

Preventing Pandemics in an Interconnected World: the COVID-19 Story

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May 12, 2020

No relevant disclosures



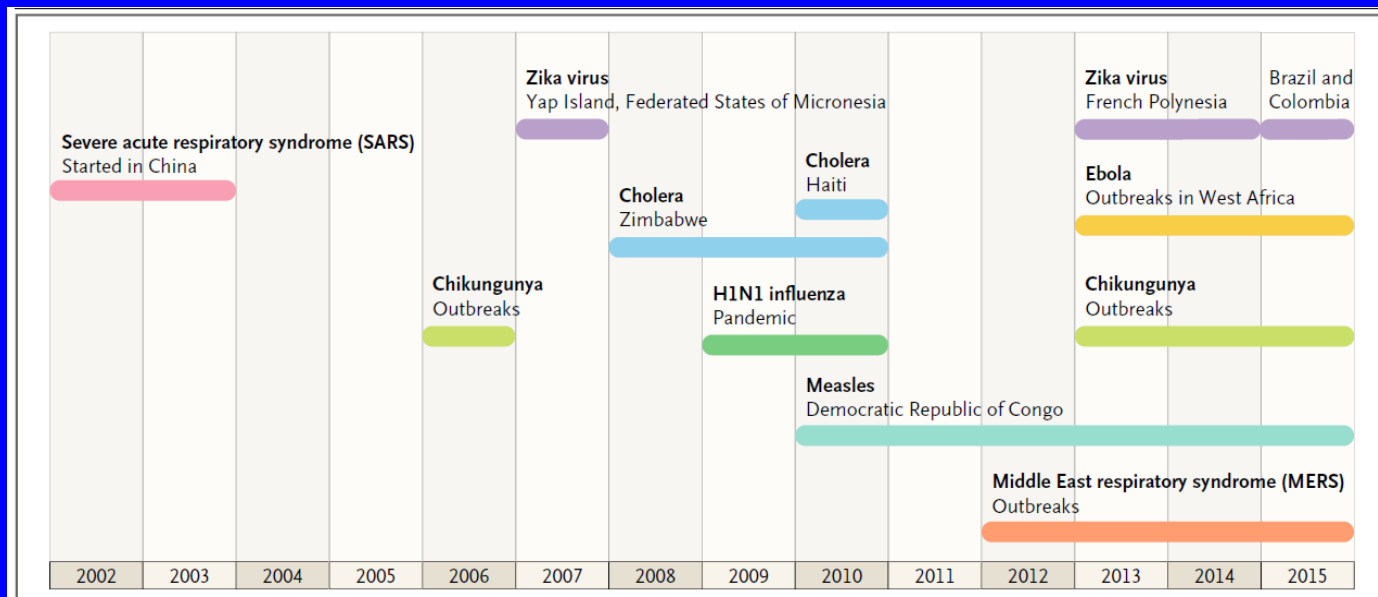
Overview

- Factors contributing to emerging disease outbreaks
- Role of the World Health Organization in pandemic recognition and control
- COVID-19 origins and epidemiology
- Prevention, diagnosis, treatment and vaccine development



Outbreaks happen

- Zika
 - 87 countries/territories with outbreaks, 58 for first time in 2015 or 2016
- H1N1 Influenza (March 2009-Aug 2010)
 - 214 countries/territories, 18,449 lab confirmed deaths
- Ebola (March 2014-March 27, 2016; 10 countries)
 - 28,646 cases, 11,323 deaths (40% case fatality)
 - <http://www.who.int/csr/disease/en/>

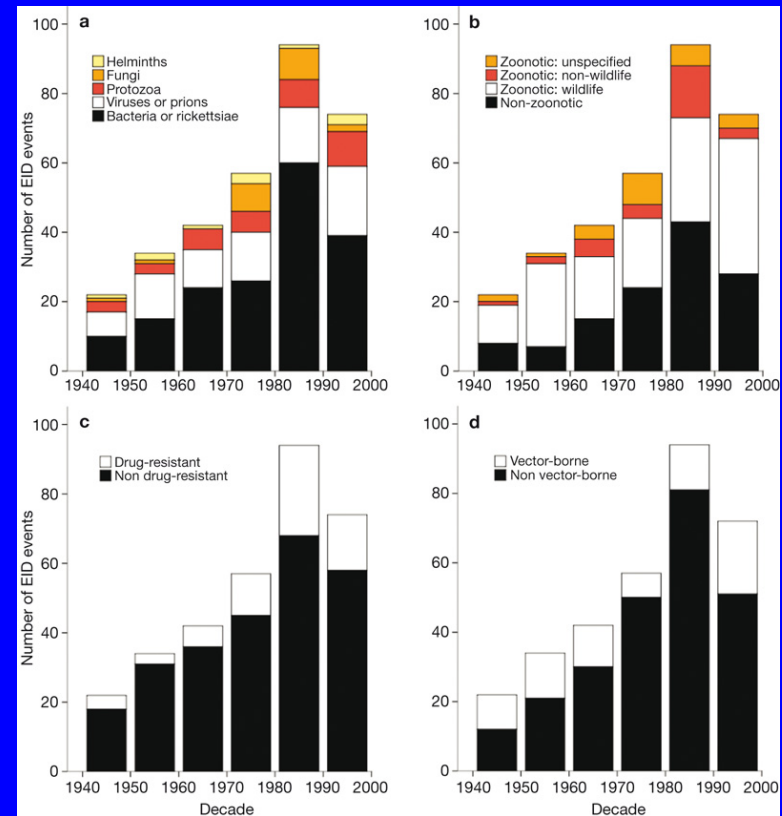


Sands. New Engl J Med 2016;374: 1281.



Are Emerging Diseases Emerging?

- Emerging diseases increased between 1940 and 2004
- Bacterial or rickettsial pathogens accounted for just over half of all “events” (54.3%)
 - Includes drug-resistance
- 60.3% of emerging disease “events” were caused by zoonoses
 - 71.8% of zoonotic events involved wildlife pathogens



Jones. Nature 2008;451:990.



