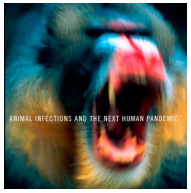
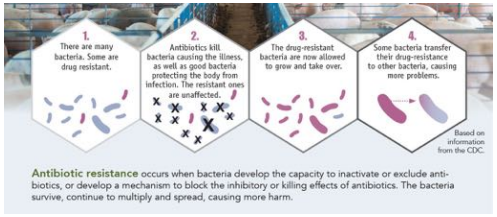


ANBI 139 Evolution of Human Disease
Pascal Gagneux Spring 2019

image from the book Spillover by David Quamen 2012: Spillover: Animal Infections and the Next Human Pandemic

---

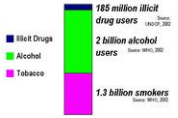
Antibiotic resistance: creating drug resistant super bugs



The discovery of antibiotics was a major step in medicine. The overuse of antibiotics is now strongly selecting for the evolution of resistant bacteria. We are making our microbial enemies worse!

Substance Abuse: slow suicide

Drug overdoses:
over 70,000 death per year in the US

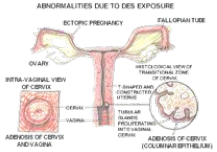


	Mortality (% of all deaths worldwide)	DALYs (% of total years of life lost)
Tobacco	8.8	4.1
Alcohol	3.2	4.0
Illicit drugs	0.4	0.8

The human brain reacts strongly to a large number of natural and human-made substances. Chronic use of such substances often includes physical dependency and leads to massive suffering, ill health and crime.

DES daughters: When medications cause disease

Diethylstilbestrol



The synthetic estrogen DES was given to pregnant women at risk for miscarriage. Unbeknownst to the doctors, this molecule causes severe malformations of the female reproductive tract of the fetus. Thousands of women in the US were affected. The same chemical was also used to chemically “castrate” homosexual men, including the famous WWII coed breaker and mathematician Alan Turing.

Thalidomide (Contergan): Medication damage

prescribed to alleviate morning sickness in pregnant women 1957: caused phocomelia in more than 10,000 children in 46 countries.

1962: FDA pharmacologist Frances Oldham Kelsey receives the Presidential Award for Distinguished Federal Civilian Service from President John F. Kennedy for blocking sale of thalidomide in the United States.

Niko von Glasow, German filmmaker

A very astute civil servant at the FDA kept this drug from being approved in the USA, saving countless children from being born without arms.

Environmental poisoning (Minamata, Japan)

chisso

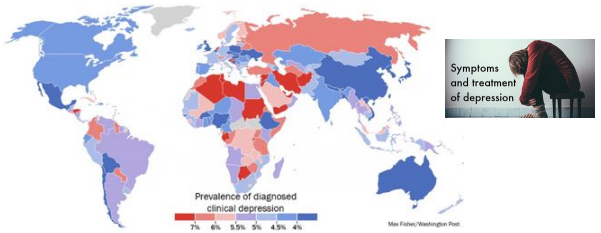
Tomoko Uemura in Her Bath (1971)
by W. Eugene Smith

Decades of discharge of Methyl mercury and other pollutants from Chisso Corp into Minimata Bay

2,265 victims have been officially certified (1,784 of whom have died)

Industrial pollution with methyl mercury is one of the most infamous assaults on child health. Similarly, lead contains paint used until fairly recently continues to contribute to neurological poisoning in children.

Mental Health: Depression



Several form of mental health could be argued to also be at least in part human-made, as these can result from how we treat each other socially.

Autism?

A spectrum of cognitive disabilities

Increase in incidence would suggest environmental causes.

Also reflects trends in diagnosis.

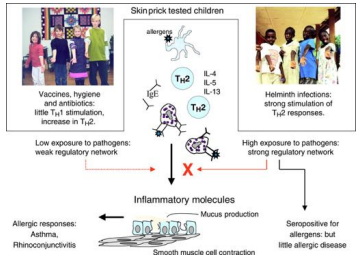
The role of de novo mutations and association with parental age could be a cultural effect.

NOT associated with vaccination, 1998 *Lancet* paper by A. Wakefield linking autism to the MMR vaccine was a fraud.

There is ZERO evidence that vaccines are associated with Autism spectrum Disorder. There might be environmental factors that help cause ASD, there clearly are large numbers of de novo mutations that cause ASD by interfering with neuronal development, usually in utero, long before birth.

Hygiene Hypothesis

The cost of too much hygiene:



Allergy, Parasites, and the Hygiene Hypothesis
Maria Yazdanbakhsh, Peter G. Kremsner, Ronald van Ree, ***Science*** **2002:**

Divergent outcome of TH2 responses in industrialized (low pathogen exposure) and developing countries (high pathogen exposure). It has been argued that improved hygiene, frequent use of antibiotics, and vaccination has led to reduced bacterial and viral infections in industrialized countries and therefore to insufficient stimulation of TH1 responses, which in turn allows the expansion of TH2 cells. TH2 responses are characterized by increased IgE to allergens, mastocytosis, and eosinophilia.

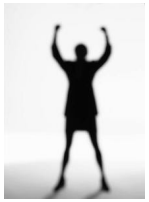
Practice question:

What is the list of the hygiene hypothesis?

Improved hygiene, frequent use of antibiotics, and vaccination deprives children

What Pathogens?

