Current Vaccines: Progress & Challenges

Influenza Vaccine – what are the challenges?

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Outline of presentation

- Virus characteristics and evolution
- Epidemiology and transmission of influenza
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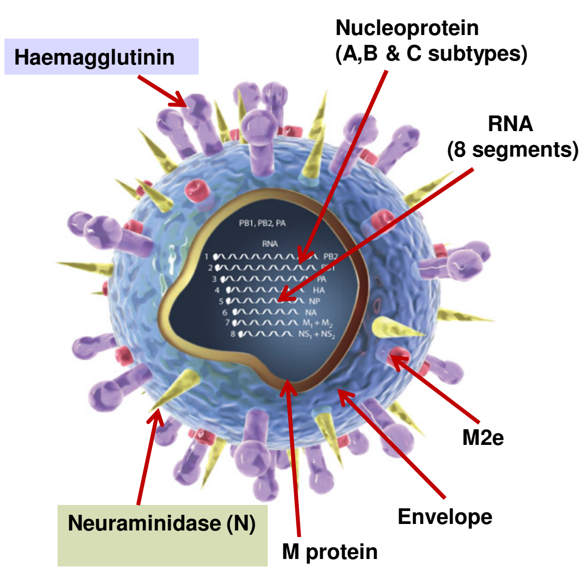
Seasonal Influenza: Ongoing Public Health Threat

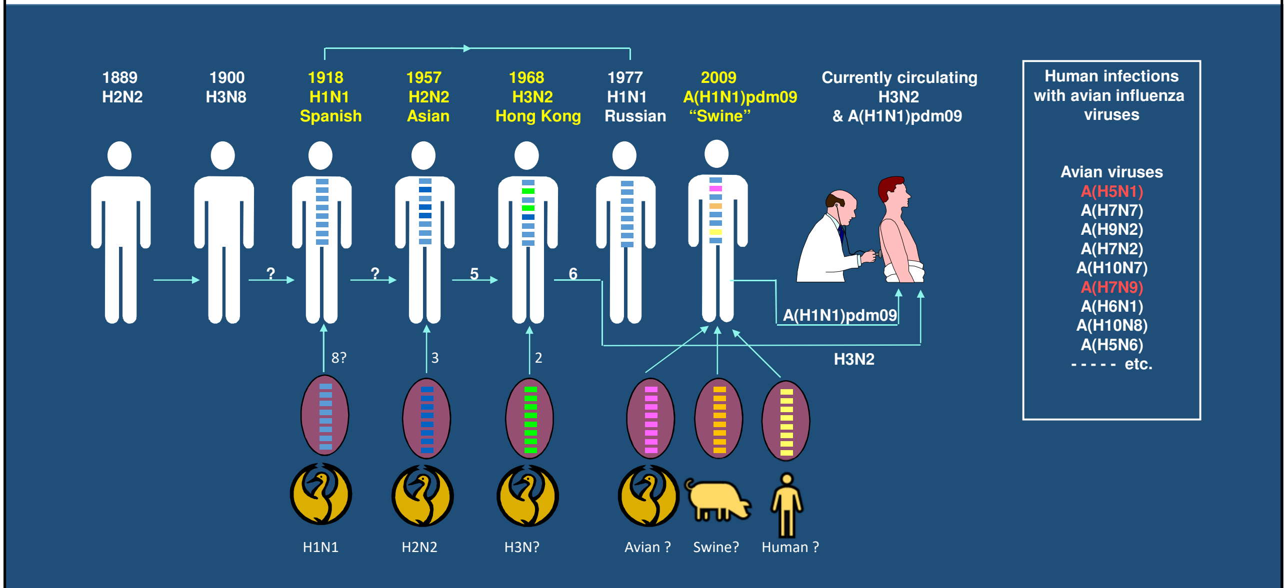
- Current influenza vaccines are moderately effective (approx. 60% effective in seasons with a good antigenic match)
- Impacts millions of people globally
  - 10-20% population; 250,000-500,000 deaths
- $80 B / yr. loss attributed to influenza disease in the USA
- Unpredictable changes in HA and NA lead to epidemics and global pandemics
  - Due to antigenic shift and antigenic drift
- Two types of influenza that affect humans: Type A and Type B
  - Type A : H1N1 and H3N2
  - Type B: Victoria and Yamagata lineages
- Emerging strains present pandemic risk to humans
  - e.g. H5N1, H7N9, H9N2, H6N1 & H10N8

