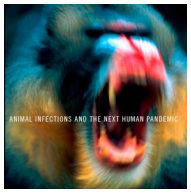
Eco Health - Emerging Disease



ANBI 139 Evolution of Human Disease
Pascal Gagneux

Winter 2021

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

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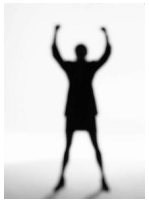
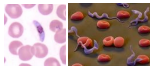
What Pathogens?

Viruses:
HIV
Polio
Hepatitis B
Hepatitis C
Influenza
Measles
Smallpox
Monkeypox
Yellow Fever
West Nile
Zika
Dengue
Chikungunya
Corona
Ebola
Hanta



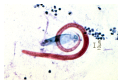
Protozoans:
Plasmodium (malaria)
Trypanosome (sleeping sickness, Chagas)
Leishmania (leishmaniosis)
Trichomoniasis (trich)
Toxoplasma gondii



Prions:
Kuru, Scrapie
Mad Cow Disease
Elk wasting disease
Creutzfeld Jakob Disease
Spongiformr encephalopathy

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

Helmitnhs:
Tapeworm
Hookworm
Spoolworm
Filaria
Shistosomes



Fungi:
Candida
Pneumocystis
Cryptococcus

Most emerging diseases are viral or bacterial.

Practice question: List five major classes of human pathogens?

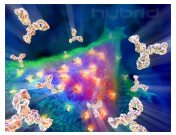
Answer: Viruses, bacteria, protozoans, helminths and fungi & prions.

Immune defenses

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

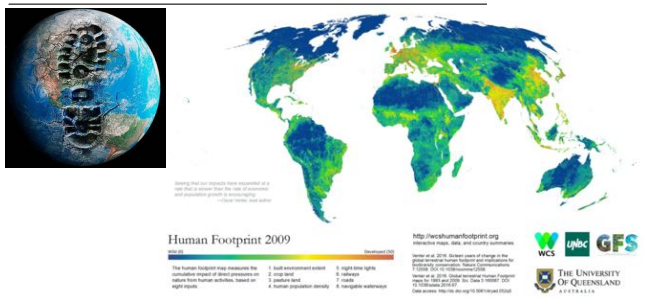
Natural killer cells attacking a tumor

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



Antibodies homing in on a tumor cell

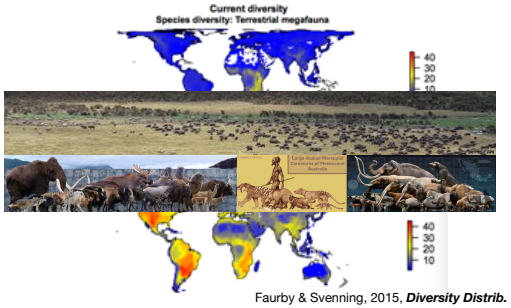
Where we live



Human footprints on the planet depend on numbers of people and the amount of energy used by those people.

Practice question: List for areas where the human footprint is particularly strong on the planet.
Answer: east Asia, South Asia, Europe, and Eastern North America.

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

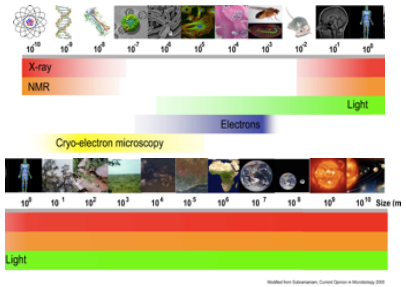
Practice question:

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!