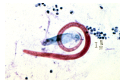
Viruses:
HIV
Polio
Hepatitis B
Hepatitis C
Influenza
Measles
Smallpox
Yellow Fever



Bacteria:
E. Coli
Mycobacterium TB
Helicobacter
Vibrio cholera
Anthrax
Neisseria meningitidis
Neisseria gonorrhoeae
Spirochete (syphillis, Lyme disease)

Protozoans:
Plasmodium (malaria)
Trypanosome (sleeping sickness, Chagas)
Leishmania (leishmaniosis)

Helmitnhs:
Tapeworm
Hookworm
Filaria
Shistosomes



Practice question:
List four major classes of parasites/pathogens.
viruses
bacteria
protozoa
helminths
and fungi

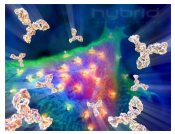
Immune defenses

Cellular arm of our immune systems:
- Macrophages
- Natural Killer Cells
- Neutrophiles

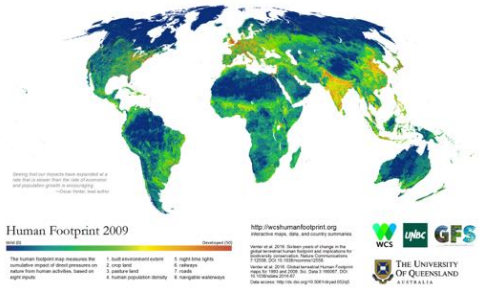
Natural killer cells attacking a tumor

Humoral (soluble molecules)
arm of our immune systems:
- Antibodies (secreted by B-cells)
- Complement

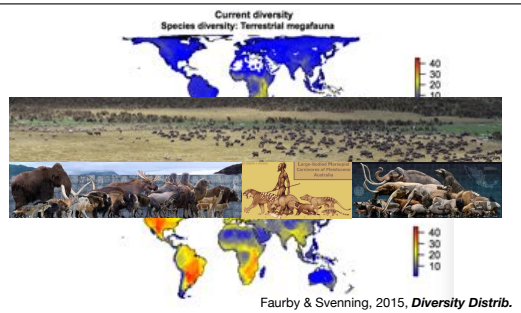
Antibodies homing in
on a tumor cell



Where we live



Missing Megafauna (>44 kg/97 lbs)?



Faurby & Svenning, 2015, ***Diversity Distrib.***

Where ever modern humans have migrated, there seem to be many missing large animals…. except in Africa, where large animals have co-evolved with humans

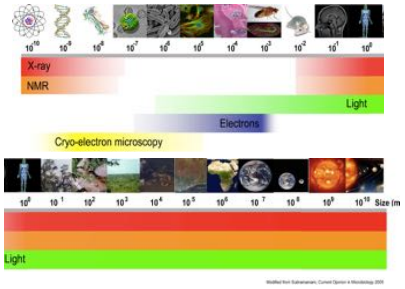
Practice question:

Why is Africa the only continent that still has such large numbers of wild animals?

African animals evolved with humans, they are people smart. Large animal on all other continents were taken by surprise when these bipedal primates with their efficient hunting tools arrived, many of them died out.

Spatial Scales: from atoms to galaxies

Relevant data to be found at every scale!

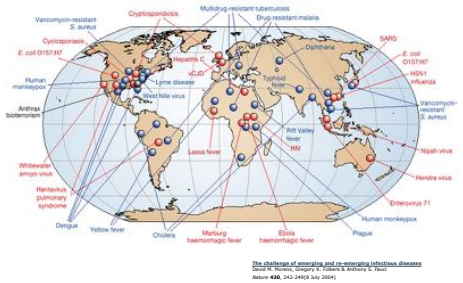


Human encroachment

Growing human populations and encroachment of wild areas lead to novel and contact.

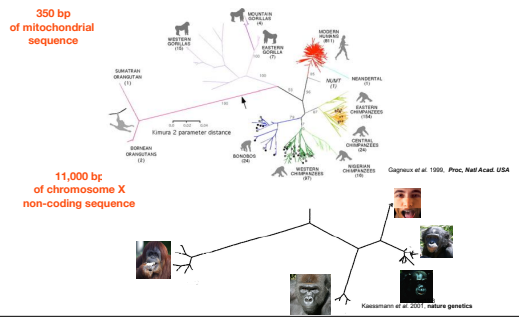
New road in the Congo

Emerging Diseases



despite the misleading impression that humans were winning the fight against infectious disease in the middle of the 20th century, there is a long list of emerging diseases around the world.

Hominid phylogenies, mitochondrial and X-linked DNA



Years ago, I collaborated with a large group of people to compare the DNA sequences of a small stretch of mitochondrial DNA. We reported that each of the grat ape species showed much more genetic variation than 800 humans from populations from all around the world.

A few years later, Svante Paboo's group sequenced a stretch of DNA 30 times longer on noncoding parts of the X chromosome and found a similar pattern. Now we have whole genomes for all these players including Neanderthals.