Influenza virus



	Human	Pig	Horse	Bird	Bats
H types					
H1	✓	✓		✓	
H2	✓	✓		✓	
H3	✓	✓	✓	✓	
H4		✓		✓	
H5	✓	✓		✓	
H6	✓			✓	
H7	✓		✓	✓	
H8				✓	
H9	✓	✓		✓	
H10	✓			✓	
H11-H16				✓	
H17-H18					✓
N types					
N1	✓	✓		✓	
N2	✓	✓		✓	
N3				✓	
N4				✓	
N5				✓	
N6	✓			✓	
N7	✓		✓	✓	
N8	✓		✓	✓	
N9	✓			✓	
N10-N11					✓

Evolution of Influenza A Virus Pandemic Strains



Adapted and modified from: BR Murphy & RG Webster "Orthomyxoviruses" in Fields Virology, 3rd Edition Lippincott-Raven Publishers

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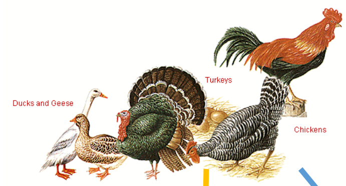
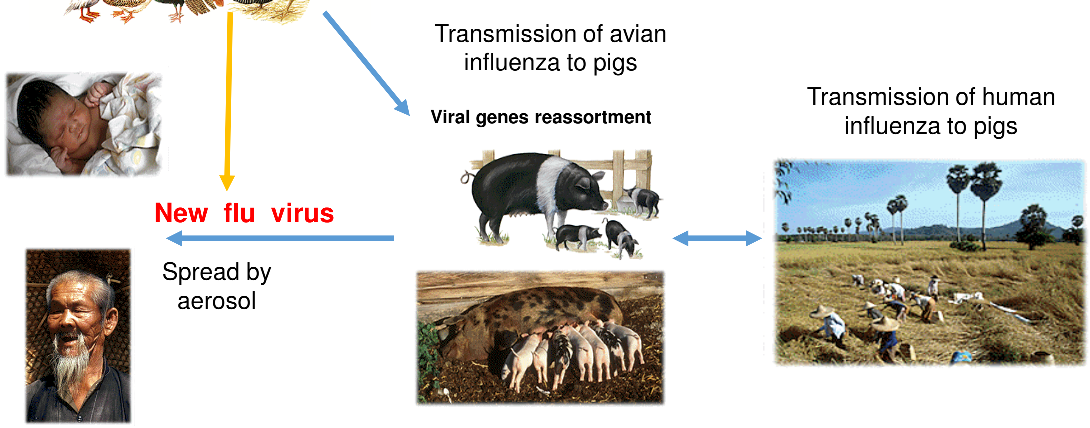
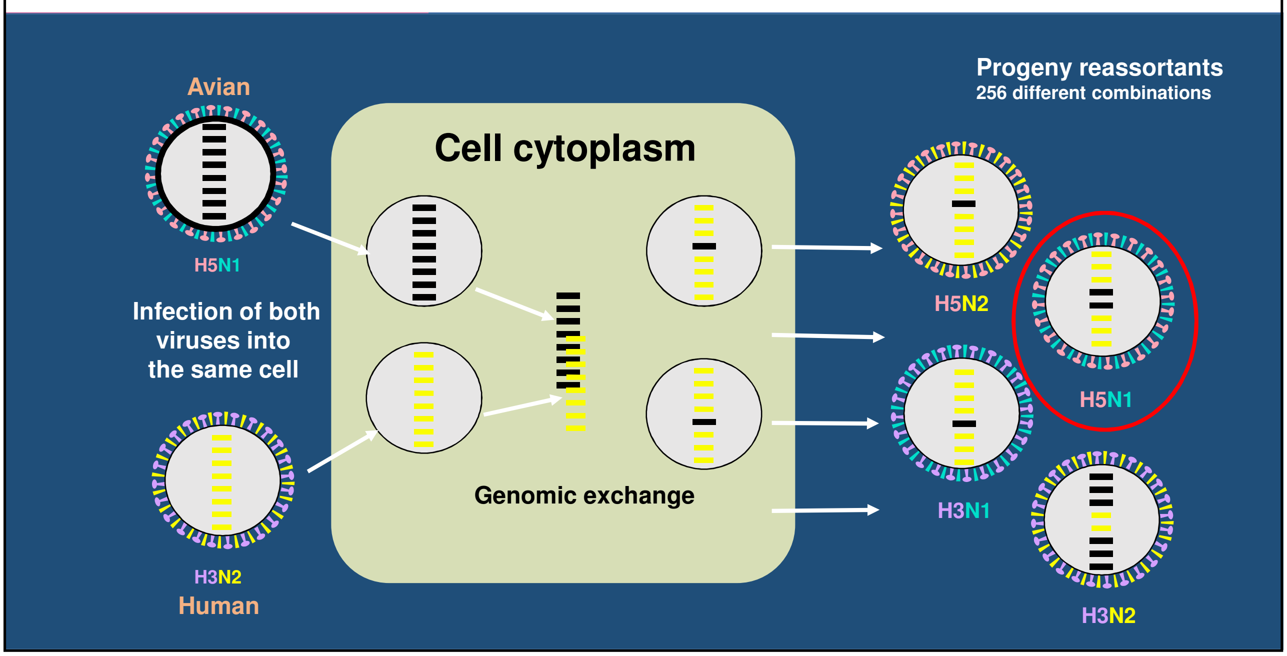
Evolution of Novel Influenza A Virus Strains (antigenic shift)



