Pathogenic Characteristics Of Pandemic Influenza Viruses

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ASPR's Mission

Save Lives and Protect Americans from 21st Century Health Security Threats

The BARDA Model

BARDA develops and makes available medical countermeasures **(MCMs)** by forming unique public-private partnerships with industry partners
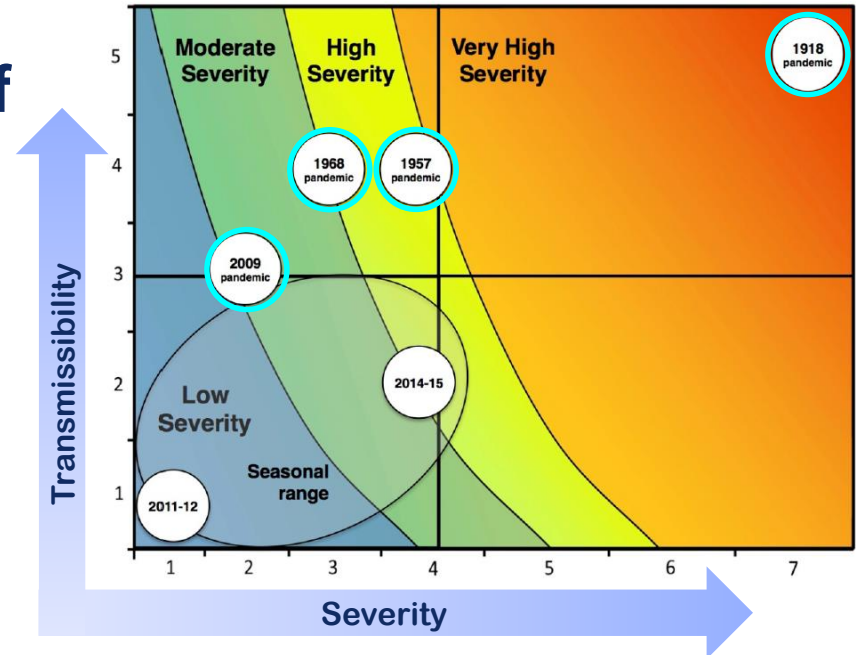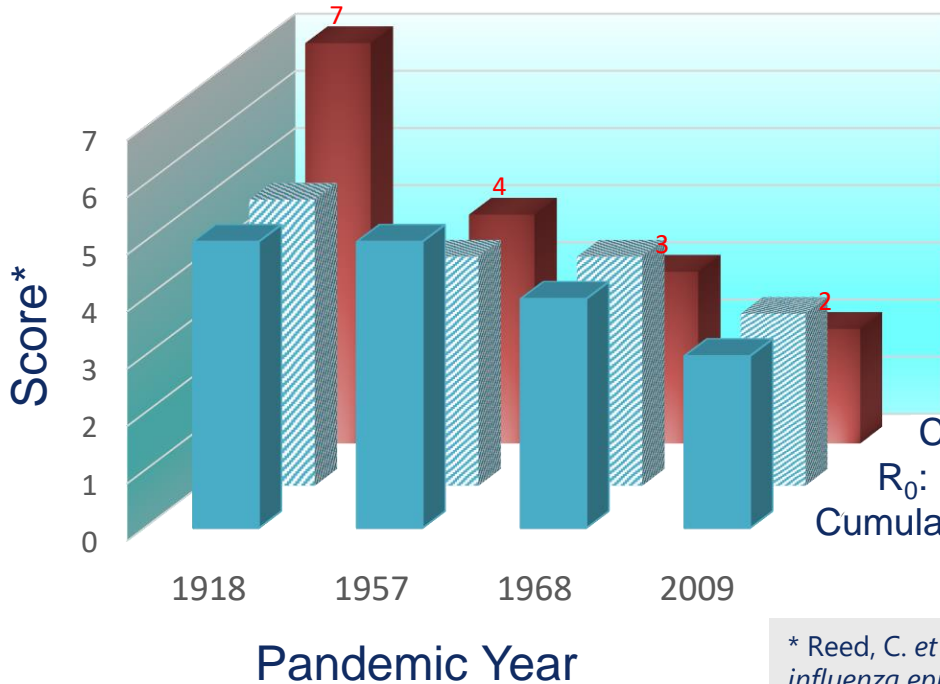
BARDA Pandemic Influenza Preparedness

Severity and Transmissibility of Pandemic Influenza

Case-fatality Ratio
R_0: Basic Reproductive Number
Cumulative ILI

PSAF
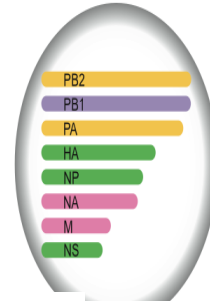
* Reed, C. et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis 19, 85-91 (2013).