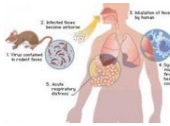
Pascal's personal journey:

David Woodruff

Jeanne Messier

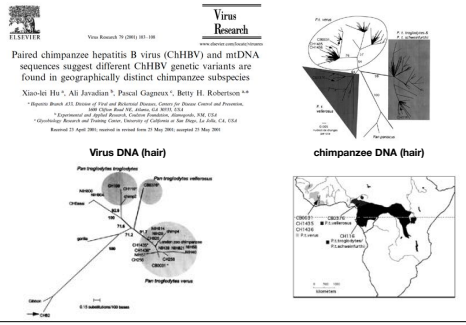
UC San Diego Grad student
victim of Hanta virus

Nicholas Mundy



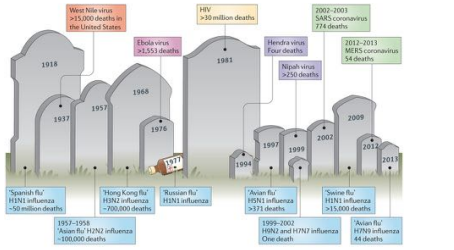
visiting graduate student in a biology lab at UCSD with the late David Woodruff.
Met Nick Mundy who had just spent there years in Gabon and sen chimpanzees with SIV infections.
Lost a friend to an emerging virus (sin hombre) haunt virus.
read Laurie Garrett's book the coming plague.

Pascal's personal journey:



Collaborated with people at the CDC on chimpanzee HBV

Zoonoses over time



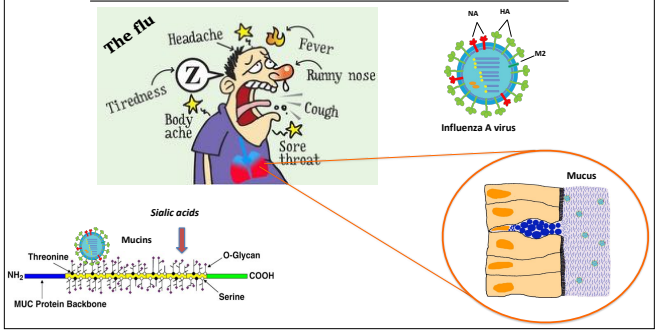
Studying immunity to zoonotic diseases in the natural host — keeping it real. Andrew G. D. Bean, Michelle L. Baker, Cameron R. Stewart, Christopher Cowled, Celine Deffrasnes, Lin-Fa Wang & John W. Lowenthal
Nature Reviews Immunology 13, 851–861 (2013)

A zoonosis (plural zoonoses) is an infectious disease of humans acquired from non-human animals.

1918 "Spanish" Flu (H1N1)

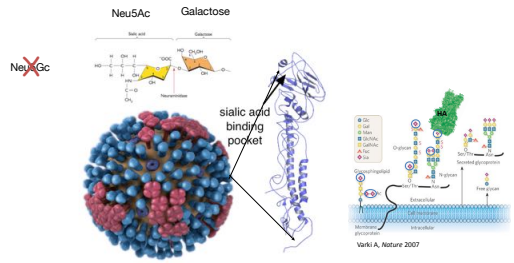
The biggest infectious event of the 20th century
killed more people than both world wars combined!

The Flu & The Goo



Our respiratory tracts secrete mucins, glycoproteins very rich in sialic acids that act as protective decoys.
The Influenza virus has evolved to counter such decoys and can clip sialic acids off muffins in order to penetrate towards the cell surface.

Viruses use host glycans as receptors

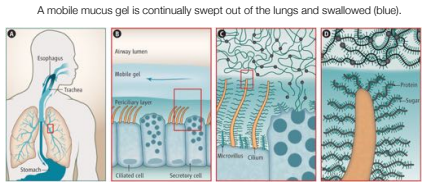


specific for monosaccharides and glycosidic linkage type!

The virus cares about the type o sugar and its linkage got the underlying sugar chain

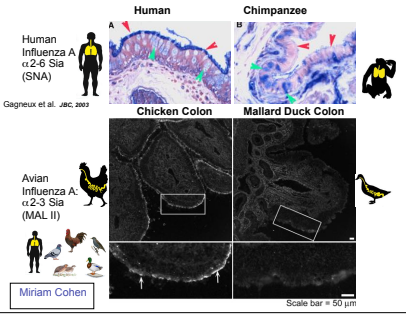
---

Defensive host glycans as barriers and



Airway mucus layers.(A) A mobile mucus gel is continually swept out of the lungs and swallowed (blue). (B) The mucus layer moves over an immobile periciliary layer. Secretory cells synthesize polymeric mucins that form the mobile gel; ciliated cells propel the gel. (C) Secretory cells release mucin polymers that travel upwards to be incorporated into the mobile gel layer. Button et al. now show that glycoconjugates (membrane-tethered mucins and mucopolysaccharides) are present in the periciliary layer at greater density than glycoconjugates (polymeric mucins) in the gel layer. (D) Densely packed sugar side chains cause membrane-tethered mucins to assume a partially extended configuration, whereas mucins in the gel layer are random entangled

Why apes do not get the flu



The sialic acid in the lung of chimpanzee are different and differently linked, they do not get the flu!

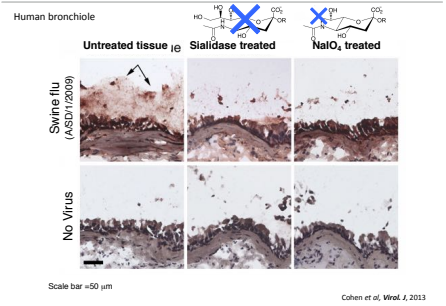
In adapting from bird host to human host, the preference of the virus for the linkage of sialic acid changes (one or two mutations in the protein sequence of the hemagglutinin are enough to cause this switch!)