- cross infection of human & avian influenza in pigs
- leading to reassortment of genes and new strains (antigenic shift)



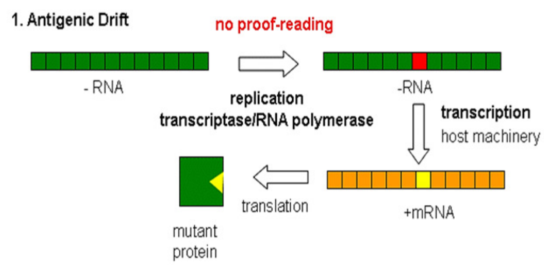
Reassortment of Influenza Virus Genes (antigenic shift)



Influenza A Virus Evolution (antigenic drifts)

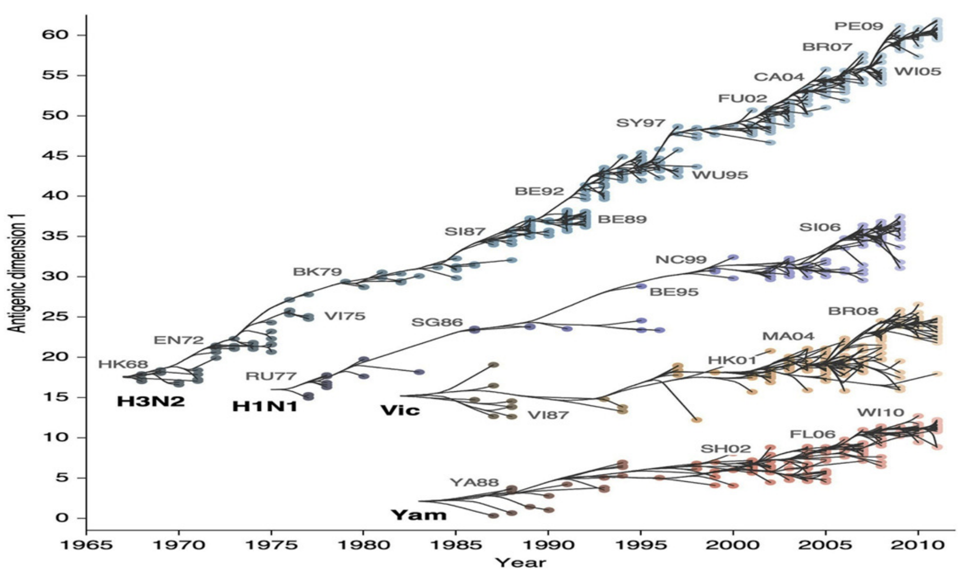
- Antigenic Drift
  - minor change, same subtype
  - caused by point mutations in gene
  - may result in epidemic
- Example of antigenic drift
  - in 2002-2003, A/Panama/2007/99 (H3N2) virus was dominant
  - A/Fujian/411/2002 (H3N2) appeared in late 2003 and caused widespread illness in 2003-2004

Replication of the RNA genome of influenza viruses is associated with a relatively high mutation rate (2.3 × 10^{-5}) because the viral RNA-dependent RNA polymerase lacks 3′-5′-exonuclease activity and therefore has no proof-reading function



Antigenic drift of A/H3N2, A/H1N1, B/Vic and B/Yam viruses