Cumulative incidence of ILI, community Ro: Basic Reproductive Number Symptomatic case-fatality ratio

Lessons Learned From 2009 H1N1 Pandemic
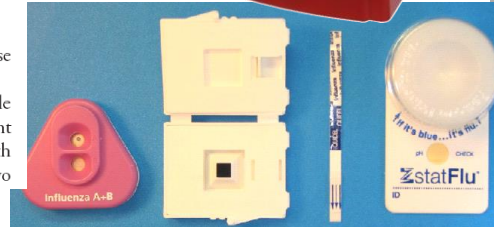
IRAT Informs Pre-pandemic Preparedness

Critical Elements

Attributes of the virus
- Receptor Binding Properties
- Transmission in Animal Models
- Genomic Variation
- Antiviral Susceptibility

Attributes of the population
- Population Immunity
- Disease Severity
- Antigenic Similarity to Vaccines

Ecology and epidemiology
- Human Infections
- Infections in Animals
- Global Distribution

Disease Surveillance

Virologic Surveillance

IRAT Emergence and Impact - Average Risk Scores

H7N9

HK/125/17 H7N9
B
Yunnan/15 H5N6 Clade 2.3.4.4
Vietnam/04 H5N1 Clade 1
H
Netherlands/03 H7N7
Bangladesh/11 H9N2 G1
IN/08/11 H3N2 variant
L
I
turkey/IN/16 H7N8
J
H9N2
K
duck/NY/96 H1N1

Impact

Emergence

https://www.cdc.gov/flu/pandemic-resources/monitoring/irat-virus-summaries.htm
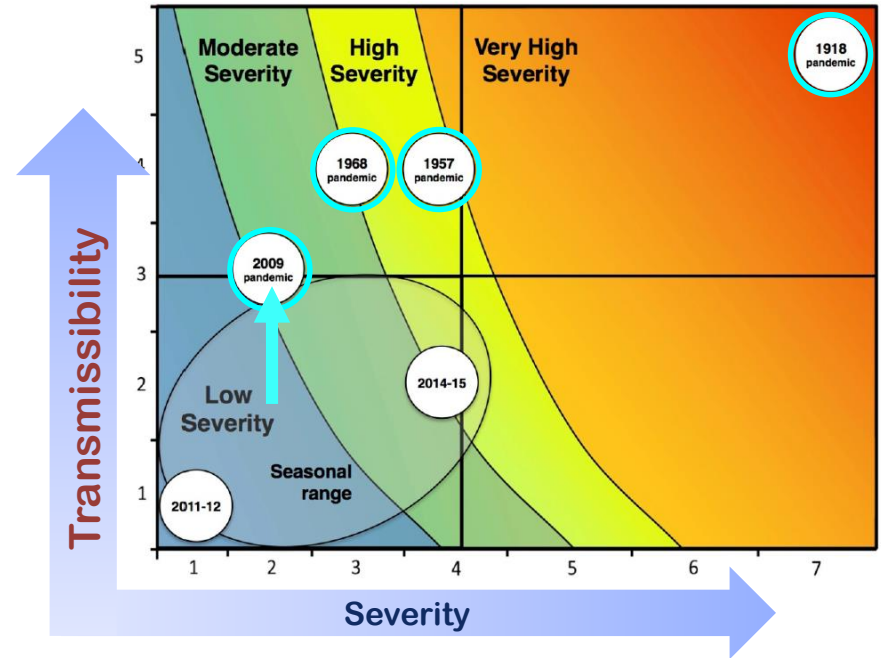
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Saving Lives. Protecting Americans.