Practice question:

What factor could cause very closely related species such a s humans and chimpanzees to have very different susceptibility to infection by a given

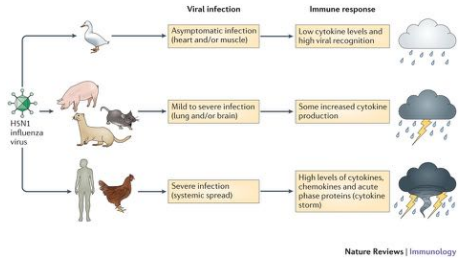
---

Influenza A binds to secreted airways mucus



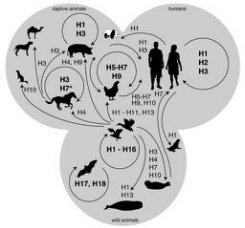
Visualizing Influenza virus trapped in mucus on human bronchial tissue (tissue section from a frozen post-mortem lung sample)

What a wild bird virus can do to us



Influenza A

Very diverse pool of viruses existing in wild aquatic birds



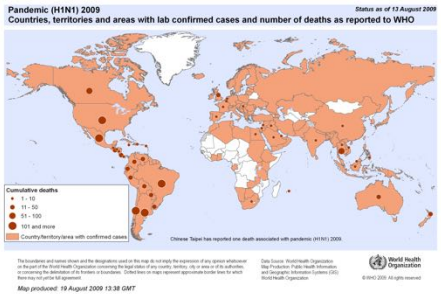
Eradication not possible, only better surveillance prevention, and treatment Short et al, *One Health*, December 2015

Practice question:

Why is it totally unrealistic to eradicate influenza viruses?

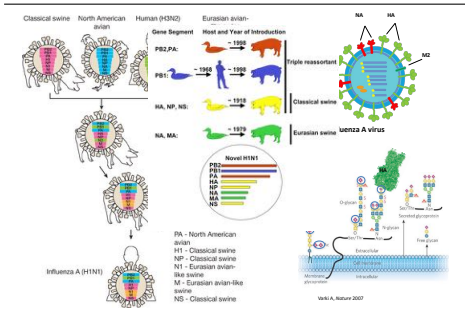
They have a gigantic reservoir in many species of wild water birds that migrate across the planet.

2009 “Pig Flu” (H1N1)



The 2009 H1N1 swine origin flu was a close call.

2009 “Pig Flu” (H1N1)



It arose through viral sex,,, multiple recombination of viral RNA segments

Contrast Legionella to HIV/AIDS

Legionellosis: high priority, AIDS: low priority

1994
Benetton
Ad

Legionella, a novel bacterium growing in the air conditioning system of a hotel and sickening members of the American Legion got immediate attention and funding

HIV, and African ape virus infecting gay men, hemophiliacs, heroin users and Haitians, did not for the longest time

---

HIV/AIDS: a chimpanzee zoonosis

It is now clear that HIV/AIDS emerged as a zoonosis bin Central Africa around the turn of the the 1900s.

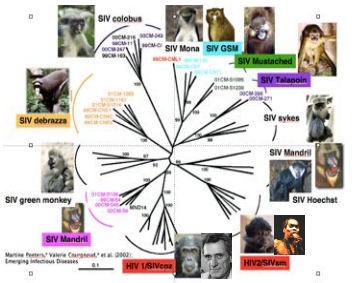
HIV infects T-lymphocytes in the blood stream, ultimately causing AIDS. Terese Winslow created this artwork to give scientists new insight into how HIV infects T-lymphocytes. The

virion is shown in the first stage of infection, when the virion attaches to the surface of the T-cell. The molecules involved in this docking process are of particular interest to scientists,

so she rendered them accurately according to the most up-to-date scientific information. These molecules include gp120 (the blue 'mushrooms' on the surface of the virus), CD4 (the

long red molecules on the cell surface), and chemokine receptors (the groups of blue cylinders on the cell surface). The artwork was created with Adobe

SIV in > 40 species of primates



Peeters *et al.* 2002. ***Emerg. Infect. Dis.***

At least two different cross-species jumps caused HIV1 and HIV2

Perfect Storms

Colonial brutality and mass medical campaigns

Large urban centers and mass migrations

Intercontinental Medical Aid

Blood Commerce

(Sex) Tourism and IV Drug use

The convergence of colonial brutality, the first large urban centers (including sex workers), intercontinental medical aid, blood commerce (plasma pheresis businesses in Haiti), and sex tourism and IV drug use formed the perfect storm.

Practice question:

Which factors helped spark the HIV/AIDS pandemic?

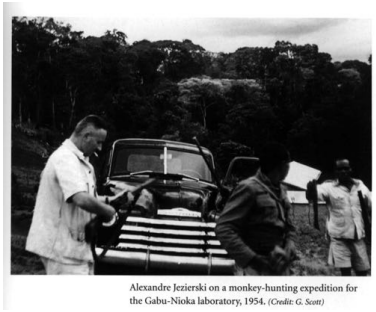
see above

Bush meat trade

Apes are still hunted for their meat throughout tropical Africa, even in the cities, bush meat is valued much more highly than farmed meat.

perfect opportunity fro cross-species infections.

Polio vaccine studies in the Belgian Congo used hundreds of wild caught chimpanzees and bonobos for testing the efficacy and safety of vaccine. These studies could not have cause the HIV1 epidemic which was well underway by the late 1950s.