Antigenic drift is shown in terms of change of location in the first antigenic dimension through time.



Trevor Bedford et al. eLife Sciences 2014;3:e01914

Consequences of Mutations in Influenza Virus Genes

- Changes in receptor binding characteristics
  - changes viral tropism - avian (α2-3 linkage SA) to human (α2-6 linkage SA)
  - increase risk of non-human subtypes to infect human
  - enhance human-human transmission
- Alteration in pathogenesis
  - aerosol transmission to airborne transmission (H5N1- lab mutation)
  - changes in targeted organs (disease clinical presentations)
- Antigenic changes in neutralizing epitopes on HA protein
  - escape-mutations leading to vaccine failure
  - reduction of vaccine efficacy and effectiveness
- Antiviral resistance
  - treatment failure in using antiviral drugs

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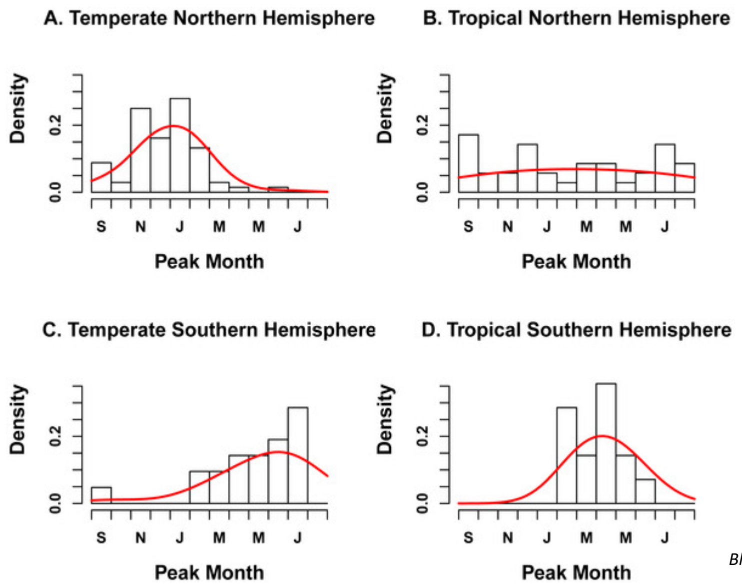
Seasonality of influenza by geographic zone (n = 77 locations)



Bloom-Feshbach K, et al. (2013)

