Lecture 5: Pox be upon all of us
One of the earliest documented cases of smallpox is of the Egyptian pharaoh Ramses V who died from smallpox in 1158 BC.
Smallpox

- Smallpox is an anthroponosis
- Smallpox has been globally eradicated

- So why are we talking about it??
  - Zoonotic protection
    - intentional zoonotic transmission!
  - Reemergent poxes
    - lack of training and surveillance
Smallpox – one of the ‘big’ diseases

• Likely zoonotic origin estimated 3000+ years ago in India or Egypt

• “Pox” derives from the Latin for “spotted”

• Got to Europe around 700 AD
  – the Americas in 1500s.

• Within two years over 3.2 million Aztecs died
  – Lack of childhood sensitization by any pox
Smallpox — one of the ‘big’ diseases

Famous deaths?

– Queen Mary II of England
– Emperor Joseph I of Austria
– King Luis I of Spain
– Tsar Peter II of Russia
– Queen Ulrika Elenora of Sweden
– King Louis XV of France
Smallpox – one of the ‘big’ diseases

• First smallpox prevention in India as early as 1000 BC
  – blew powdered smallpox scabs up people’s noses
  – scratched material from a smallpox lesion into the skin
    • “Variolation”
    • If successful → lasting immunity
    • If not → smallpox infection and continued transmission possibility
  – Variolation had a 0.5-2% mortality rate; considerably less than the 20-30% mortality rate of the disease itself.

**Smallpox – one of the ‘big’ diseases**

- Lady Mary Wortley Montagu

- Husband was an ambassador to Turkey in 1716, and she went to Istanbul with him and their two children

- Wrote famous letters ‘from the Orient’ about Muslim life

- Brought the concept of variolation back to the UK

- Spread gradually across Europe, despite suspicion and prejudice
.... The small-pox amongst us is here entirely harmless by the invention of ingrafting (which is the term they give it). There is a set of old women who make it their business to perform the operation. Every autumn in the month of September, when the great heat is abated, people send to one another to know if any of their family has a mind to have the small-pox... the old woman comes with a nutshell full of the matter of the best sort of small-pox and asks what veins you please to have opened. She immediately rips open that you offer to her with a large needle (which gives you no more pain than a common scratch) and puts into the vein as much venom as can lye upon the head of her needle, and after binds up the little wound with a hollow bit of shell, and in this manner opens four or five veins. . . . The children or young patients play together all the rest of the day and are in perfect health till the eighth. Then the fever begins to seize them and they keep their beds two days, very seldom three. They have very rarely above twenty or thirty in their faces, which never mark, and in eight days time they are as well as before the illness. . . . There is no example of any one that has died in it, and you may believe I am very well satisfied of the safety of the experiment since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England, and I should not fail to write to some of our doctors very particularly about it if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind, but that distemper is too beneficial to them not to expose to all their resentment the hardy wight that should undertake to put an end to it. Perhaps if I live to return I may, however, have courage to war with them. ...
INOCULATION

Those who are desirous to take the infection of the SMALL-POX, by inoculation, may find themselves accommodated for the purpose, by applying to.

Stephen Samuel Hawley

Fiskdale, in Sturbridge.

February 7, 1801

N. B. A Pest-House will be opened, and accommodations provided by the first day of March next.
Smallpox, cont

- Smallpox was such a huge killer (around 30%) that many cultures forbade naming babies until they survived pox, as infants.

- Of the survivors, 65-85% were left with deep pitted scars – pockmarks – particularly on the face – poxy!

- In 18th century Europe, a third of all reported cases of blindness was due to smallpox.

- In a survey conducted in Viet Nam in 1898, 95% of adolescent children were pockmarked and nine-tenths of all blindness was ascribed to smallpox.

- As late as the 18th century, smallpox killed every 10th child born in Sweden and France and every 7th child born in Russia died from smallpox.

(WHO http://www.who.int/mediacentre/factsheets/smallpox/en/)
Smallpox eradication

• 1798 – Edward Jenner’s cowpox inoculation – became widely used
  – ‘vacca’ is Latin for ‘cow
  – Hence the term “vaccination”

• Sometime in the 19th century, was replaced with vaccinia
  – unknown origin

• Early 1950s – 150 years after Jenner
  – 50 million cases of smallpox occurred in the world each year
  – fell to around 10–15 million by 1967 because of vaccination.

• 1967 WHO launched an intensified plan to eradicate smallpox
  – Smallpox threatened 60% of the world's population
  – killed every fourth victim
  – scarred or blinded most survivors, and eluded any form of treatment

(WHO http://www.who.int/mediacentre/factsheets/smallpox/en/)
MULTIPUNCTURE VACCINATION BY BIFURCATED NEEDLE

NEEDLE IS HELD PERPENDICULAR TO THE ARM

WRIST OF VACCINATOR RESTS ON THE ARM

DROP OF VACCINE IS HELD IN THE FORK OF THE NEEDLE
Smallpox eradication

• 1972 last major European outbreak in Yugoslavia
  – A pilgrim from Kosovo returned from the Middle East with smallpox
  – Infected 175 people, causing 35 deaths.
  – Authorities declared martial law
  – Enforced quarantine
  – Massive re-vaccination of the population, with the WHO.