Alexandre Jezierski on a monkey-hunting expedition for the Gabu-Nioka laboratory, 1954. *(Credit: G. Scott)*

Chimp caught in a liana net by pygmies, at one of Rollais's base camps in the north of Province Oriental, 1958. *(Credit: G. Rollais)*

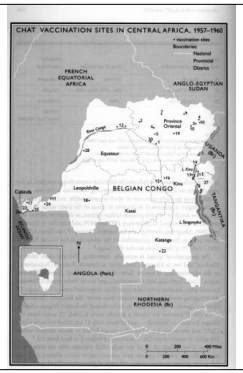
Two African assistants dismembering a dead chimp in the

Mass vaccination in Belgian Congo 1959

Agnes Flack vaccinating a "sea of Africans" with CHAT in the Ruzizi Valley, 1958. (Credit: R. Phillips)

Mass vaccination in Belgian Congo 1959: suspected by some as possible origin of HIV/ AIDS

BUT
clearly not the case
rather HIV was already circulating at the time



The Alternative hypotheses about HIV origins:

- 1.Natural Transfer: infection by killing and butchering of apes for meat, more hunting in modern times, larger cities and more travel.
- 2. Natural Transfer & syringes (aided by rural clinics with rampant reuse of unsterilized hypodermic needles).
- 3.Oral Polio Vaccine (OPV), vaccine prepared on chimpanzee tissue cultures? infected with SIV and fed to ~1 million Africans in 1957-1960.
- # 3 has been proven wrong, so likely a combination of 1 and 2.

Logging road in the DRC

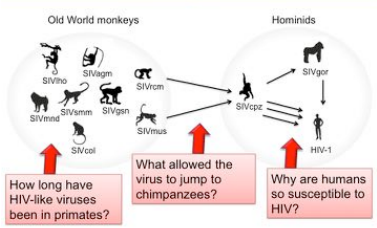
Logging roads are made by international logging companies. Once a road is made, many locals and migrant use it to enter the forests and establish camps along or near the road. These new settlers hunt for their meat and start depopulating all animal populations. They can use bush meat a a cash crop, utilizing the traffic of looking trucks to ship their meat to the cities, where bushmeat fetches much higher prices than that of domestic animals.

Practice question:

How could logging roads affect emerging diseases?

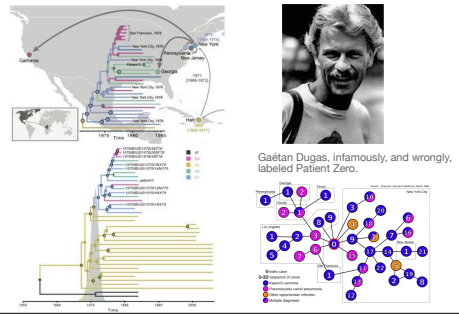
see above

What caused the virus to jump?



More than a million years in other African primates. Jump likely aided by bush meat hunting/butchering
The basis for human susceptibility are still being studied.

HIV patient ZERO?



Gaétan Dugas, infamously, and wrongly, labeled Patient Zero.

A 1984 paper linked 40 AIDS patients by sexual contact. Of those patients, Dugas was the first to experience an onset of symptoms of AIDS.
But he was not patient zero!

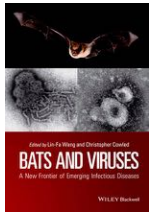
Eco Health

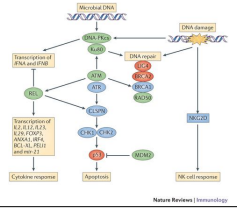
Protecting the environment and preventing diseases

The idea of Eco health is that conservation of ecosystems can contribute to our understanding of emerging diseases and too their prevention.

Bats

adapted to high viral loads?





The figure illustrates key components of the DNA damage response and DNA repair pathways. Whole-genome analysis of two bat species (*Pteropus alecto* and *Myotis davidii*) showed that a high number of genes encoding components of these pathways are positively selected in *P. alecto* and *M. davidii*. Many of these genes are positively selected in both species (these encode proteins that are highlighted in green), whereas others have been positively selected in only one of the species (these encode proteins that are highlighted in red).

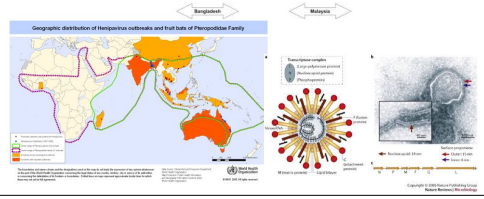
Practice question:

Why are bats so important for monitoring emerging viral diseases?

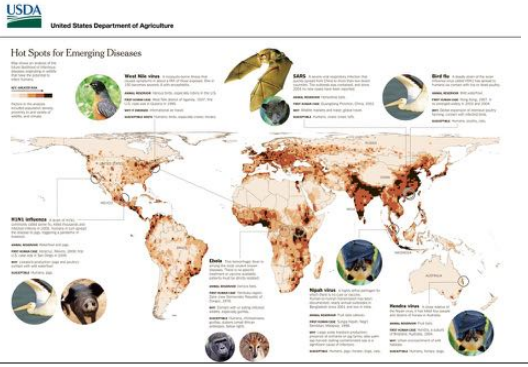
There high mobility and resistance to viruses make them ideal reservoirs.

Bats and Nipah Virus

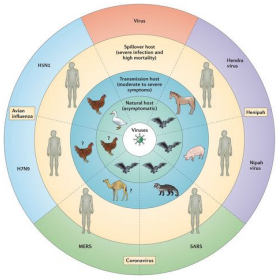
Pteropus megabat



Nipah is a highly virulent virus carried by South East Asian bats and able top infect pigs and people.



