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Virus Update

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Conflict of interest

Consultant for AstraZeneca: research study assessing efficacy of monoclonal antibodies to prevent COVID-19 in immunocompromised patients

I will not discuss any AstraZeneca products today

Objectives

1. Review viral characteristics that predispose to increased risk for pandemics
2. Discuss SARS-Cov-2 mutations and risk of new variants / pandemics
3. Understand the impact of avian influenza transmission on commercial poultry and risks to humans
4. Summarize Marburg virus situation in Africa

Epidemiology 101

- Epidemic: widespread occurrence of disease at specific time
  - May occur in a population (monkeypox)
  - May occur in geographic area (seasonal influenza)
- Pandemic: epidemic occurring on at least 2 continents
- Endemic: disease regularly occurs in a geographic area and/or population
  - Predictable / regular patterns (enterovirus in Summer / early Fall, rotavirus in winter)

Pandemic

- Large scale outbreaks in multiple geographic regions
- Increased morbidity and mortality
- Economic / social disruption
- Likelihood of pandemics increased over past century, and occurring more frequently
  - Global travel
  - Urbanization / population concentration
  - Increasing contact with remote areas of world in pursuit of rare materials (exposure to new zoonosis)
  - Exotic pets
  - Ecotourism
  - Exotic food consumption

https://www.ncbi.nlm.nih.gov/books/NBK525302/

Population density

City	Population	Population density
Detroit metro area	632,464	5,144 people / mile^2
Flint	80,628	3,065 people / mile^2
New York City	8,468,000	26,403 people / mile^2
Tokyo	37,435,191	16,480 people / mile^2
Delhi	29,399,141	29,300 people / mile^2
Sao Paulo	21,317,104	18,690 people / mile^2
Mexico City	21,671,908	16,000 people / mile^2
Manila	1,780,000	119,600 people / mile^2

U.S. Census data

https://worldpopulationreview.com/world-cities

Emerging infections

- In past decades, > 75% transmitted from animals (zoonotic infections)
- Usually, viral etiologies
  - Often vector involved in transmission
- Human expansion and decreased habitat for wildlife major risk factor
  - 1900: world population 1 billion
  - 2023: world population 7.968 billion

https://www.census.gov/popclock/

Emerging infections continued

- Vampire bat rabies in Amazon Basin from deforestation and mining
  - Twice as many cases as rabies from canines
- Kyasanur Forest disease (tickborne)
  - 1957: 300 square mile zone
  - 2023: > 2,000 square miles
- Nipah virus infection in Malaysia (1998-1999) associated with deforestation, pig farming, and planting fruit trees
- Bushmeat / contact with non-human primates: Simian foamy virus, HTLV-3, HTLV-4
- Ecotourism
  - African tick bite fever
  - herpes B from macaques

https://wwwnc.cdc.gov/eid/article/13/1/06-0480_article

CDC: pandemic threat(s)

- Outbreak usually starts in vulnerable areas (limited resources) with high population density
- Pathogens can travel from remote village to any major city in ≤ 36 hours
- Increased risk of outbreaks
  - Pathogens move from animal host to humans
  - Antimicrobial resistance
  - Pathogen spreads via global travel
  - Bioterrorism
  - Weak public health infrastructure / surveillance for novel infections

https://www.cdc.gov/globalhealth/healthprotection/fieldupdates/winter-2017/why-it-matters.html

COVID-19: endemic or pandemic?

- SE Michigan COVID inpatient numbers are low and remain steady
- No longer seeing inpatient surges
- Outpatient numbers very manageable
- I believe we are in an endemic state
- If there is significant mutation, we could return to pandemic status
- See WebMD article for various opinions on this question

https://www.webmd.com/covid/news/20230317/time-to-stop-calling-it-a-pandemic

COVID-19 variants

- Thousands of variants identified
- Relatively small number of variants have clinical significance
- Focus is on mutations in the spike protein
  - Pathogenesis
  - Transmission
- Immunocompromised patients have prolonged viral infection which increases risk of new mutations