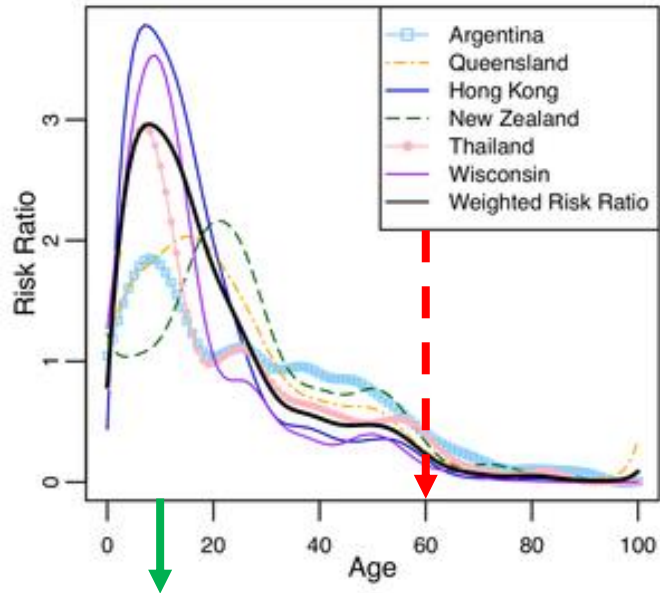# Severity and Transmissibility of 2009 H1N1 Pandemic

Low to moderately severity

- 2009 H1N1
  - "Recycled" HA from 1918
  - Eurasian avian M and NA
  - Classical and Eurasian swine genes
- Minimal adaptive changes were needed
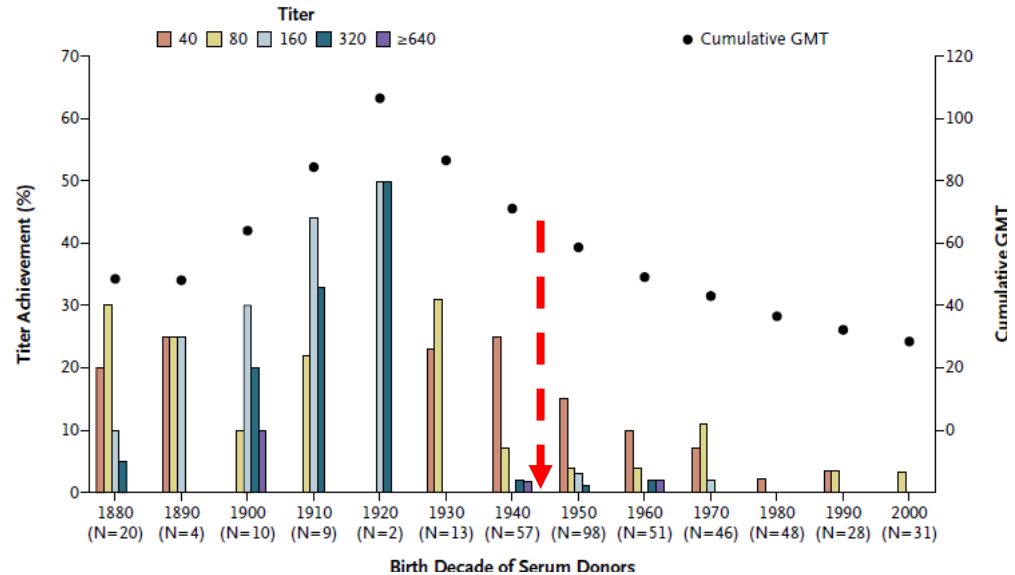 - Most genes were of human origin maintained in swine

