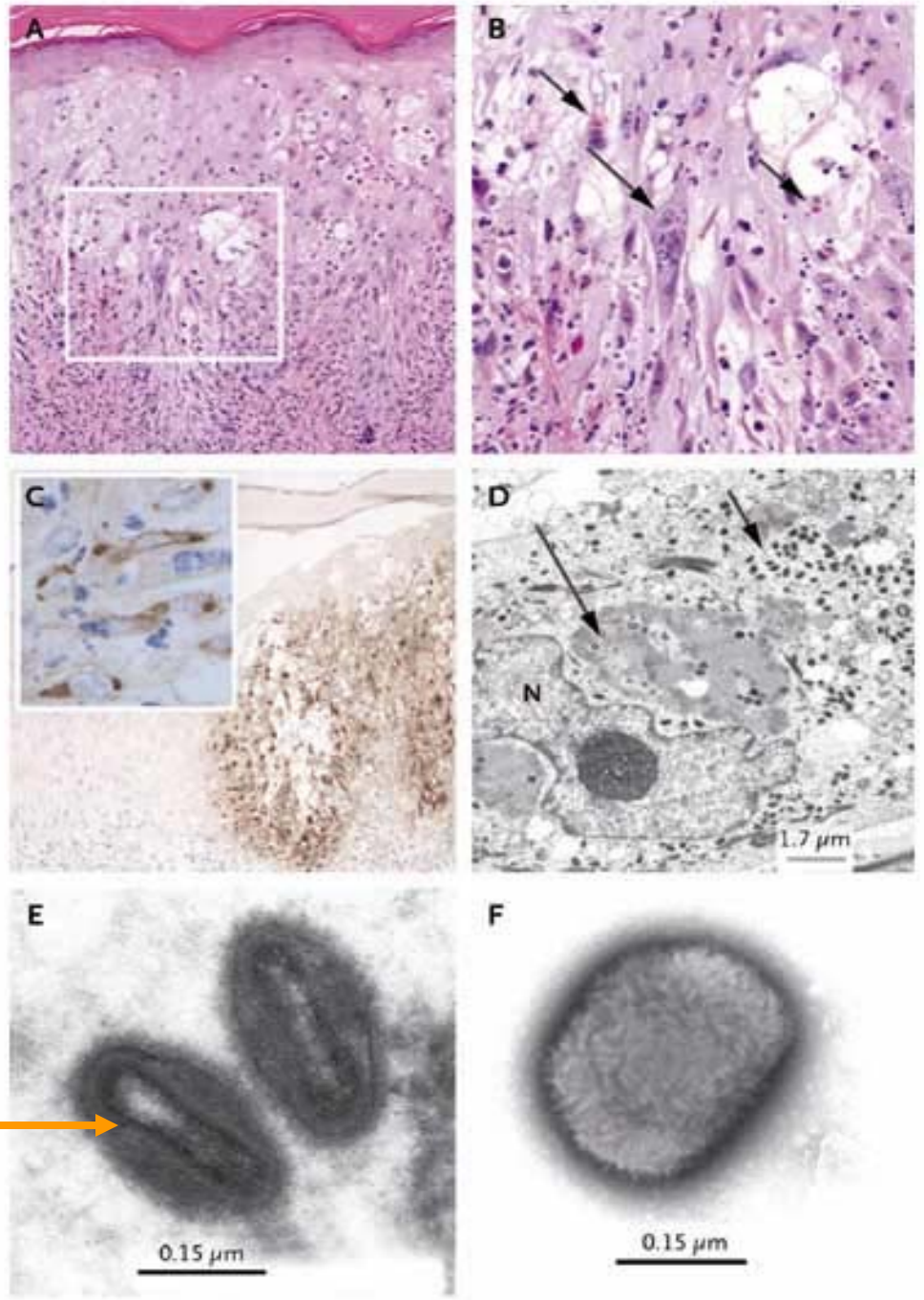
10 year-old ICU hospitalized girl with characteristic lesions along with tracheal airway compromise secondary to a large retropharyngeal abscess and cervical lymphadenopathy.

Histologic, Immunohistochemical, and Ultrastructural findings from skin biopsy of Patient #2

All are indistinguishable from smallpox lesions!

Note:

Dumb-bell shaped core

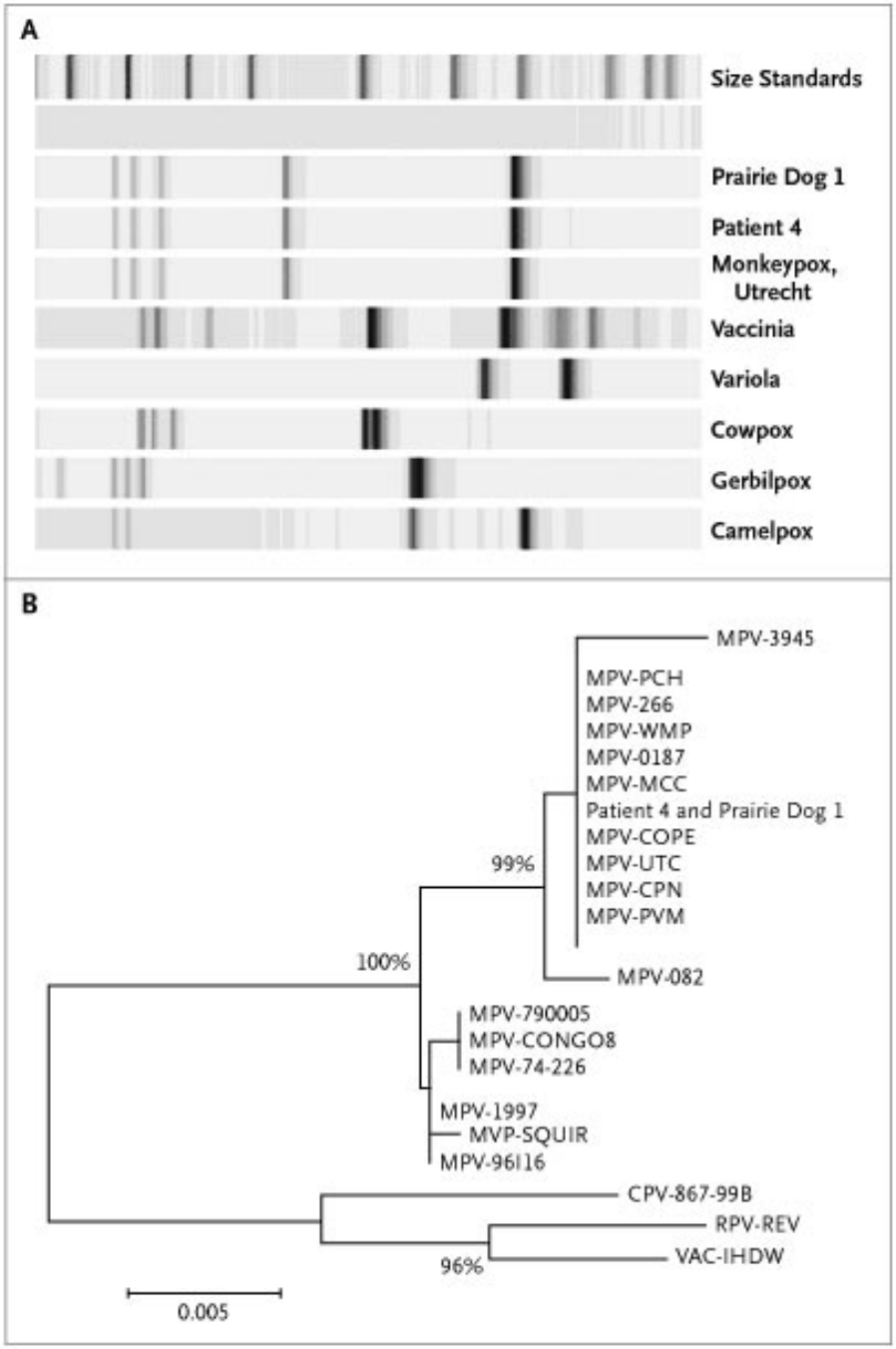


Monkeypox!