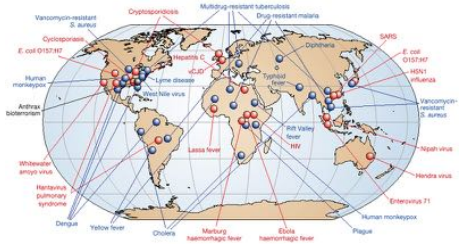


Human encroachment

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

New road in the Congo

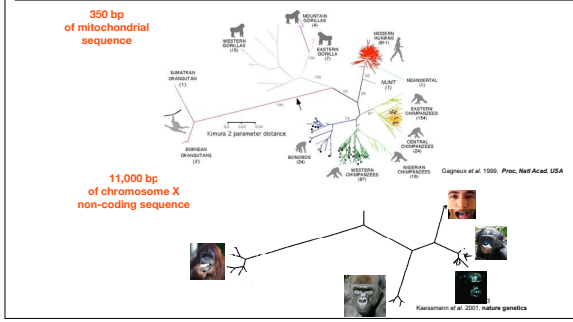
Emerging Diseases



The challenge of emerging and re-emerging infectious diseases
David M. Morens, Gregory K. Folkers & Anthony S. Fauci
Nature 430, 242-249(8 July 2004)

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 great 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.

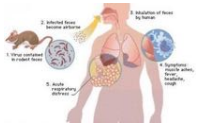
Pascal's personal journey:

David Woodruff

Jeanne Messier

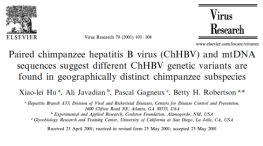
UC San Diego Grad student
victim of Hanta virus

Nicholas Mundy



Visiting graduate student in a biology lab at UCSD with the late David Woodruff.
Met Nick Mundy who had just spent three years in Gabon and seen 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:

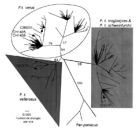


Virus Research

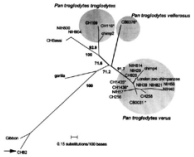
Paired chimpanzee hepatitis B virus (ChHBV) and mtDNA sequences suggest different ChHBV genetic variants are found in geographically distinct chimpanzee subspecies

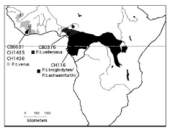
Xiao-lei Hu, Ali Javadian, Pascal Gagneux, Betty H. Robertson

Virus DNA (hair)



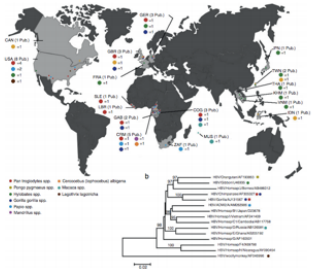
chimpanzee DNA (hair)

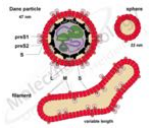


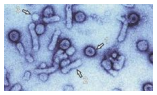


Collaborated with people at the CDC on chimpanzee HBV, chimpanzee genetics gives us clues o the evolution of Hepatitis B viruses.

Hepatitis B, an Orthohepadnavirus



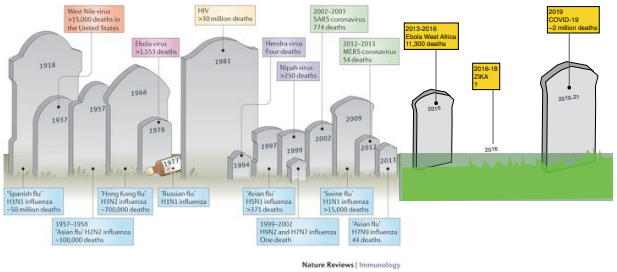




Breno et al Braz J Infect Dis . 2 0 1 4;18(5):535–543

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)

Zoonoses over time

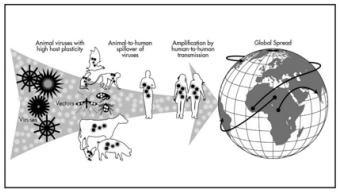


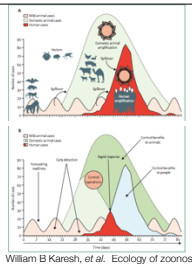
Studying immunity to zoonotic diseases in the natural host — keeping it real. Andrew G. D. Bean, Michelle L. Baker, Cameron R. Stewart, Christopher Cowled, Celine Deffrasnes, Lin-Fa Wang & John W. Lowenthal Nature Reviews Immunology 13, 851–861 (2013)

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

These can get out of hand or resolve relatively quickly.

