Influenza Overview

- case study
- vaccine types and effectiveness
- vaccine timing

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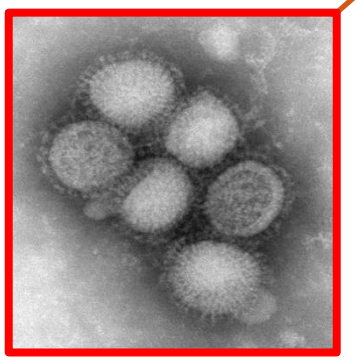


"I had a little bird, and its name was Enza,
I opened the window, and in-flew-Enza."

David Speers

39 year old woman

- **Presented with fever, cough and headache**
- **Admitted for SOB and treated with ceftriaxone, azithromycin, oseltamivir, vancomycin**
- **Deteriorated with increasing respiratory rate, confusion, type II respiratory failure**
- **Hypotensive and tachycardic (150 bpm)**
  - Intubated and transferred to ICU

- **PMHx**
  - IVDU and hepatitis C
  - Alcoholism
  - Obesity (98.5kg)

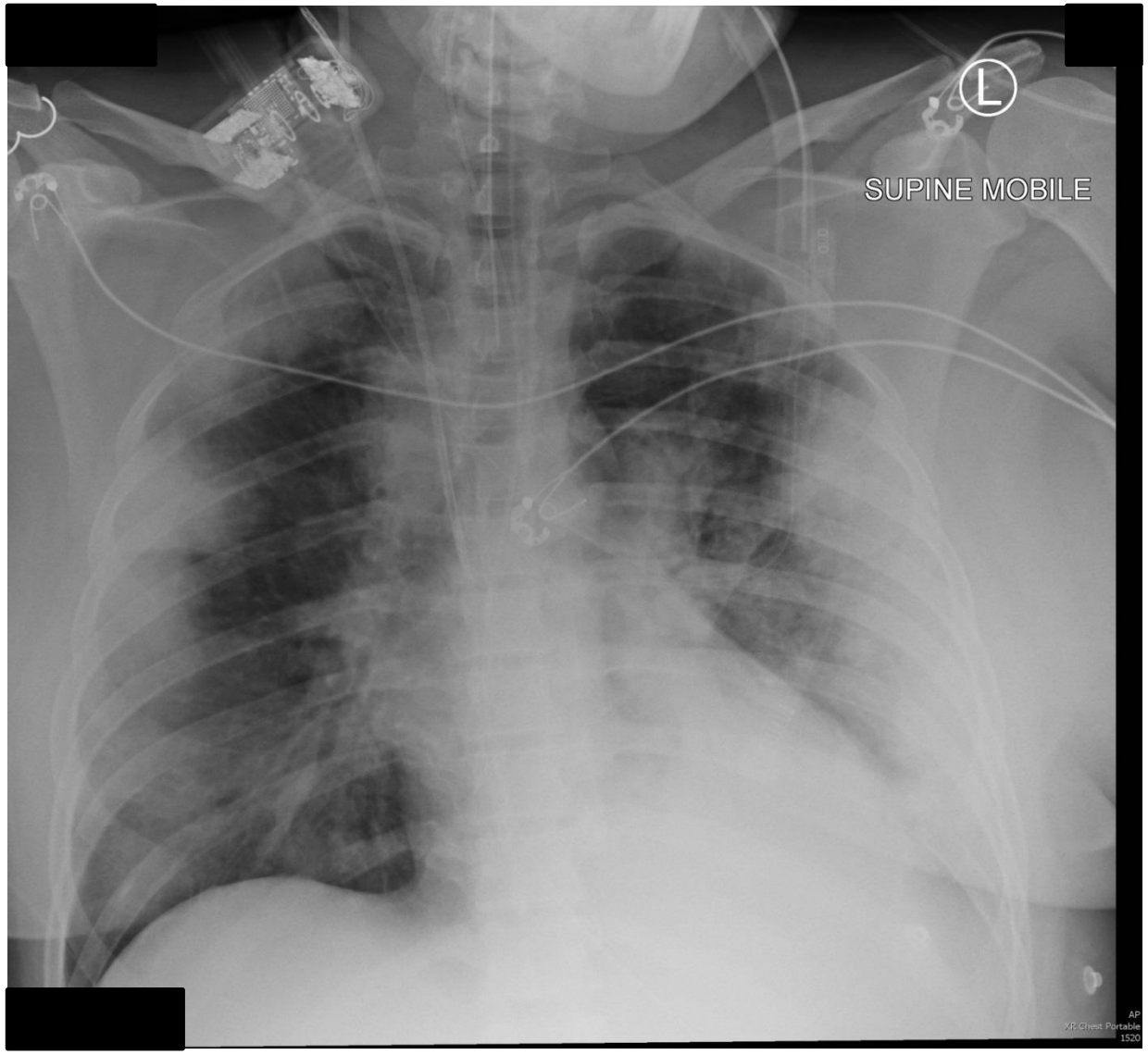
Microbiology

- **Blood cultures –ve**
- **Sputum:**
  - Moderate WBCs
  - no significant bacterial growth

- **Nose and Throat Swab**

Human Metapneumovirus RNA	**NOT Detected**
Influenza A virus RNA (A/H1N1 09) .	**Detected**
Influenza B virus RNA	**NOT Detected**
Parainfluenza 1 RNA	**NOT Detected**
Parainfluenza 2 RNA	**NOT Detected**
Parainfluenza 3 RNA	**NOT Detected**
Respiratory syncytial virus RNA . . .	**NOT Detected**

