"Asian Pacific Vaccinology Meeting 2015"
30 November-3 December in Bangkok, Thailand

Influenza Vaccines

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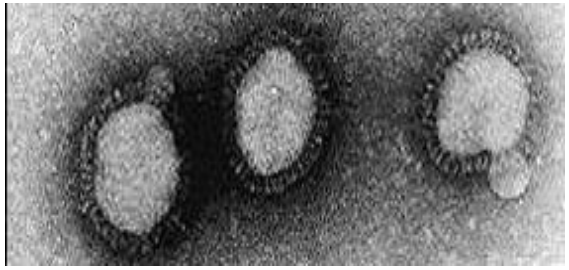
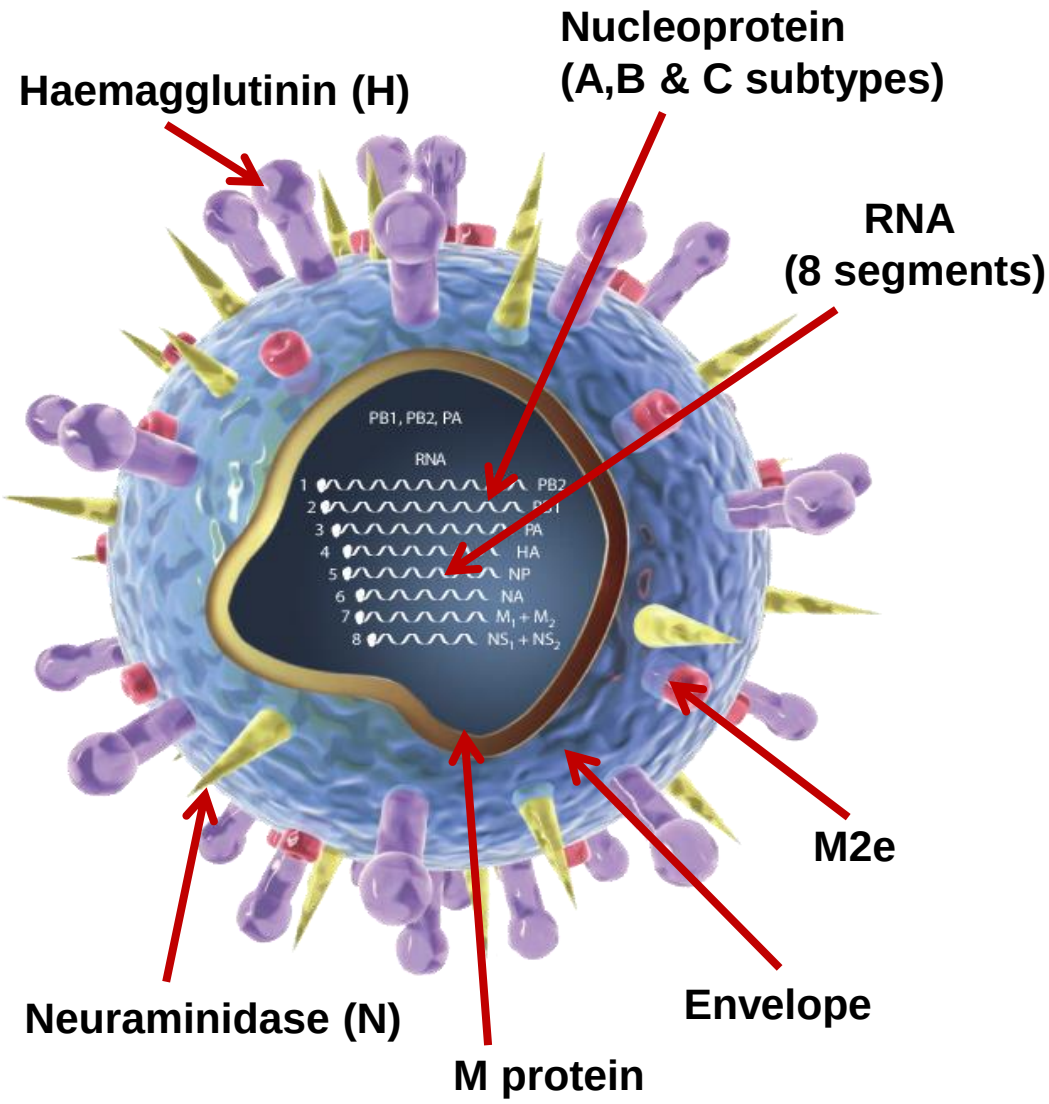
Influenza virus



