14 SATURDAY
WEEK 37

14.7.2020

SEPTEMBER, 2013

EMERGING VIRUSES

- causative agent of a new or previously unrecognized infection.
- the term became popular in 1990s, but emerging viruses are not new.
- since the rise of agriculture - 11,000 years ago - new infectious agents have invaded human populations because they can be sustained by numbers that were unknown before agriculture & commerce.
- only recently have we become good at detecting emerging viruses.
- KILLER VIRUS: BEYOND THE EBOLA SCARE
  WHAT ELSE IS OUT THERE

15 SUNDAY
WEEK 37

- FEVER!

LASSAVIRUS (RODENT RESERVIOR)

A TRUE MEDICAL DETECTIVE THRILLER WITH ALL THE DRAMA OF THE ANDROMEDA STRAIN
· THE HUNT FOR A NEW KILLER VIRUS.

SEPTEMBER						2013
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NOTES

before agriculture, humans were hunter-gatherers. they lived in small communities, didn't support much infection; certainly there were infections. they didn't typically spread beyond them.

EMERGING VIRUS

- expanded host range with an increase in disease not previously obvious.

- transmission of a virus from wild or a domesticated animal to humans - <u>zoonosis</u>.

- cross-~~vi~~ species infection (spillover) may establish a new virus in the population (SIV moving from chimps to humans, SARS-CoV-2).

- often cross-species infection (spillover) cannot be sustained. (eg. ebolavirus from bats to humans, MERS-CoV from camels to humans).

OVER-RIDING FACTORS DRIVING THE EMERGENCE OF INFECTIOUS DISEASES OF HUMANS AND ANIMALS

- human population growth and incredible change ocurring in all ecosystems brought about by human occupation of almost every corner of the planet.

0: 0.3b 1500: 0.5b 1700: 1b 2000: 7.1b
past world popolation growth.

NOTES zika virus - was discovered in 1947, however it wasnt until 2015 that we recognized that that moquito transmitted flavivirus could cross the placenta, and cause microcephaly & other congenital birth defects.

SEPTEMBER						2013
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14.7.2020
3

ECOLOGICAL AND ANTHRPOGENIC ACTIVITIES THAT PROMOTE VIRUS EMERGENCE

• humans continuosly devise new ways to encounter viruses.

- dams & water impoundments
- irrigation
- massive deforestation
- rerouting of wildlife migration patterns.
- wildlife parks.
- longdistance transport of livestock & birds. exotic pets
- climate change
- natural disasters
- air travel
- uncontrolled urbanization
- day care centers
- hot tubs
- air conditioning
- millions of used tires mosquitos
- blood transfusion
- xenotransplantation
- societal changes with regard to drug abuse & sex.

SEPTEMBER						2013
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8	9	10	11	12	13	14
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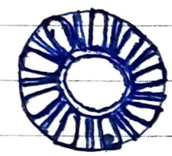
NOTES

THE AMAZON NORTH REGION OF BRAZIL

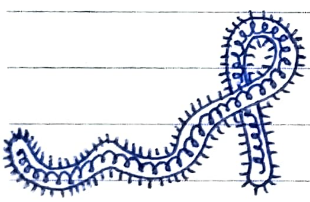
home to 183 arthropod-borne and other vertebrate viruses.

FACTORS THAT LEAD TO EMERGENCE OF NEW VIRUSE

- dengue virus — flaviviridae — urban population density; open water storage favoring mosquito breeding (e.g., millions of used tires).



- ebola virus — filoviridae — human contact with unknown natural host (africa).



- hantaan virus — bynyaviridae — agricolture: human-rodent contact during rice harvest.

NOTES

SEPTEMBER 2013

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8	9	10	11	12	13	14
15	16	17	18	19	20	21
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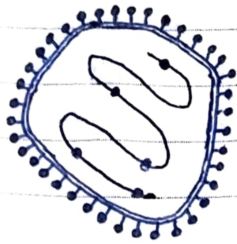
14.7.2020
5

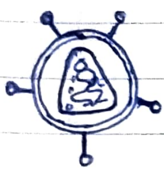
19 THURSDAY
WEEK 38

SEPTEMBER, 2013

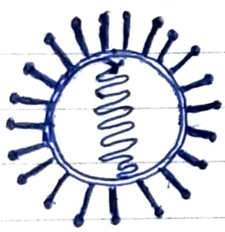
• hendra virus	paramyxoviridae	proximity of froit bats favors transmission to horses & Stable workers.