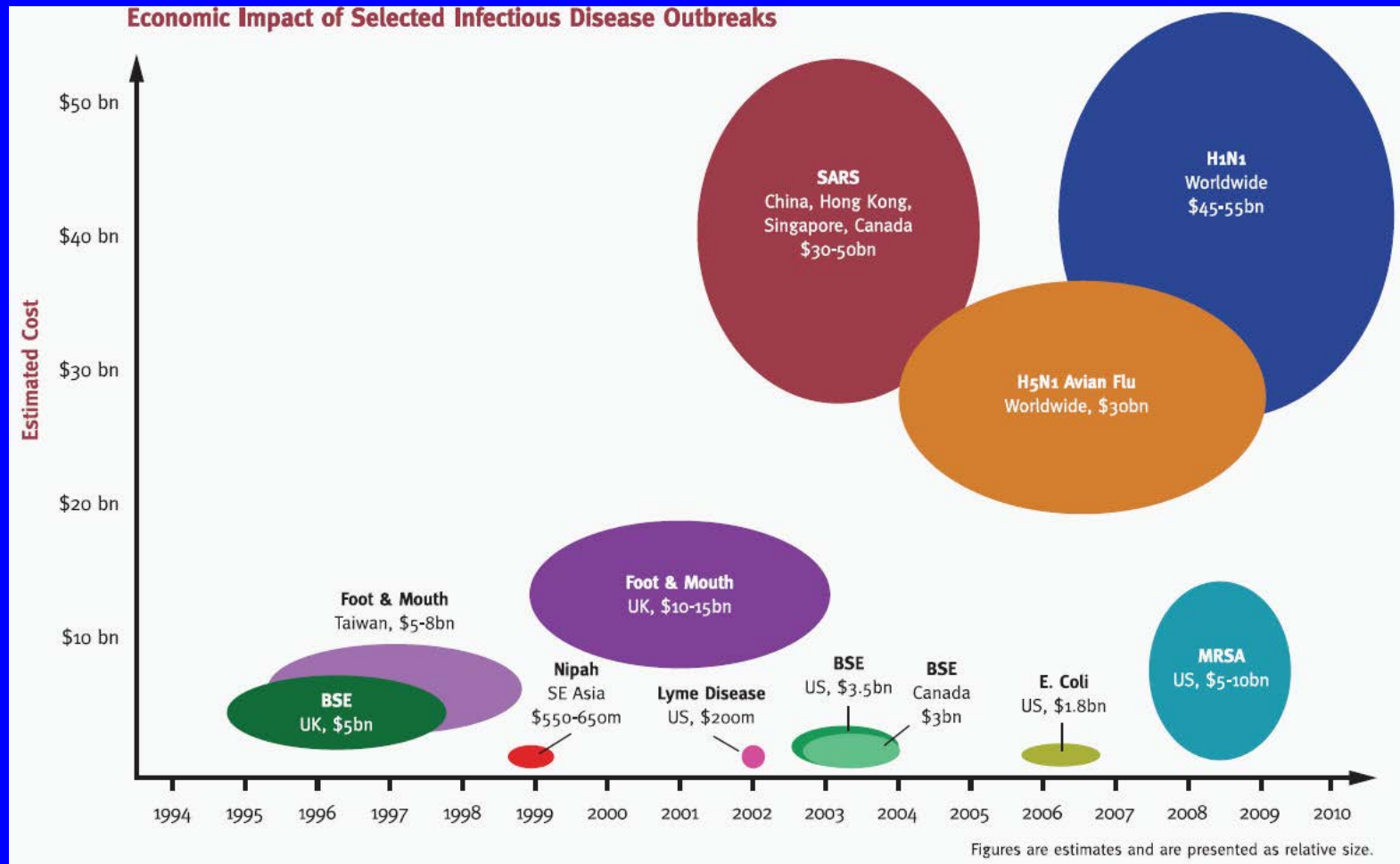
Year	Agent	Disease	Re
1973	Rotavirus	Major cause of infantile diarrhea worldwide	
1975	Parvovirus B19	Fifth disease; Aplastic crisis in chronic hemolytic anemia	
1976	<i>Cryptosporidium parvum</i>	Acute enterocolitis	
1977	Ebola virus	Ebola hemorrhagic fever	
1977	<i>Legionella pneumophila</i>	Legionnaires' disease	
1977	Hantaan virus	Hemorrhagic fever with renal syndrome (HFRS)	
1977	<i>Campylobacter</i> sp.	Enteric pathogens distributed globally	
1980	Human T-cell lymphotropic virus-I (HTLV I)	T-cell lymphoma leukemia	
1981	<i>Staphylococcus</i> toxin	Toxic shock syndrome associated with tampon use	
1982	<i>Escherichia coli</i> O157:H7	Hemorrhagic colitis; hemolytic uremic syndrome	
1982	HTLV II	Hairy cell leukemia	
1982	<i>Borrelia burgdorferi</i>	Lyme disease	
1983	Human immunodeficiency virus (HIV)	Acquired immunodeficiency syndrome (AIDS)	
1983	<i>Helicobacter pylori</i>	Gastric ulcers	
1988	Human herpesvirus-6 (HHV-6)	Roseola subitum	
1989	<i>Ehrlichia chaffeensis</i>	Human ehrlichiosis	
1989	Hepatitis C	Parenterally transmitted non-A, non-B hepatitis	
1991	Guanarito virus	Venezuelan hemorrhagic fever	
1992	<i>Vibrio cholerae</i> O139	New strain associated with epidemic cholera	
1992	<i>Bartonella</i> (= <i>Rochalimaea</i>) <i>henselae</i>	Cat-scratch disease; bacillary angiomatosis	
1993	Hantavirus isolates	Hantavirus pulmonary syndrome	
1994	<i>Sabia</i> virus	Brazilian hemorrhagic fever	

Some Major Diseases and Agents identified since 1973

Social, economic and environmental factors are believed to contribute to the emergence of new diseases, but the extent and relative importance different factors are unknown.