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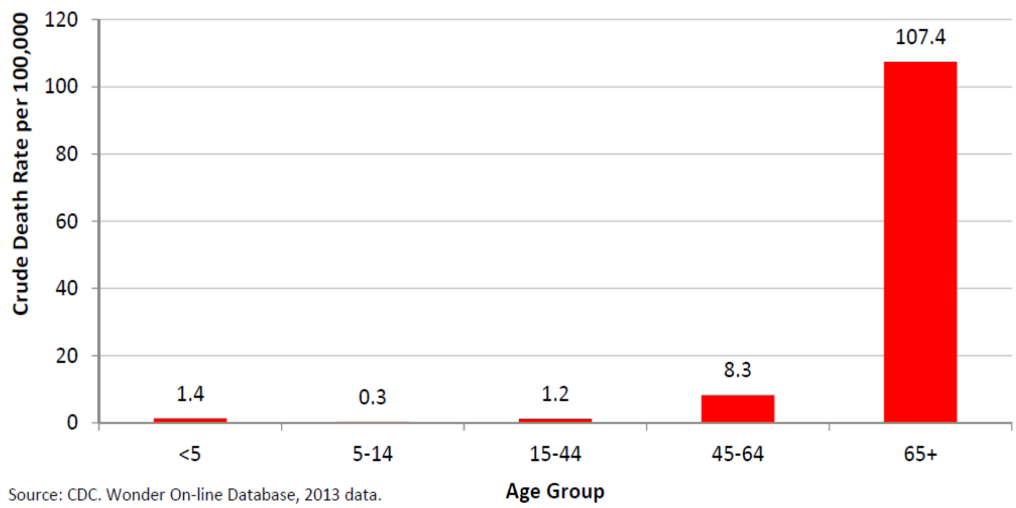
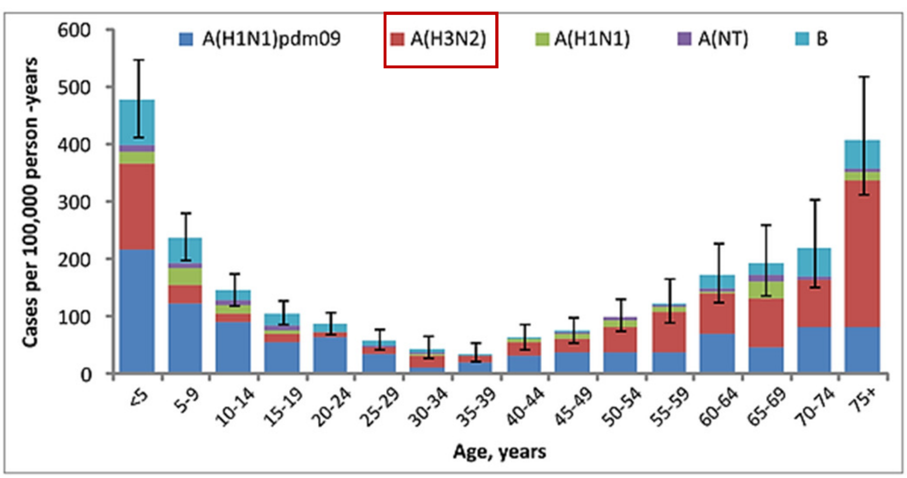
Age-specific mortality rate of influenza & pneumonia, USA 2013