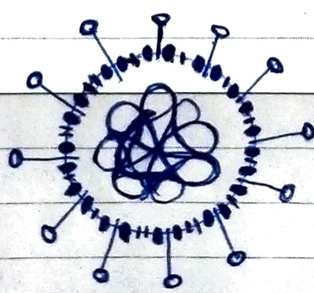
• human immunodeficieny virus type I	retroviridae	hunting and butchering of infected primates (bushmeat trade).



• influenza virus	orthomyxoviridae	reservoir in aquatic birds, expansion of bird & pig farming.



• middle east respiratory syndrome (MERS) coronavirus	coronaviridae	camel husbandry, contact with humans.



SEPTEMBER 2013

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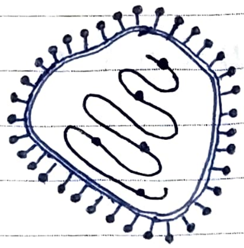
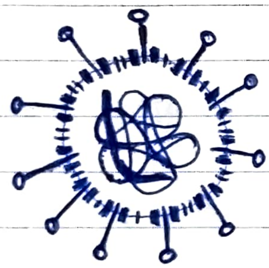
14.7.2020

6

- nipah virus — paramyxoviridae — proximity of fruit bats, the natural reservoir, favors transmission to pigs & then to humans.

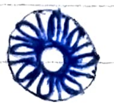


- severe acute respiratory syndrome (SARS) coronavirus — coronaviridae — open-air meat markets



- sin nombre virus — hantaviridae — natural increase of deer mice and subsequent human-rodent contact.

- west nile virus — flaviviridae (from israel). — mosquito transmission from bird reservoir, global travel.



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- zika virus — flaviviridae — mosquitoes, global travel.

SEPTEMBER 2013

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15	16	17	18	19	20	21
22	23	24	25	26	27	28
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SARS-CoV-2 — coronaviridae — ? likely bat)

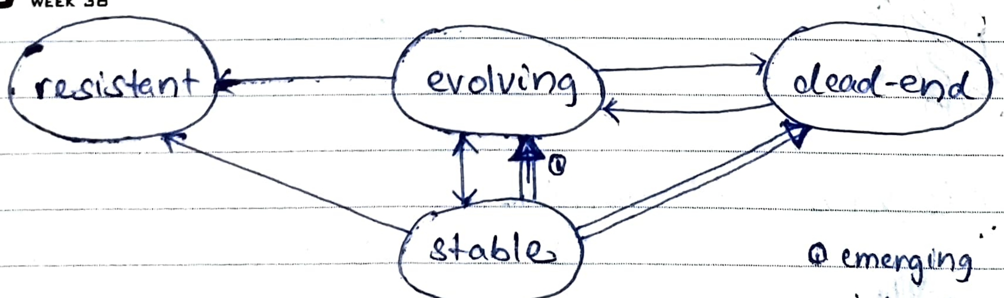
ROLES OF EVOLUTION

- leads to biodiversity of pathogens existing in nature (quasispecies)
- adaptation to new host & environments (through variation & selection).

GENERAL CATEGORIES OF INTERACTION BETWEEN HOSTS AND VIRUSES

- stable: maintains virus in ecosystem.
- evolving: passage of virus to naive population (same ~~of~~ or different host)
- dead-end: one way passage to different species.

- resistant host: infection blocked.



① emerging infections

many of these viruses are emerging RNA viruses, and populations are incredibly diverse.

Somewhere in that diversity of viruses in those animals, there is a virus that could infect humans perhaps, just randomly arising by the enormous diversity.

STABLE HOST-VIRUS INTERACTIONS

- both participants survive & multiply
- some are effectively permanent
  - humans are sole natural host for measles virus, herpes simplex virus, HCMV, smallpox
- may include infection of more than one species
  - influenza A virus, flaviviruses, togaviruses.

EVOLVING HOST VIRUS RELATIONSHIP

- hallmarks of instability & unpredictability
- outcome of infection may range from benign to death.
  - introduction of small pox & measles to natives of americas by old world colonists & slave traders (wiped them out)
  - introduction of west nile virus into western hemisphere, 1999. (established in native birds)
  - introduction of myxoma virus to eliminate rabbits into australia.