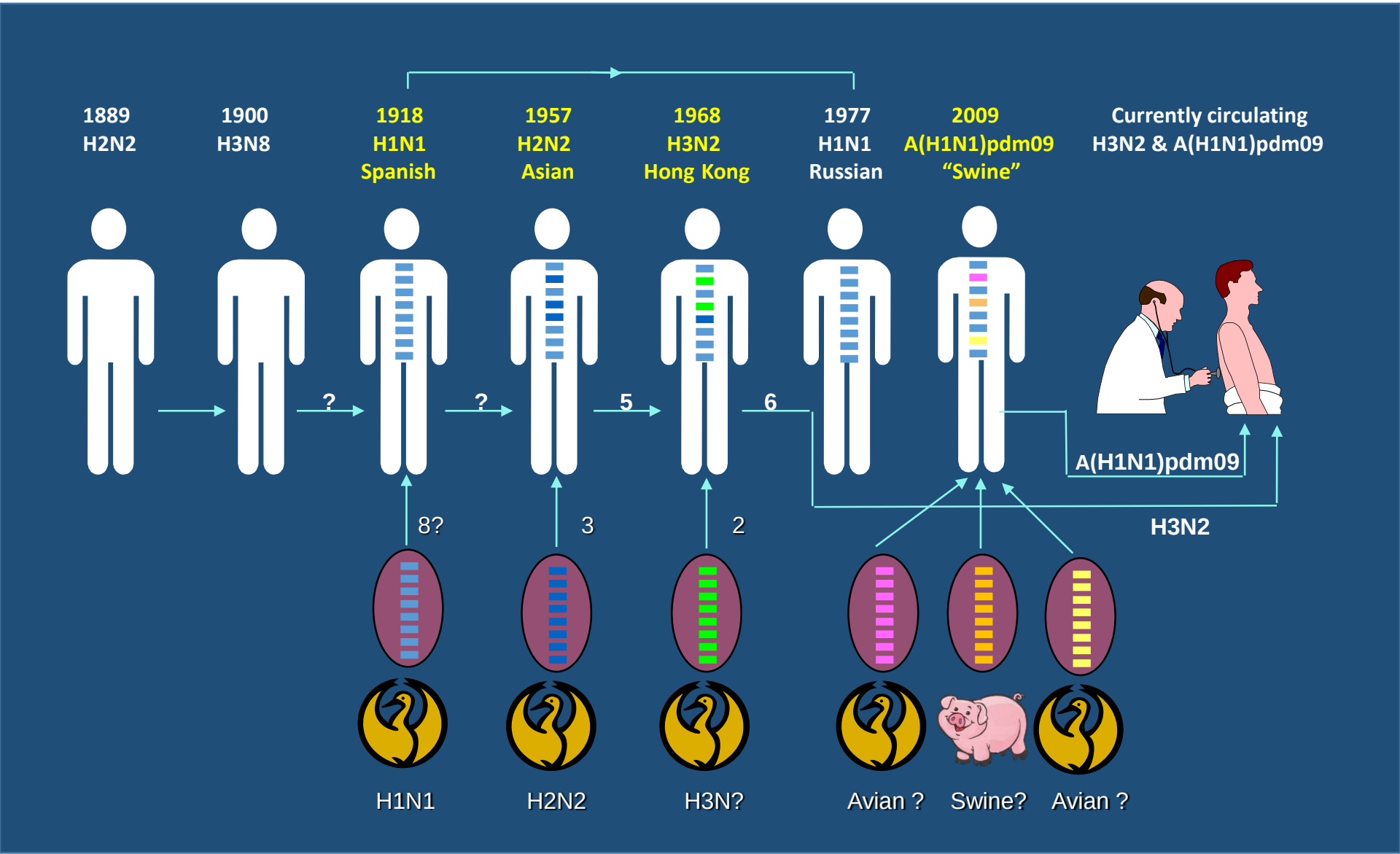


	Human	Pig	Horse	Bird
H types				
H1	✓	✓		✓
H2	✓	✓		✓
H3	✓	✓	✓	✓
H4		✓		✓
H5	✓	✓		✓
H6	✓			✓
H7	✓		✓	✓
H8				✓
H9	✓	✓		✓
H10	✓			✓
H11-H16				✓
H17-H18				
N types				
N1	✓	✓		✓
N2	✓	✓		✓
N3				✓
N4				✓
N5				✓
N6	✓			✓
N7	✓		✓	✓
N8	✓		✓	✓
N9	✓			✓
N10-N11				