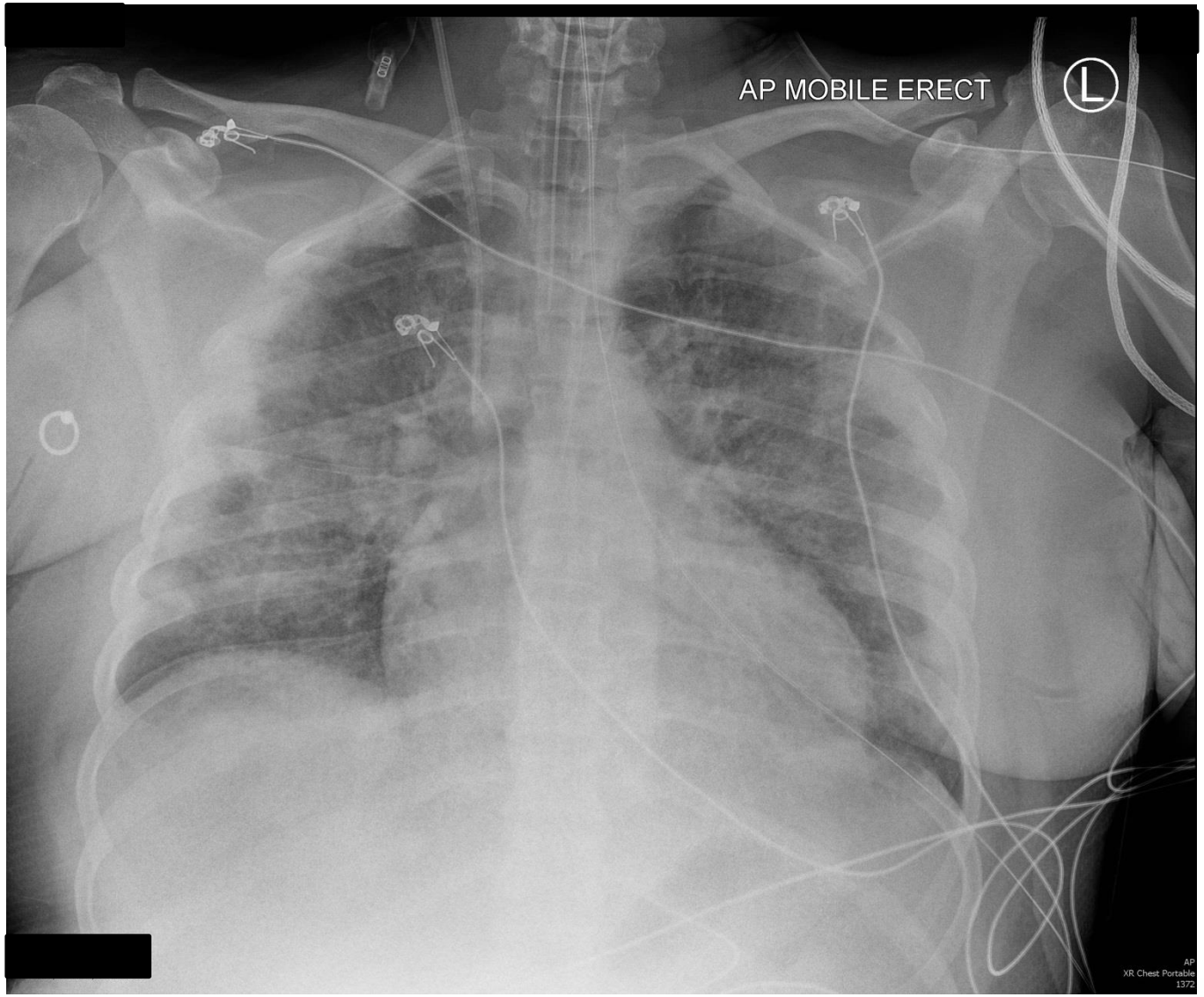
Day 1 ICU

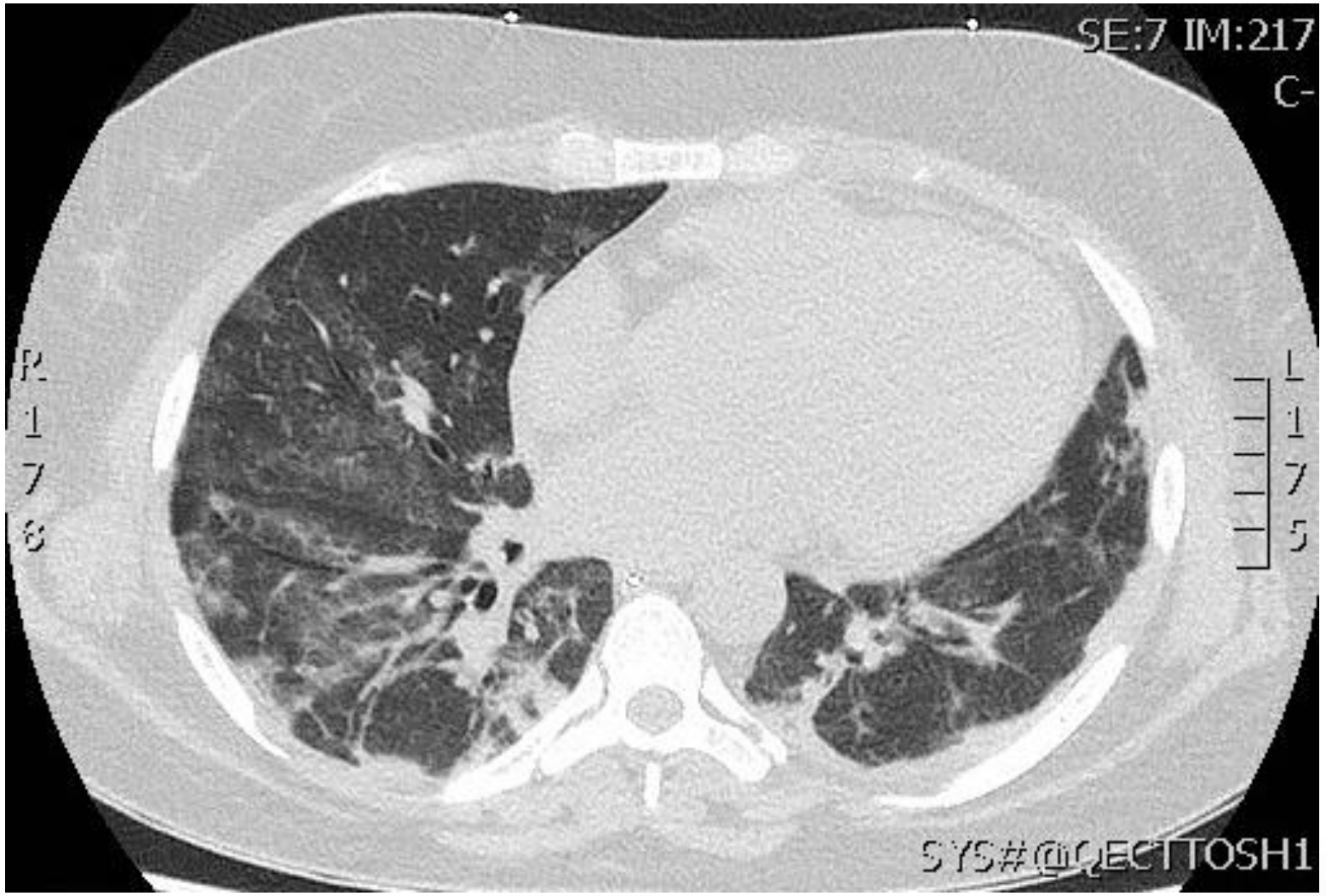


Progress

- **Received broad spectrum antibiotics and oseltamivir**
- **Developed ARDS secondary to viral pneumonia**
- **Persisting fevers, acute kidney injury, tachycardia**
  - escalating antibiotics
  - dialysis
  - aspiration pneumonia
  - IDC associated UTI
  - Hypoxic encephalopathy and critical illness myopathy
  - autonomic dysregulation
- **Myocarditis**
  - FluA H1N1 PCR +ve in blood