2009 H1N1: Transmissibility and Population Immunity

Laboratory-confirmed Influenza

Serum Antibody to A(H1N1)pdm09

Median age: 12-15 years

Hancok K et al. NEJM (2009) 361(20):1945-52

Jacobs JH, et al. (2012) PLOS ONE 7(8): e42328.
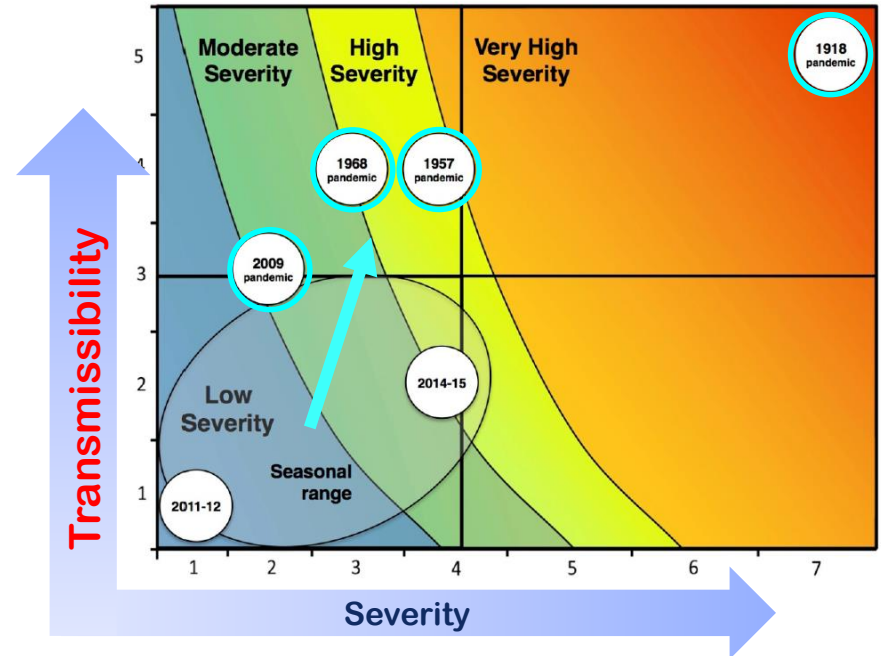CDC. MMWR 2009;58(33):913–918.

Severity & Transmissibility of '57 H2N2 and '68 H3N2

High severety

- 1957 H2N2 subtype
  - Novel H3 HA + N2 NA
  - Avian PB1

Moderate severety

- 1968 H3N2 subtype
  - Novel H3 HA
  - New avian PB1
  - Immunity to N2 dampened severity?

Reed, C. et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis 19, 85-91 (2013).
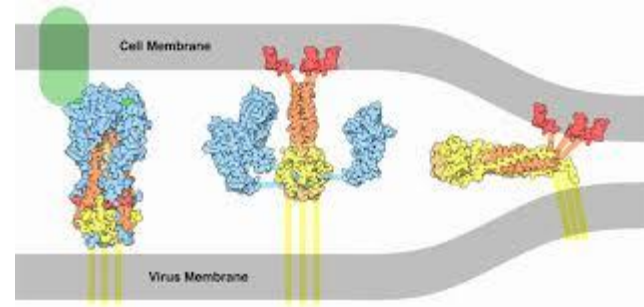
Animal-origin HA/NA Adaptation to Human Host

HA adaptation
- Recognize 2-6 sialic acid-containing receptors in the human upper airway tract
- Optimal acidic pH trigger for fusion (stability)
- Appropriate susceptibility to specific proteases as activators of fusion function
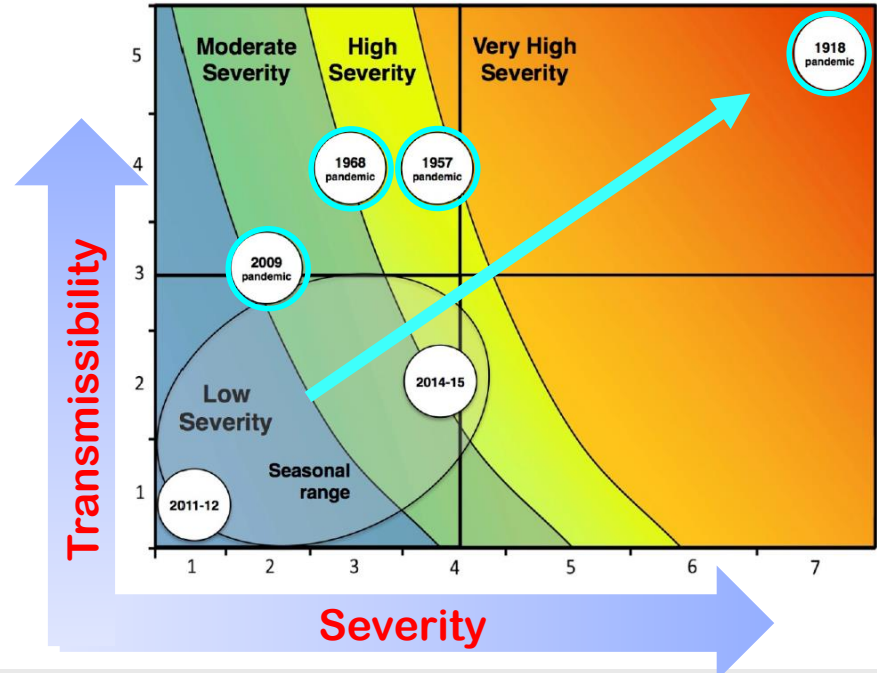
NA adaptation
- Altered enzymatic activity for functional balance with HA