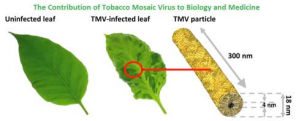
Many paths for a zoonotic virus to human hosts



Studying immunity to zoonotic diseases in the natural host — keeping it real. Andrew G. D. Bean, Michelle L. Baker, Cameron R. Stewart, Christopher Cowled, Celine Deffrasnes, Lin-Fa Wang & John W. Lowenthal
Nature Reviews Immunology 13, 851–861 (2013)

The notion of "viruses" is very recent

Dmitri Iwanowski, discovered viruses in plants in 1892.



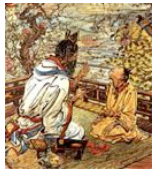
"Messieurs Dames, les microbes auront le dernier mot"
Ladies and gentlemen, microbes will have the last word!

However, it was Robert Koch & Louis Pasteur who jointly proposed the 'germ theory' of disease in the 1880s .

Plants could be infected with fluid pressed from infected plants that had been filtered through ceramic filters (Pasteru- Chamberland filters that exclude bacteria because the porcelain has pores that measure 0.1 to 1 microns (100 nm to 1 um).

"Virus"

Virus = "poison" in Latin
Only discovered in the 1890s.
Old idea of "fighting poison with poison"
"variolation" against smallpox in 16th century China



Small Pox

smallpox is often deadly and leave survivors with nasty scars.

Vaccination

On 14th May 1796, Jenner vaccinated an 8 year old boy, James Phipps, with material from a cowpox lesion on the hand of a milkmaid, Sarah Nelmes.

"Vacca" means cow in latin, vaccination started as the use of cow pox virus to immunize against the much nastier smallpox virus.

Lady Mary Wortley Montagu was a prominent member of society, noted beauty and the wife of the British Ambassador to the Ottoman Empire. In 1715, she contracted smallpox & suffered severe facial scarring and loss of her eyelashes (!) In 1718, while living in Turkey, she had her 6 year old son variolated, despite the violent opposition of the British Embassy staff in Constantinople.

Public acceptance of vaccination?

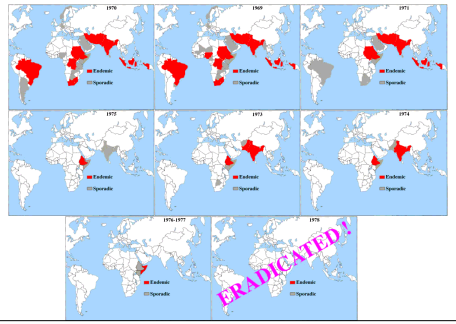
Against the will of God

Introduces beast into humans

Linked to serious infections

From the get go there were people who objected to vaccination.

Eradication of Smallpox : from 20 million in 1920 to 0 in 1978



vaccines have allowed the eradication of infectious diseases!

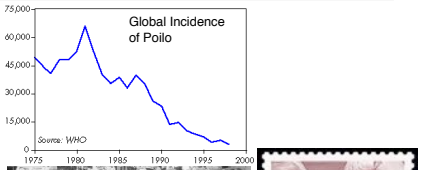
The bad news is that some countries still keep stocks of live smallpox virus for their bioweapons programs….

Polio (poliomyelitis), the disease:

Poliomyelitis virus causes paralysis due to immune attack of infected nervous tissue

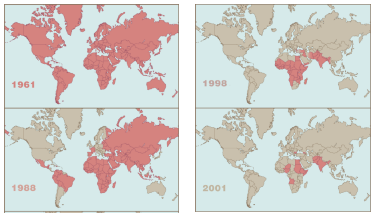
---

Introduction of the Salk vaccine in 1955



Polio has now been almost completely eradicated.

Another success story:



The near-eradication of Polio due to oral polio vaccine (OPV) Developed by Albert Sabin.

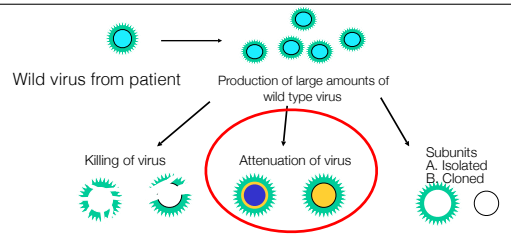
Vaccines

Single most successful intervention of western medicine.

Kinds of vaccines:
inactivated: dead whole pathogen
attenuated: live infectious pathogen manipulated to generate a non-pathogenic state.
subunit vaccines: only part of the pathogen (surface glycoprotein) is used, non-infectious
conjugated vaccines: part of the pathogen is linked with a "famous" antigenic molecule such as cholera toxin or bacterial glycolipid.

There are different ways of manufacturing vaccines.
Vaccines can have risks, but moire than half a century of studies have shown that overall the benefits of mass immunization far outweigh the risks to the individuals.

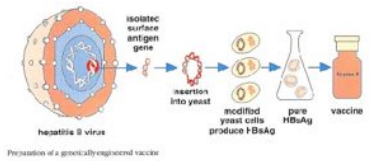
Different ways of making a vaccine



Test for efficacy: Does it produce lasting and adequate immune response?
Test for safety: Are their any side effects?
Test for safety of attenuation: Are the viruses stable?
Are there back mutations?