Day 8 ICU

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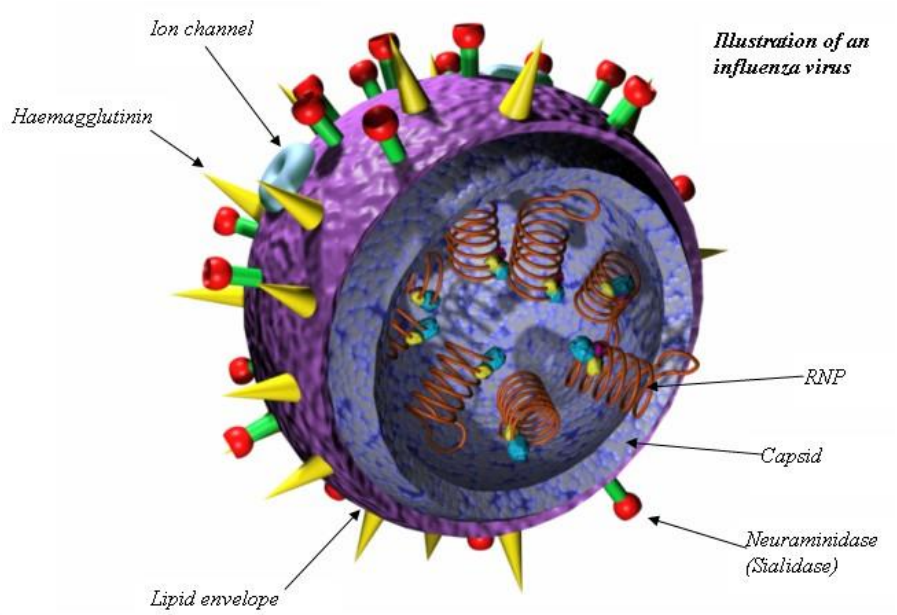
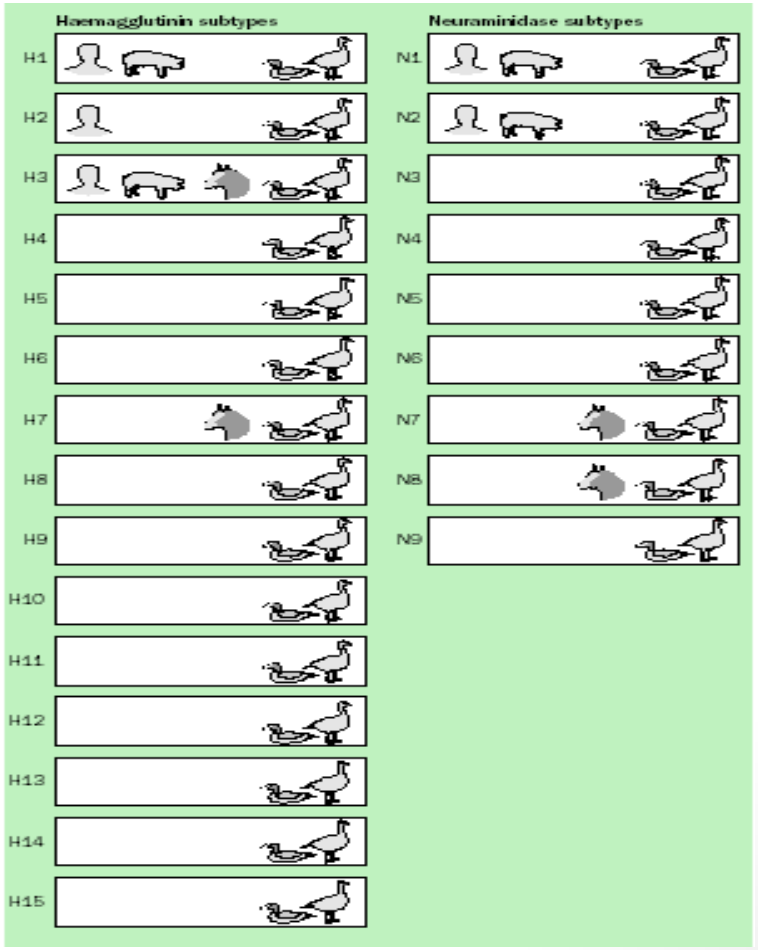
Further progress

- **26 day ICU stay**
- **3 month and 22 day hospital admission**
- **Transferred to transitional care**
- **Died 2 months later**

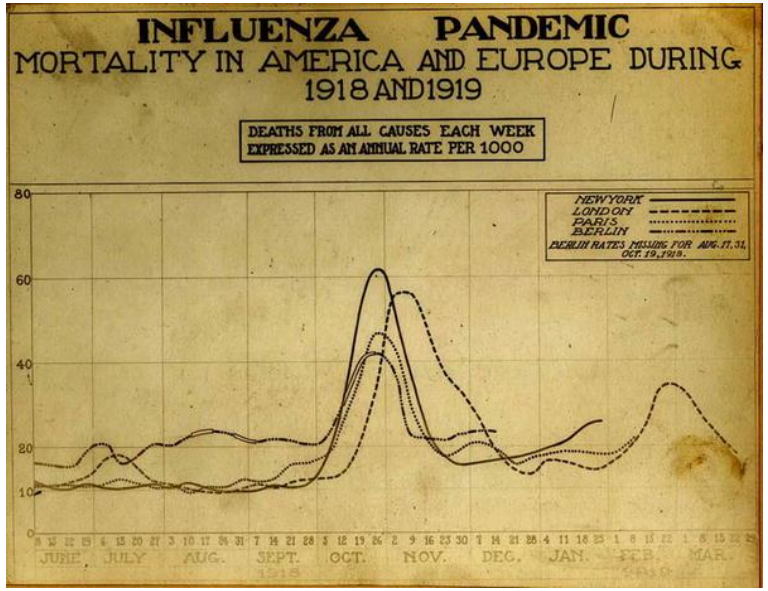
The origin of influenza A viruses

- **Aquatic birds**
  - intestinal tract infection by all subtypes
  - faecal-oral spread into lakes by migrating wild ducks
  - enough virus in 1g of contaminated manure to infect 1 million birds