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8714679/

SARS-Cov-2 classifications

Greek letter	Nextstrain (based on genetic relationship)	Pango (based on parental ancestry)
Alpha	20I	B.1.1.7
Beta	20H	B.1.351
Gamma	20J	P.1
Delta	21A	B.1.617.2
Omicron	Multiple	Multiple

https://covariants.org/variants/21A.Delta

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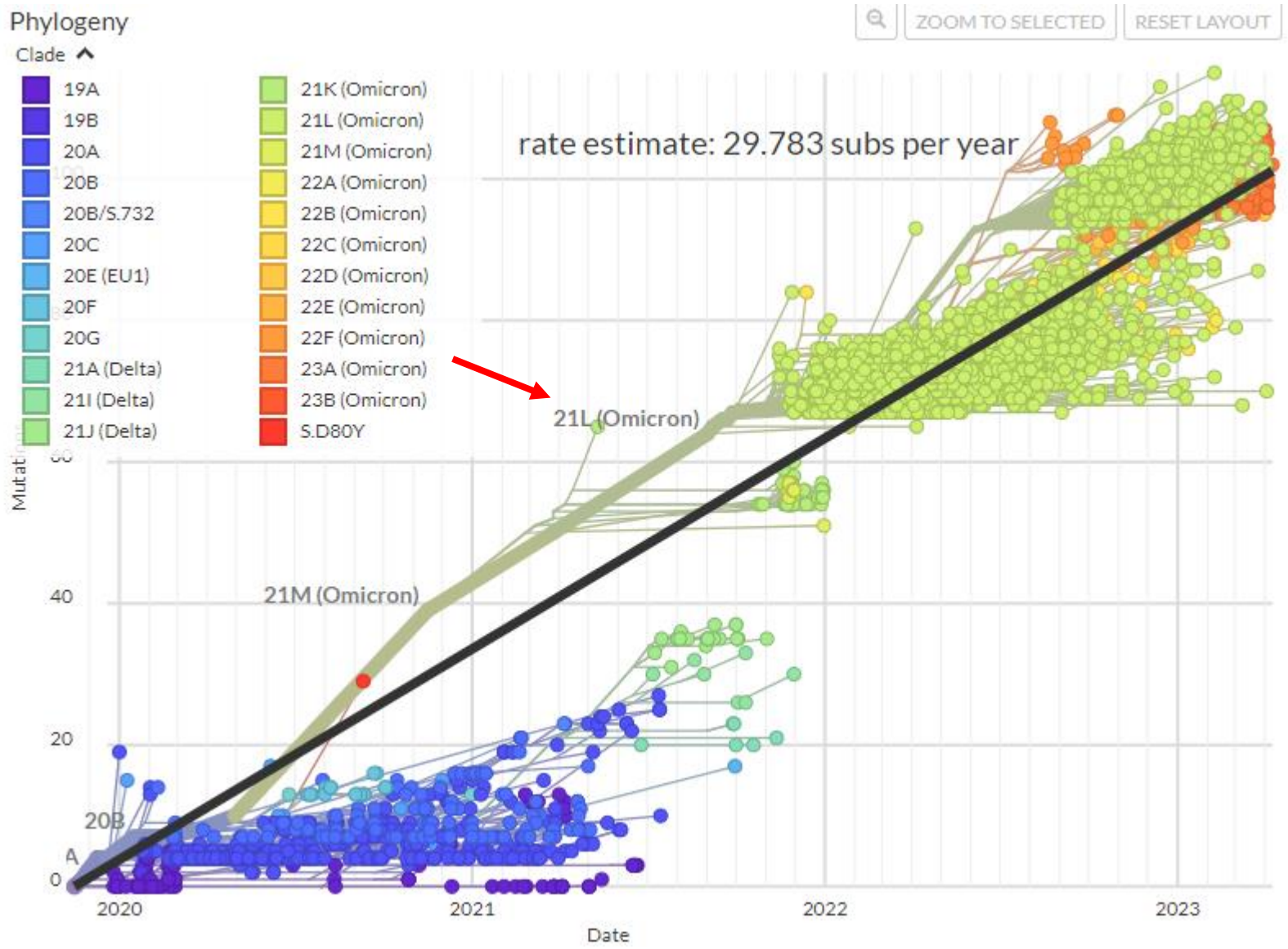
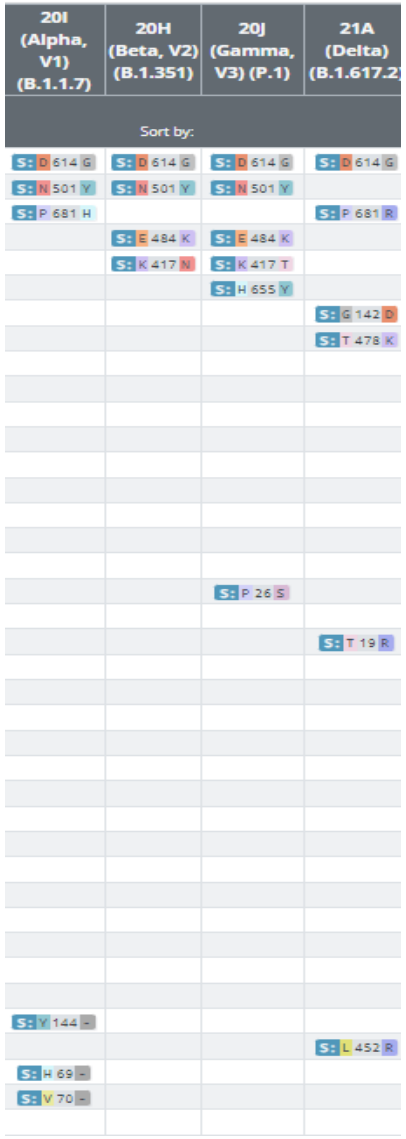
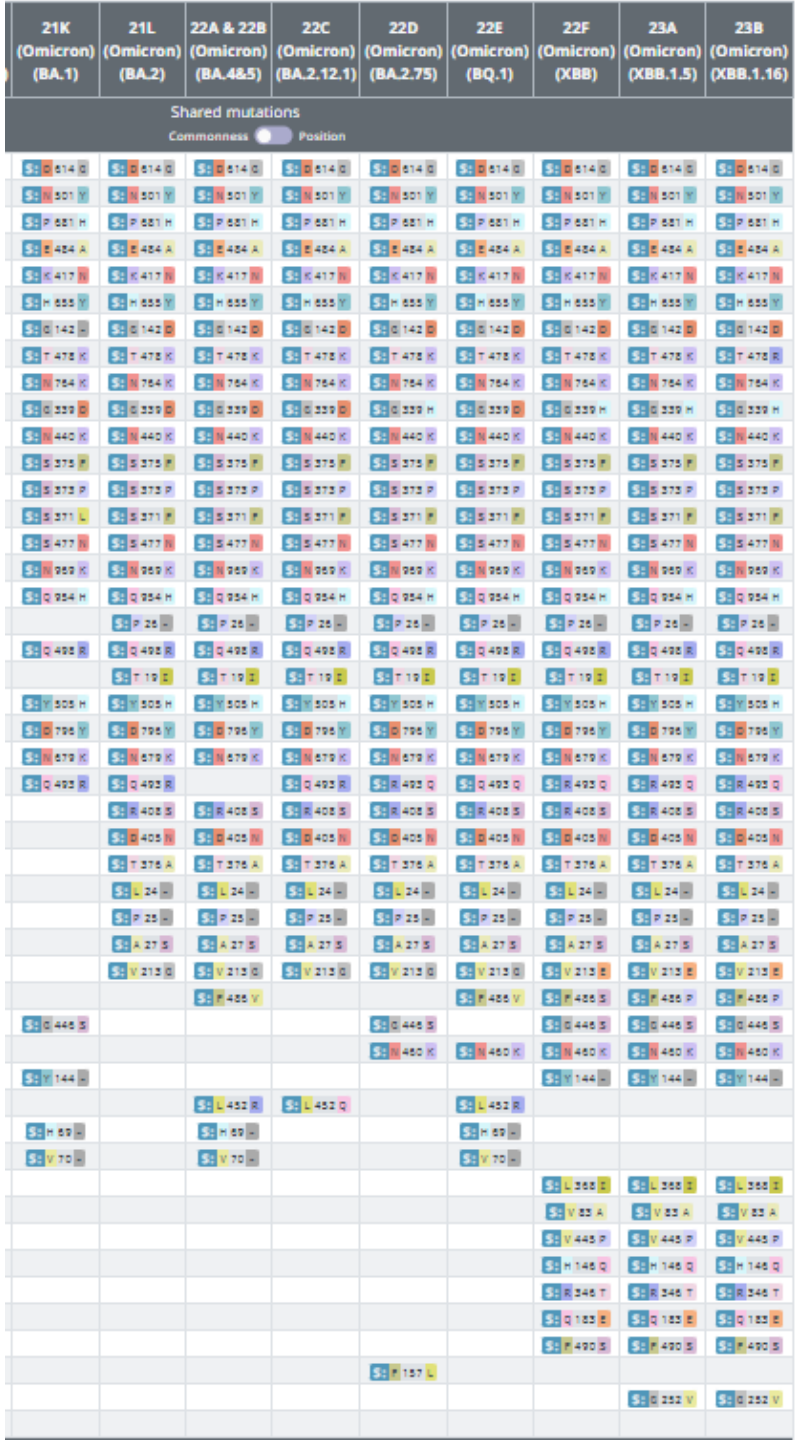
- 21K (BA.1)
- 21L (BA.2)
- 22A (BA.4)
- 22B (BA.5)
- 22C (BA.2.12.1)
- 22D (BA.2.75)
- 22E (BQ.1)
- 22F (XBB)
- 23A (XBB.1.5)
- 23B (XBB.1.16)