PCR-RFLP Results of HA gene from patient

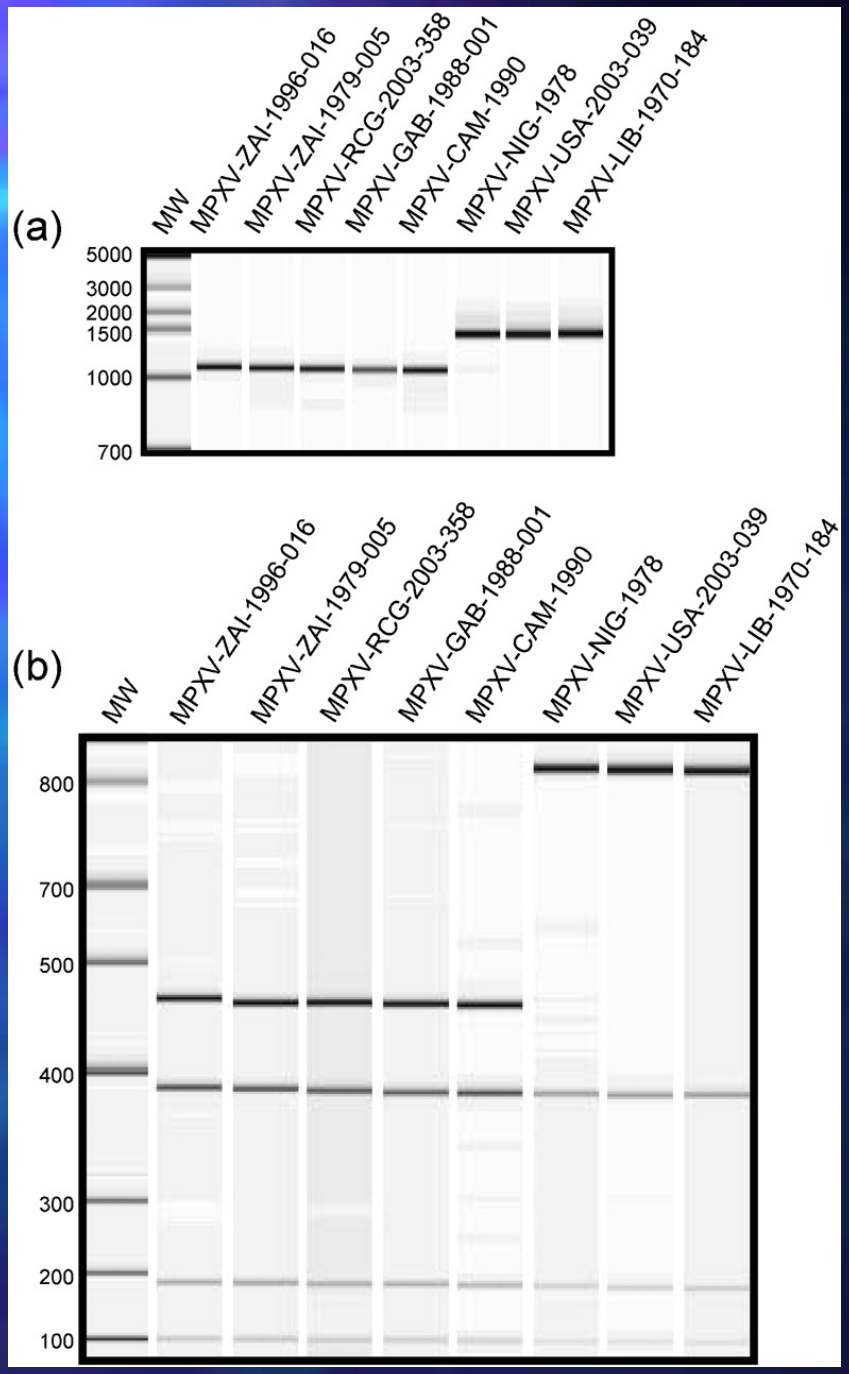
Note: MPV-UTC is West-African origin

Dendogram of gene sequence alignment



Single-gene PCR of MPXV isolates (A-type inclusion gene)

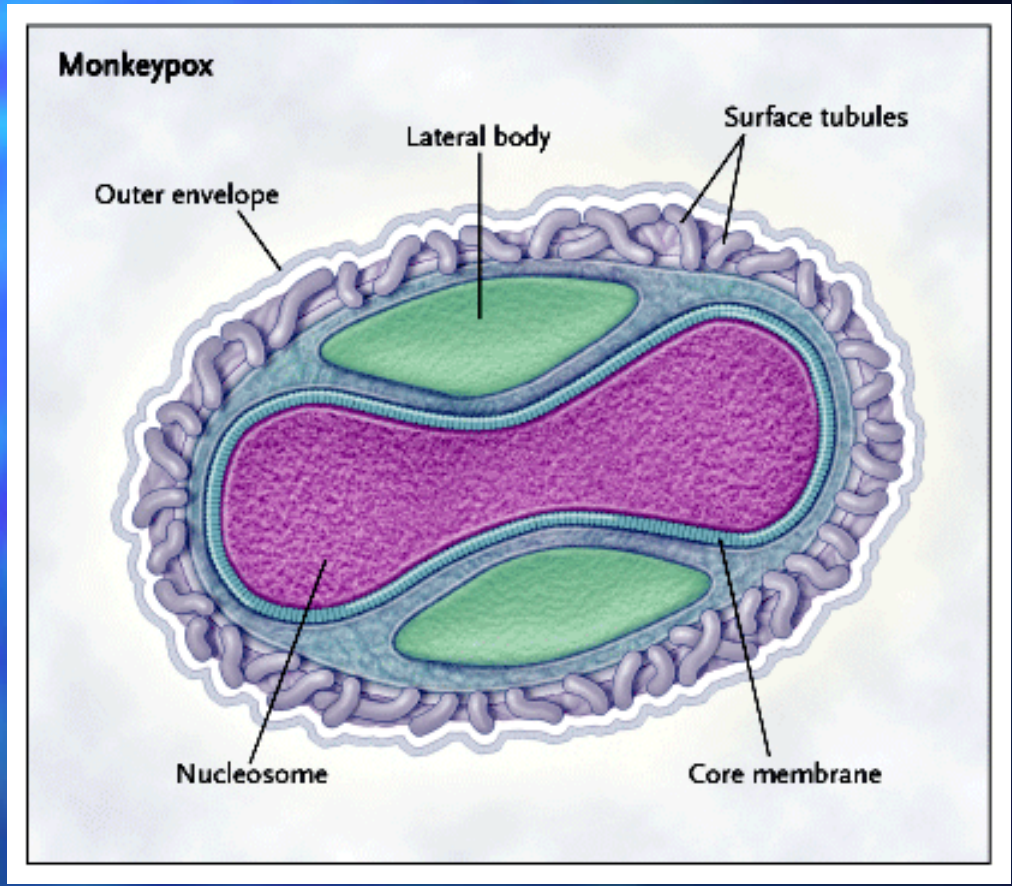
RFLP analysis using XbaI of the ATI-PCR product



1958

First seen in research cynomolgus monkeys in Denmark… hence,

“Monkeypox”



Genome: 196,858 bp, 96.3% identical to variola (smallpox)

World Health Organization

May 8, 1980

The last naturally-occurring case of smallpox in the world was contracted in October, 1977 by a young man in Merka Town, Somalia.

Monkeypox was diagnosed in 1970 in a child from the Democratic Republic of Congo, Nine months after smallpox was eradicated from that region.

- Broad host-range….
- Squirrels,
- Rats,
- Monkeys,
- Humans

Monkeypox is the most important orthopoxvirus of humans since the eradication of smallpox

Table. Poxviruses That Infect Humans and Cause Disease.