NOTES

SEPTEMBER						2013
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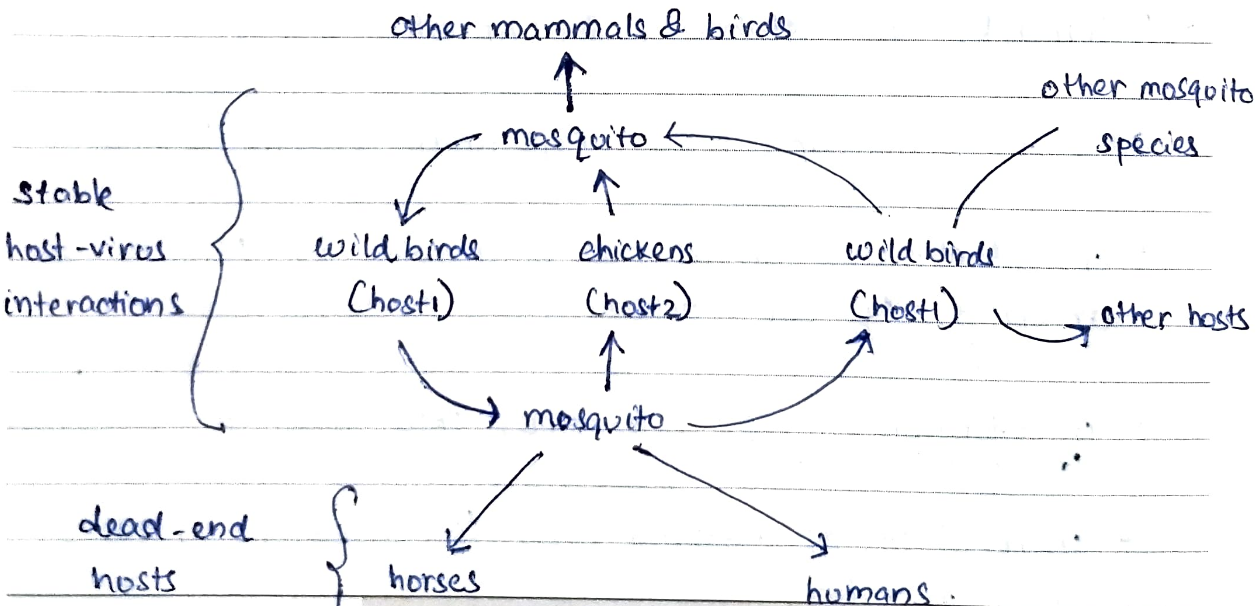
DEAD-END INTERACTION

- (very) frequent outcome of cross-species infection
- no sustained transmission from new infected host to others of the same species.
- ebolavirus: humans, chimps, gorillas.
- influenza H5N1 virus (highly pathogenic avia influenza virus) (rarely come into humans, short chains)
- contribute little to the spread of infection.

EXAMPLES OF STABLE AND DEAD-END HOST VIRUS RELATIONSHIP.



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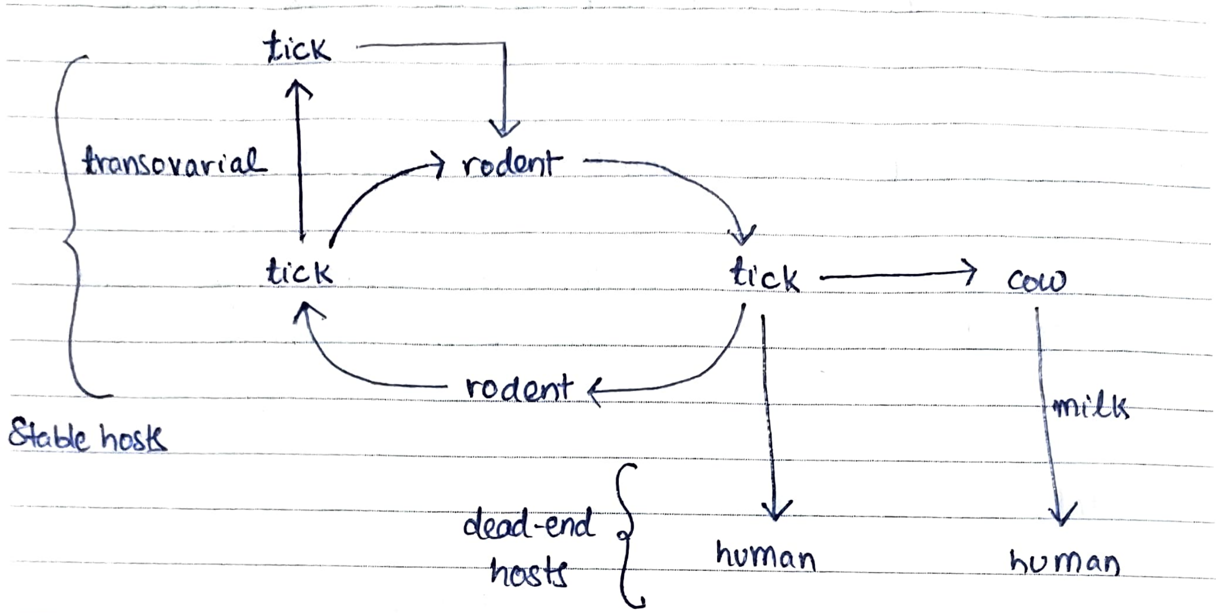
22	23	24	25	26	27	28
29	30					