https://nextstrain.org/groups/neherlab/ncov/21L.Omicron?l=clock

COVID-19 mutations





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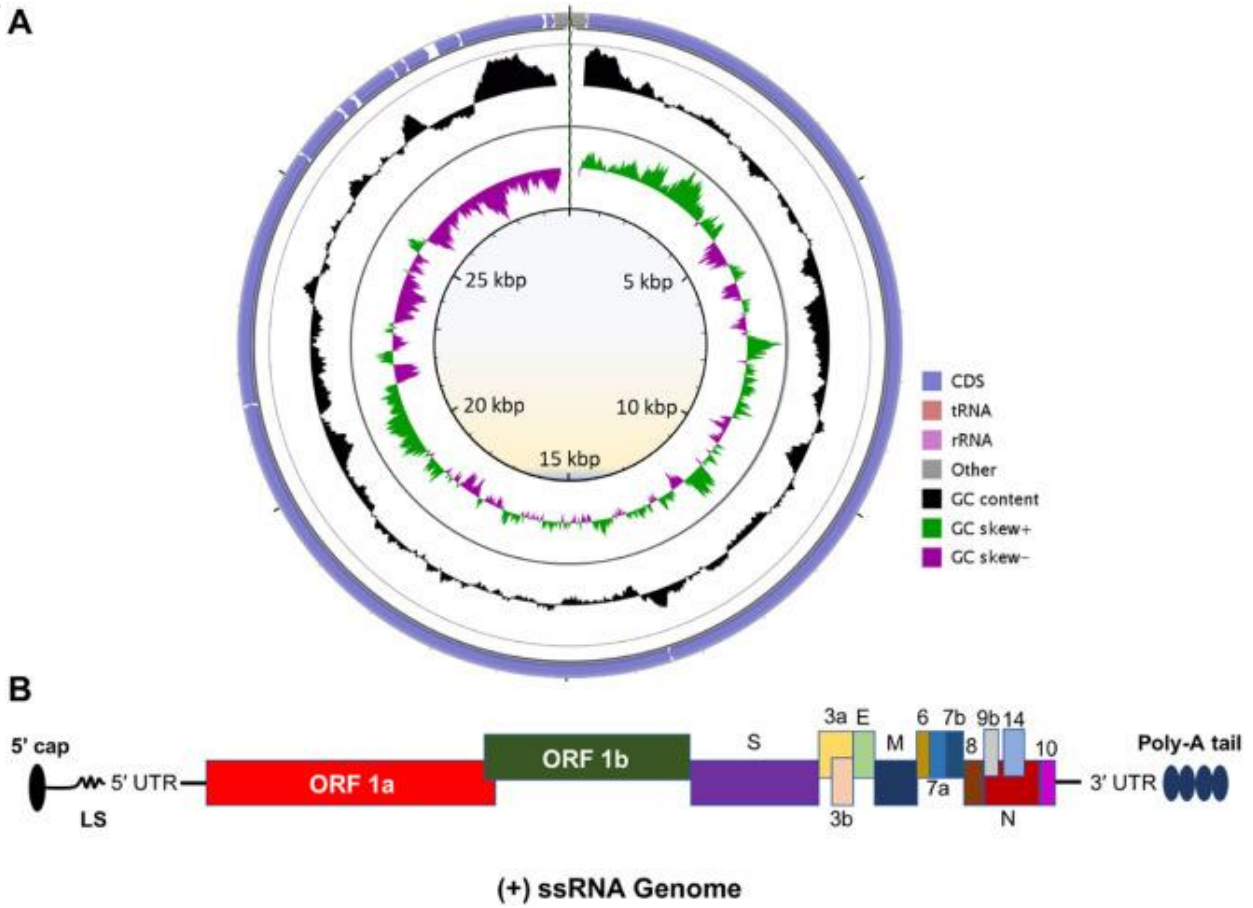
SARS-Cov-2 genetics