Seasonal Influenza: Ongoing Public Health Threat

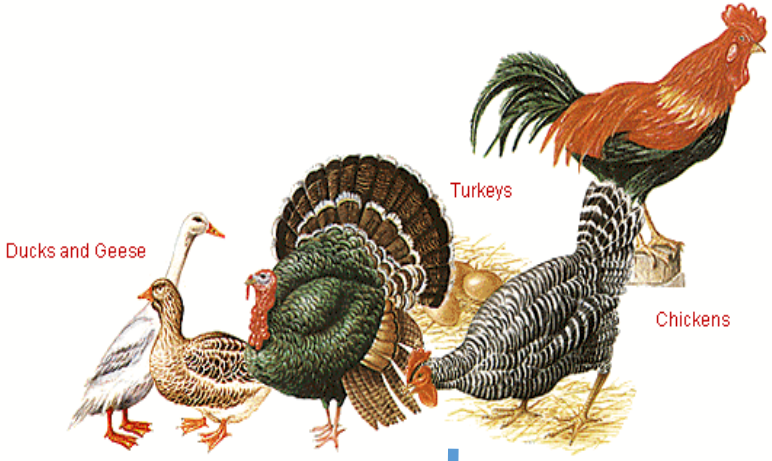
- Current influenza vaccines are moderately effective (approx. 60% effective in seasons with a good antigenic match)
- Impacts millions of people globally
  - 10-20% population; 250,000-500,000 deaths
- $80 B / yr. loss attributed to influenza disease in the USA
- Unpredictable changes in HA and NA lead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

Evolution of Influenza A Virus Pandemic Strains
(Antigenic Shift)