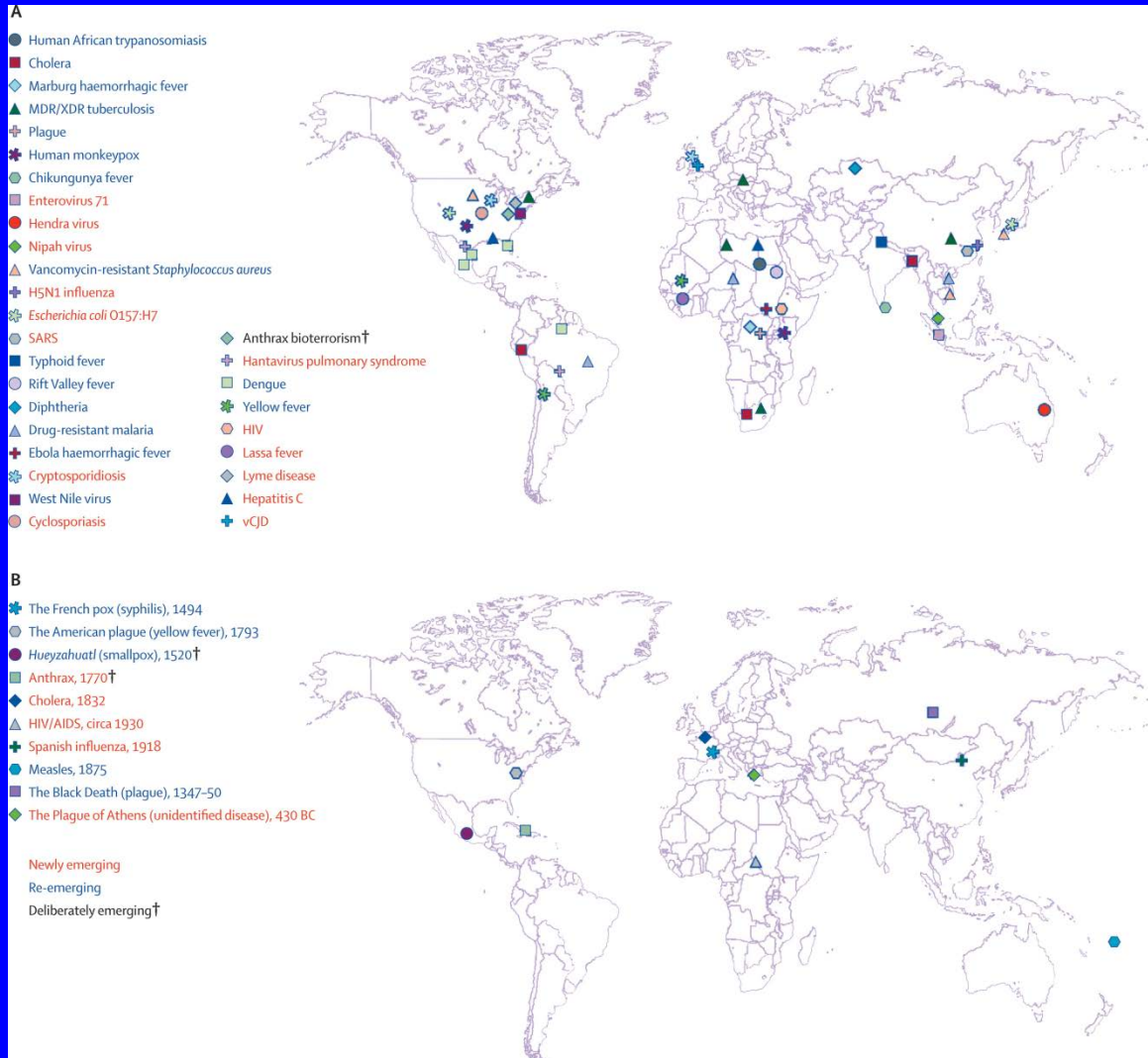
Economic impact of selected outbreaks



Newcomb J. The economic impact of selected infectious disease outbreaks. Cambridge, MA: Bio Economic Research Associates, 2011.



Where Emerging Diseases Emerge



Morens. Lancet Infect Diseases 2008;8:710.



Why outbreaks emerge

Genetic and biological factors

- Microbial adaptation and change
- Human susceptibility to infection

Physical environmental factors

- Climate and weather
- Economic development and land use

Ecological factors

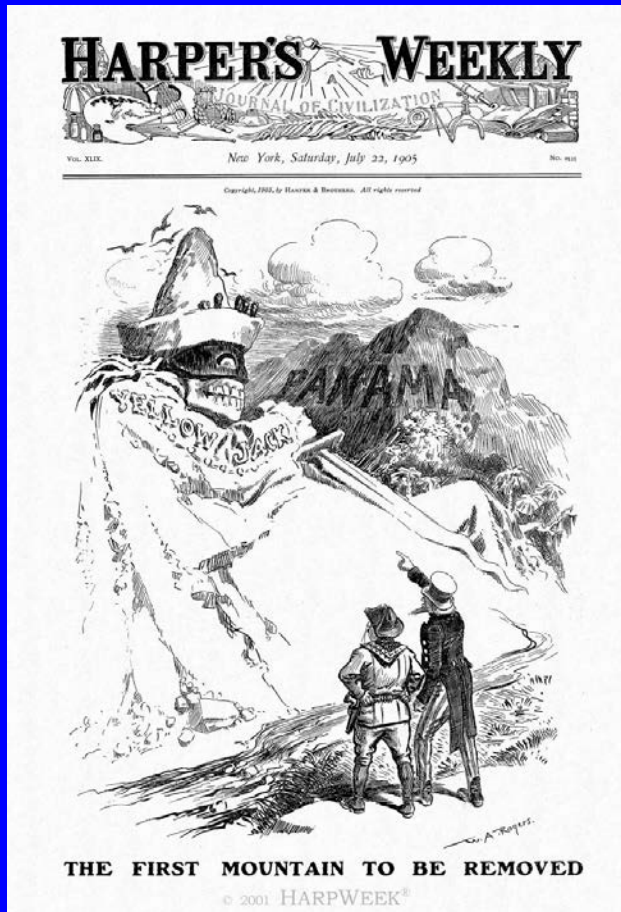
- Changing ecosystems
- Human demographics and behavior

Social, political, and economic factors

- International travel and commerce
- Poverty and social inequity
- War and famine
- Lack of political will
- Intent to harm



Human environment interface



- French period, 1881-1889
 - As many as 22,000 workers die from Yellow Fever & malaria
- US Period 1904-1909
 - Malaria deaths drop from 11.59/1,000 (1906) to 1.23/1,000 (1909)
 - http://www.cdc.gov/malaria/about/history/panama_canal.html

http://www.nytimes.com/learning/general/ontisday/harp/0722_big.html



Human animal interface

- Middle East Respiratory Syndrome coronavirus (MERS-CoV)
 - 2494 cases, 858 deaths as of May 8th
 - MERS-CoV genetic sequences and antibodies found in camels and humans
 - People who work with camels at higher risk
 - Limited human to human transmission
 - <http://www.who.int/emergencies/mers-cov/en/>

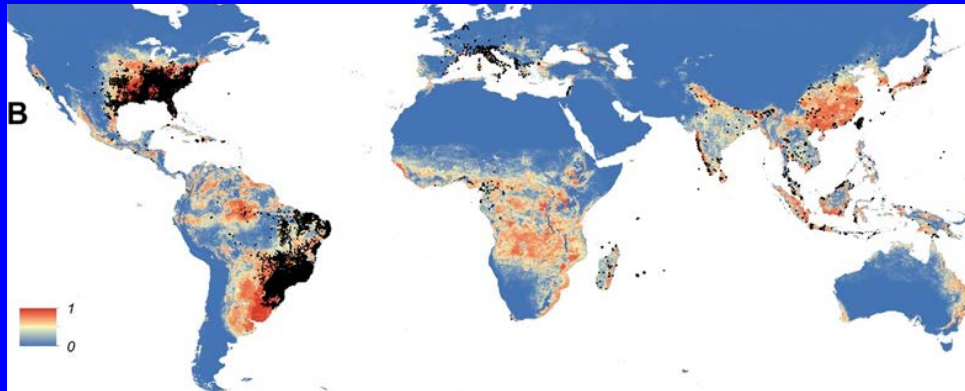


Humans, animals and the environment

- Malaysia/Singapore Nipah Virus Outbreak
 - 276 cases between 1998-1999
 - 105 deaths (40%)
 - Natural reservoir flying foxes
 - *Pteropus hypomelanus*
 - Respiratory illness in pigs
 - Epstein. *Curr Infect Dis Rep* 2006; 8:59-65.
 - Encephalitis in humans