Modern Zoonoses and there dynamics





Kreuder Johnson, C., Hitchens, P., Smiley Evans, T. et al. Spillover and pandemic properties of zoonotic viruses with high host plasticity. ***Sci Rep*** 5, 14830 (2015). https://doi.org/10.1038/srep14830

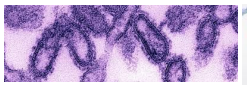
William B Karesh, *et al.* Ecology of zoonoses: natural and unnatural histories ***The Lancet*** V380, 9857, P1936-1945, 2012 https://doi.org/10.1016/S0140-6736(12)61678-X

Figure: Clinical relevance of disease ecology

(A) Transmission of infection and amplification in people (bright red) occurs after a pathogen from wild animals (pink) moves into livestock to cause an outbreak (light green) that amplifies the capacity for pathogen transmission to people.

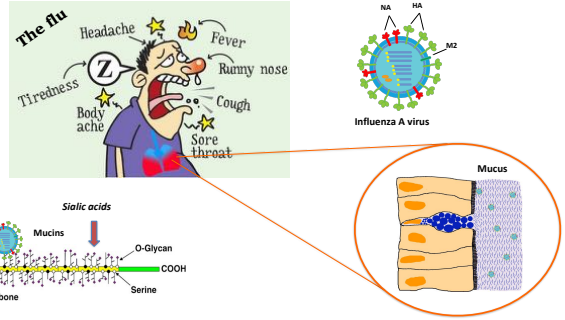
(B) (B) Early detection and control efforts reduce disease incidence in people (light blue) and animals (dark green). Spillover arrows shows cross-species transmission.

1918 “Spanish” Flu (H1N1)



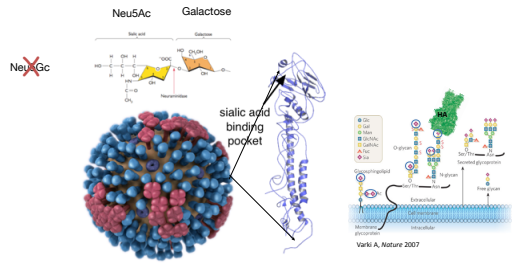
The biggest infectious event of the 20th century killed more people than both world wars combined!

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 mucins in order to penetrate towards the cell surface.

Viruses use host glycans as receptors

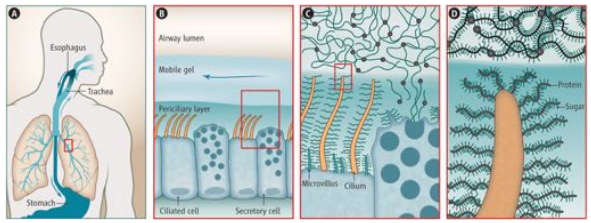


specific for monosaccharides and glycosidic linkage type!

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

Defensive host glycans as barriers and decoys

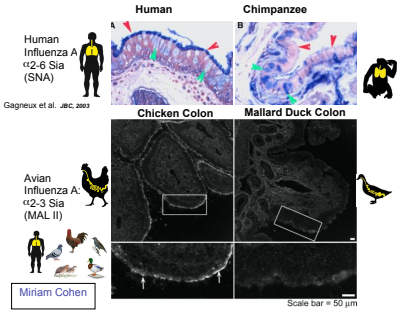
A mobile mucus gel is continually swept out of the lungs and swallowed (blue).



B. F. Dickey *Science* 2012

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 coils.

Why apes do not get the flu



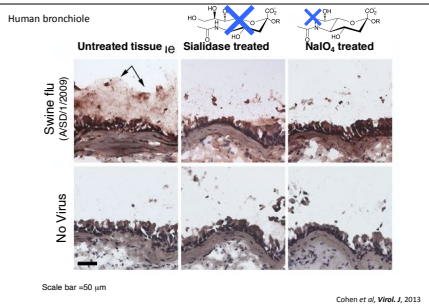
The sialic acid in the lung of chimpanzee are different and differently linked, they do not get the flu! In adapting from bird host to human host, the preference of the virus for the linkage of sialic acid changes (one or two mutations in the protein sequence of the hemagglutinin are enough to cause 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 virus?