Genus and Species (Disease)	Primary Reservoir	Geographic Region	Mode of Transmission	Protection Provided by Vaccinia Vaccination
Orthopoxvirus				
Cowpox	Rodents	Europe, Africa, central and northern Asia	Direct contact	Yes
Monkeypox	Rodents	Central and West Africa	Direct contact, respiratory droplets	Yes
Vaccinia	Unknown*		Direct contact	
Variola (smallpox)†	Humans	U.S., Russia	Direct contact, respiratory droplets	Yes
Yatapoxvirus				
Tanapox	Nonhuman primates	Kenya, Zaire	Direct contact	No
Yabapox	Nonhuman primates	Central Africa	Direct contact	No
Parapoxvirus				
Pseudocowpox (milker's nodules and paravaccinia)	Ungulates	Worldwide	Direct contact	No
Bovine papular stomatitis	Ungulates	U.S., Canada, Africa, Australia, New Zealand, Great Britain, Europe	Direct contact	No
Orf	Ungulates	North America, Europe, New Zealand	Direct contact	No
Sealpox	Seals	North Sea, Pacific Ocean, Atlantic Ocean	Direct contact	No
Molluscipoxvirus				
Molluscipox (molluscum contagiosum)	Humans	Worldwide	Direct contact	No

* Genetic analysis of vaccinia reveals it to be different from cowpox; its origin is unknown, but it may be an extinct horsepox virus.
† Smallpox was declared eradicated in 1980.

Table 1. Evaluation criteria for the differential diagnosis of patients with monkeypox, smallpox, and chickenpox.

Variable	Monkeypox	Smallpox	Chickenpox
Incubation period, days	7–17	7–17	12–14
Prodrome period, days	1–4	2–4	0–2
Symptom			
Fever, severity	Moderate	Severe	Mild or none
Malaise, severity	Moderate	Moderate	Mild
Headache, severity	Moderate	Severe	Mild
Lymphadenopathy, severity	Moderate	None	None
Lesions			
Depth (diameter in mm)	Superficial to deep (4–6)	Deep (4–6)	Superficial (2–4)
Distribution	Centrifugal (mainly)	Centrifugal	Centripetal
Evaluation	Homogenous rash	Homogenous rash	Heterogeneous rash
Time to desquamation, days	14–21	14–21	6–14
Frequency of lesions on palms or soles of feet	Common	Common	Rare

NOTE. Signs and symptoms of the diseases are not age-specific.

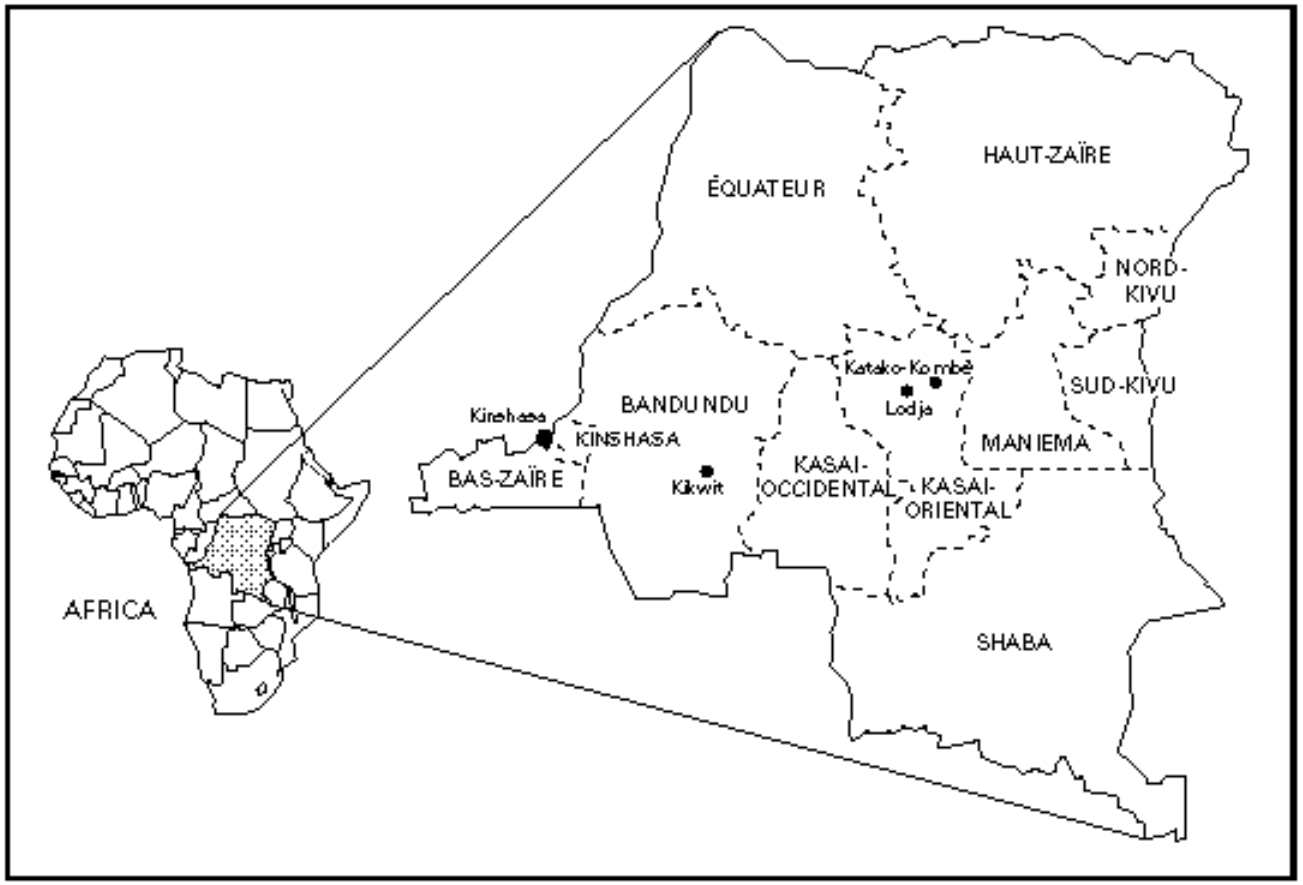
From: Nalca et al. Reemergence of Monkeypox: Prevalence, diagnostics, and countermeasures. Clin Infect Dis 2005;41:1765-71.

MMWR April 11, 1997.

Human Monkeypox – Kasai Oriental, Zaire, 1996-1997

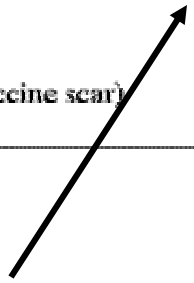
- 71 cases
- 6 deaths
- 13 villages

FIGURE 1. Location of Katako-Kombe health zone, Sankuru subregion, Kasai Oriental, Zaire



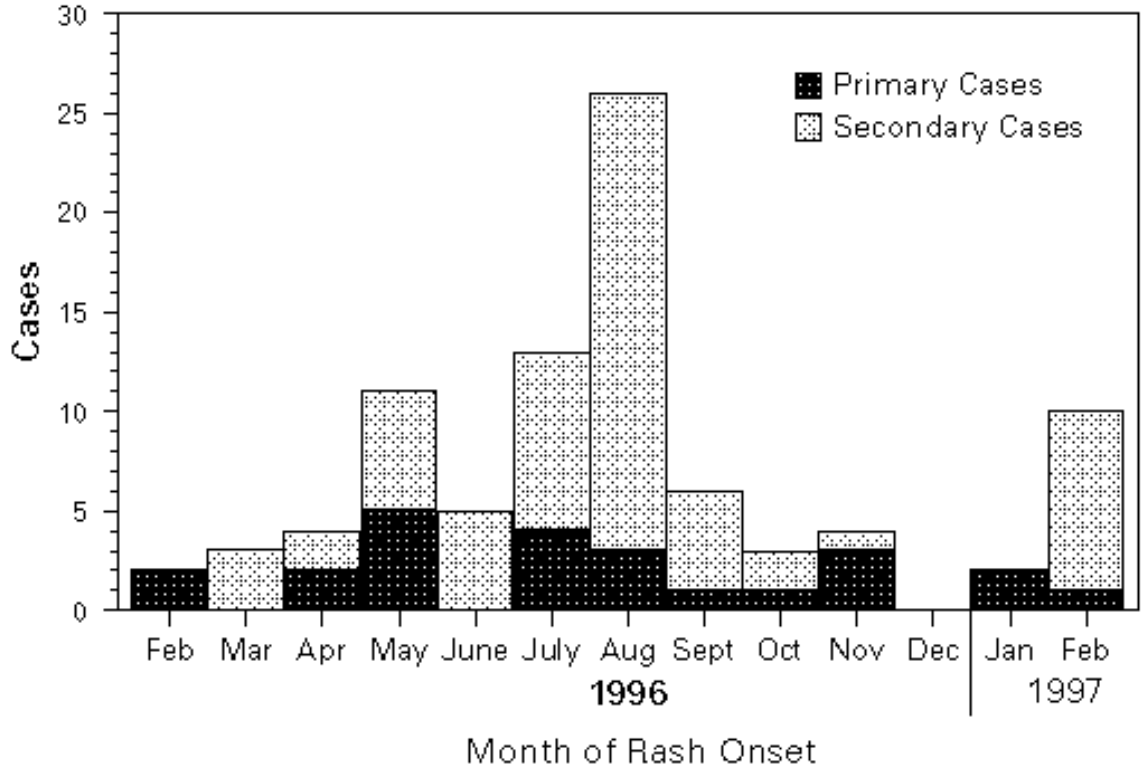
Comparison of epidemiological features of human monkeypox by surveillance period and epidemiological setting