Severity and Transmissibility of 1918 H1N1

Very high severity

- Direct avian to human?
- Avian to swine to human?
- HA + NA + Internal genes
- Tumpey et al. H1N1
- Herfst et al. H5N1
- Imai et al. H5N1/H1N1

Tumpey, et al. (2005) Science 310; p77-80

* Reed, C. et al. Novel framework for assessing epidemiologic effects of influenza epidemics and pandemics. Emerg Infect Dis 19, 85-91 (2013).

The Reconstruction of 1918 H1N1

- 1918 H1N1 virus recued by RG
  - Landmark achievement
    - ✓ Tumpey *et al* 2005
    - ✓ Taubenberger et al. 2001
  - Experimental infections
  - In vitro and in vivo
  - Structural biology
  - Omics
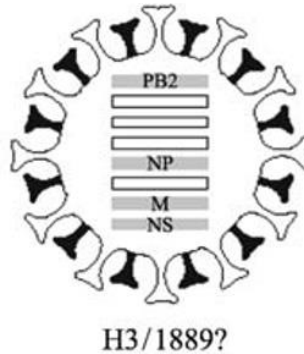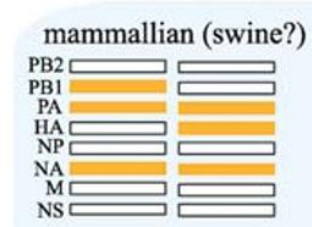
Darisuren Anhlan et al. RNA 2011;17:64-73

Guan et al. Protein Cell. 2010 1(1):9-13.

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1918 H1N1 Pathogenicity: Viral Replication & Transmission Machinery In Animal Models

Salomon, R. *Cell* **136**, 402-410 (2009).
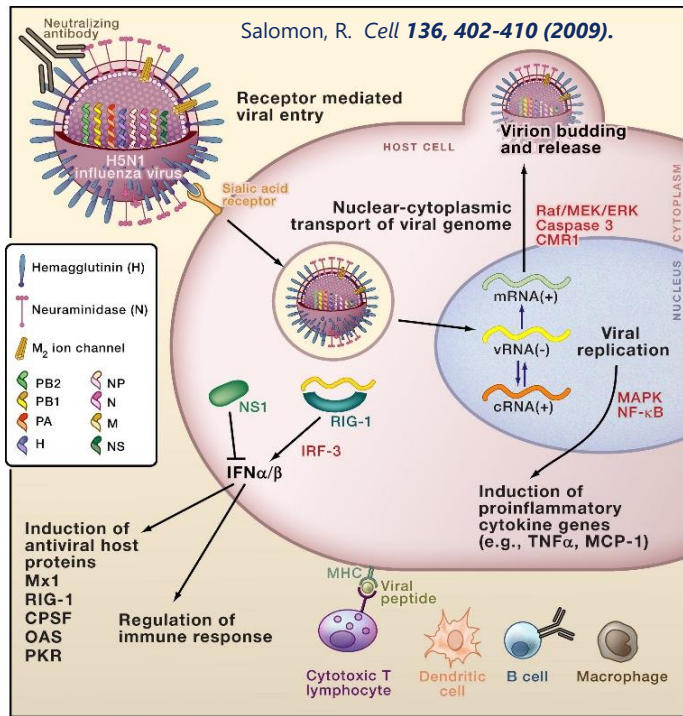
| HA | Protease cleavage activation |
	Sialoside receptor binding specificity
	Membrane fusion/pH optima
NA	Glycan cleavage catalysis optima
M2	Ion channel activity, uncoating, folding
NS2	Nucleocytoplasmic traffic
PB1	Replicase and transcriptase, fidelity
PB2	RNA Cap-binding
PA	RNA Cap endonuclease
NP & M	Genome structure and virion assembly
NS1	Host response modulation