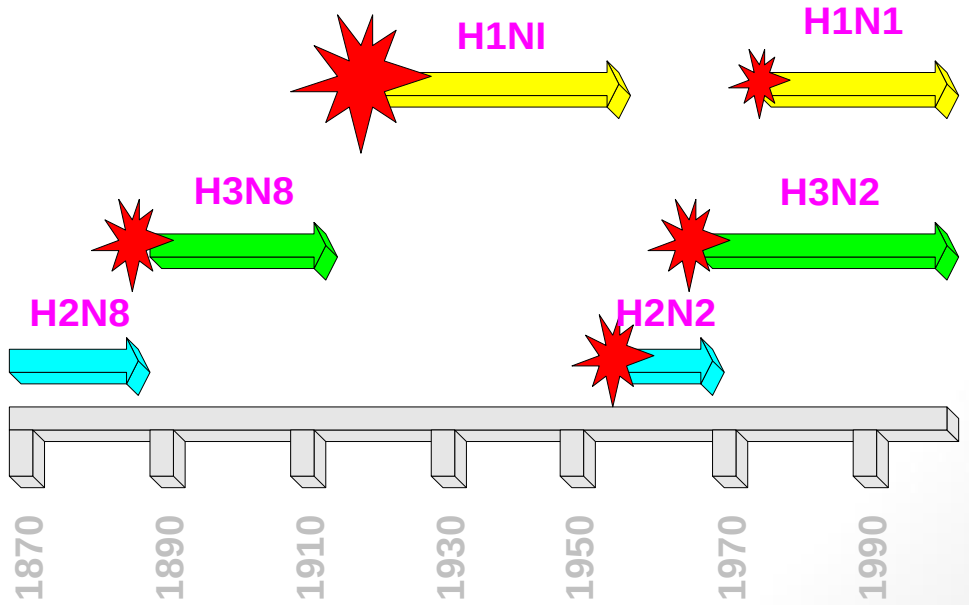
Death, Taxes, and Influenza - the certainties in life



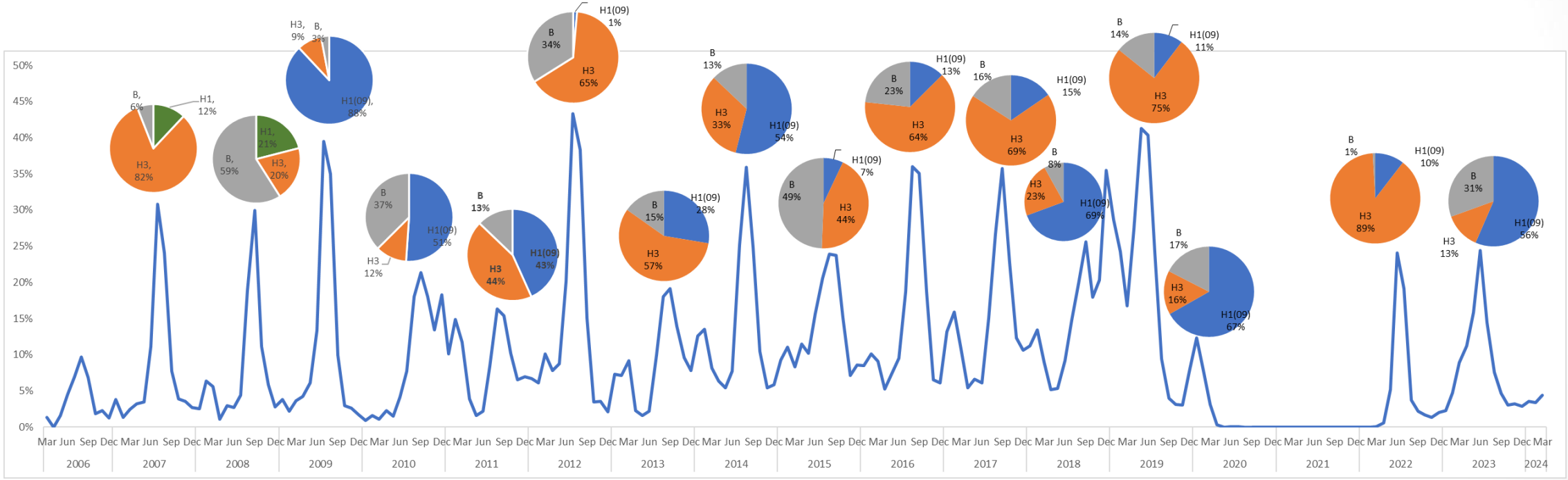
- **Flu A Pandemics**
  - Requires new haemagglutinin, ability to replicate in humans, immunologically susceptible population, ability to spread person-to-person
  - about 31 pandemics since 1580 (average of one every 14 years)

- **20th Century pandemics**
  - 1918-19 H1N1 (Spanish): 20-50 million deaths
  - 1957 H2N2 (Asian): 1-2 million deaths
  - 1968-69 H3N2 (Hong Kong): 700,000 deaths

- **21st Century pandemic**
  - 2009 A(H1N1)pdm09 (Swine flu): 284,000 deaths
    - Quickly evolved to a seasonal pattern



WA influenza 2006-current (PW data)