• Smallpox was finally pushed back to the horn of Africa
  – 1977 - a single last natural case, Somalia
  – 1978 - a fatal laboratory-acquired case, United Kingdom

(WHO http://www.who.int/mediacentre/factsheets/smallpox/en/)
"Reward--Recompense $1000."

Gauch, Rene.
World Health Organization, 1977

Le fine print:
The World Health Organization offers US $1000 to the first person reporting an active smallpox case resulting from human-to-human transmission and confirmed by laboratory tests. Valid until global eradication is certified.
The global eradication of smallpox was certified, based on intense verification activities in countries, by a commission of eminent scientists in December 1979 and subsequently endorsed by the World Health Assembly in 1980.

(Source: WHO)
Smallpox eradication

• Routine childhood vaccination discontinued in the USA in 1972
• Routine vaccination of healthcare workers discontinued in 1976
• Vaccination of military recruits stopped in 1990, except Middle East deployment
• Now primarily recommended for laboratory workers at risk for occupational exposure
• Mass smallpox vaccination was abandoned in most European countries in the early 1970s
Smallpox eradication

- Despite intensive searching, no other cases have been detected since 1978

- Smallpox virus remains only in laboratory deep freezers in Moscow and Atlanta, USA, awaiting a politico-scientific decision for final extinction

- Clinton (1999) decided *not* to let the lab samples be destroyed

- Genetic sequence information is stored in computer memory banks

- Post September 11 2001 the American and UK governments have had increased concern over the use of smallpox or smallpox-like disease, in bio-terrorism.
**Smallpox virus**

Smallpox belongs to the **Orthopox** virus group.

Poxviruses are very large, brick-shaped viruses about 300 x 200 nm (the size of small bacteria).

Complex internal structure: large double-stranded DNA genome (about 200 kbp in size) enclosed within a core flanked by 2 lateral bodies.

Virus particle surface covered with filamentous protein components, particles have the appearance of a "ball of knitting wool".

Particle is enclosed in an envelope derived from the host cell membranes.
Smallpox virus

There are two clinical forms of smallpox.

- **Variola major** is the severe and most common form of smallpox, with a more extensive rash and higher fever.

- Historically, variola major has an overall fatality rate of about 30%; however, flat and hemorrhagic smallpox usually are fatal.

- **Variola minor** is a less common presentation of smallpox, and a much less severe disease, with death rates historically of 1% or less.
There are four types of *Variola major* smallpox:

- **ordinary**
  - the most frequent type, accounting for 90% or more of cases

- **modified**
  - mild and occurring in previously vaccinated persons

- **Flat and hemorrhagic**
  - both rare and very severe
Smallpox illness

- **Spread**: close contact, eg. within households, via droplet infection of pharyngeal secretions (ulcers in pharynx).

- **Incubation**: 10 - 12 days.

- **Major illness**: Rather similar to severe chicken pox (varicella). Abrupt onset of fever and prostration with a macular rash on the third day (head, limbs, hands and feet rather than trunk, including palms and soles).
  - Progresses to vesicles which become pustular, ulcerated, scabbed, healed with scarring ("pock marked face").
  - Also inside mouth.
Smallpox illness

- Laboratory diagnosis of pox viruses may be undertaken by electron microscopy of negatively stained vesicle fluid or lesion material.

- Smallpox recognition not taught as much anymore

- Eradication meant that there was no need

- Other poxes described as “rare” and “exotic”

- What happens if someone presents with pox?

- How should we deal with pox-like illnesses?
Poxviruses

- Poxviruses have amazing cross-antigenic properties
- Most poxviruses are host-species specific
  - *Buffalopox virus*  *Camelpox virus*
  - *Cowpox virus*  *Ectromelia virus*
  - *Monkeypox virus*  *Rabbitpox virus*
  - *Raccoonpox virus*  *Sealpox virus*
  - *Skunkpox virus*  *Taterapox virus*
  - *Uasin Gishu disease virus*
  - *Variola virus*  *Volepox virus*

- Spillover to humans are truly zoonotic – cowpox, monkeypox

- **Vaccinia** is an exception and a mystery
  - Multiple hosts
  - Unclear origins
Poxviruses

- **Vaccinia** (Orthopoxvirus)
  - Origins are not known but it seems to be a genetically distinct type of pox virus which grows readily in a variety of hosts.
  - In man it causes a localised pustule with scar formation.
  - In immunocompromised persons or eczematous persons can cause severe generalized vaccinia infection.

- **Cowpox** (Orthopoxvirus)
  - acquired by humans usually by milking cows;
  - manifests as ulcerative lesions (sometimes called "milkers nodules") on the hands of dairy workers.
  - Despite its name, rodents are the main reservoir of cowpox
  - Spreads secondarily to cows and domestic cats.