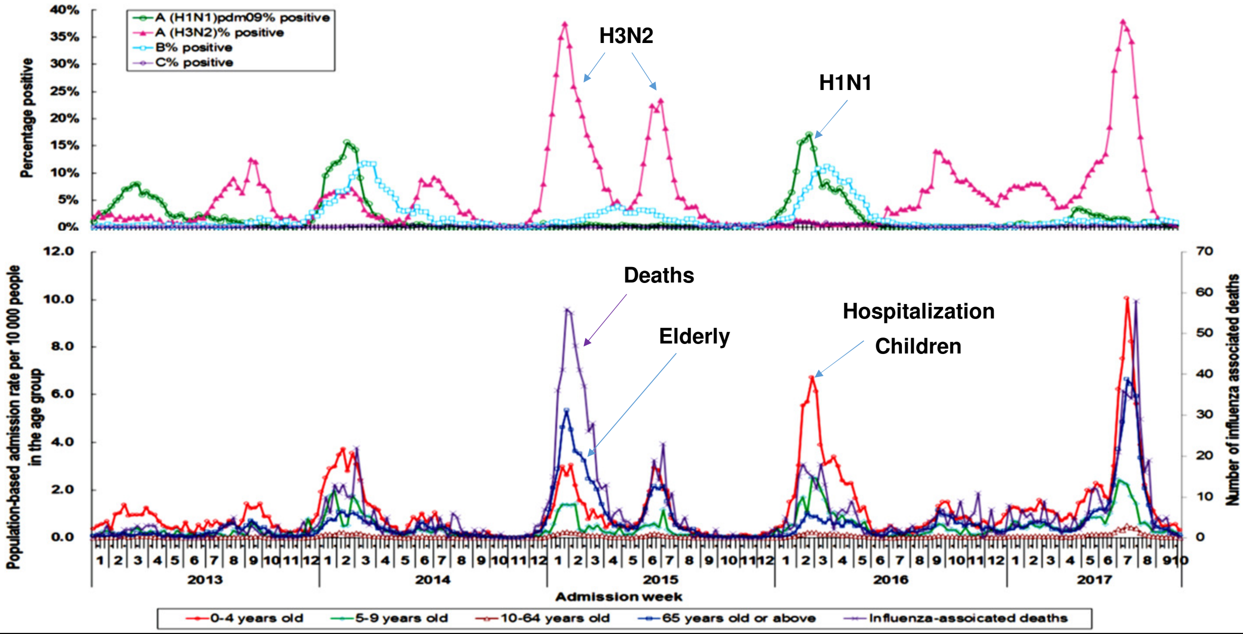
Source: CDC. Wonder On-line Database, 2013 data.

Age-specific incidence rate of influenza-associated acute lower respiratory infection hospitalizations in Thailand 2009 - 2010

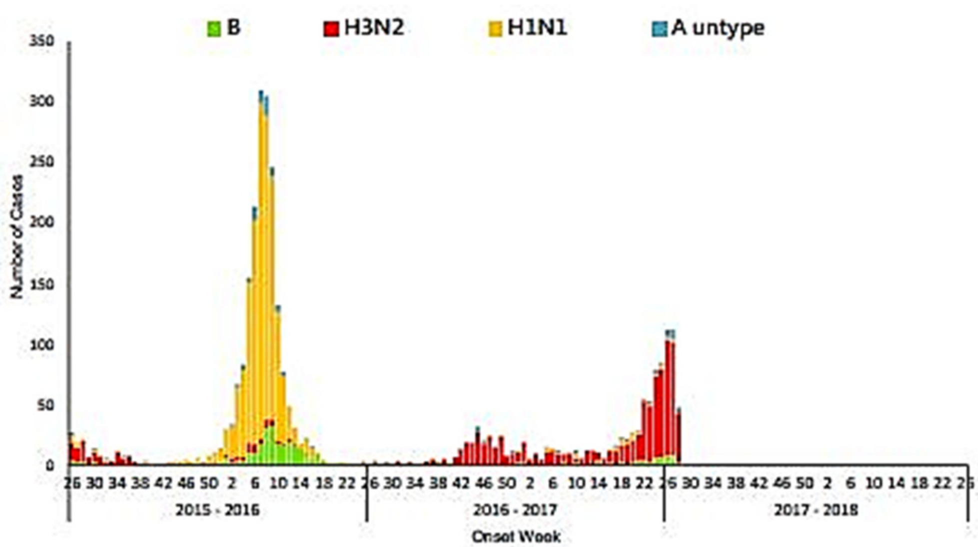


Baggett HC, Chittaganpitch M, Thamthitiwat S, Prapasiri P, Naorat S, et al. (2012) Incidence and Epidemiology of Hospitalized Influenza Cases in Rural Thailand during the Influenza A (H1N1)pdm09 Pandemic, 2009–2010. PLOS ONE 7(11): e48609. doi:10.1371/journal.pone.0048609