Practice question:
List three major types mod vaccines:
killed
attenuated
subunit

Hepatitis B subunit vaccine



First successful anticancer vaccine

Your Hepatitis B vaccine was tested for safety in chimpanzees!

Studies by Alfred Prince and his team at the Vilab in Liberia
have paved the way for a Hepatitis B vaccine.The vaccine is now produced in yeast cells.

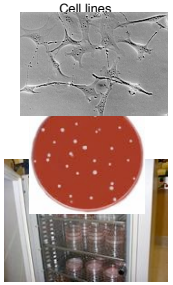
Growing virus to make vaccines:

Primary tissue culture

Primate Kidneys

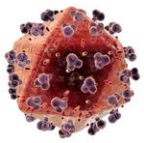
Hens' eggs

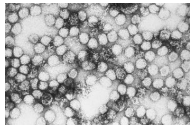
Cell lines



The substrate used for making vaccine contributes to certain risks of the vaccine, e.e. Influenza vaccine made in chicken eggs can cause reactions in people who have egg allergies.

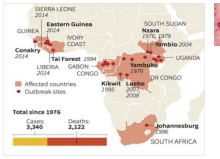
Yellow Fever, a flavivirus

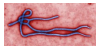




yellow fever is the only flavivirus that can be prevented with a very efficient vaccine.

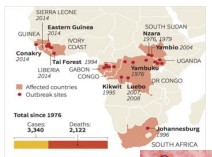
Ebola, a filovirus

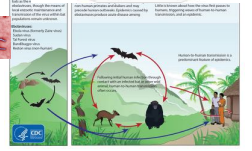




A recently developed vaccine against ebola is a big hope for many.

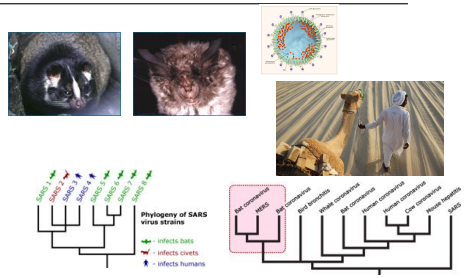
Ebola





My friend and colleague was patient zero for the Ebola Ivory Coast outbreak in 1994.
She infected herself while helping a veterinarian conduct an autopsy of a dead wild chimpanzee.

SARS MERS and other coronaviruses

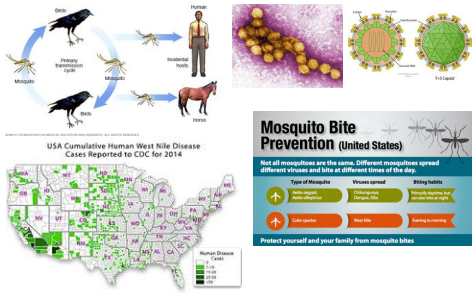


Severe Acute Respiratory Syndrome virus (SARS). News update, July 2013
Since September 2012, a mysterious respiratory infection has been spreading through hospitals in Saudi Arabia and has popped up in nearby countries. MERS (Middle East Respiratory Syndrome) is a coronavirus, like SARS, and has health workers thinking about the devastating effects of that outbreak. So far the new virus, which can cause severe pneumonia and kidney failure, has infected 64 people and killed 38. Some cases are unexplained, but many were contracted from other infected people in the hospital. The ease with which the virus spreads from person to person suggests that it has the potential to trigger an epidemic.

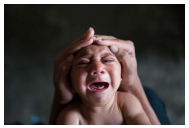
SARS cases 2001 to 2003

The outbreak of SARS corona virus in 2001 to 2003 was controlled in an exemplary way by Chinese Health authorities.

West Nile, a flavivirus

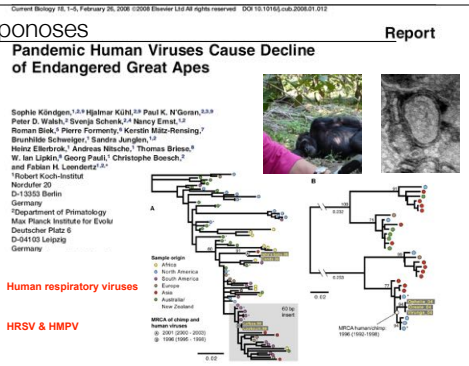


ZIKA, a flavivirus



Mosquito borne, causes massive developmental derailments in brains of fetuses…..microcephaly.

Anthroponoses



Current Biology 16, 1–5, February 26, 2006 ©2006 Elsevier Ltd All rights reserved DOI 10.1016/j.cub.2006.01.012

Report

Pandemic Human Viruses Cause Decline of Endangered Great Apes

Sophie Köndgen,[1,2,5] Hjalmar Kühl,[2,3] Paul K. N'Goran,[2,3,5] Peter D. Walsh,[2] Svenja Schenk,[2,4] Nancy Ernst,[1,2] Roman Biek,[2] Pierre Formenty,[2] Kerstin Mätz-Rensing,[7] Brunhilde Schweiger,[7] Sandra Junglen,[1,2] Heinz Ellerbrok,[1] Andreas Nitsche,[1] Thomas Briese,[6] W. Ian Lipkin,[6] Georg Pauli,[1] Christophe Boesch,[2] and Fabian H. Leendertz[1,2,*]

[1]Robert Koch-Institut
Nordufer 20
D-13353 Berlin
Germany
[2]Department of Primatology
Max Planck Institute for Evolu
Deutscher Platz 6
D-04103 Leipzig
Germany