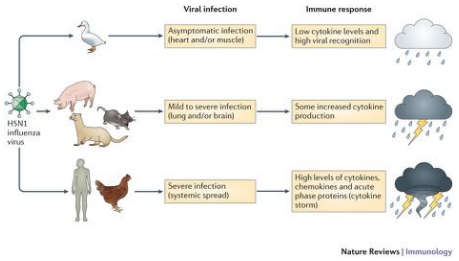
Changes in nature and/or distribution of cell surface molecules (proteins, glycasn or lipids)

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)

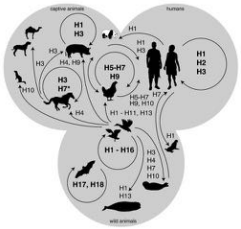
What a wild bird virus can do to us



H5N1 bird flu has dangerous potential! Mutations identified can let the bird virus switch to airborne transmission in humans!

Influenza A

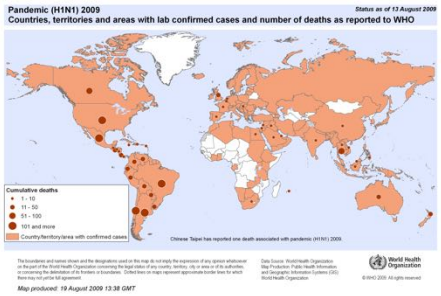
Very diverse pool of viruses existing in wild aquatic birds



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

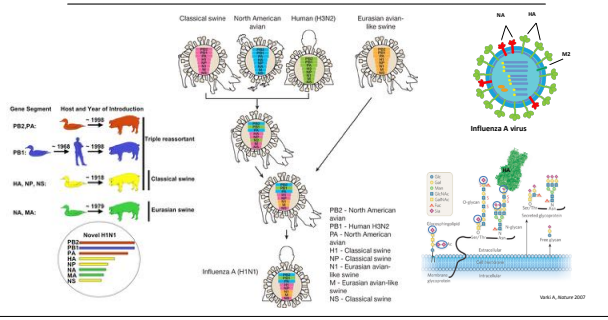
Practice question:
Why is it totally unrealistic to eradicate influenza viruses?
They have a gigantic reservoir in many species of wild water birds that migrate across the planet.

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

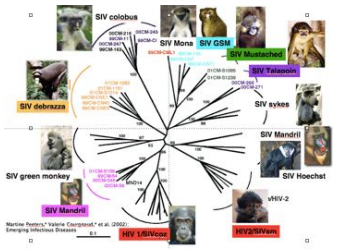
It is now clear that HIV/AIDS emerged as a zoonosis bin Central Africa around the turn of the the 1900s.

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).

Again, no depiction of the many complex glycan molecules on both, the virus glycoprotein “mushrooms” or the host cell surface.

All other African primates have their own SIV

SIV in > 30 species of primates

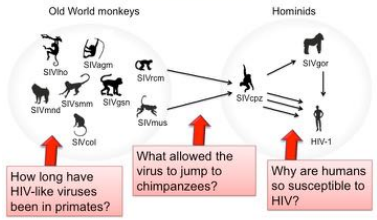


Humans only acquired HIV from African primates at the beginning of 1900s.

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

Most African non-human primates each have their own versions of HIV, named SIV (simian immunodeficiency virus, a misnomer, as most other African primate species do not get sick).

What caused the virus to jump?



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

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)*

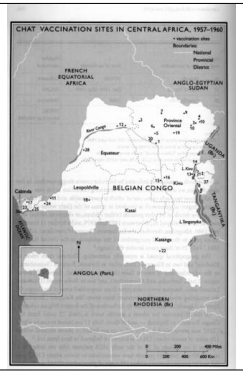
Two African assistants dismembering a dead chimp in the

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

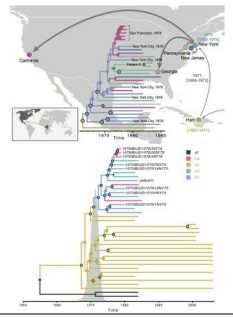
Logging roads are made by international logging companies. Once a road is made, many locals and migrant use it to enter the forests and establish camps along or near the road. These new settlers hunt for their meat and start depopulating all animal populations. They can use bush meat a a cash crop, utilizing 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:

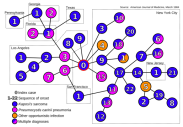
How could logging roads affect emerging diseases?

see above

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

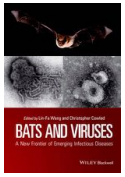
Protecting the environment and preventing diseases

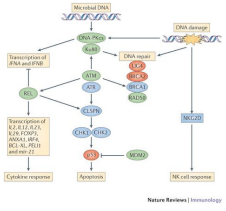
The idea of Eco health is that conservation of ecosystems can contribute to our understanding of emerging diseases and too their prevention.