Pathology:1918 and Subsequent Pandemics

- 1918 pathologic findings are similar to those of autopsies from the 1957 and 2009 pandemics
- No unique pathological mechanisms
  - similar cell tropism
  - similar virus distribution
- Co-morbidities; obesity, cardio

Trachea   Lung   Lung

Trachea   Lung
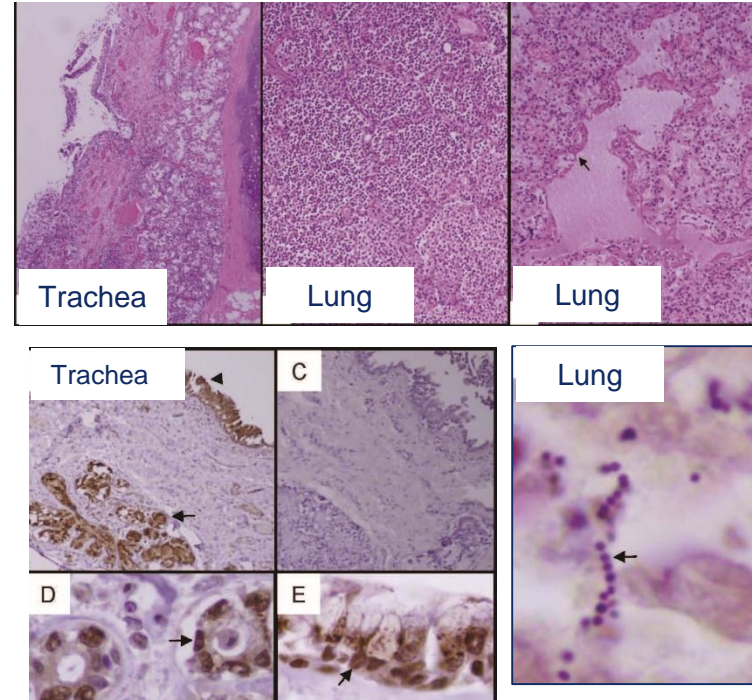
Gill, J. R. et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch Pathol Lab Med **134, 235-243 (2010).**

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1918 H1N1: Bacterial Superinfection