Trade: intended and unintended global distributions



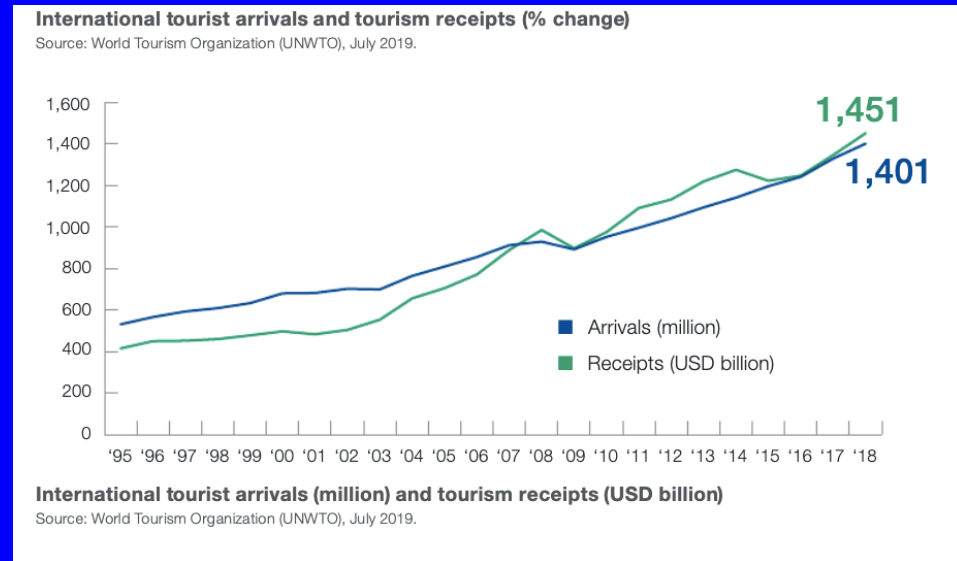
Kraemer et al. eLife 2015;4:e08347

- *A albopictus* mosquitoes were introduced through used tires into the United States in 1986 and spread broadly, and was the main vector identified in the dengue outbreak in Hawaii in 2001-02



Travel is faster, and more people are traveling

- 1.4 billion tourists traveled internationally in 2019
 - Increased every year since 2010
- Singapore to New York
 - 15,353 kms, 17.8 hours
 - <https://upgradedpoints.com/longest-nonstop-flights-in-the-world>



<https://www.e-unwto.org/doi/pdf/10.18111/9789284421152>



When Outbreaks do become International Concerns?

- Unknown disease
- Potential for spread beyond national borders
- Serious health impact or unexpectedly high rates of illness or death
- Potential for interference with international travel or trade
- Strength of national capacity to contain the outbreak
- Suspected accidental or deliberate release



International Health Regulations (IHR)

- Legally binding agreement adopted by 194 countries in 2005
 - Went into effect June 15, 2007
- Important changes
 - All public health threats
 - “illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans”
 - Obligation of member states
 - Develop minimal core public health capacity
 - Notify WHO about possible public health emergencies of “international concern”



West Nile Virus

- Single stranded RNA virus (*Flavivirus*)
 - Member of Japanese encephalitis serocomplex
 - Includes St. Louis encephalitis
 - Initially described in humans in 1937 in Uganda
 - Confined to Africa, the Middle East and Europe.
 - First North American case reported in August, 1999 in Queens, New York
 - Peterson et al. *Ann Intern Med* 2002;137:173.