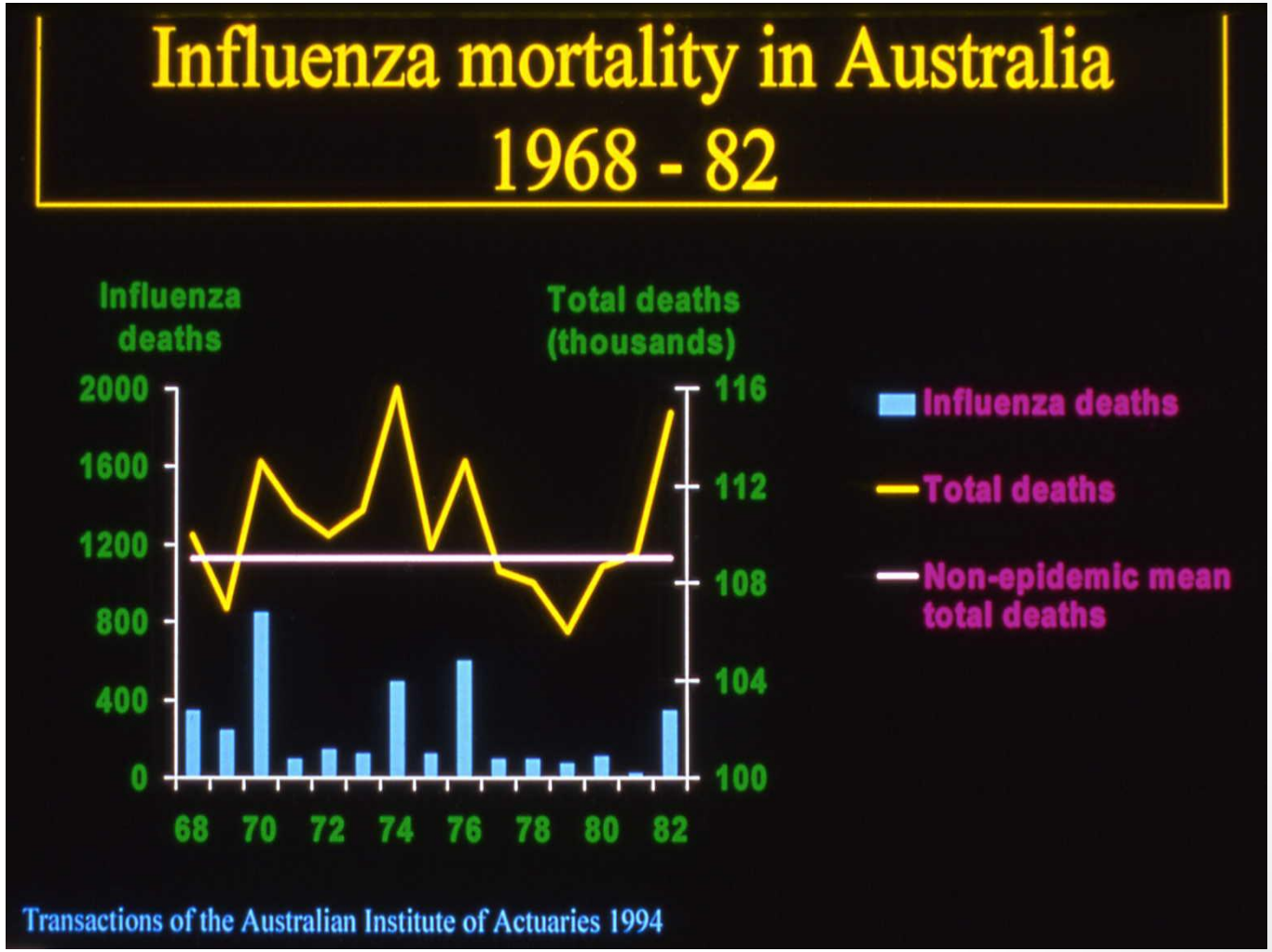
Previous seasonal H1N1

H1N1pdm09

Cara Minney-Smith

Burden of disease

- **Influenza causes 3-5 million cases of severe illness and 290,000-650,000 deaths/yr (0.1-0.2% CFR)**
- **Direct and excess mortality**
- **Risk groups for vaccine protection:**
  - Older adults (>65 yr) 4-5X hospitalisation
  - Comorbidities 3-4X hospitalisation
  - Pregnancy 7X hospitalisation
  - HCWs
  - Children < 5 yr
- **Greatest impact of vaccination on community transmission:**
  - School aged children



Vaccine types

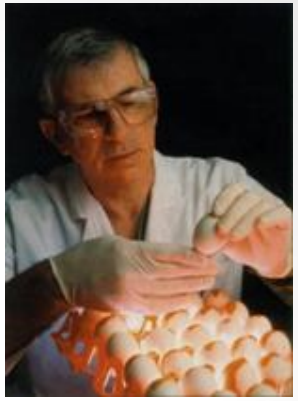
- **Candidate vaccine viruses:**
  - Inactivated egg or cell based vaccines
    - Usually subunit vaccine of HA and NA antigens to reduce adverse reactions
    - For pregnant women, older, HCWs, immunocompromised
    - >65 yr vaccine require more immune boost:
      - Increased antigen (60mcg vs 15 mcg), multiple doses, adjuvants (alum, squalene)
  - Live attenuated
    - Single dose nasal spray, produced in eggs with required HA, NA
    - Cold adapted to be temperature sensitive
    - Used in Russia since 1987 and in USA, Canada, Europe since 2012
    - More protective in children above 2 years (2 to 17 - 59 yr), lower efficacy for adolescents and adults
    - Not recommended in the immune compromised
- **Recombinant vaccines**
  - Produce 45mcg rHA using DNA technology with a baculovirus expressed in an insect cell line
  - Avoids egg adaptive mutations
- **Universal vaccine (none in use)**
  - DNA, mRNA, viral vector, nanoparticle vaccines underdevelopment
  - Target conserved (non-HA) regions or mosaic vaccines with mRNA from all HA subtypes

Vaccine strain manufacture

- **Egg-based methods**
  - Slow (5-8 months), dependent on egg supply
  - Prone to antigenicity changes due to egg adaptation
  - ?risk to people with egg allergies
    - No vaccine has >1 mcg ovalbumin
    - ATAGI: People with egg allergy, including anaphylaxis, can be safely vaccinated with any egg-based influenza vaccine unless they have reported a serious adverse reaction (up to 2% mild reaction)
  - Used for inactivated vaccines and live attenuated vaccines

- **Cell culture methods**
  - Faster production, avoid egg adaptation
  - Vulnerable to contamination
  - Limited current production capacity, would require overhaul of manufacturing facilities