Bats

Adapted to high viral loads?

Active flight shaped the immune system of bats.





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). Professor Linfa Wang studies bats in Singapur for their immunity to viruses and their capacity to avoid cancer.

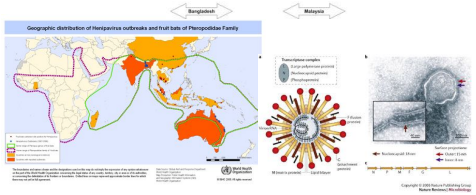
Practice question:

Why are bats so important for monitoring emerging viral diseases?

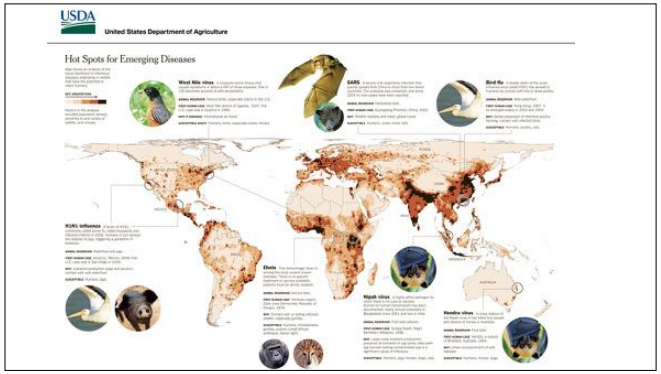
Their high mobility and resistance to viruses make them ideal reservoirs.

Bats and Nipah Virus

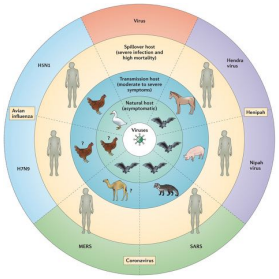
Pteropus megabat



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



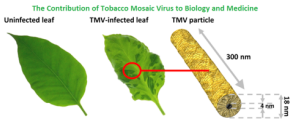
Many paths for a zoonotic virus to human hosts



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 (Pasteur- Chamberland filters that exclude bacteria because the porcelain has pores that measure 0.1 to 1 microns (100 nm to 1 um).

Vaccines: Most Successful Intervention of Medicine

Inactivated: dead whole pathogen
Attenuated: live infectious pathogen manipulated to generate a non-pathogenic state.

Down sides:
not as good an antigen

potential reversal to pathogenic

Subunit vaccines: only part of the pathogen (surface glycoprotein) is used, non-infectious

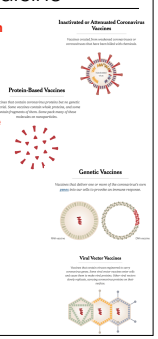
not presenting diverse enough"face" of virus

Genetic vaccines: RNA or DNA encoding viral antigens In viral vector or lipid nanoparticle.

new, limited on longterm risk

Viral vector vaccines: DNA from the virus is Inserted into the capsid of a Harmless virus as delivery vehicle.

little information on longterm risk, limited antigen



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

Practice question: List three types of different anti-viral vaccine with regard to how these are produced and delivered to humans.
Answer: Inactivated, attenuated live, subunit, genetic, viral vector.