- Bacterial superinfections in fatal pandemic flu
  - ~90% in 1918
  - ~75% in 1957
  - ~55% in 2009
  - *Streptococcus pneumoniae*
  - *Haemophilus influenza*
  - *Mycoplasma pneumonia*
  - *Staphylococcus aureus*
- A future 1918-like pandemic would be much less severe due to antibiotic therapy
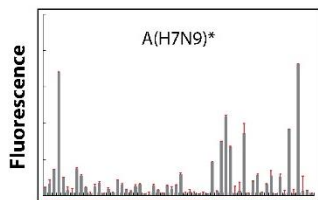- **The search for answers on 1918 virulence continues!**
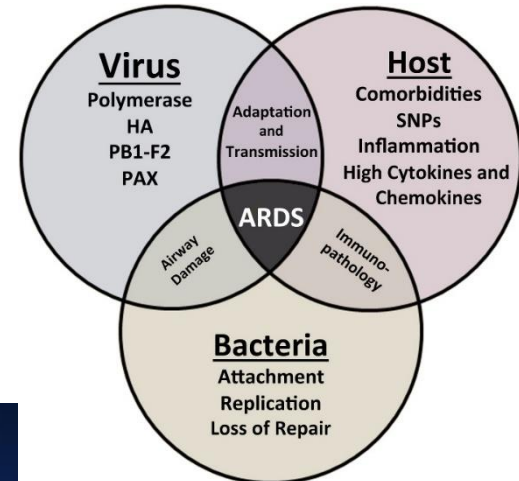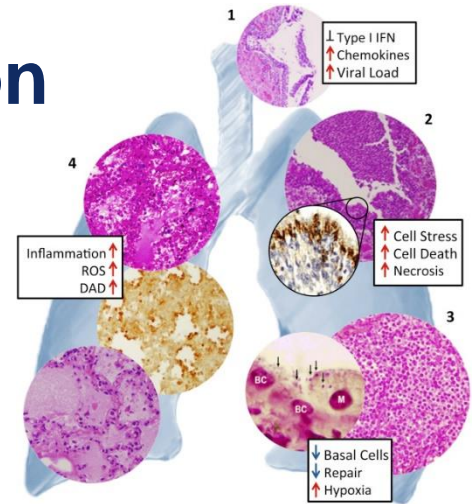
Kash, J. C. & Taubenberger, J. K. *Am J Pathol 185, 1528-1536,*
Gill, J. R. *et al. Arch Pathol Lab Med 134, 235-243 (2010).*
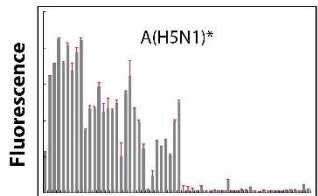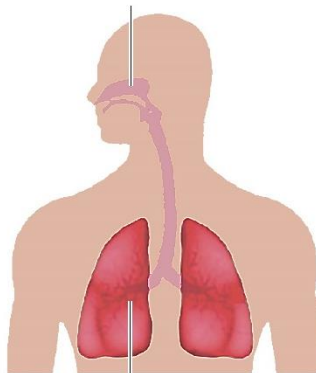
H7N9 IRAT Pandemic Emergence Risk: 6.5
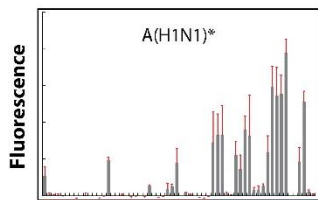
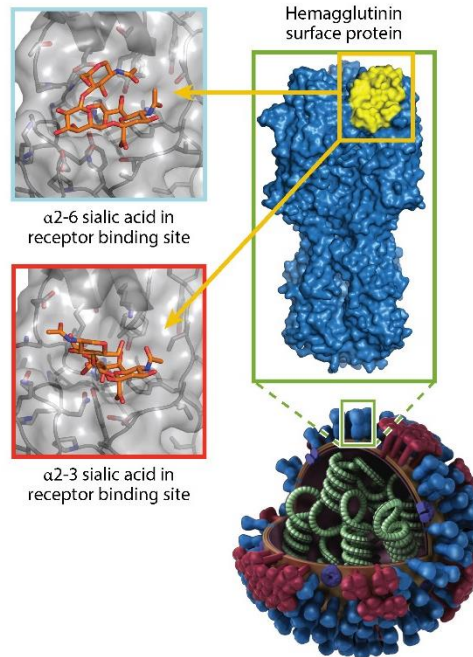Jernigan, D. Ann Rev Med 66, 2015 pp 361-371

H9N2 Pandemic Emergence Risk: 5.6

Virus	Emergence Score	Impact Score
H7N9 [A/Hong Kong/125/2017]	6.5	7.5
H9N2 G1 lineage [A/Bangladesh/0994/2011]	5.6	5.4
H5N1 Clade 1 [A/Vietnam/1203/2004]	5.2	6.6

Similarities

- Human infections: sporadic
- Receptor: significant 2-6 binding
- Internal genes: shared ancestry
- Evolution: multiple reassortments and antigenic drift