- Large virus (30,000 base pairs)
  - RNA viruses mutate more easily than DNA viruses
- 11 ORFs (open reading frames)
- 1/3 genome encodes structural proteins
- 2/3 genome encodes non-structural proteins (NSP)



https://www.imrpress.com/journal/FBL/27/2/10.31083/j.fbl2702065

Figure from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7293463/

Structural Proteins

- Spike protein
  - S1 attach to ACE1 receptors on human cell
  - S2 fuse virus with human cell
- Envelope protein: facilitates virion assembly and release
- Membrane protein and nucleocapsid proteins **inhibit** immune response
  - M protein: inhibit NFκB (nuclear factor kappa-light chain enhancer impacts cytokine production)
  - N protein: inhibit IFNβ innate defense against viruses by activating signal transducer proteins

https://www.imrpress.com/journal/FBL/27/2/10.31083/j.fbl2702065

Non-structure proteins

- NSP14 – exonuclease – removes nucleotide(s) at end of RNA strands which facilitates mutations
- ORF3a: Prevents lysosome from fusing with autophagosomes (blocks autophagy)
- ORF6, ORF7a and ORF8: aid N protein by blocking interferon 1 pathway
- ORF10: function not identified
- ORF1a and ORF1b: proteins help replicate genome

https://www.imrpress.com/journal/FBL/27/2/10.31083/j.fbl2702065

Mutations

- Shown to evade protective antibodies
- Increase infectivity (more easily transmitted)
- Increase pathogenicity (as seen with Delta)
- Potential future mutations
  - Bind to different / additional receptors
  - Resistance to protease inhibitor (nirmatrelvir)
  - Resistance to nucleoside analogue (remdesivir)

Future of COVID

- Historically COVID variants started in high density populations
- Will there be new variants (change from Omicron)? Probably
- Cannot assume that newer variants will be less virulent
  - Good news
    - Ability to modify and produce mRNA vaccines quickly
    - Effective antiviral agents (remdesivir, nirmatrelvir/ritonavir)
    - New C5a inhibitor to treat COVID-19 (vilobelimab)
    - Immunomodulators (glucocorticoids, JAK inhibitors, IL-6 inhibitors)
  - Not so good news
    - Virus mutates and travels fast
    - Virus unpredictable

