

# Universal Influenza Vaccines

**Kanta Subbarao**

WHO Collaborating Centre for Reference and Research on Influenza  
Department of Microbiology and Immunology, University of Melbourne,  
Peter Doherty Institute for Infection and Immunity

2020 Global Vaccines and Immunization Forum



# The burden of influenza



## Global seasonal influenza-associated respiratory mortality
































- Previous estimates were 250,000 to 500,000 deaths globally/year
- New estimates from 47 countries (1995-2015)
  - 291,243 to 645,832 deaths annually ~ 4.0 to 8.8/100,000 persons
  - Highest in sub-Saharan Africa, southeast Asia and persons older than 75 years (17.9-223.5/100,000 persons)
  - In children <5 years: 9,243-105,690 deaths annually
- 36,000 deaths and >200,000 hospitalisations/year in the US
- Ever present threat of pandemic influenza

# Characteristics of the last 4 influenza pandemics and economic impact of a future pandemic

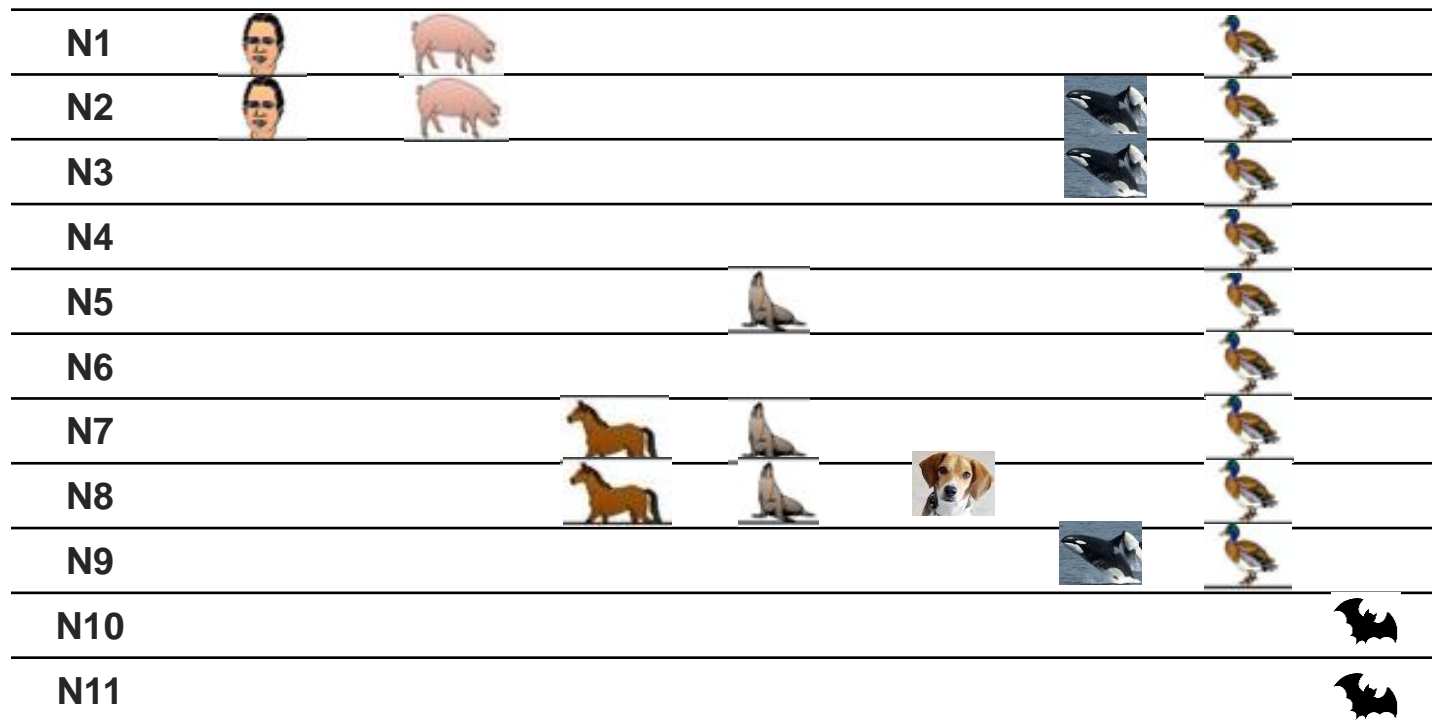
Pandemic year of emergence and common name	Area of origin	Influenza A virus subtype (type of animal genetic introduction/recombination event)	Estimated reproductive number (34,	Estimated case fatality	Estimated attributable excess mortality worldwide	Age groups most affected
<b>1918</b> "Spanish flu"	Unclear	H1N1 (unknown)	1.2–3.0	2–3%	20–50 million	Young adults
<b>1957–1958</b> "Asian flu"	Southern China	H2N2 (avian)	1.5	<0.2%	1–4 million	All age groups
<b>1968–1969</b> "Hong Kong flu"	Southern China	H3N2 (avian)	1.3–1.6	<0.2%	1–4 million	All age groups
<b>2009 -2010</b> "influenza A(H1N1) 2009"	North America	H1N1 (swine)	1.1–1.8	0.02%	100 000–400 000	Children and young adults