Vaccine composition

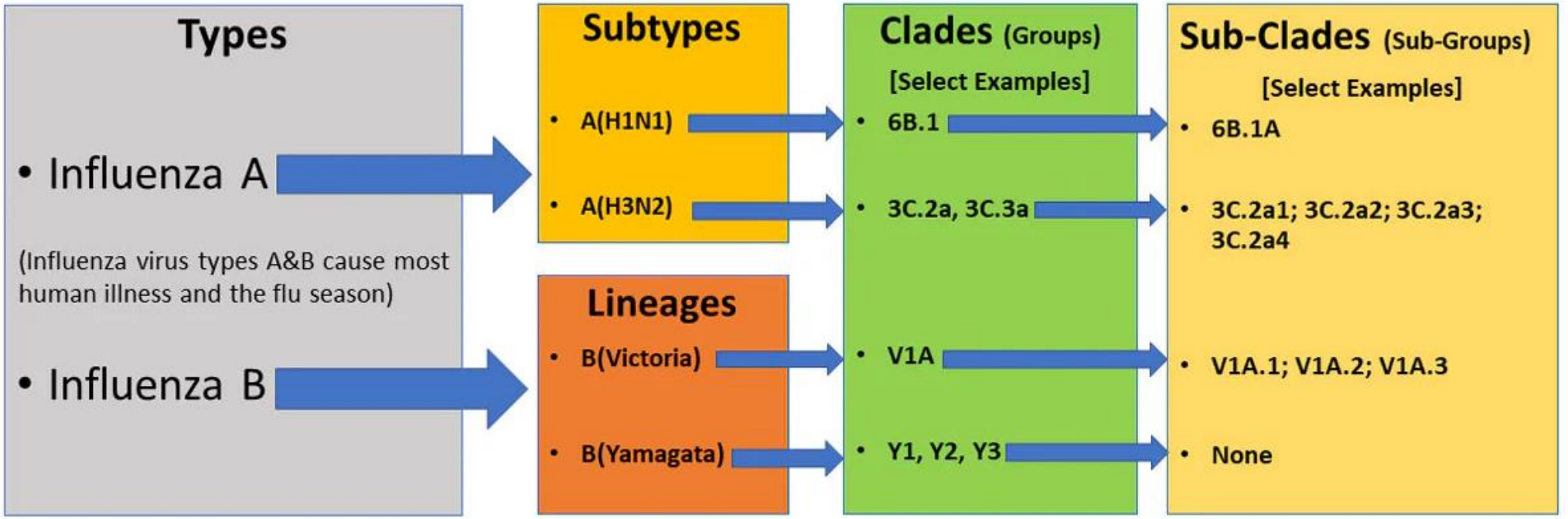


- **Trivalent and quadrivalent contain the same H1 and H3 flu A vaccine strains**

- **Vaccine Composition Meeting (VCM) convened in Feb (NH) and Sep (SH) to review GISRS network data (WHO collaborating laboratories)**
  - Meet 6-8 months prior to expected peak influenza season for production and distribution
  - Review the antigenic and genetic characteristics of circulating viruses
  - Review vaccine effectiveness and antiviral resistant strains
    - HI titres $\geq$ 40 used as surrogate for clinical protection (50% protection)
    - Previously used ferrets, now use human serum post-vaccination
    - Better as across age groups, accounts for previous vaccines

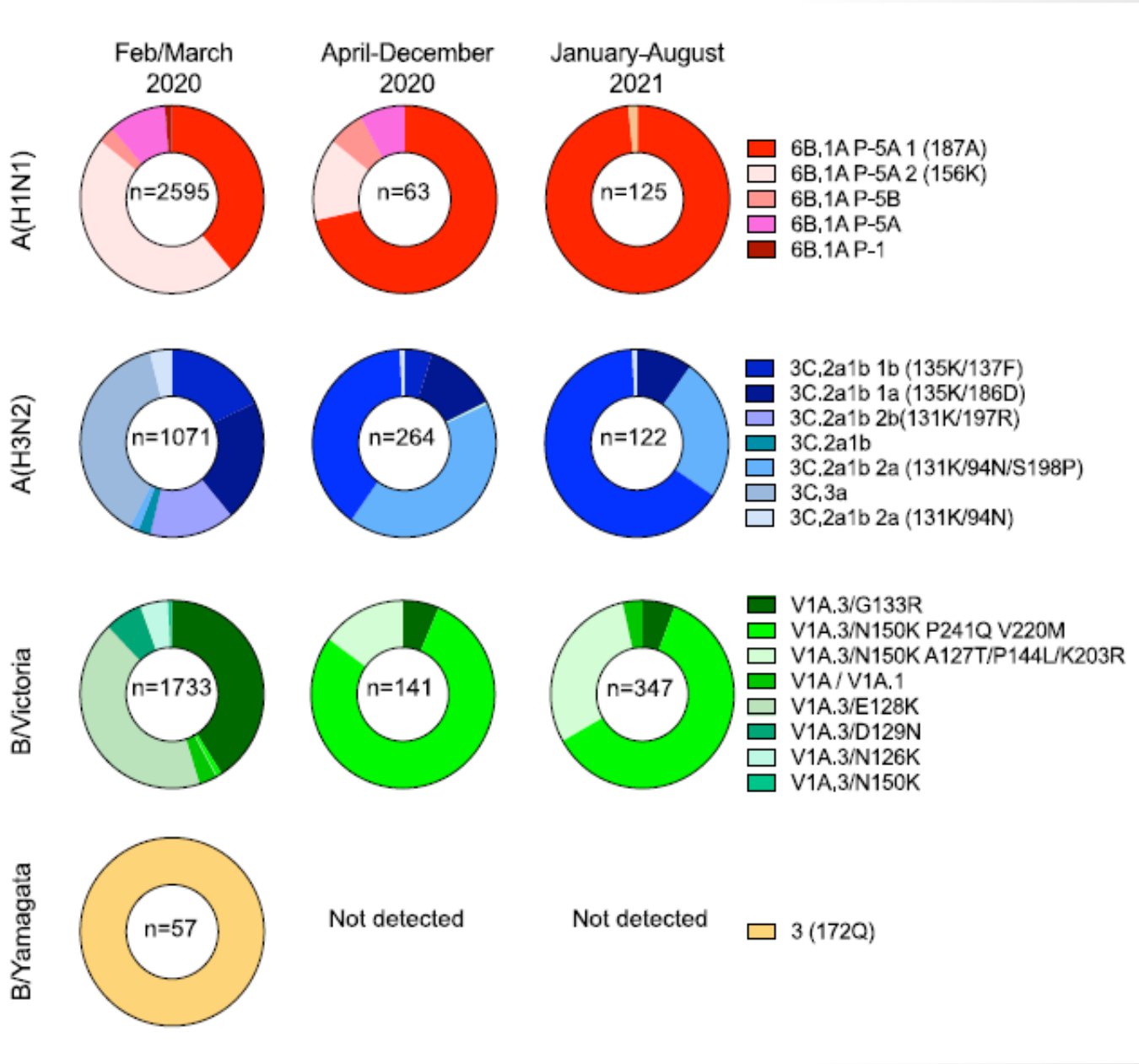
- **Data used to:**
  - Forecast the strains likely to circulate
  - Make recommendations to inform the development of candidate vaccine viruses