Avian influenza

- Spread via migratory aquatic birds (reservoir for all influenza A viruses)
- Migratory birds may not have symptoms but transmit virus to susceptible birds
- U.S. record in past year: loss of 58 million commercial fowl from H5N1 costing more than $670 million dollars
  - Died of infection
  - Culled herds to decrease spread of disease
- Debate on role for vaccines
  - Most nations do not vaccinate as concern for exporting infected but asymptomatic birds → increased spread
  - With current outbreak, many nations reconsidering use of avian influenza vaccines

https://www.cidrap.umn.edu/avian-influenza-bird-flu/us-poultry-farms-reduce-avian-flu-outbreaks-usda-begins-vaccine-testing

https://www.reuters.com/business/healthcare-pharmaceuticals/bird-flu-alarm-drives-world-towards-once-shunned-vaccines-2023-02-17/)

https://www.agriculture.com/news/business/cost-of-fighting-bird-flu-outbreaks-tops-670-million

Avian influenza continued

- Infects **intestines** & respiratory tract
  - Primary spread fecal-oral
  - Stability of virus in water
  - Higher concentration in cloacal samples versus tracheal swabs
- Waterfowl natural reservoirs: ducks intrinsically resistant because of retinoic acid-inducible gene I (RIG-1)
    - Recognize viral RNA in cytoplasm and express INF-1 & cytokines
    - Gene lost in domesticated chickens 10,000 years ago
- Very contagious, highly virulent (90-100% mortality in chickens)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332658/

https://macleans.ca/society/health/why-dont-ducks-ever-get-the-flu/

Types of avian influenza

- Low pathogenic avian influenza: no symptoms to mild symptoms in poultry
  - Decreased egg production, ruffled feathers
  - No symptoms in wild aquatic birds
  - Potential to mutate into more pathogenic strains
- Highly pathogenic avian influenza: H5N1 and H7N9 specific strains
  - Approach 100% mortality in poultry within 48 hours
  - Spread from wild birds → domestic poultry → wild birds which increases geographic spread
  - Potential to cause disease in wild birds
  - Recent avian flu isolates survive 6 days in aquatic environments versus typical 2 days

HPAI

- Lack of energy
- Decreased appetite
- Loss of coordination
- Bruising / swelling
- Diarrhea
- Nasal discharge, coughing, sneezing
- Reduced egg production
- Abnormal eggs (soft shells, misshapen)
- Sudden death

https://www.osha.gov/sites/default/files/publications/avian_flu_animal_handlers.pdf

https://www.avma.org/resources-tools/animal-health-and-welfare/animal-health/avian-influenza/avian-influenza-companion-animals

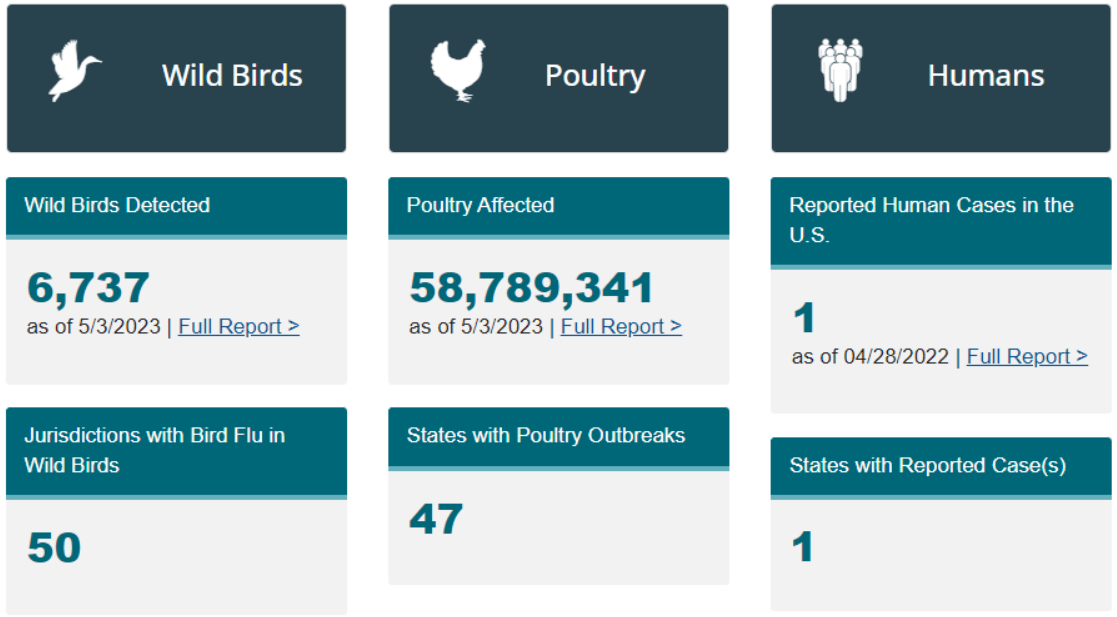
Photo from https://www.shutterstock.com/search/chicken-mask?image_type=photo