- The economic impact of a severe pandemic similar to 1918 could be ~5% of the global gross domestic product.
- The annual global cost of moderately severe to severe pandemics is ~\$570 billion, or 0.7% of global income.
- In contrast, pandemic preparedness has been estimated to cost \$4.5 billion, or less than \$1 per person

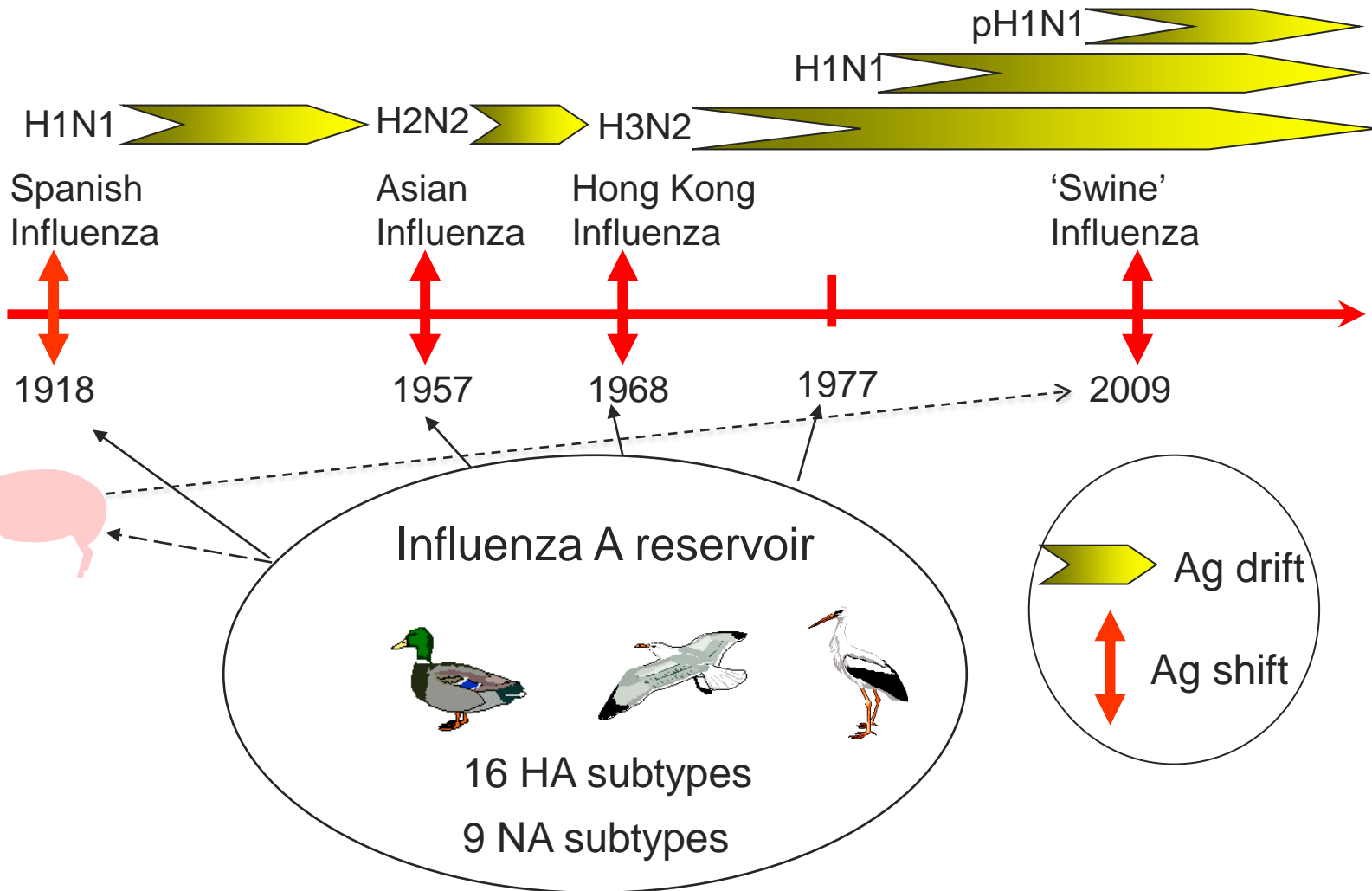
# Distribution of influenza A haemagglutinin subtypes in nature