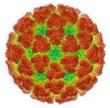
Human respiratory viruses

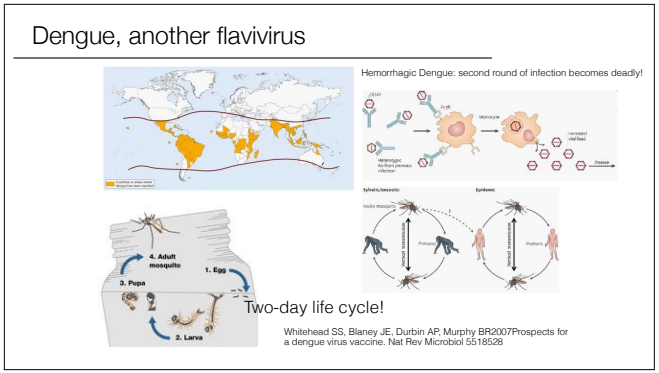
HRSV & HMPV

Humans can also pas dangerous viruses to non-human primates, such as these respiratory viruses that caused the death of wild chimpanzees.

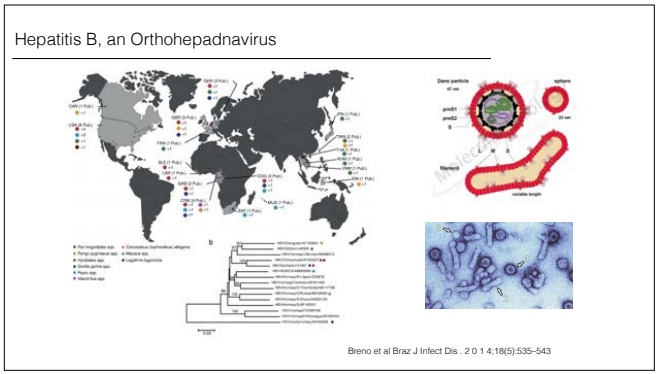
Chikungunya, a togavirus

Another virus from forest primates of Africa

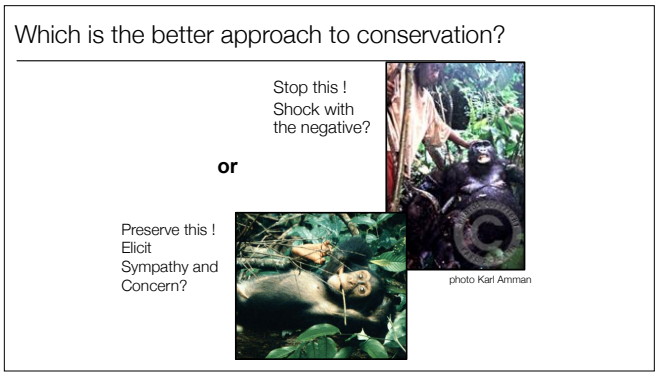




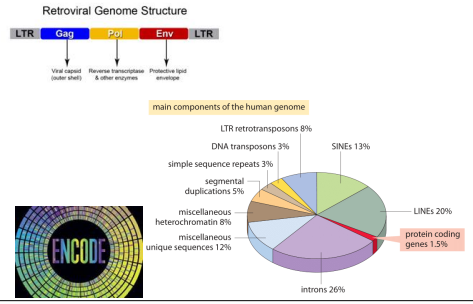
Female *Aedes aegypti* commonly lay eggs on the inner walls of artificial containers. When the containers fill with water, mosquito larvae hatch from the eggs. After developing through four larval stages, the larvae metamorphose into pupas. Like the larval stage, the pupal stage is also aquatic. After two days, a fully developed adult mosquito forms and breaks through the skin of the pupa. The adult mosquito can fly and has a terrestrial habitat.



Primate origins of HBV: Right: Geographical distribution of publication relating to non-human primates which were detected with some HBV genotype. Sample animals are listed by genera in Table 1. (B) The evolutionary history was inferred by Neighbor–Joining method using differences between DNA sequences..
(left graphic): Electron Microscop Presentation of HBV Particles. The round 42 nm particles (1) represent infectious virions (Dane particle). The small empty spheres (3) and the filaments (3) are non infectious. The preparation was enriched in virus particles (EM picture by courtesy of H.-W. Zentgraf, Heidelberg)



Molecular Parasites in your genome: rubbish or opportunity?



More about viruses as active, creative agents in evolution in a later lecture.

Summary

Humans have increasingly encroached on wild ecosystems.

This has provided many opportunities for cross-species infections.

Colonial history, mass migration and urbanization, combined with biomedical interventions have provided great opportunities for emerging diseases.

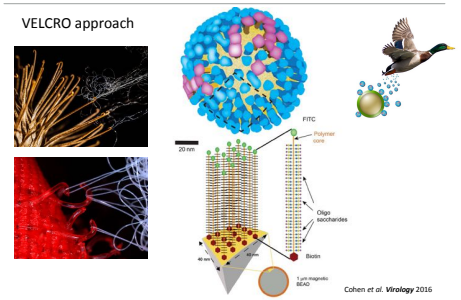
Birds and bats, carry many infectious agents and share these with humans and other species.

Agricultural practices facilitate the evolution of novel pathogens.

Climate change is changing the range of many vector borne diseases.

Conservation and prevention of emerging diseases care many goals (Ecohealth).

3-D Multivalent glycan bead array



The Gagneux lab developed special glycan probes on magnetic beads to capture influenza A virus from cloacal samples of wild birds, or nasal swabs of seals.