Avian influenza jumping species

- Infect mammals that eat birds
  - Sea lions, bears, foxes, skunks, mink, tigers, lions, stray cats & dogs
- Rare cases of disease in humans (zoonosis), primarily H5N1 and H7N9
  - Asymptomatic to severe disease and death
  - Transmission when virus has contact with mucous membranes (including inhalation)
    - Droplets
    - Inhaled dust?
  - Rare cases of human-to-human transmission (fortunately few cases)
  - Important to look for mutations that enhance infection in mammals
- Pandemic potential: no cross-protection from human influenza infections and immune naive population

Avian influenza in U.S. as of 5/3/2023

- Wild birds: widespread
- Poultry flocks: sporadic outbreaks
- Mammals: sporadic infections
- People: 1 case after exposure to infected bird
- Person to person spread none



https://www.cdc.gov/flu/avianflu/avian-flu-summary.htm

Testing humans for avian influenza

- Test only if patient:

- Meets epidemiologic criteria **AND**

- Meets clinical criteria or public health response criteria (testing exposed individuals)

Human cases of avian influenza

- 4/2023: China H3N8 (3rd case in humans, all occurred in China)
- 3/2023: Chile H5N1
- 1/2023: Ecuador H5N1
- Scattered human cases in U.S. from 2014-2017
- Almost all cases had known exposure to infected poultry

Mutations can increase risk to mammals

- H gene: increased affinity for human cells
- M gene (mutations impact ability to infect a species)
  - M1 matrix
  - M2 membrane
- N gene (neuraminidase) N1, N2
- PB2 (polymerase basic protein 2): RNA polymerase changes increase efficacy in mammals
  - Leads to increased disease severity and transmission
- Look for antiviral resistance
  - Neuraminidase mutations → resistance to oseltamivir, zanamivir, peramivir
  - PA (polymerase gene) mutations → baloxavir resistance
  - M2 mutations → amantadine, rimantadine resistance

https://www.cdc.gov/flu/avianflu/spotlights/2022-2023/chile-first-case-h5n1-addendum.htm

Epidemiologic criteria

- Exposure to birds infected with H5, H7, H9
  - Close exposure (2 meters) to birds with confirmed H5, H7, or H9 viruses (handling, slaughtering, defeathering, butchering, culling, or prepping birds for consumption)
  - Direct contact with surfaces contaminated with feces/body parts from infected birds
  - Visiting live poultry market with confirmed avian influenza and a documented human case
  - Exposure to infected person (2 meters) without PPE
  - Laboratory exposure without PPE

- Public health labs have rRT-PCR (real time reverse transcriptase PCR) to look for specific RNA sequences from avian influenza
  - look for RNA sequences that are specific to a variant

https://www.cdc.gov/flu/avianflu/case-definitions.html

Clinical criteria

Persons with signs and symptoms consistent with acute or lower respiratory tract infection or conjunctivitis, or complications of acute respiratory illness without an identified cause. Examples include but are not limited to:

- Mild flu-like illness (cough, sore throat, fever or feeling feverish, rhinorrhea, fatigue, myalgia, arthralgia, headache) or conjunctivitis (red eye, discharge from eye)
- Moderate to severe illness: shortness of breath or difficulty breathing, altered mental status, seizures
- Complications: pneumonia, respiratory failure, acute respiratory distress syndrome, multi-organ failure, meningoencephalitis

https://www.cdc.gov/flu/avianflu/case-definitions.html

Management of human cases of avian influenza

- Standard, contact and airborne precautions (N-95, eye protection, gown, gloves)
- Minimize number of staff caring for patients
- Treatment https://www.cdc.gov/flu/avianflu/clinicians-evaluating-patients.htm
  - Empiric antiviral therapy with neuraminidase inhibitor
  - Contact state health department / CDC
  - Consider other etiologies

- Human disease severity does not correlate to designation of low or high avian pathogenicity

Influenza pandemics

- Interval between pandemics ranges from 3 to 56 years
- Severe pandemic every 100 to 300 years?
- U.S. government regional stockpiles to respond to natural or manmade infectious risks
  - Antibiotics
  - Antivirals
  - Vaccines for novel pathogens such as H5N1 and H7N9
  - Protective equipment

https://www.sciencedirect.com/science/article/pii/B9780128019801000167

Marburg virus

- Member of the filoviruses, and closely related to Ebola
- Caused by Marburg virus, Ravn virus, or coinfection
  - 1 case of Ravn virus from Kenya
- RNA viruses that infect primates
- 1967 outbreaks in multiple labs after exposure to African green monkeys or tissue
- Reservoir is Egyptian rousette bat (fruit bat)
  - Shed in saliva, feces, urine
- Sporadic outbreaks in sub-Saharan Africa, often after mine workers in bat infested caves

Marburg continued

- Incubation 2-21 days
- Infectious once symptoms appear
- Sudden onset fever, chills, HA, myalgia which is nonspecific
- Macular-popular rash on day 5
  - May have nausea, vomiting, chest pain, sore throat, abd pain, diarrhea
  - Late stage: jaundice, pancreatitis, delirium, shock, liver failure, MSOF, hemorrhage
- Mortality 23-90%

- Differential diagnosis includes malaria, typhoid fever, Lassa fever, Ebola, Dengue, shigellosis, rickettsia illnesses, meningitis

February 2013

First case Marburg in Equatorial Guinea

17 confirmed and 23 probable cases in Equatorial Guinea and Tanzania

Case fatality rate in confirmed cases 78.6%

Outbreak is over when no new cases for twice the upper limit of the incubation period (42 days)

Marburg treatment

- Supportive care
- Fluid/electrolyte management
- Maintain blood pressure
- Maintain oxygenation
- Replacing lost blood and clotting factors

Treatment of Marburg virus in non-primates

- No FDA approved human treatments
- Animal Efficacy Rule of 2005 allows extrapolation of data from animal models when human studies not feasible /ethical
- Promising results in animal studies for:
  - Lipid nanoparticles delivering interfering small interfering RNA particles
    - 20-40 base pairs of double stranded RNA that degrades mRNA and prevents translation
  - Vesicular stomatitis virus-based vaccines
  - Monoclonal and polyclonal antibodies
  - Phosphorodiamidate morpholino oligomers (synthetic DNA analogs inhibit gene expression)
- Less promising
  - Remdesivir (improved efficacy if combined with monoclonal antibody_

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4502585/

https://pubmed.ncbi.nlm.nih.gov/33767178/

Viruses in the news May 2023

Crimean-Congo hemorrhagic fever (Pakistan)
Murray Valley encephalitis (Australia)
Ebola new case (DR of Congo)
Monkeypox (increased cases in Chicago and Pakistan)
Schmallenberg virus (Sweden)

Pandemics

- The question is not IF.
- The question is when will the next pandemic start?
- Luck and hope are not good strategies.
- As a nation, we need to remember the importance of investments in public health and lab technology including surveillance.
- Murphy's Law: anything that may go wrong will go wrong.

I’m willing to make one prediction

- My employment prospects as medical director of infection prevention remain favorable!!! This is confirmed by my Magic 8 Ball.

- THANK YOU for inviting me to return to this conference.