H1						
H2						
H3						
H4						
H5						
H6						
H7						
H8						
H9						
H10						
H11						
H12						
H13						
H14						
H15						
H16						
H17						
H18						

# Distribution of influenza A neuraminidase subtypes in nature

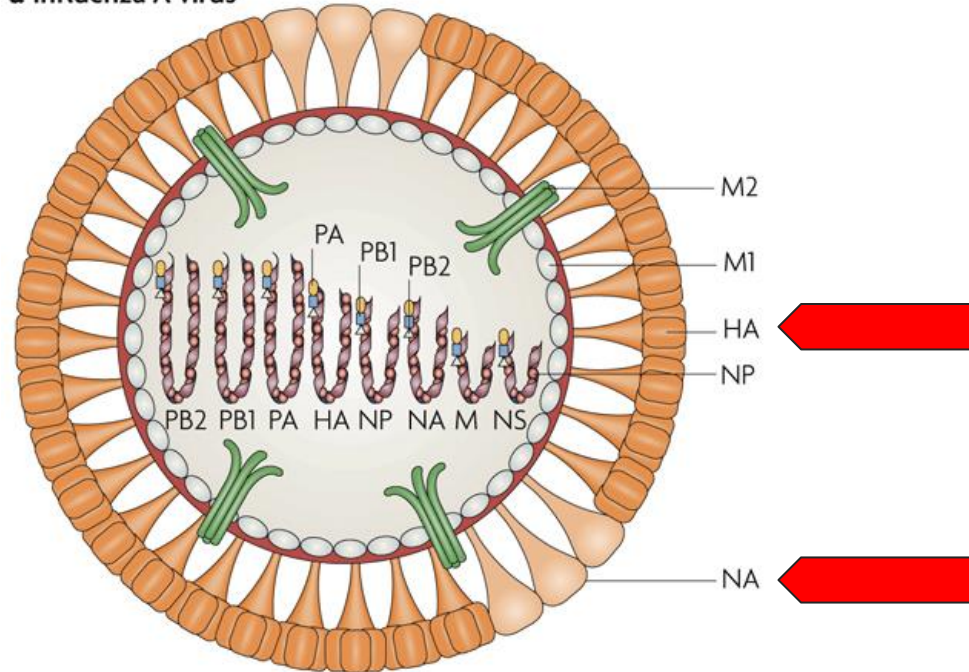


# Circulation of influenza A viruses in humans in the last century

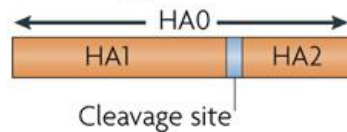


# The haemagglutinin and neuraminidase are the main targets of the protective antibody response

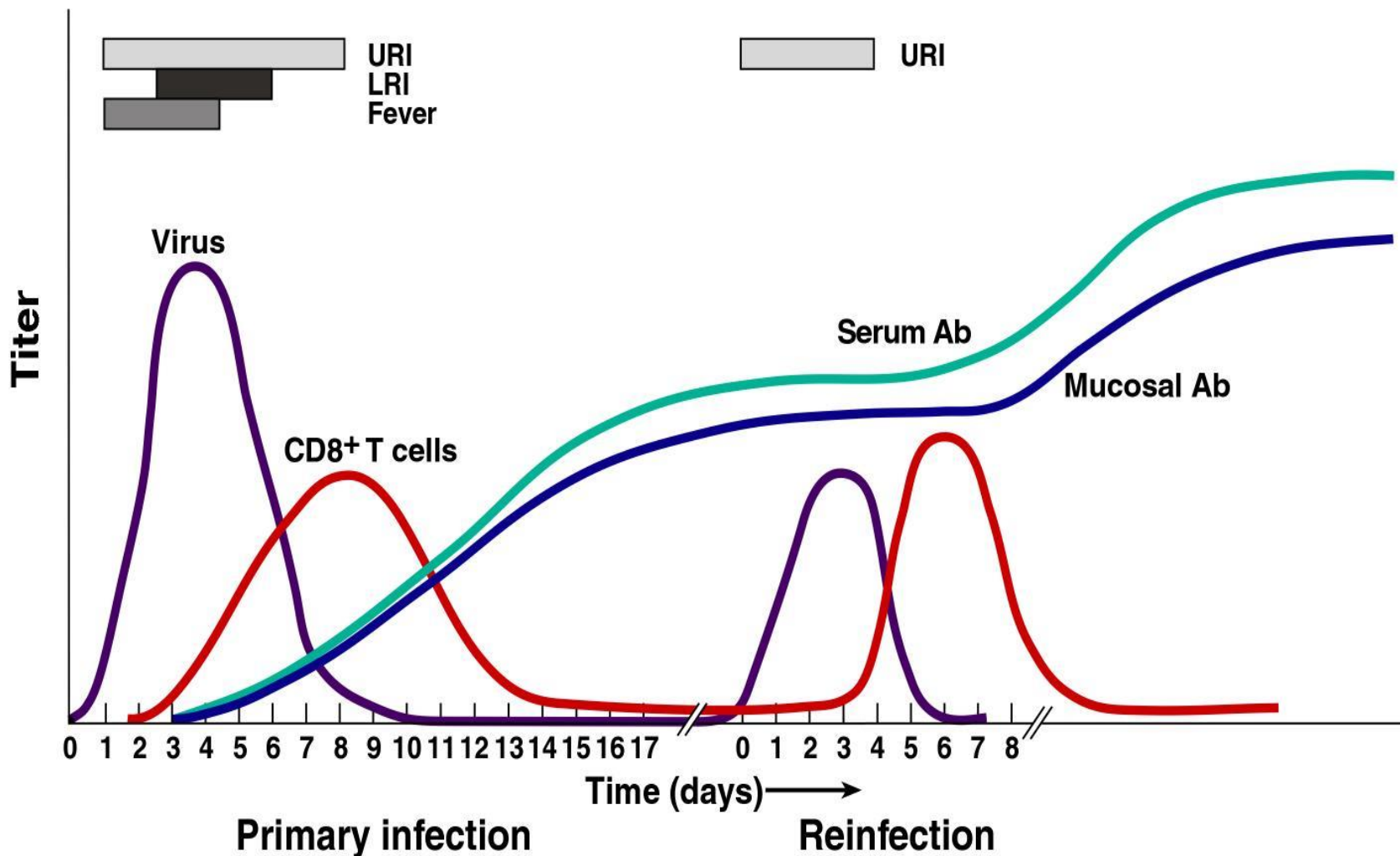
**a** Influenza A virus



**b** Haemagglutinin



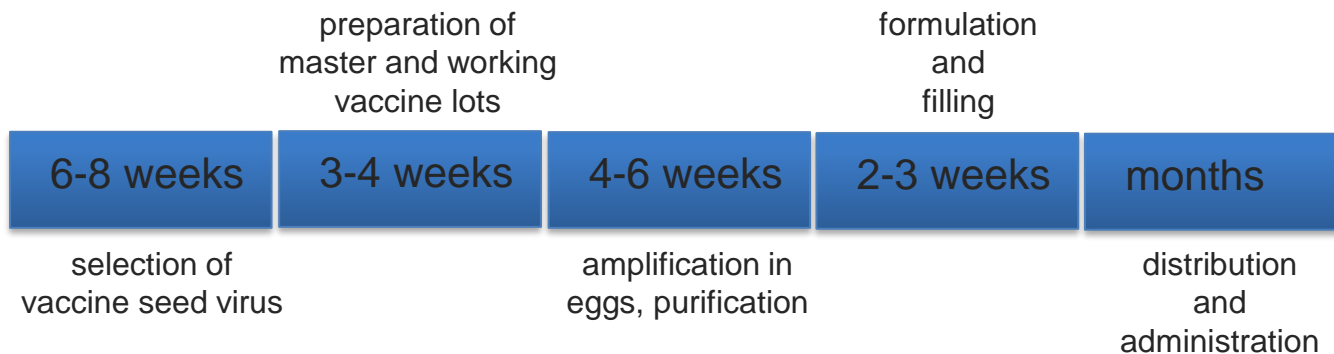
# Course of Immune Response During Influenza Infection





# Limitations of current influenza vaccines

- Vaccines require months to manufacture
- Reduced effectiveness when vaccine and epidemic strains are antigenically mismatched
- Suboptimal efficacy in the elderly
- Short duration of protection