Feature	1970–79	1981–86	1996–97	2003
Location	Central and western Africa	Democratic Republic of Congo	Democratic Republic of Congo	Central USA
Epidemiological setting	Passive surveillance	Active surveillance	Outbreak	Outbreak
Number of reported cases	47	338	419*	81
% laboratory confirmed	87	100	Not known	40
Median age (years)	4	Not known	Not known	27
Suspected primary source(s)	Not known	"Forest animals"	Not known	Prairie dog, Gambian giant rat
Primary cases (%)	91	72	22	100
Secondary cases (%)	9	28	78	0
Secondary attack rate (%)	3·3	3·7†	8·0	0
Case-fatality rate (%)	17	10	1·5	0
Previous vaccinia vaccination	9% (with vaccine scar)	13%	6% (with vaccine scar)	25%‡



Note difference

FIGURE 2. Number of possible monkeypox cases, by date of rash onset — 12 villages, Katako-Kombe health zone, Sankuru subregion, Kasai Oriental, Zaire, February 1996–February 1997*



*n=89 (24 primary and 65 secondary cases).

Risk factors in Africa:

Hunting, skinning, preparing, eating infected rodents and monkeys.

What could this mean…

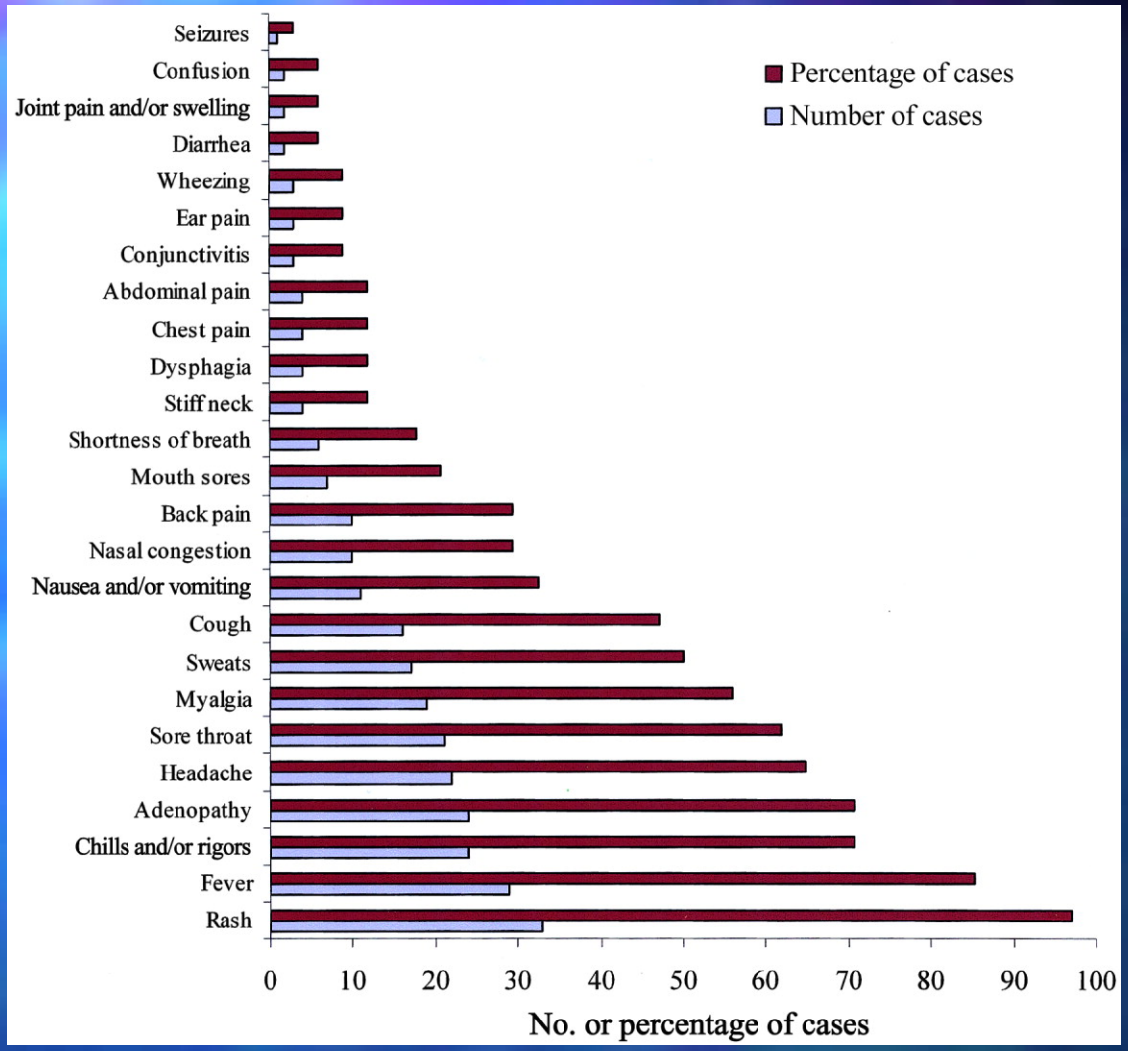
- To the public?
- To health care providers?
- To pet trade?

Patient History

- ✓ 6 of the 11 Wisconsin cases had received a single childhood dose of smallpox vaccine.
- ✓ Incubation period range: 4 – 24 days (median 15 days)
- ✓ All cases appeared to be via direct contact

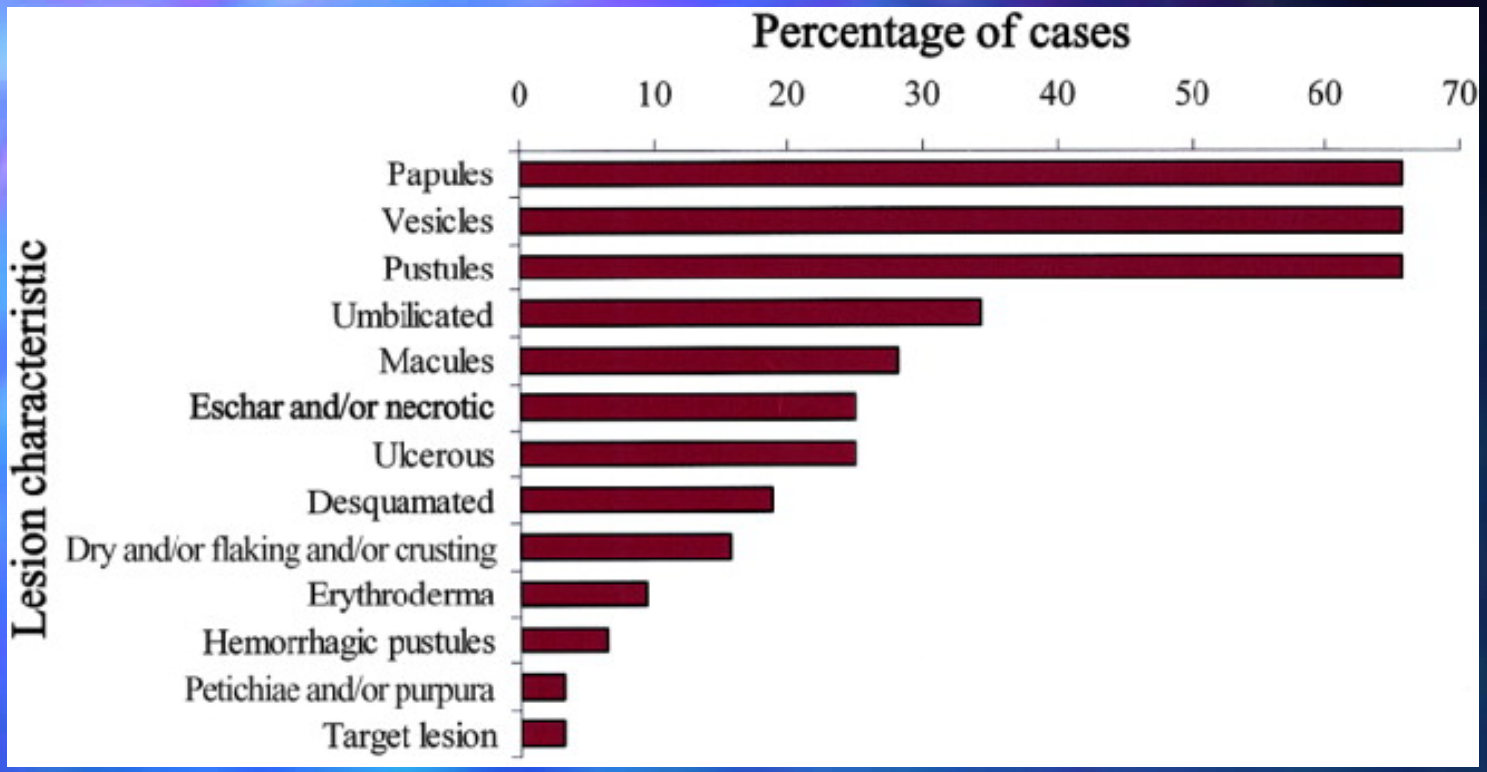
Typical Prodrome:

- Fever
- Headache
- Sweats
- Lymphadenopathy
- Then skin lesions (~ 1-4 days later)
- Lesions may be localized or systemic
- No deaths in the USA, <10% deaths in Africa



Signs and symptoms for 34 patients with confirmed monkeypox in the USA in 2003

From: Huhn et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis 2005;41:1742-51.



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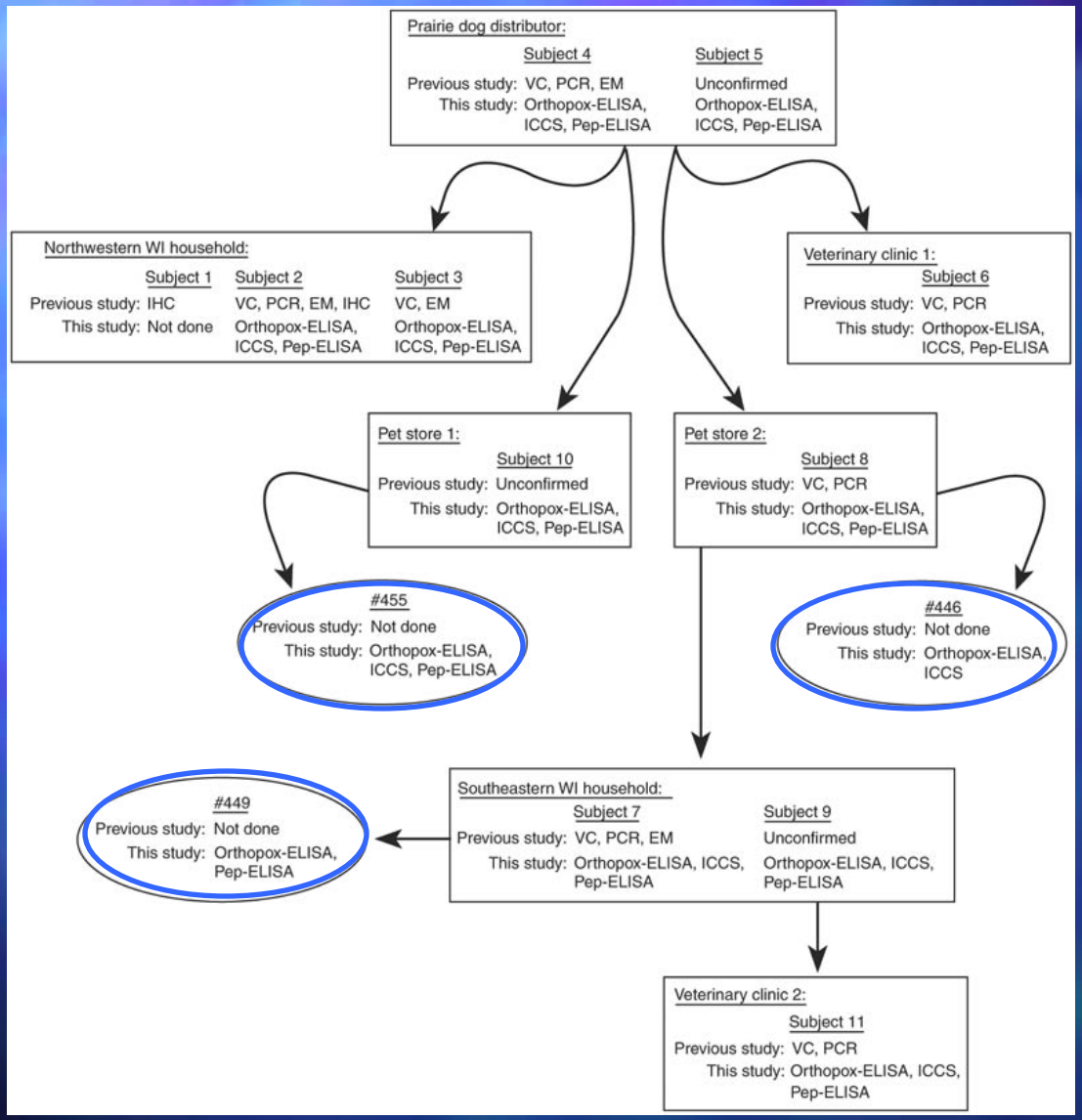


New diagnostic methods; reported and unreported infections in 2003 Wisconsin monkeypox outbreak

Hammarlund et al. Nature Medicine 2005;11:1005-11

Role of smallpox vaccination

- Half of USA population routinely vax^{ed} before 1972
- 85% protection for MPX in some studies
- 6 of 11 Wisconsin MPX cases had been vaccinated
- Pre-exposure : esp. health care workers, veterinarians, field investigators, animal control staff in regards to monkeypox cases
- Post-exposure? 4 days to 2 weeks?

Treatment:

- Cidofovir?
- Vaccina immune globulin?

Table 1. Demographic information for 34 patients with confirmed monkeypox infection, United States, 2003

Characteristic	No. (%) of patients
Sex	
Male	18 (52.9)
Female	16 (47.1)
Age >18 years	24 (70.6)
State of residence	
Wisconsin	18 (52.9)
Illinois	9 (26.5)
Indiana	7 (20.6)
Ethnicity	
White	29 (85.3)
Black	1 (2.9)
Unknown	4 (11.8)
Exposure setting	
Home	19 (55.9)
Work	2 (5.9)
Pet store	4 (11.8)
Veterinarian's office	9 (26.5)
Previous smallpox vaccination (age range)	
Yes (33–47 years)	7 (20.6)
No (6–31 years)	24 (70.6)
Unknown (28–35 years)	3 (8.8)
Underlying medical condition[a]	8 (23)

NOTE. There were 37 total confirmed monkeypox cases during the 2003 US outbreak (J. Cono, Centers for Disease Control and Prevention, personal communication)

[a] Includes hepatitis C, hepatitis (unspecified type), asthma, hydrocephaly, pregnancy, lupus nephritis, receipt of a bone marrow transplant, and hemophilia.

From: Huhn et al. Clinical characteristics of human monkeypox, and risk factors for severe disease. Clin Infect Dis 2005;41:1742-51.

Summary from 37 total confirmed monkeypox cases during 2003 outbreak.

What do you need....?