NOTES

typically the stable hosts are fine with the virus, they dont get sick. these are long-standing infections that have evolved for many many years.

STABLE AND DEAD-END RELATIONSHIPS: TICK BORNE ENCEPHALITIS VIRUS



EMERGING INFECTIONS: TWO STEPS

- introduction
- establishment & dissemination

ENCOUNTERING NEW HOSTS

- rare chance encounters of viruses with new hosts may never be detected.
- Single-host infections are not transmitted among humans for many reasons

NOTES

rodents dont get sick typically
tick-rodent cycle

SEPTEMBER 2013

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8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

eggs of a female tick can harbor the virus, when the female lays eggs, and they hatch into new ticks, the ticks will have the virus.

14.7.2020
11

EXPANDING VIRAL NICHES

- successful encounters require access to susceptible & permissive cells.

- population density & health are important factors.

- virus populations will endure in nature only because of serial infections (a chain of transmission).

ORIGINS OF SMALLPOX VIRUS

- phylogenetic analysis of related viruses & their hosts suggest emergence 3000-4000 years ago in east africa, transmitted from camels.

- camels were introduced to africa 3500-4500 years ago.

- camels likely infected with a smallpox virus ancestor from gerbills.

a rodent

SEPTEMBER						2013
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NOTES

Smallpox has been eradicated, looking at all varieties of pox viruses & their hosts, we think that this virus emerged 3000-4000 years ago in easter africa, transmitted to humans, from camels.

ORIGINS OF MEASLES VIRUS

- measles virus is closely related to rinderpest virus, a bovine pathogen.

- probably evolved from an ancestral rinderpest virus when humans first began to domesticate cattle (11th - 12th centuries, 1000-1200)

- established in the middle east when human populations began to congregate in cities (MV maintenance requires populations of 250,000-500,000.

- spread around the world by colonization & migration, reaching americas in 16th century & destroying native americans.

DISEASES OF EXPLORATION AND COLONIZATION

- explosive epidemic spread may occur when a virus enters a naive population.

- Smallpox reached europe from the far east in 710 AD, attained epidemic proportions

- Smallpox changed the balance of human populations in the new world - killed 3.5 million aztecs in 2 years (1520. spread from hispaniola), allowing conquest by Cortez.

NOTES

SEPTEMBER						2013
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15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30					

CHANGES IN HUMAN POPULATIONS AND ENVIRONMENTS

- emergence of epidemic poliomyelities in the begining of the 20th century.
- known since 4000 years ago, sporadic cases, stable host-virus relationship.

POLIOMYELITIS: A DISEASE OF MODERN SANITATION

- pre-1900, poliovirus circulated freely and infected mostly shortly after birth.
- maternal antibodies prevented paralysis.
- improved sanitation (toilet & sewers) delayed infection until later in life = epidemic poliomyelitis.

- had there been genome sequencing in 1908, would the emergence of epidemic polio been blamed on mutation?

SEPTEMBER						2013
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NOTES

paralysis due to polio is only 1 in 100. so there is lots of infections, lots of spread. fecal or oral spread of this virus, but suddenly at the begining of 1900s this virus started to cause epidemics of bigger & bigger size, until in the US alone 20-30,000 cases.