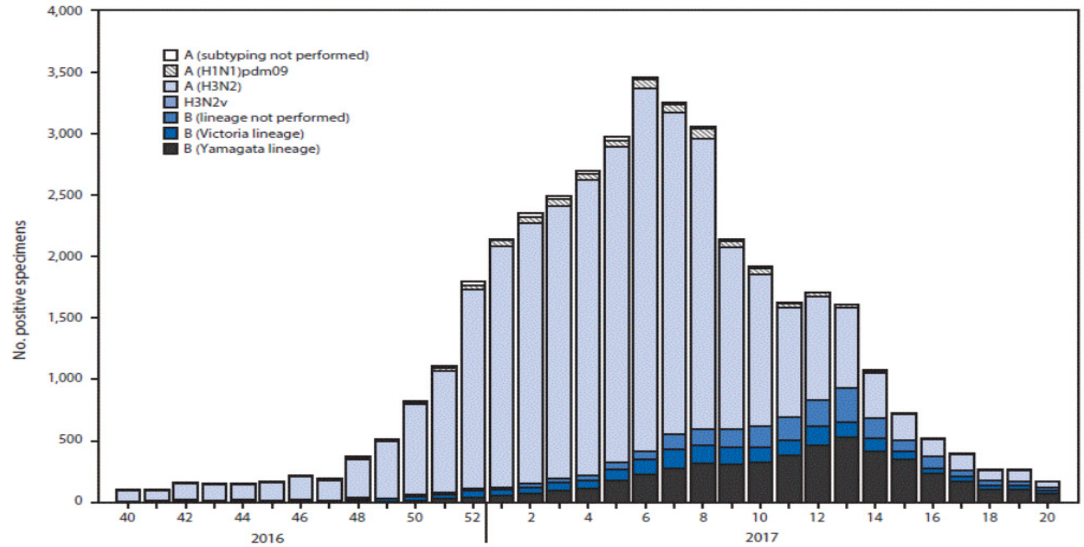
Influenza-associated hospital admission & deaths in Hong Kong 2013-2017



Number of severe complicated influenza cases reported by week of onset, Taiwan 2015 - 2017

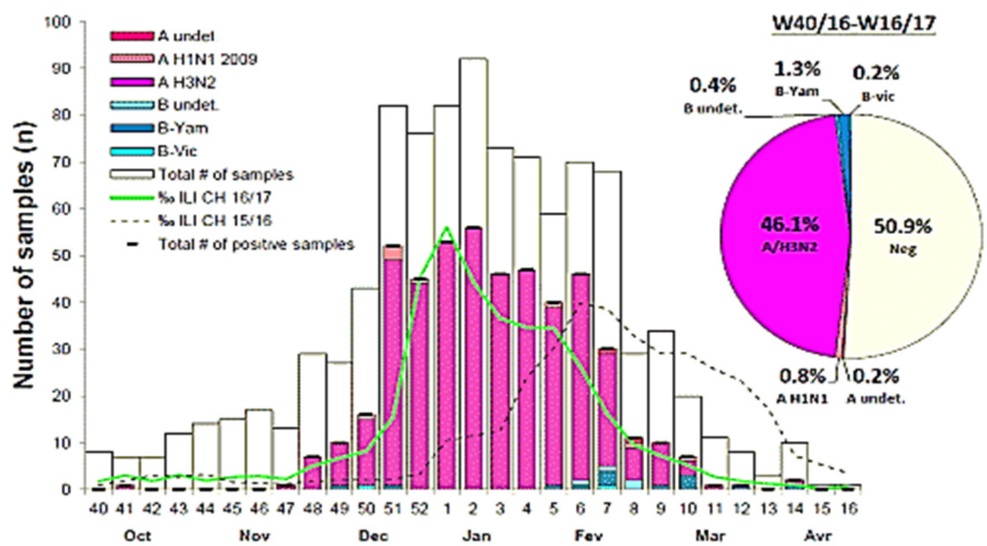


Number of respiratory specimens positive for influenza reported by public health laboratories, by influenza virus type, subtype/lineage, and surveillance week — United States, October 2, 2016–May 20, 2017