Vaccine composition to match circulating sub-clades



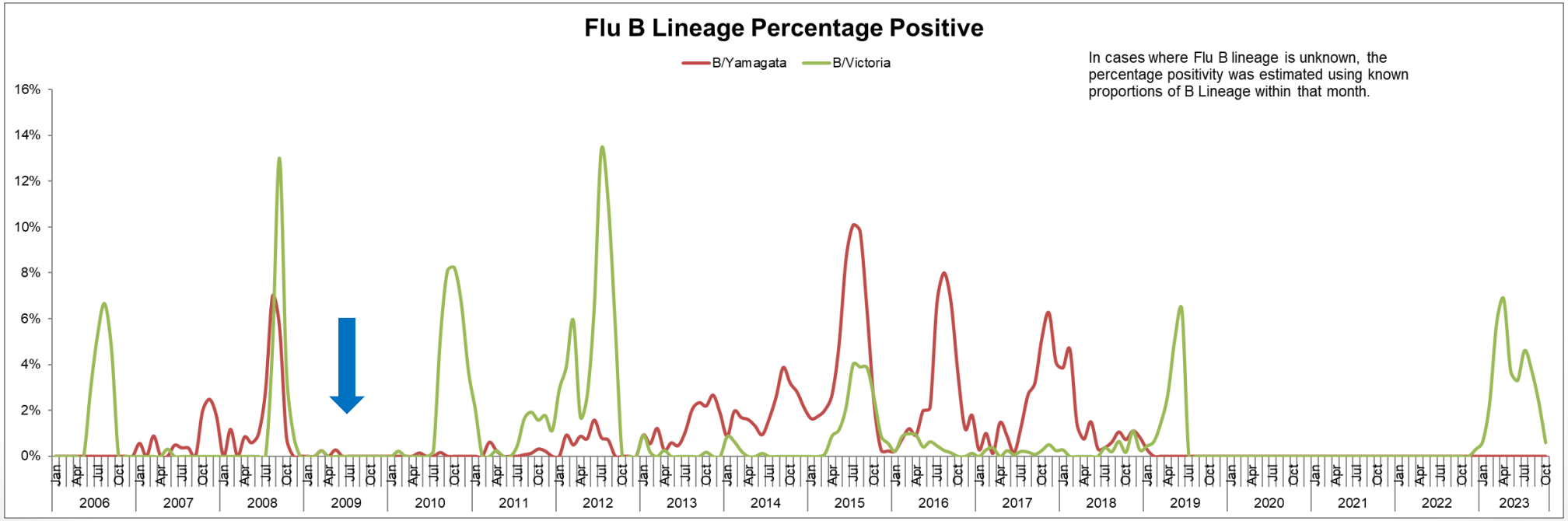
COVID-19 measures

- **Resulted in dramatic reduction in virus diversity in flu A and B and other respiratory viruses, e.g. RSV**



Flu B Yamagata lineage may be extinct

- **Flu B lineages can go into dormancy for years, e.g. Victoria in 1990's then dominated in 2000's**
- **Yamagata lineage has lower effective reproductive number than Victoria (shorter transmission chain, slower growth phase), long-lived clades become extinct**
- **COVID-19:**
  - Yamagata affects adults > 25 yr more c.f. Victoria which affects more children
  - more global spread of Yamagata c.f. Victoria possibly due to adult travellers
  - Yamagata at low level going into COVID-19 pandemic



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Vaccine efficacy and effectiveness

- **No established correlate of protection as response involves both humoral and CMI**
- **VE estimates vary across seasons and population groups**
  - Confounders incl. immunosenescence in older, varying study design, different vaccines, mismatches and egg adaptation
- **Healthy adults (18-65 yr):**
  - Pooled efficacy across 12 yr: 59% , reduced risk of flu from 2.3% to 0.9% (RR 0.41)
  - Cell based trivalent vaccine 18-49 yr: 70% overall, 52% for flu B
  - Live attenuated vaccine: 53%
  - Recombinant HA vaccine: 45%
- **Older (>65 yr)**
  - Lower VE overall, (H3N2) lower than for A(H1N1)pdm09 and type B viruses
  - High dose vaccine higher VE (24%), adjuvant vaccine 45%
- **Children (< 17 yr)**
  - Inactivated vaccine 64% in those > 2 yr (range 45-91%), live attenuated vaccine 72-78%
  - Lower VE in < 2 yr
- **Pregnancy**
  - RR of 0.4-0.5
- **Immune compromised**
  - High dose and adjuvanted vaccines immunogenic in immune compromised

The efficacy of the vaccine varies between strains and years

- **Usually due to H3N2 variants or trivalent flu B lineage difference**
  - If no Flu B Yamagata then consider two H3N2 strains

- **H3N2 antigenic variants can occur in three ways**
  - More sub-clade diversity between years (antigenic drift)
  - More rapid natural mutation within seasons after the vaccine strains are chosen (September for Australia)
    - 2014/15 northern hemisphere (NH) season: 80% infections H3N2 variant with 13% efficacy
  - Mutation of vaccine strain during vaccine manufacture (adaption to egg growth)
    - 2017 Southern and 2017/18 Northern Hemisphere season:
    - 55% H3N2 infections with 42% overall efficacy
      - H3N2 33%, H1N1 50%, flu B 57%

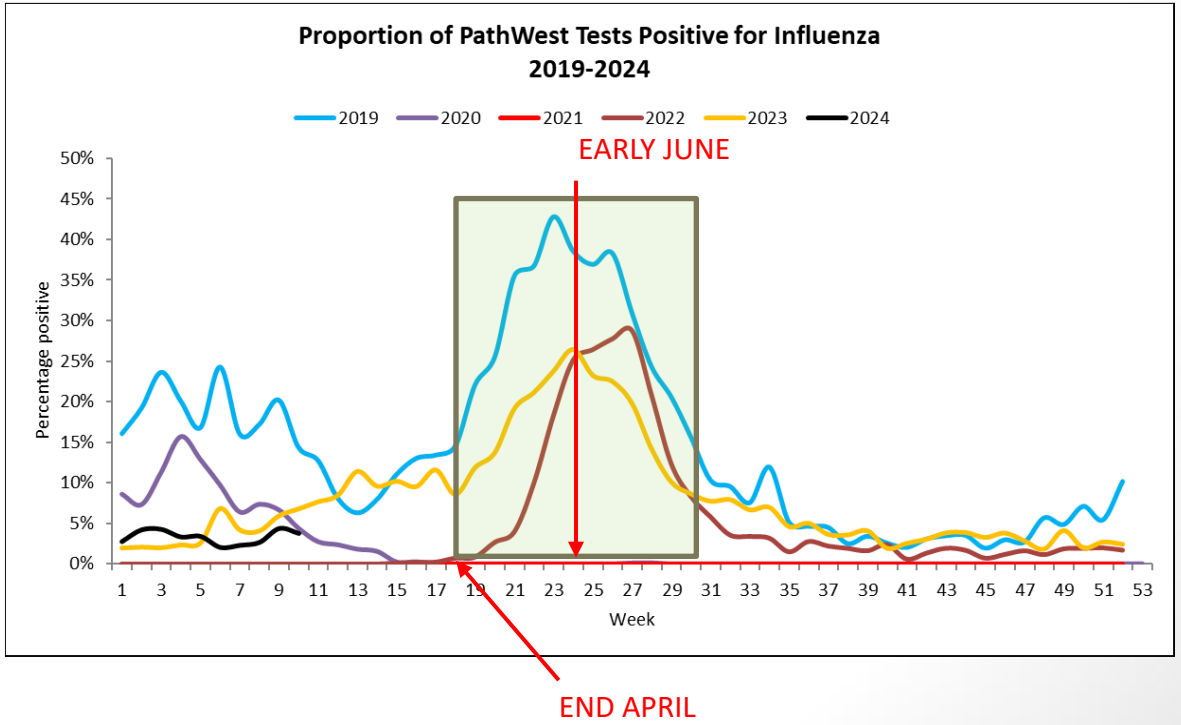
- **Efficacy also varies by individual immune response, including past infection and vaccination**
  - VE for Flu A and Flu B higher in current year vaccinated only c.f. current and prior year vaccination
  - Both significantly higher than prior year vaccination only