CHANGING CLIMATE AND ANIMAL POPULATIONS

- hantavirus pulmonary syndrome - first noted in four corners area of new mexico, 1993.
- disease is caused by sin nombre virus, endemic in deer mouse (peromyscus maniculatus, 30% virus positive)
- originally called muerto canyon virus, but residents objected. (bunya viridae)

CHANGING CLIMATE AND ANIMAL POPULATIONS

- in 1992-1993, abundant rainfall produced a large crop of piñon nuts, food for humans & the deer mouse. mouse population rose, contact with humans increased.
- virus is excreted in mouse feces; contaminated blankets or dust from floors provided opportunities for human infection.
- humans are not the natural host for sin nombre virus, human disease is rare.
- not new, earliest known case 1959.

NOTES
HPS - a very serious respiratory disease
sin nombre - no name

HPS BY STATE, JANUARY 2017 n=728
RANGE OF P. MANICULATUS

SEPTEMBER 2013

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22	23	24	25	26	27	28
29	30					

14.7.2020
15

BATS: A SOURCE OF ZOONOTIC INFECTIONS

- many new paramyxoviruses + measles. found in flying foxes since 1995, including nipah & hendra viruses.
- cause severe disease in domestic animals (horses & pigs) & infect humans.
- bats host major mammalian paramyxoviruses
  66 new paramyxoviruses from 119 bat & rodent species.

HENDRA VIRUS

- discovered in hendra, australia, september 1994
  - outbreak killed 14 racehorses & a trainer.
- spread from flying foxes to horses, then to humans.
- horses continue to acquire infection.
- vaccine for horses: one world health: (approach)

OCTOBER						2013
S	M	T	W	T	F	S
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NOTES

bats - flying foxes - 3ft from top to bottom
dracula embodied.

these infections (hendra v) continued for a no. of years. finally a vaccine was developed for horses specifically.

NIPAH VIRUS

- first outbreak, malaysia 1998.
  - outbreak of respiratory & neurological disease on pig farms.
  - 105 human deaths, 1 million pigs culled.
- fruit bats are unaffected, excrete virus in urine
- pig farmers plant mangoes near pigpens
- pigs spread infection to humans.
- Subsequently humans infected by consuming date palm sap contaminated by bats (india, bangladesh).
- human to human transmissions; infections continue.

OUTBREAKS OF EBOLAVIRUS DISEASE

each outbreak represents a new zoonotic spillover.

NOTES

in perak region of malaysia (started).
CEPI has prepared a nipah vaccine and its ready for phase 1 trials. (using donations).

OCTOBER						2013
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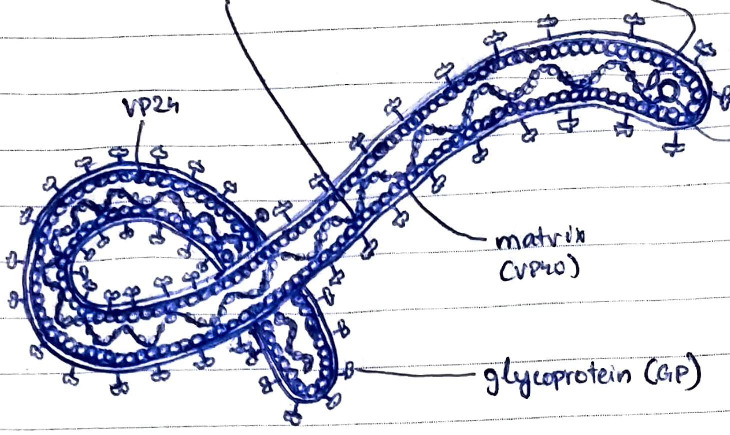

(-)-strand RNA

3' ∿∿∿∿∿∿∿∿∿∿∿∿∿∿∿∿∿∿∿∿ 5'

↓ mRNA synthesis

(+)-strand RNA

5' [C] ∿∿ AnAOH 3' → NP

5' [C] ∿ AnAOH 3' → VP35 IFN antagonist

5' [C] ∿ AnAOH 3' → VP40 IFN antagonist

5' [C] ∿∿ AnAOH 3' → GP tetherin antagonist

5' [C] ∿ AnAOH 3' → VP30 RNA synthesis

5' [C] ∿ AnAOH 3' → VP24 IFN antagonist

5' [C] ∿∿∿∿∿∿∿ AnAOH 3'

↓ translation

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20	21	22	23	24	25	26
27	28	29	30	31		

NOTES

HOW ARE HUMANS INFECTED?