  - Antigenic drift results in need for annual reformulation
  - Antigenic shift requires a new vaccine component
- Most of the currently licensed influenza vaccines are generated in embryonated eggs



# Goal of a Pandemic Influenza Vaccine



To prevent severe illness and death from pandemic influenza and its complications.

An ideal influenza vaccine will

- induce a systemic and mucosal immune response directed at the HA, NA and conserved internal proteins of the virus
- protect against a broad range of influenza viruses, within a subtype and across subtypes

# 3 Options for Pandemic Influenza Vaccines



---

Option A

---

Option B

Option C

---

Conventional  
Approach

Enhance the  
breadth of cross  
reactivity

The 'game changer'  
Approach

---

Strain Specific  
Vaccines

Subtype Specific  
Vaccines

Universal Vaccine

---

# The Conventional Approach: Strain-specific vaccines



- **Principle:** Elicit strain-specific immunity
- **Process:**
  - Monitor genetic and antigenic drift in nature through surveillance
  - Determine when antibody elicited against previous vaccines fail to cross-react with drift variants
  - Prepare a new vaccine candidate

# Approaches to improve breadth of immunity



- **Principle:** Elicit broadly cross-reactive subtype-specific immunity
- **Goal:**
  - Enhance the cross-reactivity of the Ab response
- **Processes:**
  - Oil-in-water adjuvants
  - Whole virion vaccines
  - Combine vaccine platforms
  - Select different viruses for development of CVVs
    - Select among existing influenza viruses
    - Select antigenically advanced variants
    - An ancestral/computationally optimized broadly reactive HA
  - Multivalent vaccine e.g. VLPs expressing different HAs
  - Combinations of antigens e.g. NP + M1 ± HA or T cell epitope vaccine + HA