#1: To work up this outbreak and record cases…

#2: To get the word out…

#3: To limit spread in the community

CDC's Updated Interim Case Definition for Human Cases of Monkeypox

July 2, 2003, 11:30 AM ET

The previous case definition (published June 17, 2003) has been updated as follows:

•Exclusion criteria have been revised

•Suspect, probable, and confirmed case classifications have been edited

Clinical Criteria

Rash (macular, papular, vesicular, or pustular; generalized or localized; discrete or confluent)

Fever (subjective or measured temperature of ≥99.3° F [≥ 37.4° C])

Other signs and symptoms

•Chills and/or sweats

•Headache

•Backache

•Lymphadenopathy

•Sore throat

•Cough

•Shortness of breath

Epidemiologic Criteria

•Exposure[1] to an exotic or wild mammalian pet[2] obtained on or after April 15, 2003, with clinical signs of illness (e.g., conjunctivitis, respiratory symptoms, and/or rash)

•Exposure[1] to an exotic or wild mammalian pet[2] with or without clinical signs of illness that has been in contact with either a mammalian pet[3] or a human with monkeypox

•Exposure[4] to a suspect, probable, or confirmed human case of monkeypox

Laboratory Criteria

•Isolation of monkeypox virus in culture

•Demonstration of monkeypox virus DNA by polymerase chain reaction testing of a clinical specimen

•Demonstration of virus morphologically consistent with an orthopoxvirus by electron microscopy in the absence of exposure to another orthopoxvirus

•Demonstration of presence of orthopoxvirus in tissue using immunohistochemical testing methods in the absence of exposure to another orthopoxvirus.

Rapidly Spreading

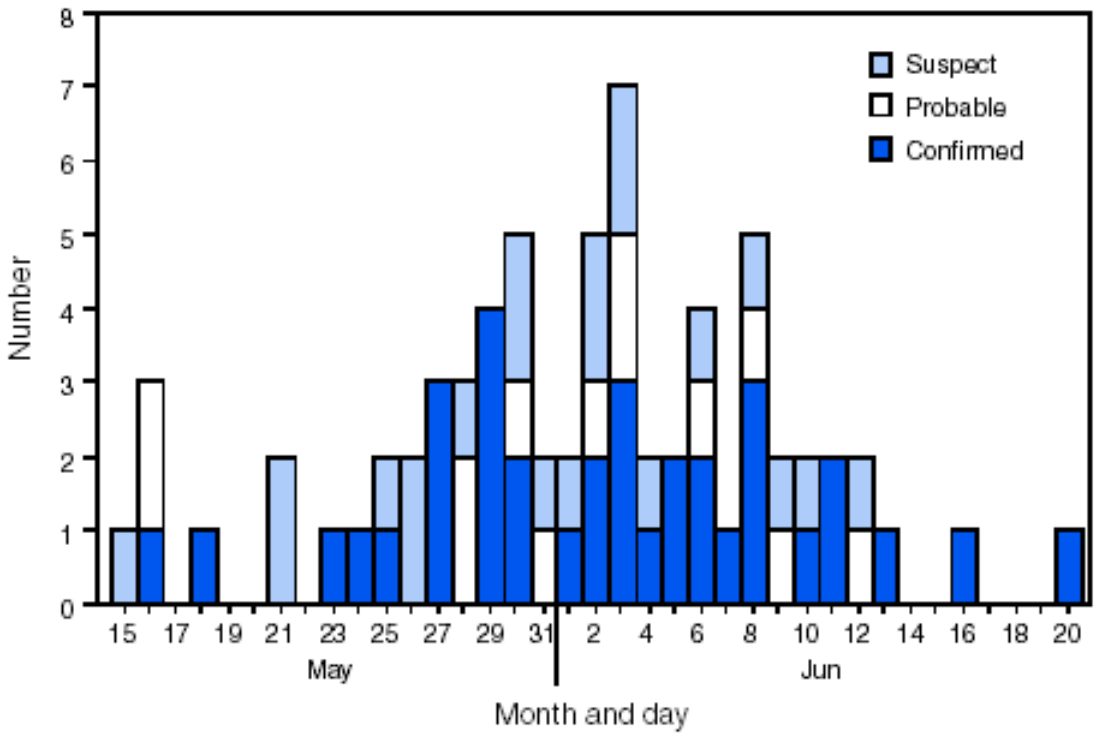
- 71 cases within 4 weeks
- Five adjacent states involved (WI, IN, IL, OH, KS)
- Where did it come from?
- How did it move so quickly?
- Was this a natural event or man-made?
- What policy decisions are indicated now?

TABLE 1. Number and percentage of laboratory-confirmed monkeypox cases, by selected characteristics — United States, 2003

Characteristic	No.	(%*)
State		
Illinois	8	(23)
Indiana	7	(20)
Kansas	1	(3)
Missouri	2	(6)
Wisconsin	17	(49)
Age group (yrs)		
6–18	11	(31)
19–51	24	(69)
Sex		
Female	18	(51)
Male	17	(49)
Possible sources of monkeypox exposure		
Prairie dog(s)	14	(40)
Prairie dog(s) and human case(s)	14	(40)
Premises housing prairie dogs	6	(17)
Premises housing prairie dog(s) and human case	1	(3)
Clinical features		
Rash†	34	(97)
Fever	29	(85)
Respiratory symptoms§	27	(77)
Lymphadenopathy	24	(69)
Hospitalized¶	16	(46)
Previous smallpox vaccination**	8	(33)

* Totals might not add to 100 because of rounding.
† Excludes one patient who had a single atypical, plaque-like skin lesion and no further lesions.
§ One or more of the following symptoms: cough, sore throat, shortness of breath, and nasal congestion.
¶ Some persons were hospitalized for isolation precautions and not because of severe illness.
** Information was available for 25 (71%) of the laboratory-confirmed cases.

FIGURE 1. Number of monkeypox cases*, by date of illness onset — Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003†



* N = 69 of 71 cases with known date of illness onset.
† As of July 8, 2003.

Total: 71 cases identified, 49% lab confirmed

Risk factors: Handling exotic and native mammalian wildlife as pets

So how did the prairie dogs become infected?

??

??

??

Gambian giant rat

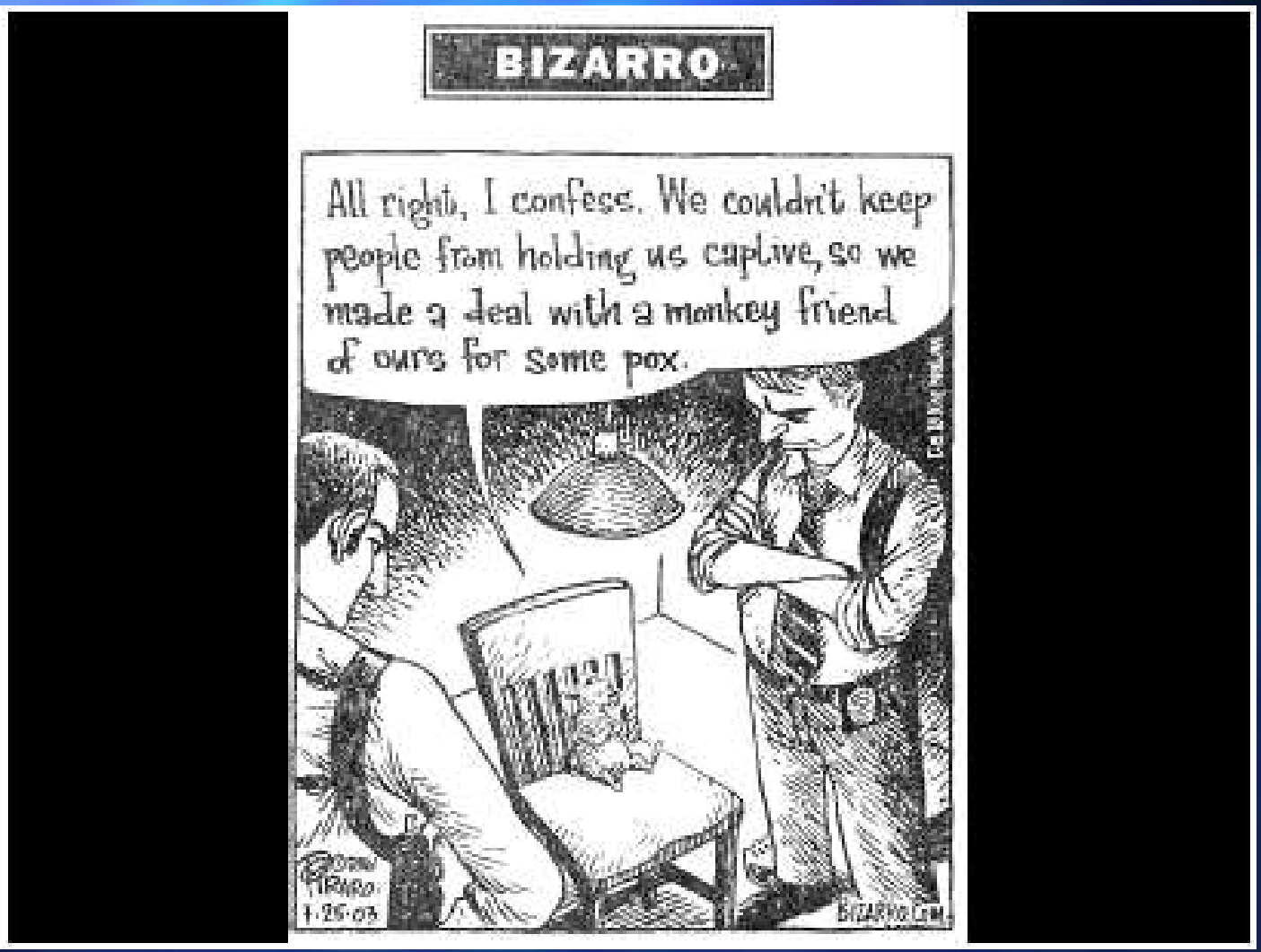
(*Cricetomys* spp.)