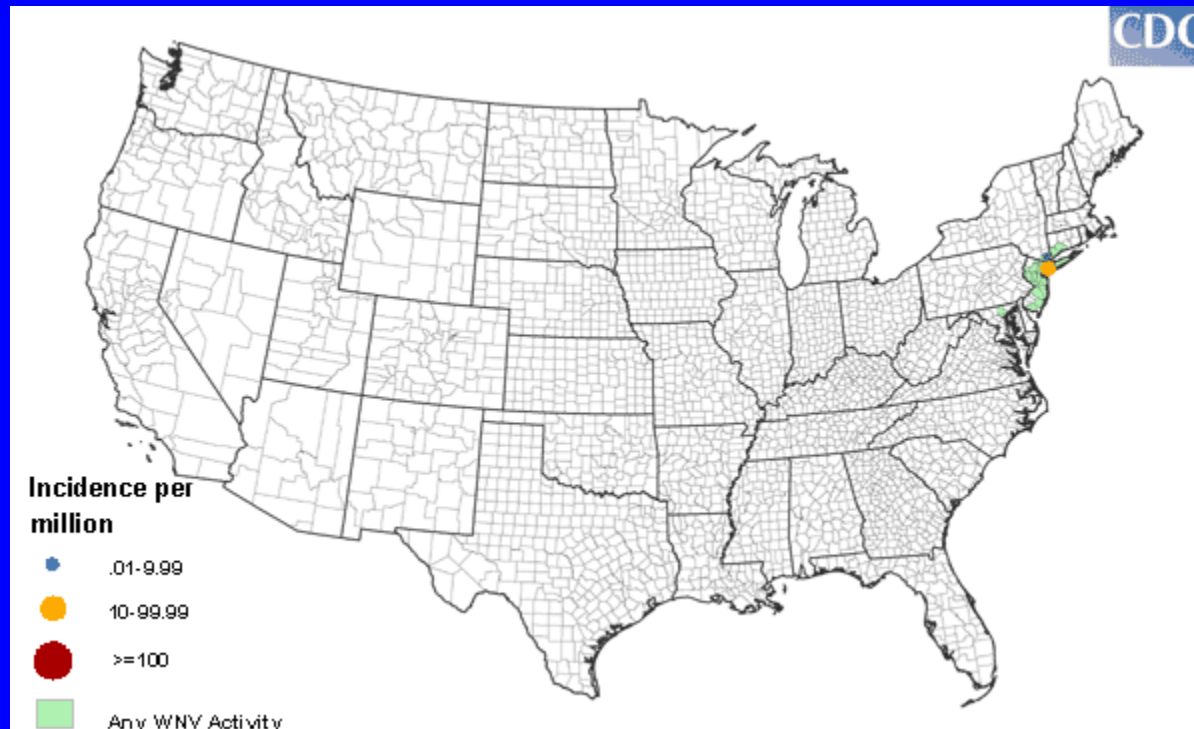
A Tale of Two Birds



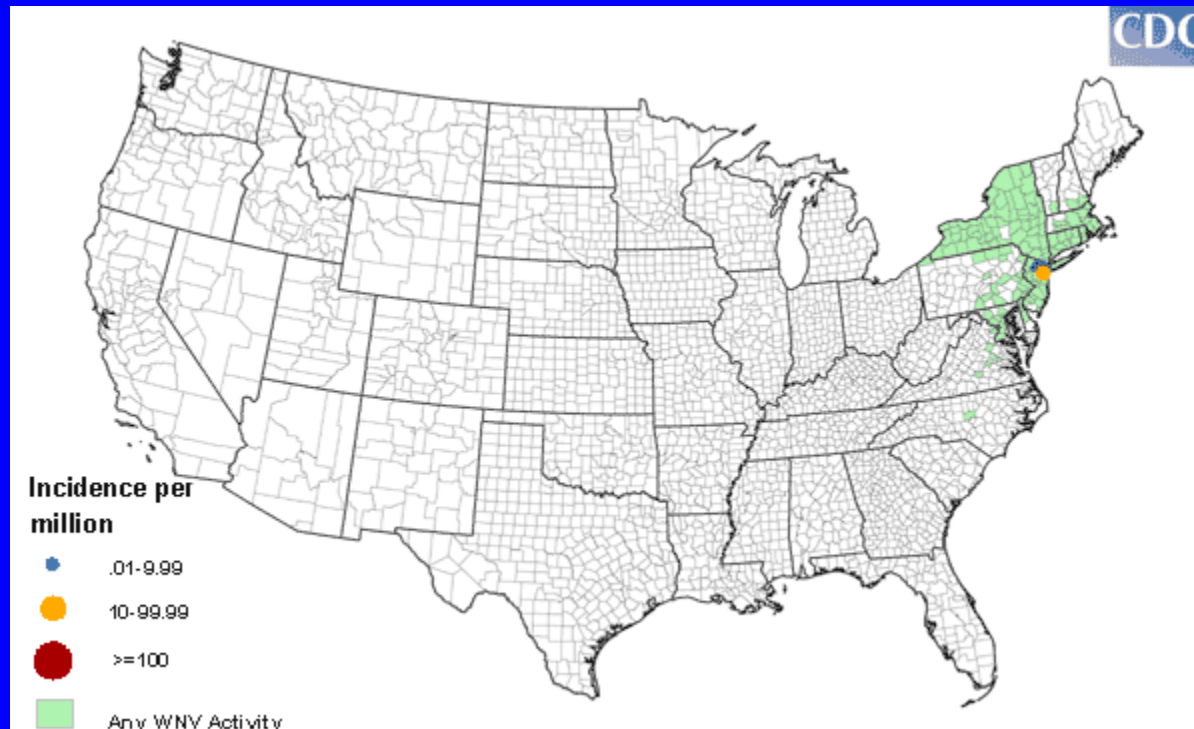
Lanciotti. Science 1999;286:2333



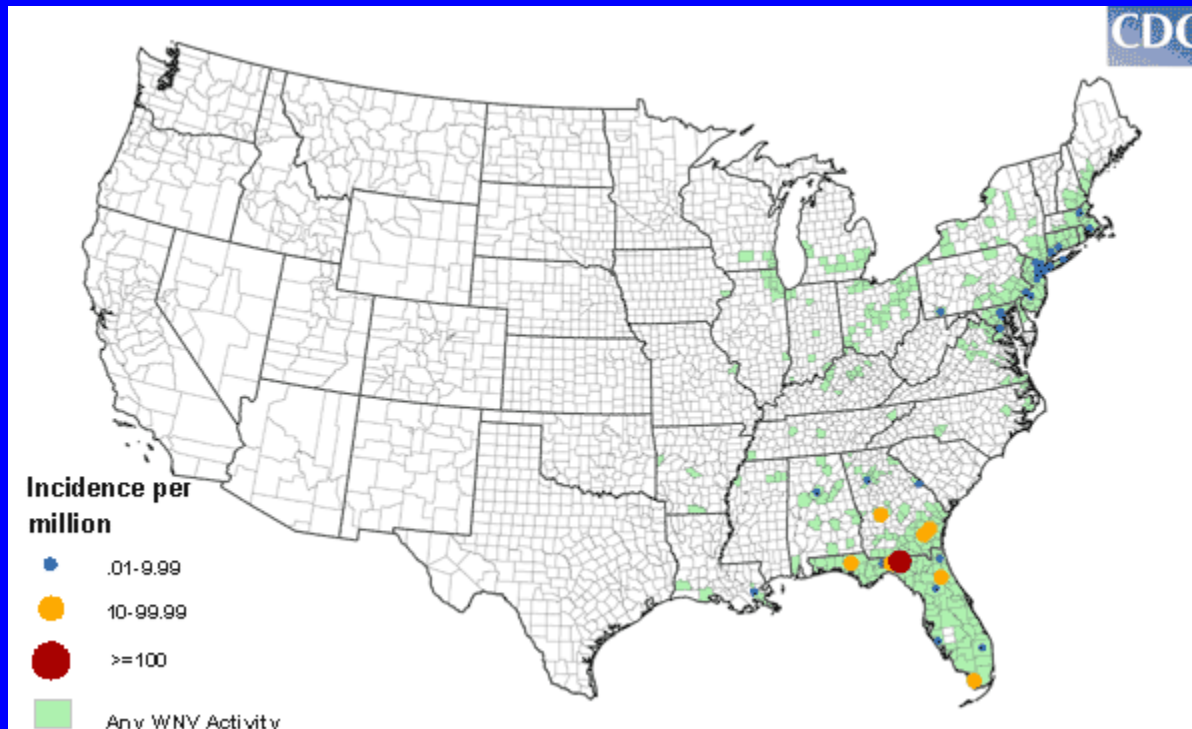
West Nile Incidence, USA 1999



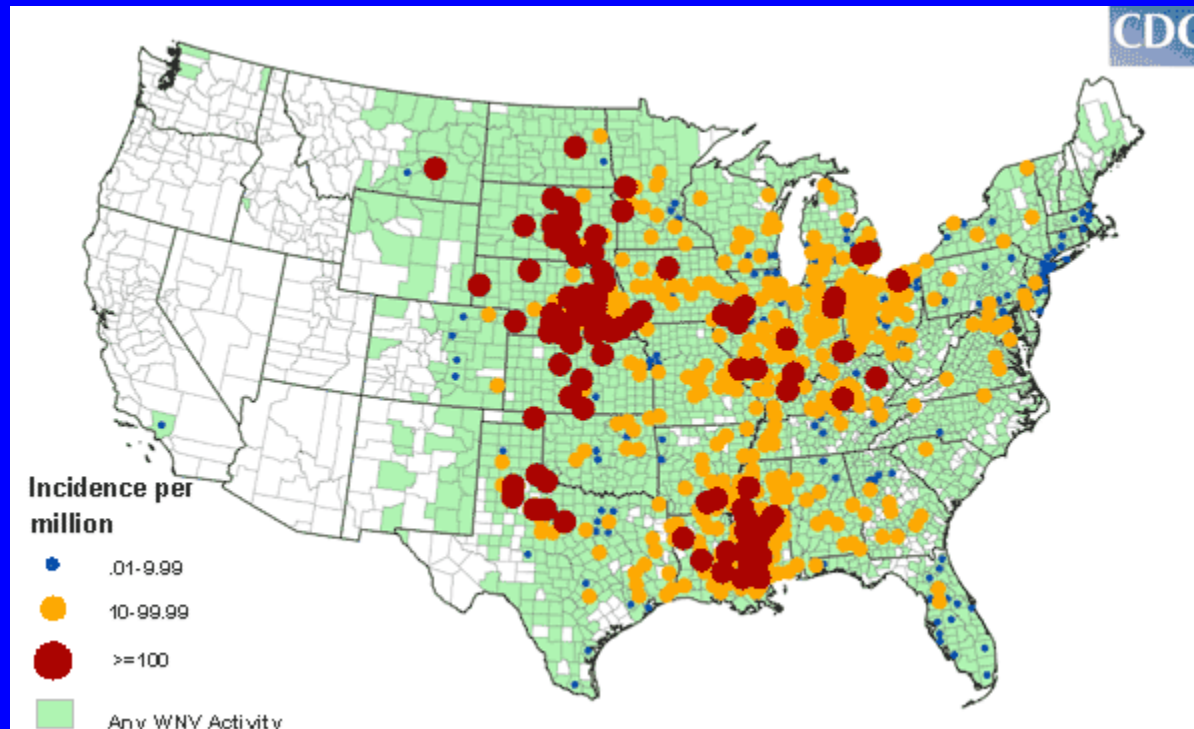
West Nile Incidence, USA 2000



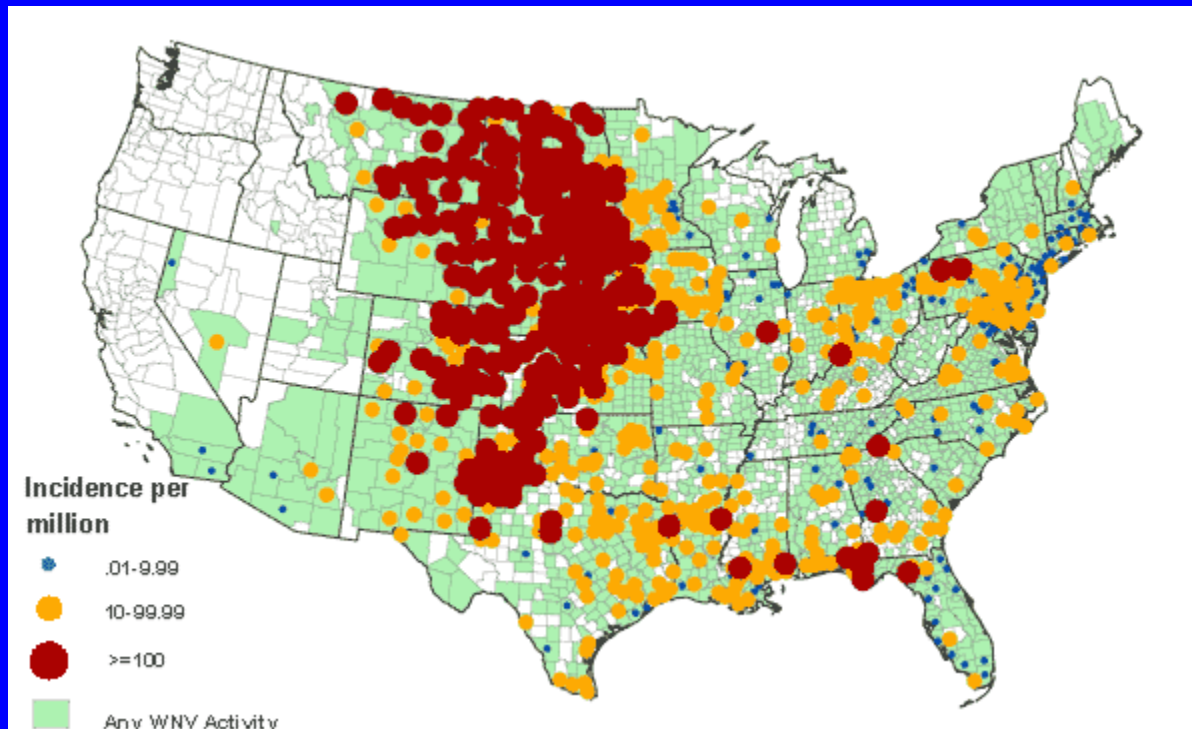
West Nile Incidence, USA 2001



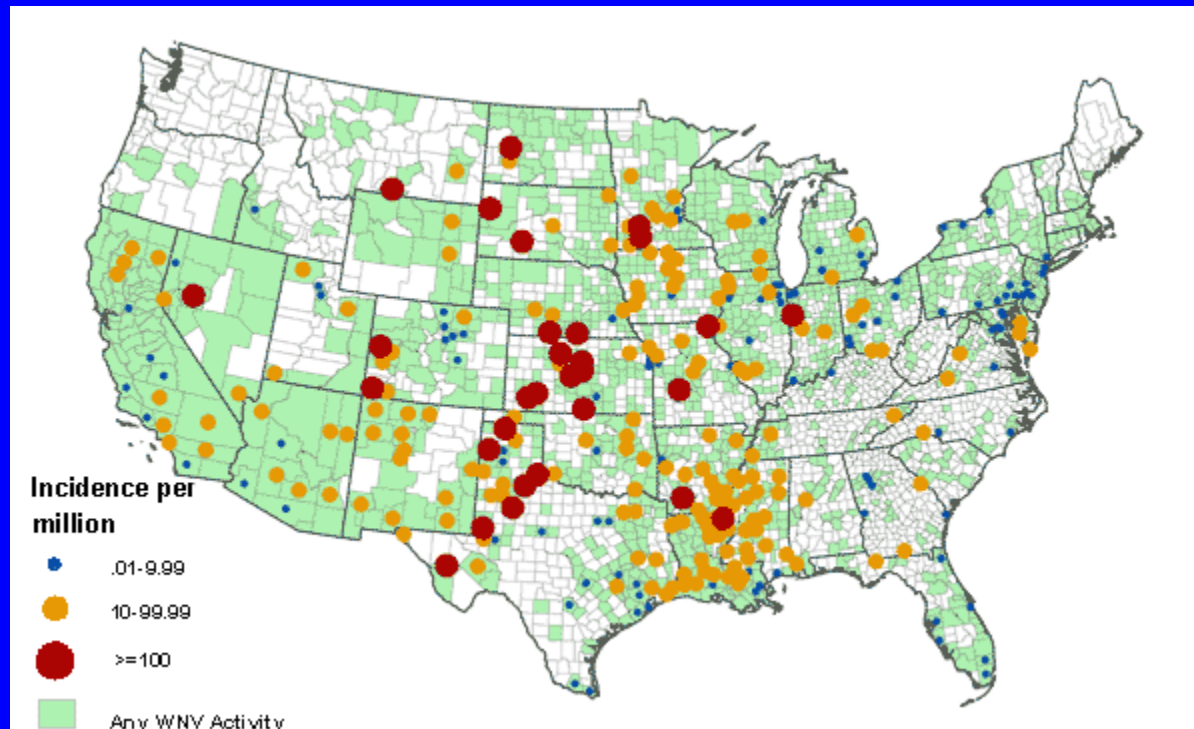
West Nile Incidence, USA 2002