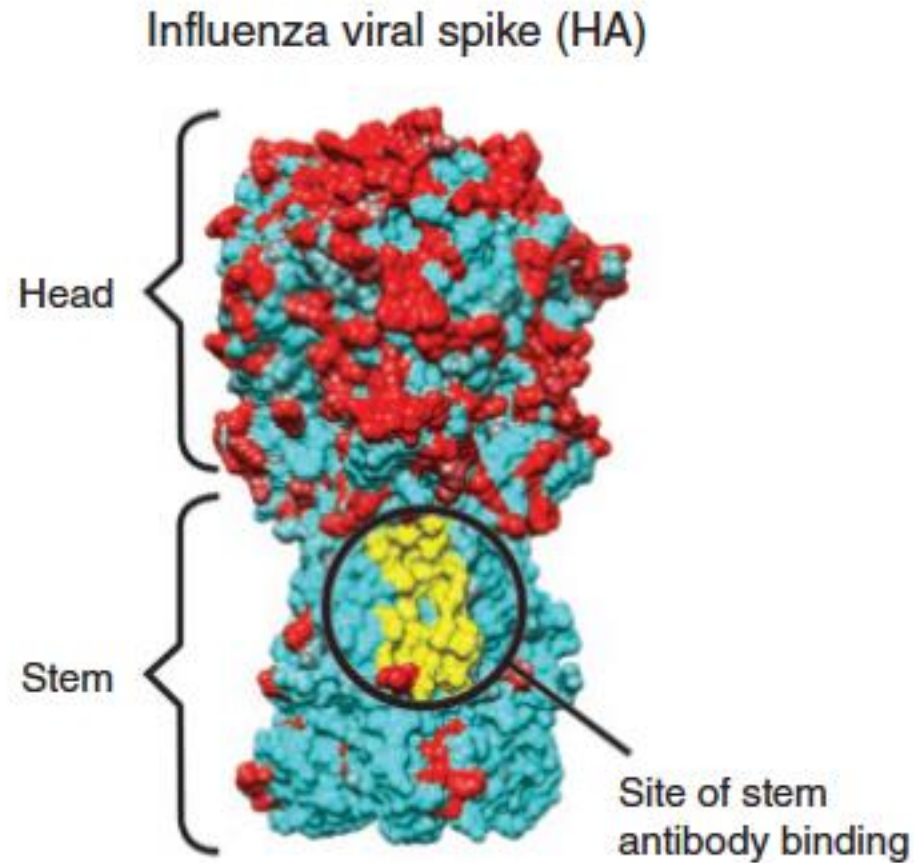
# Universal influenza vaccines



## Targets

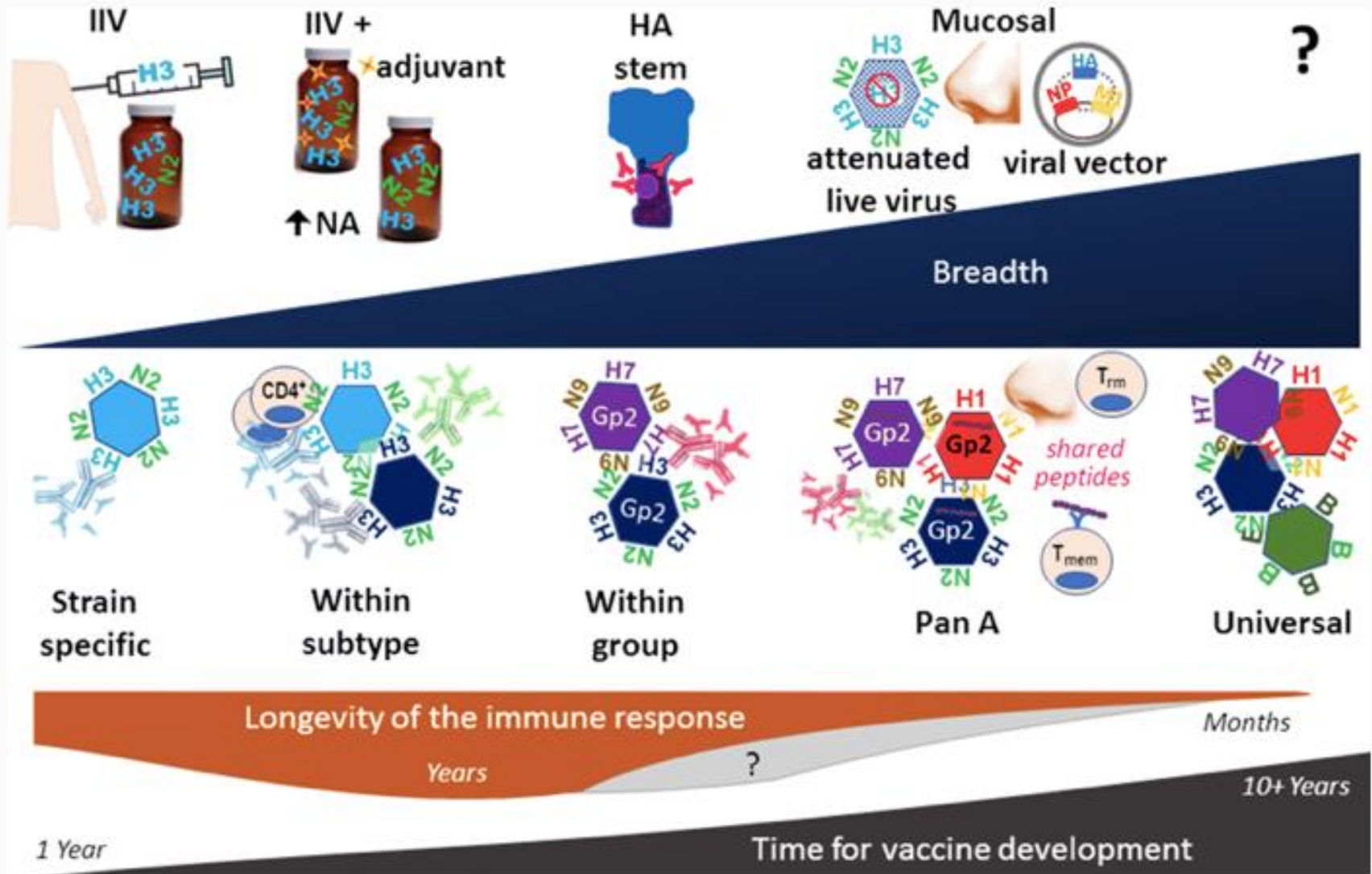
- Hemagglutinin
  - Head
  - Stem
- Neuraminidase
- M2
- NP + M1
- T cell based protection

# The most exciting development in the field: the HA stem epitope



Red: highly variable  
Yellow: highly conserved

# Increasing the breadth of vaccine protection





# The challenges of universal influenza vaccine development

## **Technical challenges:**

- Identify targets that are conserved across a wide range of influenza viruses
- Develop a vaccine strategy to induce an immune response that is
  - Sufficiently robust to confer protection
  - Elicited at the appropriate site (serum/mucosal antibody, pulmonary T cells)
  - Without adverse effects e.g. immunopathology

## **Regulatory challenges:**

- Immune correlates of protection and assays to measure them

## **Implementation:**

- Who should be vaccinated, when and how often?



**Seasonal  
Influenza  
Preparedness**

**Pandemic  
Influenza  
Preparedness**

**Thank you!**

The WHO Collaborating Centre for Reference and Research on Influenza in Melbourne is supported by the Australian Government Department of Health