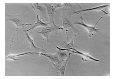
Growing virus to make vaccines:

Primary tissue culture

Primate Kidneys

Hens' eggs

Cell lines

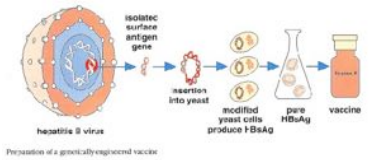


Bioreactor

N-1 at 40 L
Xcellerex XDR-200

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. Animal or human cell lines each carry risks of disease transmission, plant cells are also used, latest technology uses cell-free reactors to synthesize viral RNA (e.g. Pfizer)

Hepatitis B subunit vaccine

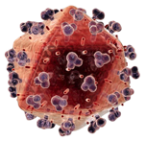


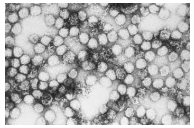
First successful anticancer vaccine

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.

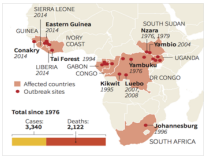
Yellow Fever, a flavivirus





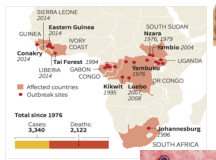
yellow fever is the only flavivirus that can be prevented with a very efficient vaccine.

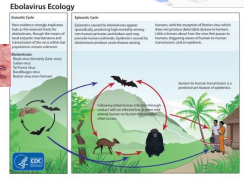
Ebola, a filovirus



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

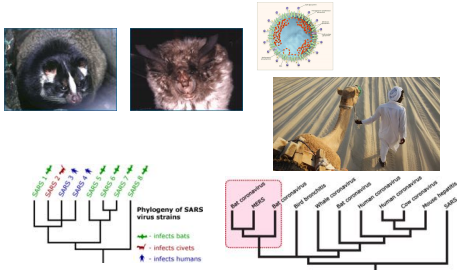
Ebola





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



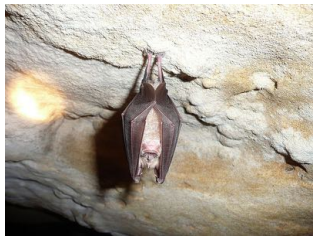
Severe Acute Respiratory Syndrome virus (SARS). News update, July 2013
Since September 2012, a mysterious respiratory infection has been spreading through hospitals in Saudi Arabia and has popped up in nearby countries. MERS (Middle East Respiratory Syndrome) is a coronavirus, like SARS, and has health 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.

Bats affected by novel diseases themselves

white nose syndrome in little brown bat, USA East Coast



greater horse shoe bat Rhinolophus

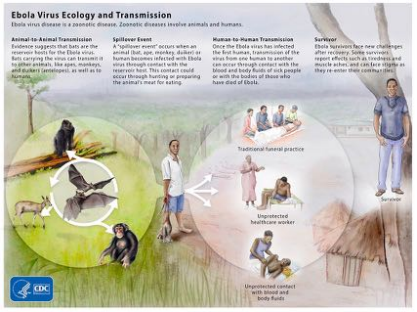
Bats affected by fungal “white nose” disease shed much more corona viruses in their feces!
Davy, C.M.; Donaldson, M.E.; Subudhi, S.; Rapin, N.;Warnecke, L.; Turner, J.M.; Bollinger, T.K.; Kyle, C.J.; Dorville, N.A.S.; Kunkel, E.L.; et al. White-nose syndrome is associated with increased replication of a naturally persisting coronaviruses in bats. Sci. Rep. 2018, 8, 15508.

Ebola (a very scary filovirus)

Virus hides in plain sight and travels widely via fruit bat hosts who do not get sick, but carry plenty of viruses.

Epauletted fruit bat

Hammerhead fruit bat



Epauletted fruit bat (Epomops franqueti) and Hammerhead fruit bats (Hypsignathus monstrosus) have been found to carry Ebola virus but show no signs of disease!