West Nile Incidence, USA 2003



West Nile Incidence, USA 2004

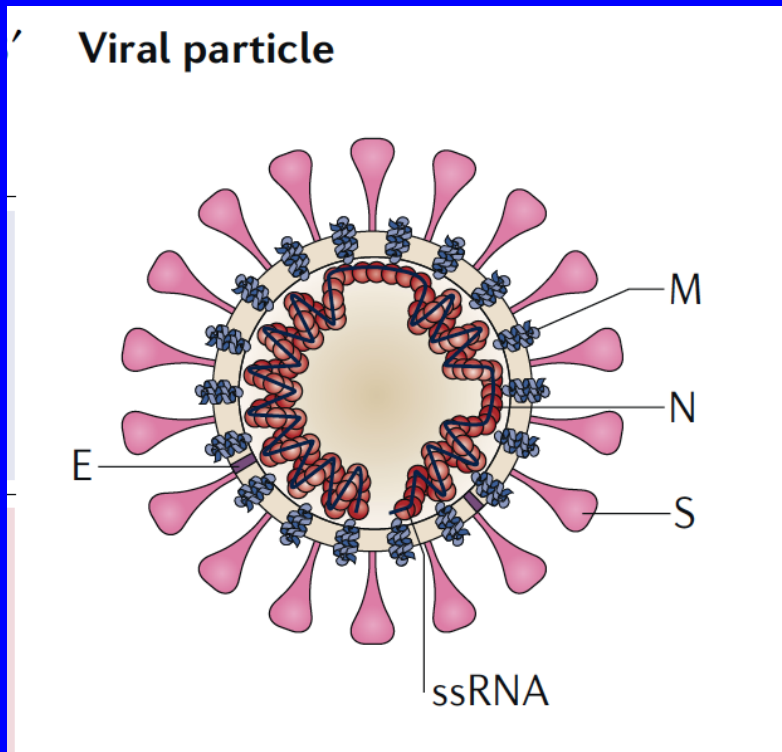


Why do epidemics occur-summary

- Infectious diseases outbreaks are increasingly being recognized worldwide
 - Improved technology and reporting
 - Social and environmental changes drive new outbreaks
 - Urbanization, poverty, civil unrest, climate change
 - Travel and trade contribute to spread of infectious diseases