- a classic zoonosis
- index case: contact with animal carcass* (bushmeat)
- transmitted to other humans by close contact with infected fluids
- chains of human infection short
- $R_0 = 2$

EBOLAVIRUS OUTBREAK EXAMPLES

- gabon, 1996 (zaire ebolavirus, 37 cases) a chimpanzee found dead in the forest was eaten by people hunting for food. eighteen people who were involved in butchering the animal became ill. ten other cases ocurred in their family members.
- gabon, 1996-97 (zaire ebolavirus, 60 cases) the index case was a hunter who lived in a forest camp. a dead chimpanzee found in the forest at the time was infected with ebolavirus.

NOTES
EBOLAVIRUS EMERGENCE IN GUINEA

OCTOBER						2013
S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

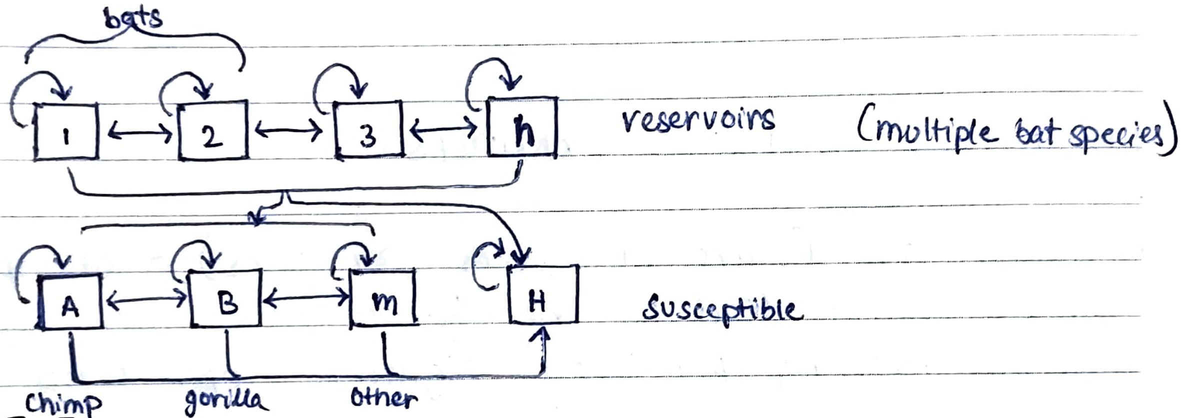
05 SATURDAY
WEEK 40

OCTOBER, 2013

FILOVIRUS ECOLOGY

- marburg virus has been isolated from cave-dwelling fruit bat Crousettus aegyptiacus)
- zaire ebolavirus RNA, antibodies found in three tree-roosting bats (but not infectious virus).
- humans, gorillas, chimpanzees are dead-end hosts.

WHAT IS THE ORIGIN OF EBOLAVIRUSES?



06 SUNDAY
WEEK 40

HUMAN-HUMAN TRANSMISSION

- contact with infected blood or body fluids (urine, saliva, sweat, feces, vomit, breast milk, semen) from someone who is sick, or has died.

OCTOBER 2013

S	M	T	W	T	F	S
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NOTES

- contact with contaminated objects (needles, syringes)
- not by insects, water, food, or aerosol.

HOST ENTRY

- mucosal surfaces
- breaks or abrasion in skin
- parenteral (e.g. contaminated needles)
- virus detected in skin, body fluids, nasal secretions, blood, semen.
- incubation period 2-21 days (not contagious)

CLINICAL FEATURES: MULTISYSTEM INVOLVEMENT

- systemic (prostration)
- gastrointestinal (anorexia, nausea, vomiting, abdominal pain, diarrhea)
- respiratory (chest pain, shortness of breath, cough)
- vascular (conjuctival injection, postural hypotension, edema)
- neurological (headache, confusion, coma)

NOTES

- 30-90% case fatality ration in africa.

OCTOBER						2013
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SARS - RISE AND FALL OF A ZOONOTIC INFECTION
(feb, 2003) (promedmail.org)

SARS • (SEVERE ACUTE RESPIRATORY SYNDROME)

- outbreak of severe atypical pneumonia, unknown etiology, guangdong province, china, nov 2002.
- - 305 cases, 5 deaths
- incubation period 2-10 days
- illness begins with prodrome of fever
  - chills, headache, malaise, myalgia (flu-like)
- next phase: dry cough, shortness of breath
- 10-20% may require mechanical ventilation.