Rope Squirrel

(*Funisciurus* spp.)

Tree Squirrel

(*Heliosciurus* spp.)


BIZARRO
All right, I confess. We couldn't keep people from holding us captive, so we made a deal with a monkey friend of ours for some pox.
1-25-03
BIZARRO.COM

How did those animals get here from Africa in 2003?

How did those animals get here from Africa in 2003?

- First cases of monkeypox in USA except for lab monkeys (rare)
- 800 small mammals imported from Ghana to Texas as pets
- Six genera of African rodents (squirrels, giant rats, dormice, striped, mice, brushtail porcupine)

Texas → Iowa animal vendor → Chicago pet distributor, co-housed with prairie dogs → pet dealers in Wisconsin and beyond….. **Human cases within 5 weeks of animal import.**

Geographic distribution of MPXV & Origin of the 2003 outbreak

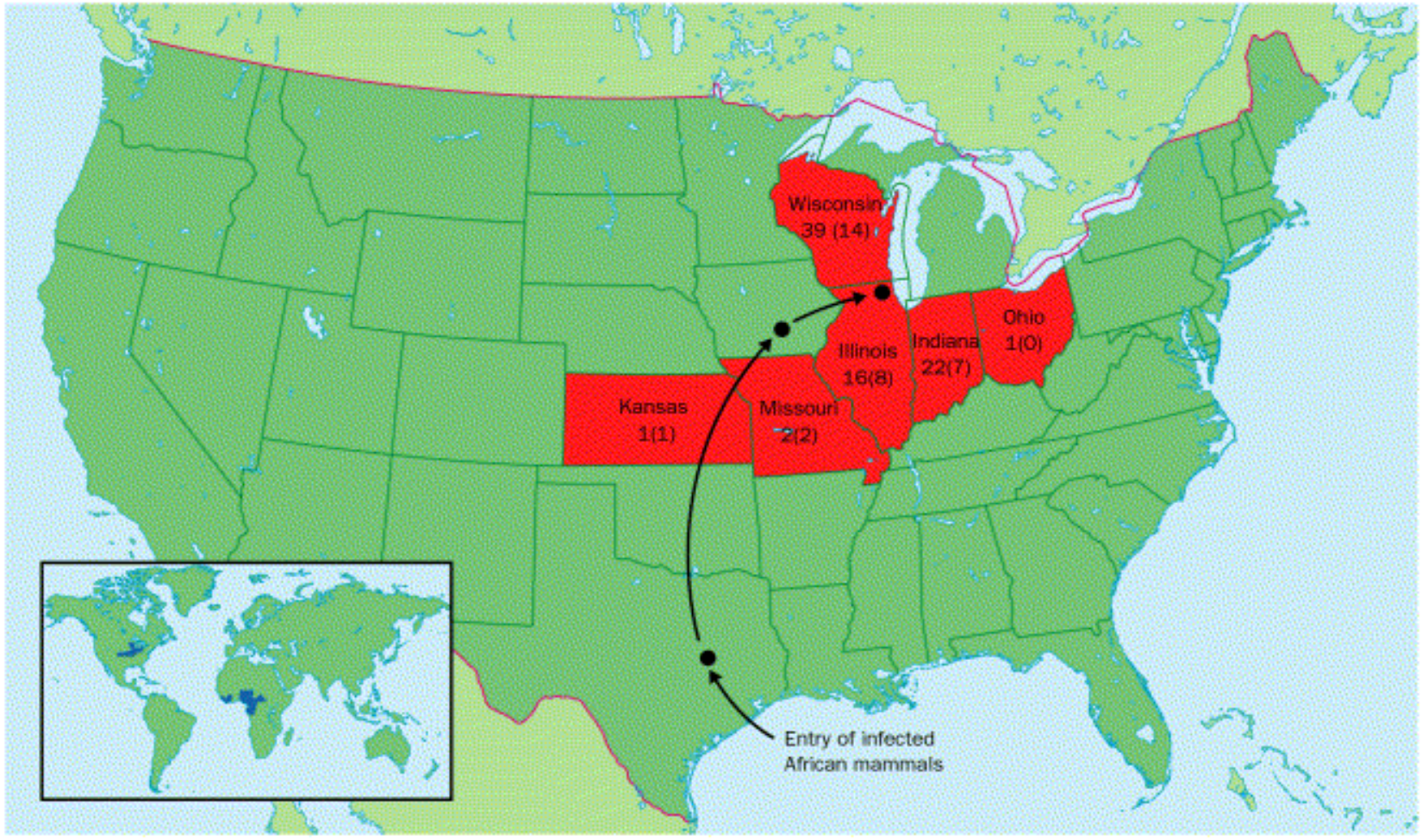
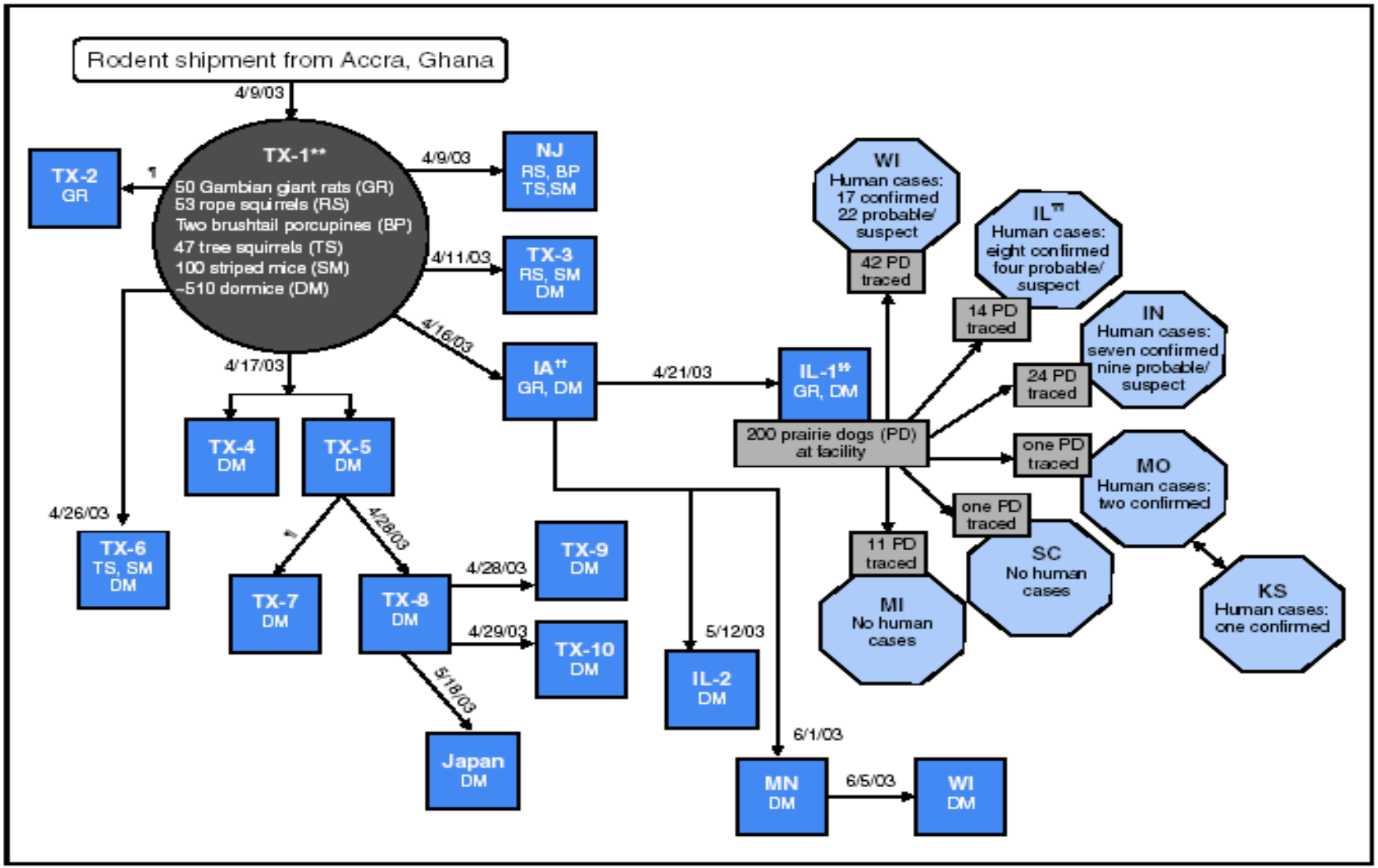