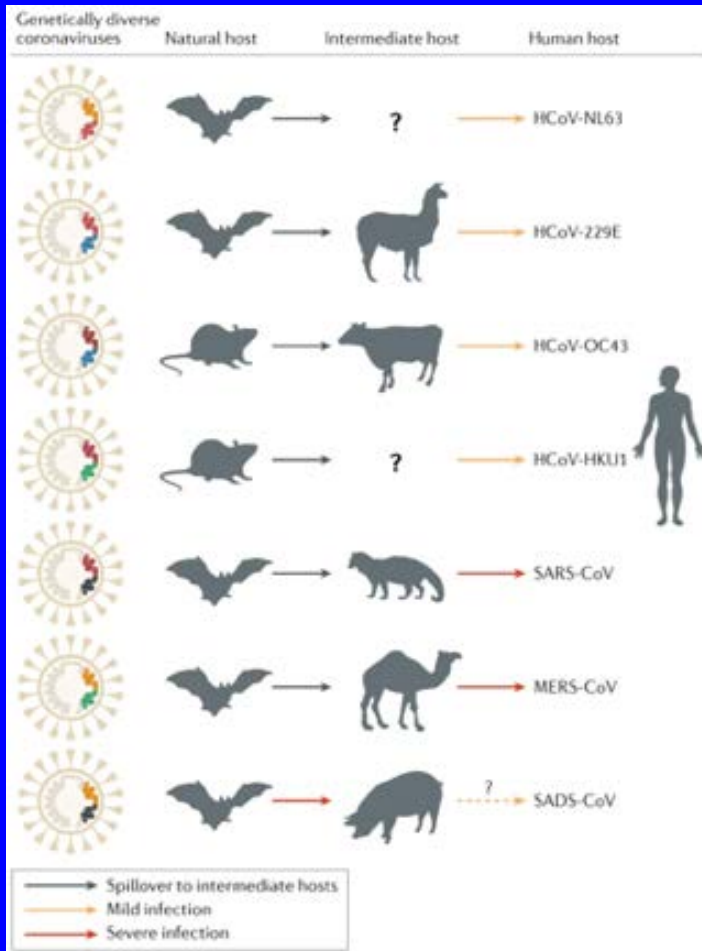


Coronaviruses



- Large single stranded RNA viruses
 - 4 genera α , β , γ , δ
 - α - and β coronaviruses
 - Respiratory tract infections in humans
 - Gastroenteritis in animals

SARS-CoV-2



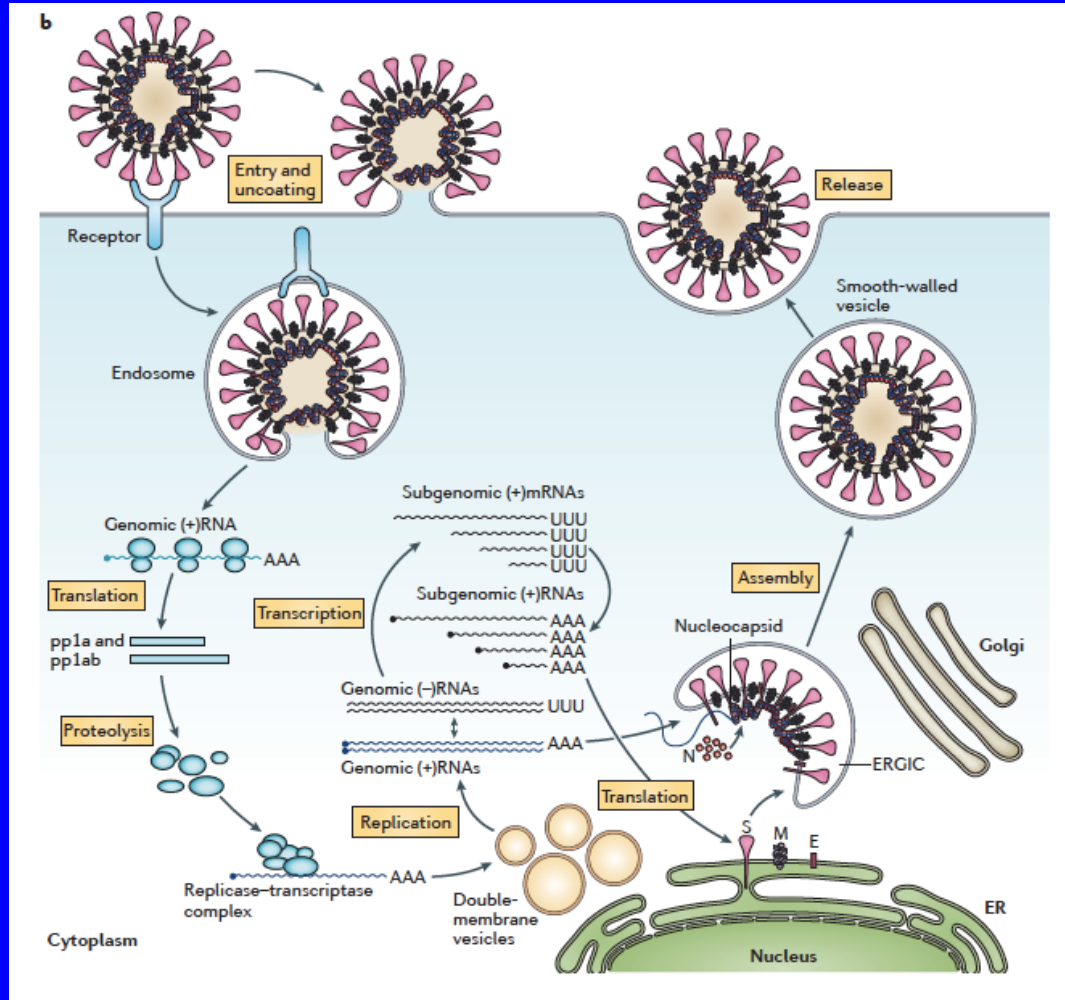
- Zoonosis

- Closely related to bat viruses (SL-CoVZC45 & SL-CoVZXC21)
- Likely intermediate host animal
- Binds to ACE-2 receptor in humans
 - Lu. Lancet 2020;395:565-74.

Cui. Nature Rev Micro 2019;17:181-92.