Timing of WA flu seasons

- **Antibody titres peak 2-4 weeks post-vaccination**
  - In older adults significantly decline by 180 days

- **Meta-analysis to see if antibody decline translates into reduced VE**
  - 14 test negative design studies

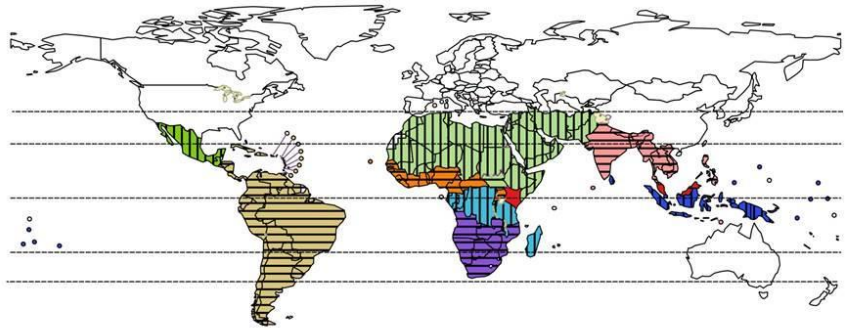
Virus	Vaccine Effectiveness	
	15-90 days	91-180 days
Influenza A(H3)	45	13
Influenza A(H1)	62	54
Influenza B	62	43



Influenza vaccine in tropics and subtropics

- **multiple peaks and identifiable year-round activity**
- **Vaccination timing**
  - countries where the primary influenza activity starts after October
  - countries where the primary influenza activity starts after April.
- **Which formulation**
  - Use either NH or SH vaccine, no recommendation for a third composition

Influenza vaccination timing



Influenza Vaccination Zones

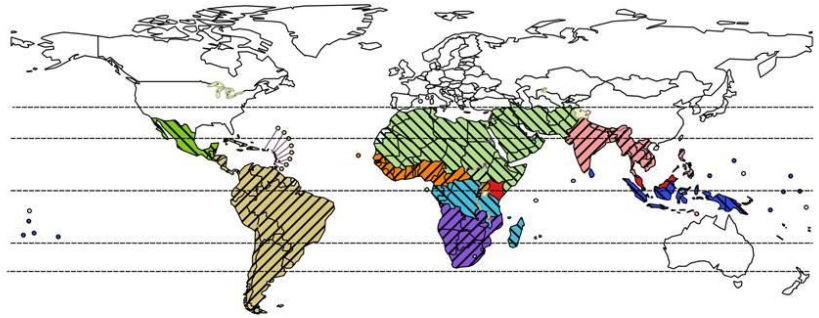
North America
South America
North Africa & Middle East
Western Africa
Equatorial Africa
Southern Africa
Tropical Asia
Equatorial Asia
Year-round

Vaccination timing

April
October

World Health Organization

Influenza vaccine formulation



Influenza Vaccination Zones

North America
South America
North Africa & Middle East
Western Africa
Equatorial Africa
Southern Africa
Tropical Asia
Equatorial Asia
Year-round

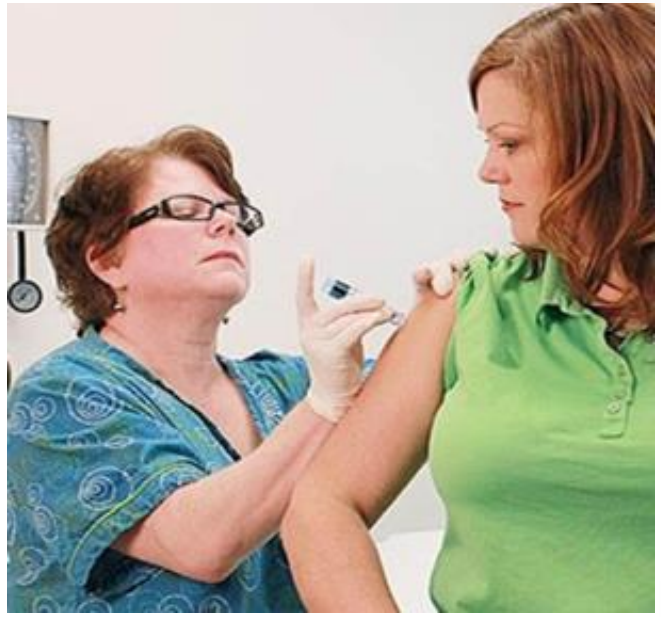
Vaccine Formulation

SH
NH

World Health Organization

Summary of vaccine effectiveness

- **Prevents ILI but less effective in elderly**
  - 60% effective in healthy adults < 65 yr, 43% effective in > 65 yr
- **Australian Sentinel Practices research Network:**
  - Protection from medical presentation 12% for children, 23% all ages but 67% for > 65 years
- **Preventing hospitalisation or pneumonia (US data)**
  - 45% effective for > 65 years
- **Preventing death**
  - 60% effective for > 65 years
- **Cardiovascular complications**
  - to prevent one cardiovascular event need to give 58 vaccines
  - If recent cardiovascular event need to give 8 vaccines to prevent another event



Slowly he would cruise the neighborhood, waiting for that occasional careless child who confused him with another vendor.