Monitoring bats and their viruses

A team of researchers from the Wuhan Institute of Virology and the EcoHealth Alliance have trapped bats in caves all over China, like this one in Guangdong, to sample them for coronaviruses.
A research group sent fecal and other bodily samples from bats they trapped in caves to the Wuhan Institute of Virology to search for coronaviruses.
As part of a long-running effort to see what viruses bats harbor, researchers in China examine one temporarily captured in a cave in Guandong. ECOHEALTH ALLIANC

Professor Zhengli Shi from the Wuhan Institute of virology has long studied bat corona viruses. In a paper from 2019. she and her colleagues essentially predicted the current pandemic: https://www.mdpi.com/1999-4915/11/3/210

Wildlife trade, bush meat (wet) markets

Shenzhen, China

N. Sulawesi, Indonesia

Democratic Republic if Congo

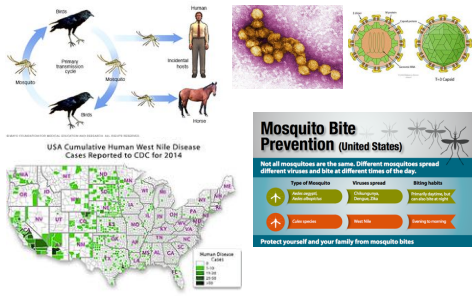
San Diego

Wuhan, China

Seattle

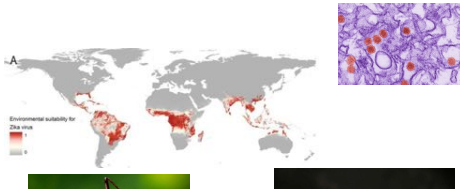
“Wet Markets” where animals caught in the wild are directly sold to customers for food.

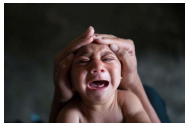
West Nile, a flavivirus



WNV is a bird virus that can cause deadly infections in mammals.

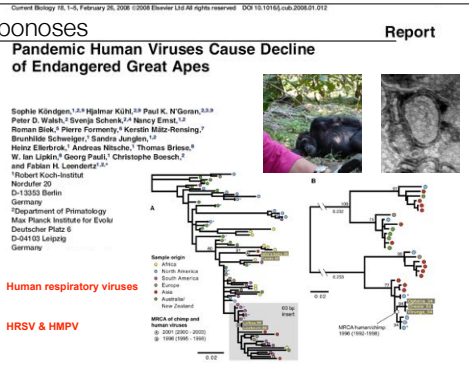
ZIKA, a flavivirus





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

Anthroponoses



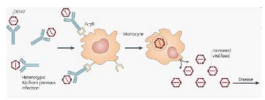
Humans can also pas dangerous viruses to non-human primates, such as these respiratory viruses that caused the death of wild chimpanzees.

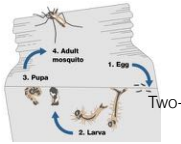
Practice question: What do you call a disease in non-human animals caused by a human pathogen?

Answer: An Anthroponosis.

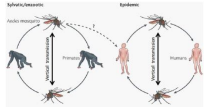
Dengue, another flavivirus

Hemorrhagic Dengue: second round of infection becomes deadly!





Two-day life cycle!



Whitehead SS, Blaney JE, Durbin AP, Murphy BR2007Prospects for a dengue virus vaccine. Nat Rev Microbiol 5518528

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.

Which is the better approach to conservation?

Stop this ! Shock with the negative?

or

Preserve this ! Elicit Sympathy and Concern?

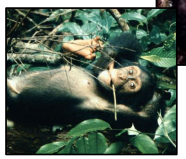
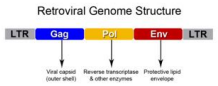
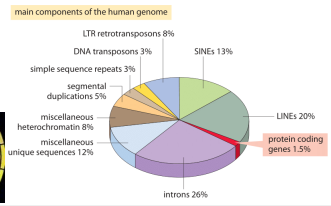


photo Karl Amman

Molecular Parasites in your genome: rubbish or opportunity?



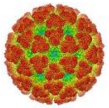


More about viruses as active, creative agents in evolution in a later lecture.

Chikungunya, a togavirus

Another virus from forest primates of Africa





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).

Summary

Humans have become a planet-altering force.

Human contact with wildlife is ever more invasive: it is the main facilitator of emerging diseases.

Microbes inhabit all animals and can become pathogenic after crossing into novel species: emerging disease!

Wild animals can also be affected by novel diseases and this can increase the chance of them spreading pathogens to humans.

We have to stop the uncontrolled pillaging of wild animals for human consumption.

We have to rethink how we use animals in the context of emerging diseases: spill over infections and antibiotic resistance in farm animals.