Coronavirus life cycle



De Wit. Nature Rev Micro 2016;14:523.



COVID-19 Epidemiology

- Severe pneumonia of unknown etiology recognized in Wuhan, China in December, 2019
 - Initial cases had exposure to live seafood market or Wuhan
 - Isolated from respiratory secretions, saliva, stool
 - 16% (173/1099) had severe disease; 1.4% died
 - Guan. New Engl J Med 2020



SARS-CoV-2 transmission

- Primarily respiratory droplets
 - 3 to 6 feet highest risk
 - Can survive on surfaces for hours to days
 - Up to 72 hours on plastic or stainless steel
 - Asymptomatic and pre-symptomatic transmission occurs
 - Aerosol transmission possible but not assumed to be major contributor
 - Lai. Inter J Antimicrob Ag 2020;55; van Doremalen. New Engl J Med 2020; Rothe. New Engl J Med 2020; WHO Joint Commission China Report 2020.



COVID-19 May 10th

- 3.9 million cases; 274,361 deaths (world)
 - Case fatality rate 7.0%
- 1.3 million cases; 78,771 deaths (US)
 - CFR 6.1%
- 66,680 cases; 2745 deaths (CA)
 - CFR 4.1%
- 31,677 cases; 1530 deaths (LA)
 - CFR 4.8%
 - WHO, CDC, CADPH, LACDPH



Clinical Characteristics

- 5 to 6 day incubation
 - Range 1 to 14 days
- Fever, cough, dyspnea most common
 - Sore throat, loss of smell or taste, diarrhea, myalgias, fatigue
 - Rhinorrhea uncommon
 - Vasculitis (Kawasaki syndrome) and blood clots reported
 - Zhou. Lancet 2020;395:1054; Lai. Intern J Antimicrob Ag 2020;55; WHO Joint Commission China Report 2020.



COVID-19 Clinical Course

- 80% of patients have mild to moderate disease
- 14% have severe disease requiring hospitalization
 - RR \geq 30, O2 sat \leq 93%, PaO₂/FiO₂ < 300
- 6% have critical disease requiring ICU care
 - Respiratory or multiorgan failure or shock
 - WHO Joint Commission China Report 2020.



Clinical course for hospitalized patients

- 13 day median onset to dyspnea
- 20 days median viral shedding
- 22 days median illness onset to hospital discharge
- 18.5 days median time to death
 - Zhou. Lancet 2020;395:1054.



Age as risk factor for serious/critical disease/death

- Laboratory confirmed hospitalization rates (per 100,000 population)
 - ≥ 65 years old 162.2
 - 50-64 years old 79.0
 - 18-49 years old 26.2
 - 5-17 years old 1.0
 - 0-4 years old 2.4
- 9/37,308 deaths (0.02%) ≤ 14 years old
- 7.9% deaths (2965) < 55 years old
 - <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html#hospitalizations>



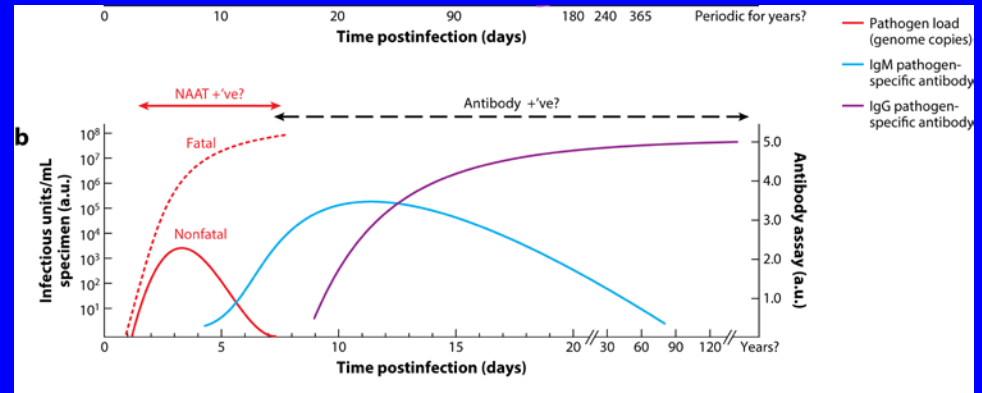
Risk factors in hospitalized patients

- Comorbid disease (adults)
 - Hypertension (59%), obesity (50%), diabetes (42%), CV disease (35%)
 - Only 8.5% of hospitalized patients without comorbid condition
- Gender and race
 - African Americans 27.5% cases, 36.8% of hospitalizations, 21.2% of deaths (18% of population)
- 42% of pediatric cases did not have a comorbid condition
 - 38% had obesity
 - <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html#hospitalizations>



Viral diagnostics

- Pathogen based
 - PCR (NP swab, sputum, stool, saliva)
 - Antigen (NP swab, saliva)
- Immune based (serology)
 - Blood, plasma



- Bird BH. Ann Rev Animal Biosci 2018;6:121.



Some testing issues

- 1,343 persons with COVID-19 symptoms in New York
 - 113/624 with PCR confirmed COVID-19 were weakly antibody positive or negative on initial testing
 - Optimal time for testing at least 3-4 weeks after symptom onset
 - 249 (19%) tested positive for nasopharyngeal SARS-CoV-2 RNA 3 to 14 days after symptom resolution (longest 28 days)
 - Wajnberg. MedRxiv preprint 2020
<https://doi.org/10.1101/2020.04.30.20085613>



Radiology/laboratory findings

- Ground glass infiltrates on CT scan (86.2%) or chest x-ray
- Lymphopenia (83.2%, even with normal total WBC)
- Elevated inflammatory markers
 - CRP, D-dimer, LDH, ferritin, IL-6
- Age, D-dimer, organ failure associated with mortality
 - Guan. New Engl J Med 2020; Zhou. Lancet 2020;395:1054.



Antiviral Treatments

- Remdesivir only FDA approved treatment under EUA
 - Shortens duration of symptoms and hospitalization
- Non FDA approved treatments under study
 - Hydroxychloroquine, lopinavir/ritonavir, selinexor, favipravir, ribavirin
 - Convalescent serum



Immune modulating treatments – not FDA approved

- Cytokine storm in severe disease
- IL-6 blockers
 - Tocilizumab, sarilumab
- Janus associated kinase (JAK) inhibitors
 - Ruxolitinib, baricitinib
- CCR5 trafficking inhibitor
 - Leronlimab
- Steroids, interferon



Supportive and other care

- Oxygenation
- Pressure support
- Organ failure
 - Renal replacement
- Antibiotics for secondary infections
- Prophylactic anticoagulation



Prevention and control

- Case identification, isolation and contact tracing
- Physical distancing
- Quarantine
 - “Stay-at-home”, “lockdown”
- Hand washing
- Disinfection of surfaces
- Masks and facial coverings
- Vaccines



Containing outbreaks in an interconnected world

- Strengthen global response capacity
 - Create emergency fund, response center
- Improve regional/international coordination
- Diversify expertise
 - Few diplomats, economists, anthropologists, etc.
- Engage civil society
- Improve monitoring of International Health regulations
 - Gostin. Lancet 2015;385:1902; Sands. New Engl J Med 2016;345:1281.



Thank you

Questions