15.7.2020

SARS

- a chinese doctor who treated first patients traveled to hong kong on 21 feb 2003, stayed on 9th floor of metropole hotel.
- he died in hospital 22 february
- infection spread to 10 people in hotel, who flew to singapore, vietnam, canada, US before symptoms evident.
- infection spread to 8000 people in 29 countries, 10% mortality. ~~the~~ (travel poster: hong kong will take your breath away)

PROBABLE SARS CASES WORLDWIDE REPORTED TO WHO AS OF SEPT 26, 2003.

total: 8098 cases ; 774 deaths (9.6% case fatality)
outbreak ends july 2003.

NOTES

this virus was eventually isolated, turned out to be a coronavirus, this was a shock to everyone at the time, because we had known of 2 coronaviruses up until this point, they were isolated in the 60s caused common colds, this was the 1st time an epidemic coronavirus that caused serious illness had been identified, awakened the world to coronaviruses.

OCTOBER 2013

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27	28	29	30	31		

15.7.2020
23

ORIGIN OF SARS-CoV

- human sera collected before SARS outbreak do not contain antibodies to SARS-CoV.

- early guandong SARS cases were in handlers of animals for the exotic food market.

- animal traders had significantly higher prevalence of anti-SARS-CoV antibodies than control groups.

- highly diverse SARSr-CoV (related) found in horseshoe bats (rhinolopus) in a cave in yunnan province.

- all genetic elements needed to form SARS-CoV in this cave.

- no direct progenitor of SARS-CoV has been found.

- direct progenitor of SARS-CoV thought to have emerged in bats, then infected civet cats which were then transported to guangdong markets.

bat ⟶ civet cat ⟶ SARS-CoV

MERS-CoV

- index case September 2012: 60yo male patient, died of pneumonia, renal failure.
- virus recovered, genome sequenced, binds dipeptyidyl peptidase 4 receptor.
- closely related to bat coronaviruses
- not SARS-CoV. (ACE-2)
- spread from dromedary camels (endemic in middle east & africa)
- not all infections have camel source
- how is the virus transmitted to humans? (mainly very ill)
- why are so few humans infected? will it spread?
- virus does not transmit well among humans.
- camel vaccine in testing (one health approach).

bats $\xrightarrow{\text{at some time}}$ dromedary camels → MERS-CoV.
(with one hump)

NOTES

OCTOBER						2013
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27	28	29	30	31		

MERS- COV TRANSMISSION AND GEOGRAPHIC RANGE

2494 cases / 858 deaths / 27 countries (CFR 34.4%)

SARS-CoV-2, FIRST PANDEMIC OF THE 21ST CENTURY

- cluster of pneumonia cases, unknown cause, wuhan, december 2019.
- huanan seafood marked initially suspected as origin, no longer true.
- as of april 2020, 2.4 million reported cases, 165,000 deaths.
- R_0 2-3, 80% of infections are mild.

ORIGIN OF SARS-CoV-2

beta-CoV
96% nucleotide identity with bat CoV RaTG13 (2013)

RECOMBINATION EVENT IN AN ANCESTOR OF SARS-COV-2 ENCOMPASSES RBD

OCTOBER			2013			
S	M	T	W	T	F	S
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

NOTES

ORIGIN OF HUMAN CORONAVIRUSES, - IN NATURE, NOT IN A LAB

- bat → ? → HCoV-NL63
- bat → llama → HCoV-229E
- mouse → cow → HCoV-OC43
- mouse → ? → HCoV-HKU1
- bat → civet cat → SARS-CoV
- bat → dromedary camel → MERS-CoV
- bat → pig $\xrightarrow{?}$ SADS-CoV
- bat → ? → SARS-CoV-2

TWiV 296: THE REAL BATMAN, LINFA WANG

NOTES

SADS- severe acute diarrhea syndrome

OCTOBER 2013

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		1	2	3	4	5
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24.7.2020 → AD-FREE NETWORK
INDIA NEWS + MAGZ.

PPT SOFTWARE

15.7.2020

COMM. PROCESSORS

BIOSAFETY LEVEL 4 (BSL-4)

- high mortality
- person - person transmission
- no approved vaccine or antiviral.

HOW COMMON ARE HOST RANGE JUMPS?

- dead end: very common
- those that produce sustaining transmission: rare
- can we predict them? no
- but we can know what is out there, and react (preparedness)
- We can make pan-CoV antivirals!

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NOTES

NEIDL - national emerging infectious diseases laboratory