FIGURE 2. Movement of imported African rodents to animal distributors and distribution of prairie dogs from an animal distributor associated with human cases of monkeypox — 11 states*, 2003†§



* Illinois (IL), Indiana (IN), Iowa (IA), Kansas (KS), Michigan (MI), Minnesota (MN), Missouri (MO), New Jersey (NJ), South Carolina (SC), Texas (TX), and Wisconsin (WI). Japan is included among sites having received shipment of rodents implicated in this outbreak.
† As of July 8, 2003.
§ Does not include one probable human case from Ohio; investigation is ongoing.
¶ Date of shipment unknown.
** Identified as distributor C in *MMWR* 2003;52:561–4.
†† Identified as distributor D in *MMWR* 2003;52:561–4.
§§ Identified as distributor B in *MMWR* 2003;52:561–4.
¶¶ Includes two persons who were employees at IL-1.

Table 1. Disposition, as of July 11, 2003, of African rodents imported from Ghana to the United States on April 9, 2003

Rodents	Dead†	Alive	Lost to follow-up	Total (n = 762)
Gambian giant rats	26	20	4	50
Dormice	≈350	27	≈135	≈510
Rope squirrels	49	4	–	53
Tree squirrels	24	20	3	47
Striped mice	14	50	36	100
Porcupines	2	–	–	2

†Includes animals that died of monkeypox and those that have been euthanized.

- Efforts to locate and destroy by federal authorities
- Lack of "paper trail" to enable trace-back
- Non-linear chain of distributors
- Pet "fad" of the year… what's next?

CDC-FDA Embargo

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration 21 CFR Parts 16 and 1240 [Docket No. 2003N-0400] RIN 0910-ZA21 Centers for Disease Control and Prevention 42 CFR Part 71 Control of Communicable Diseases; **Restrictions on African Rodents, Prairie Dogs, and Certain Other Animals**

AGENCIES: Centers for Disease Control and Prevention, Food and Drug Administration (HHS). ACTION: Interim final rule; opportunity for public comment. - SUMMARY:

The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) are issuing this interim final rule to amend their regulations to establish new restrictions and modify existing restrictions on the import, capture, transport, sale, barter, exchange, distribution, and release of African rodents, prairie dogs, and certain other animals. We are taking this action to **prevent the spread of monkeypox**, a communicable disease, in the United States.

DATES: The interim final rule is effective on November 4, 2003. Submit written or electronic comments on this interim final rule by January 20, 2004.

21 CFR 1240.63(a)(1) contains several general prohibitions. In brief, under 21 CFR 1240.63(a)(1)(i), regardless of your status (such as a pet dealer, pet owner, researcher, animal trapper, zoological park administrator, etc.), you must not capture, offer to capture, transport, offer to transport, sell, barter, or exchange, offer to sell, barter, or exchange, distribute, offer to distribute, or release into the environment:

- **Prairie dogs (*Cynomys* sp.)**
- **African Tree squirrels (*Heliosciurus* sp.)**
- **Rope squirrels (*Funisciurus* sp.)**
- **African Dormice (*Graphiurus* sp.)**
- **Gambian giant pouched rats (*Cricetomys* sp.)**
- **Brush-tailed porcupines (*Atherurus* sp.)**
- **Striped mice (*Hybomys* sp.)**
- **Or any other animal so prohibited by order of the Commissioner of Food and Drugs because of that animal's potential to transmit monkeypox.**

Prairie Dog Information

At the present time: Prairie Dogs may NOT be moved, removed, transported in ANY fashion, (including walked on a leash), confiscated, bought, sold, traded, rescued (without clearance from federal health officials), taken to your vet for routine or emergency treatment (find a vet that makes house calls) , released, or relocated.

i.e. KEEP YOUR PRAIRIE DOGS AT HOME !!

Remaining Questions..

- Is there now a sylvan cycle of MPV in USA?
- If so, what would be the consequences?
- Wild animals versus urban rats?
- What is the role of pre- and post-exposure vaccinia inoculation for MPV?
- How important is person-to-person spread?
- What about immunosuppressed persons?
- What does this mean for exotic animal import and display policies? As pets?
- Are there bioterrorism implications of MPV?

Table 3. Qualitative estimation of risk to humans*

		Infection status of animal unknown	
Human exposure to animal	Animal infected	Exposure likely	Exposure unlikely
Indirect exposure/no direct contact	Low	Low	Low
Direct contact, type I* (direct contact without type II exposure)	Medium	Medium	Low
Direct contact, type II* (bite, scratch, or contact of animal's body fluid with mucous membrane or nonintact skin)	High	High	Low

*Risk was based upon type of exposure to an animal and the infection status of the animal. Type I and type II are arbitrary classifications.

Qualitative Assessment of Risk for Monkeypox Associated with Domestic Trade in Certain Animal Species, United States

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Table 2. Variables considered in characterizing risk for human monkeypox cases and the degree of uncertainty associated with these variables

Variable	Degree of uncertainty
Animal host and carrier species	High—some, but not all, host species identified
Proportion of probable host or carrier species infected with virus	High—need to assume absent data that all animals within known or probable carrier species are infected
Proportion of animals exposed during US 2003 outbreak infected with virus	High—need to assume that all exposed animals are infected
Susceptibility of naive animals to infection	High—but experience in United States and Africa suggests several species and orders can be infected with monkeypox virus
Latency in nonhuman species	High
Duration of infection or infectiousness in nonhuman species	High
Seasonality of disease	High—some indication of peak monkeypox cases in humans in July and August in African outbreaks, which may be associated with human behavior rather than characteristics of virus or host animals
Incubation in nonhuman species	High
Infection rates in exposed nonhuman species	High
Proportion of infected animals (of different species) that shed virus	High
Mode(s) of transmission across species and to humans	High—but evidence of mucocutaneous and respiratory transmission pathways
Attack rates among humans exposed to infected animals	High
Secondary attack rates among humans	High—secondary attack rates seem to be increasing in monkeypox-endemic areas due to increasing susceptibility of exposed populations, and historical data indicating low risk for human transmission may be unreliable
Fatality rates in nonhuman species	High

- END -

Giant Gambian pouched rat - *CRICETOMYS GAMBIANUS*

Possibly Endangered