MMWR June 30, 2017

Number of respiratory specimens positive for influenza reported by the Swiss Federal Office of Public Health laboratories, by influenza virus type, subtype/lineage, and surveillance week — Switzerland, October, 2016 – April, 2017



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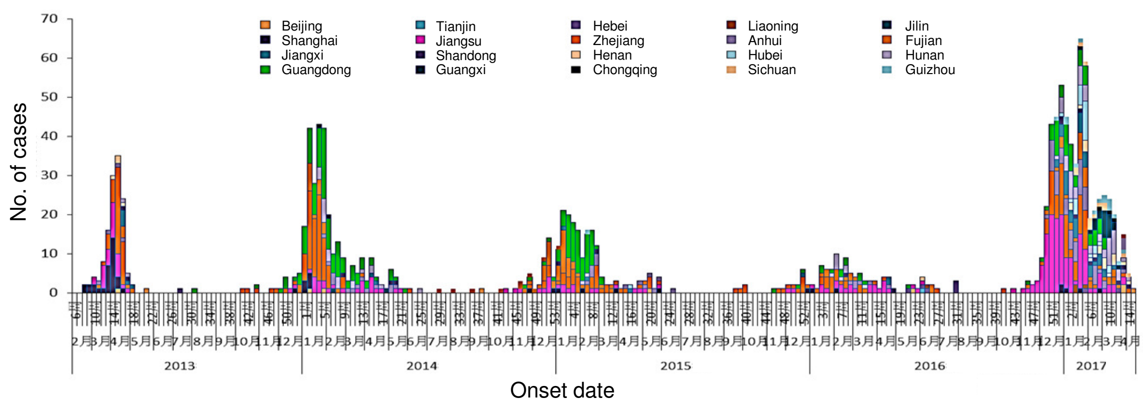
The 5th H7N9 Epidemic season: 732 cases/ 274 fatal (as of 2017-Jun-15)

Human cases reach 1507 and 595 fatal (CFR 39%) in 26 provinces, since 2013



No. of provinces	12	13	14	15	25
No. of cases	134	304	219	118	732
No. of deaths	44	127	100	48	272
Case-fatality rate	33	42	46	41	37

Summary on H7N9 infections in China

- The wave in 2017occurred earlier, higher and longer
- Wider geographic distribution
- Increase in rural cases, due to mobile poultry vendors in some provinces
- HPAI H7N9 cases occurred
- No significant in age, sex and clinical severity, and no sustained H to H transmission

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Unique characteristics of influenza vaccines

- Influenza vaccine is unique among other vaccines:
  - Include all ages and recommendations for specific groups
  - Seasonal applications (Northern vs. Southern formulations)
  - Repeated annual vaccination (changing of circulating viruses)
- Prediction of variant viruses for vaccine production:
  - Requires an extensive global surveillance system
  - Tight manufacturing schedule (2 formulations)
  - Unable to match new viruses within the manufacturing cycle
- Vaccine performance
  - Main vaccine target – severe illness
  - Approved primarily on immune correlate – ≥1:40 HI; ≥70% subjects responding to that level and ≥40% seroconversion rate, which correspond to 50% efficacy in healthy adults
  - Effectiveness varies from year to year and for different groups
  - Vaccine viruses may not correspond to circulation viruses
- Manufacturing capacity unable to match timing and volume required for PANDEMIC control