- **Molluscum contagiosum** (Molluscipoxvirus)
  - a minor infectious warty papule of the skin
  - transferred by direct contact
  - sometimes as a veneral disease
**Poxviruses**

- **Pseudocowpox** (Parapoxvirus)
  - occurs worldwide and is a disease primarily of **cattle**.
  - In humans it causes non-ulcerating "milker's nodes".

- **Orf** (Parapoxvirus)
  - Word derives from old Saxon term (Old English) for “rough”
  - a worldwide occupational disease associated with handling **sheep and goats** afflicted with "scabby mouth”
    - 2001 USDA – 40% of sheep stock had reported scabby mouth or ‘sore mouth’
  - Has also been found transmitted by **reindeer** (hello santa)
  - In humans it manifests as a single painless, papulo-vesicular lesion on the hand, forearm or face.
Poxviruses

- **Yatapoxes** are only found in tropical Africa, *unless we move them*

- **Yabapox (Yatapoxvirus)**
  - Rare, caught from monkeys
  - Cases have occurred in the USA, in primate colonies

- **Tanapox (Yatapoxvirus)**
  - Tana river, Kenya
    - Outbreaks in late 1950s and 1960s
  - Causes pustules and 3-4 days of aches and fevers
  - Likely has a vertebrate host (monkeys, apes?)
  - May be arthropod transmission involved
    - Case in 2004 of a college student studying orphan chimps in the DRC, came back to New Hampshire with it
Poxviruses

Monkey pox (Orthopoxvirus)

- a rare smallpox-like disease of children in central Africa.
- acquired from monkeys or wild squirrels,
- **occasionally spread from man to man** in unvaccinated communities
  - Estimated around 1/3 of cases are anthroponotic
- Antigenically cross-reacts with other poxviruses.
- Sick monkeys have not been identified, but apparently healthy animals have antibodies.
- Called "monkeypox" because it was first discovered in laboratory monkeys in 1958.
- The virus was identified in 1970 as the cause of a smallpox-like illness in humans in remote African locations.
Monkeypox, cont.

- Since monkeypox cases were found in Africa in the 1970s AFTER the WHO believed that smallpox was eradicated, they set up surveillance (this is rare)

- Only 400 cases were reported worldwide from the time infection by monkeypox virus was first observed in 1970 to the time when surveillance ceased in 1986

Because the pox can be quite prolific and can cause open lesions on the skin, it can allow secondary infections

Remote area hunters in Africa can get this, and often don’t want to be caught for bushmeat trade, so getting treatment from western-based clinics is hard
Monkeypox, 2003: USA midwest

- First human cases in Illinois, Indiana and Wisconsin, June 2003
- Spread to people by infected prairie dogs sold from a dealer in Villa Park, IL
- Prairie dogs and exotic animals, including rodents from Africa, were housed together in Texas.
- Cases also reported in Missouri, Ohio and Kansas.
- No human deaths related to this outbreak.

(Illinois Dept. Public Health)
Monkeypox, 2003: USA midwest

- “Western” problems
  - lack of recognition
  - Healthcare worker unwillingness – work hazard?

Why Were Doctors Afraid to Treat Rebecca McLester?

By GRETCHEN REYNOLDS
Published: April 10, 2004

The pediatrics ward at SwedishAmerican Hospital in Rockford, Ill., was busy last June 20, its 10 or so patients suffering from the usual ailments of the young. Linda Wildey, the director of women and children’s services at the hospital, was looking forward to the end of her workweek when she received a visit from the manager of the hospital’s pediatrics department. A 10-year-old girl was heading for SwedishAmerican’s emergency room, and she was suspected of having monkeypox.
Monkeypox, 2003: USA midwest

• Pediatric ward:
  • None of the nurses had been vaccinated for smallpox

• Pediatric nurses aren’t trained for quarantine circumstances

Little knowledge about monkeypox at the hospital

“The hospital staff believed, "that monkeypox could be contagious between people, and that it had a fairly high death rate in Africa. "”


!!! 10 of the people infected in the outbreak had childhood smallpox vaccine
Dr. Paul Hunter doesn't mind admitting that he thought about it (smallpox). Hunter, who lives in Milwaukee, treated one of the other monkeypox cases in late May. His patient was a meat inspector and a dealer in exotic pets, whose kitchen was stacked with cages of chattering prairie dogs and chinchillas. "We thought he might have contracted tularemia or plague," Hunter said. But when the man didn't respond to antibiotics, and his rash erupted with oozing sores, Hunter and his colleagues reluctantly began to harbor other suspicions. "The rumor about smallpox went around the hospital fast," he said.
Allpox vaccination?

- List of doctors who had been vaccinated
  - Would you want to be on the list?

- One doctor, heard about Middle East soldiers getting vaccinated, got a shot himself
  - Availability?
    - WHO not sure they are viable stocks
  - Should we make more?
  - Resistant pox?
    - Vaccination complications can arise
    - Is the risk of vaccination complications higher or lower than epidemic risk?
Allpox vaccination?

- Vaccinia is a really nice vaccination vector*
  
  *different use of vector than we commonly see in zoonotic disease
  
  Has been used in rabies control in animals successfully
  
  Should we keep ‘playing’ with it?
Networking time!!