Wu ZQ, Int. J. Environ. Res. Public Health 2017, 14, 263; Stephenson I., Lancet. 2003 Dec 13;362(9400):1959-66.
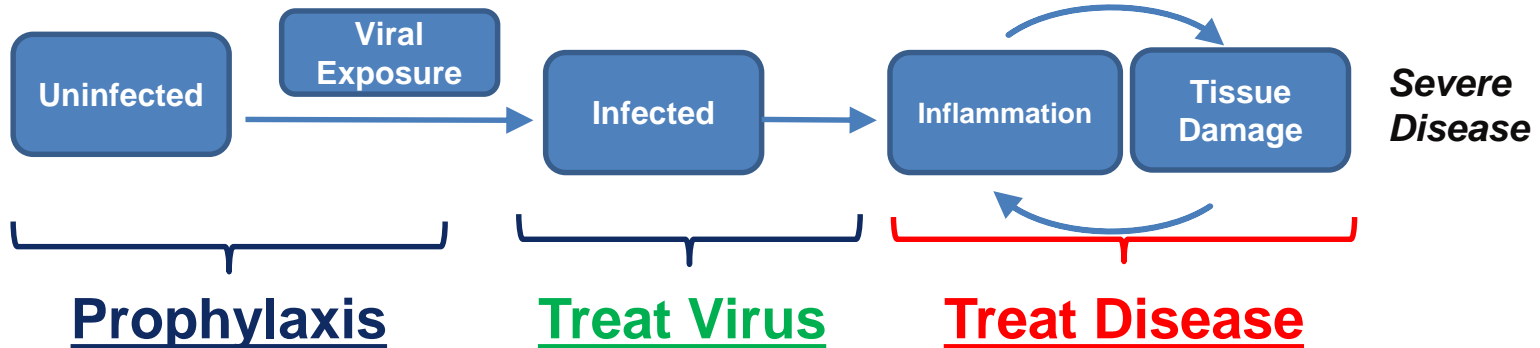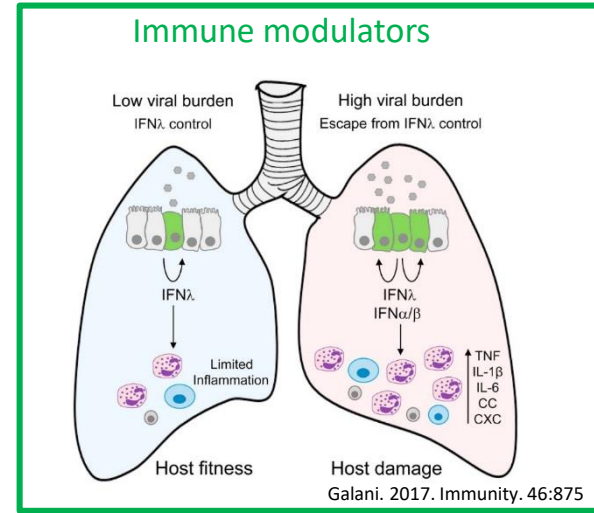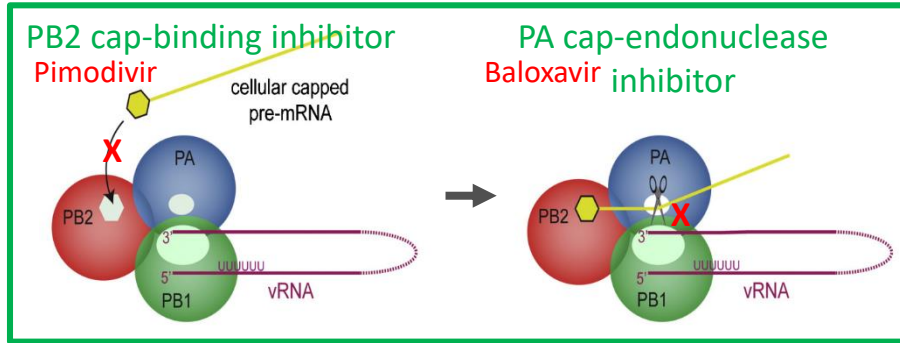
Differences

- Severity in humans: H7N9 CFR: ~30%
- Immunity in humans: H9N2 > H7N9
- Age distribution: H9N2 median =13 years, H7N9 median = 61 years
- Geographic distribution: H7N9 1 country, H9N2 widely in 2 continents
- H9N2 frequently detected in swine

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Predictable Unpredictability of Pandemic Influenza

- Global Challenges
  - Unknown pathogenic characteristics of the next pandemic virus
  - Faster spread than ever
  - Greater potential for societal disruption

- Global Opportunities
  - Better global pandemic surveillance
  - Faster communications, international collaboration
  - Improved pandemic response capabilities
  - Better and faster diagnostics, masks, vaccines and drugs

Antiviral Drugs:
Viral and Host Targets

PB2 cap-binding inhibitor
Pimodivir

PA cap-endonuclease inhibitor
Baloxavir

cellular capped pre-mRNA

PA
PB2
PB1
vRNA

Immune modulators

Low viral burden
IFNλ control

High viral burden
Escape from IFNλ control

IFNλ

IFNλ
IFNα/β

Limited Inflammation

↑TNF
IL-1β
IL-6
CC
CXC

Host fitness

Host damage

Galani. 2017. Immunity. 46:875

Uninfected → Viral Exposure → Infected → Inflammation ⇄ Tissue Damage → *Severe Disease*

Prophylaxis   **Treat Virus**   **Treat Disease**

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Thank You!