EVOLUTION OF NEW INFLUENZA VIRUS

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



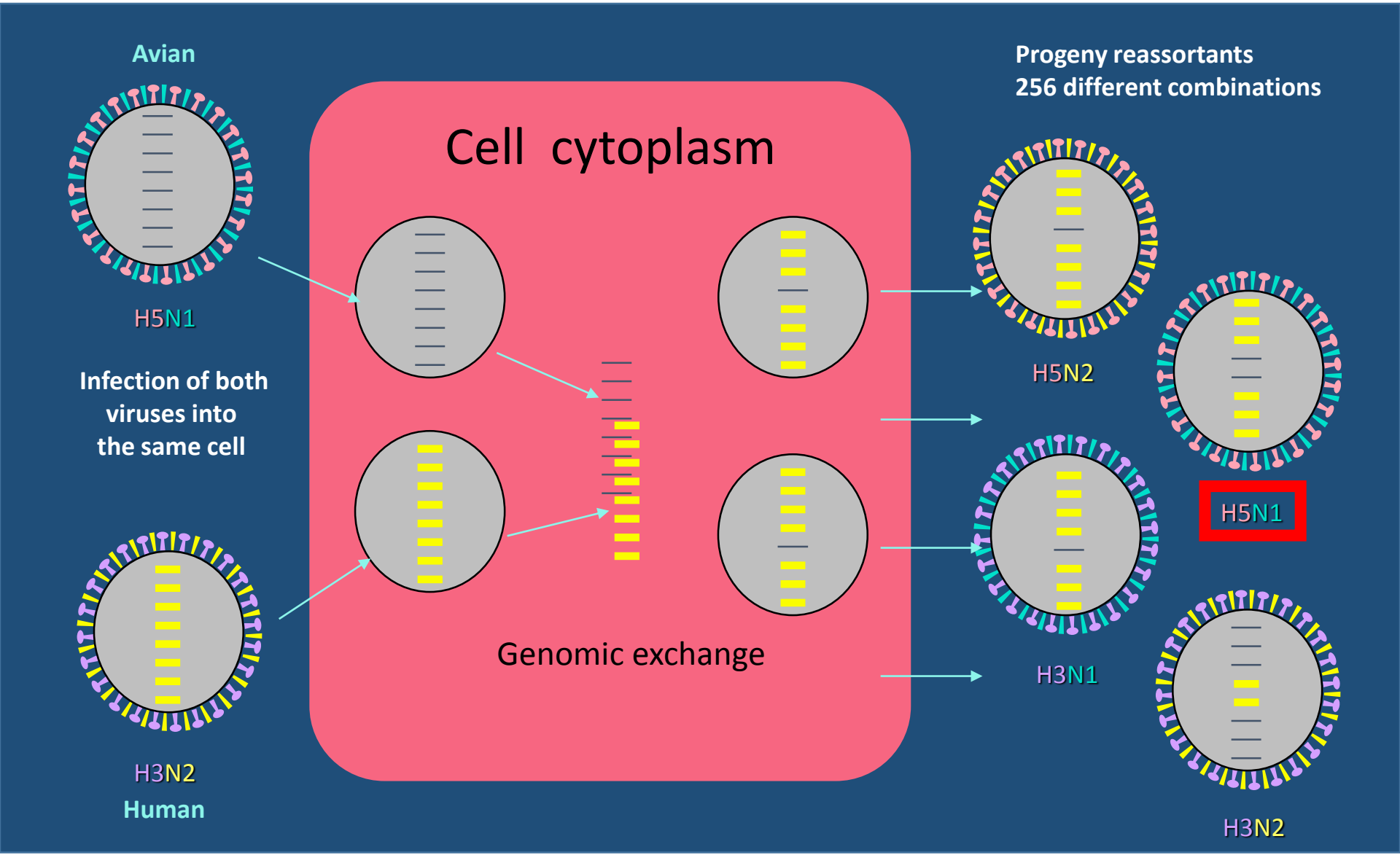
Transmission of avian flu to pigs

Transmission of human flu to pigs by aerosol

New flu virus

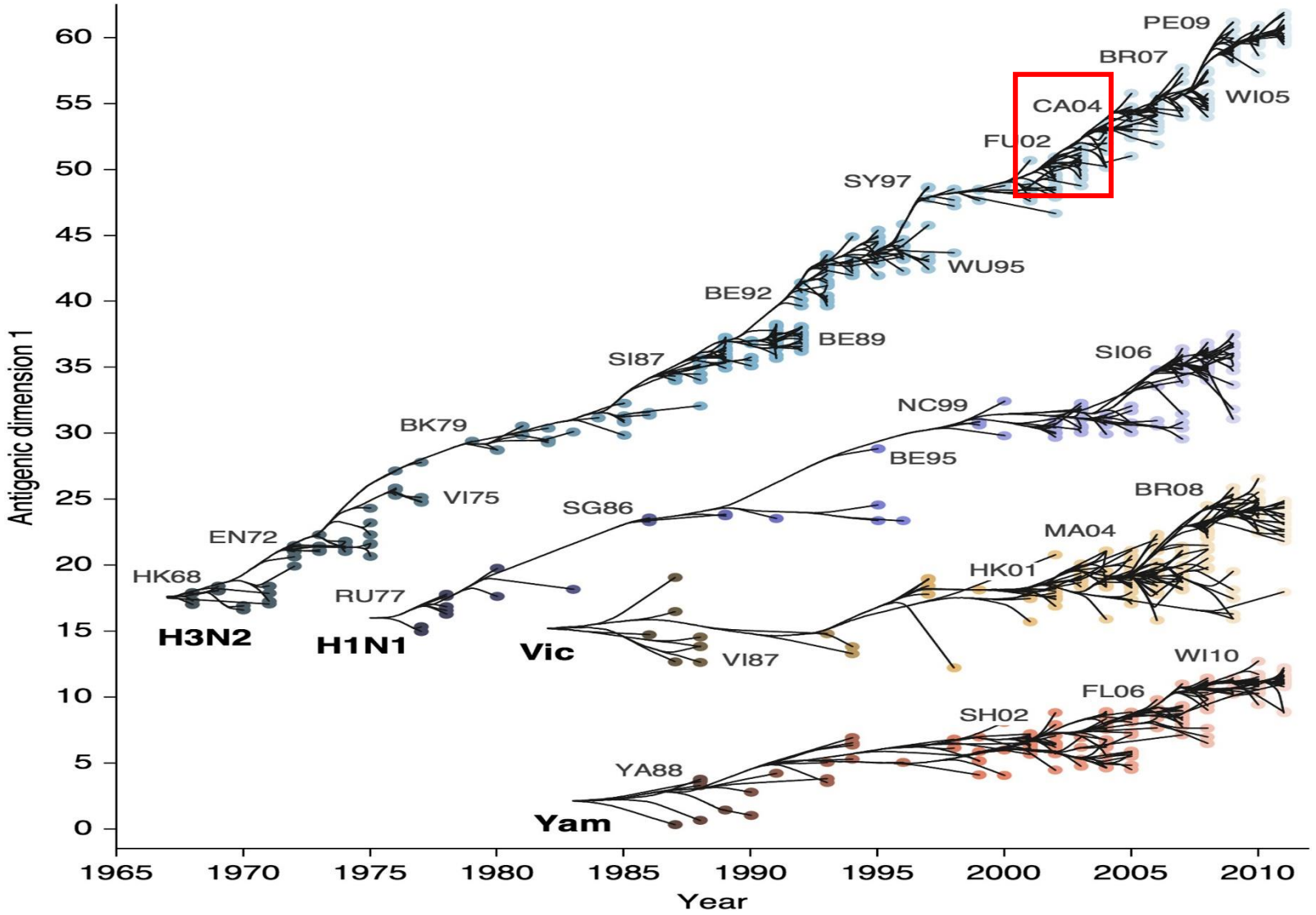
Spread by aerosol

Generation of new influenza viruses (reassortment process)



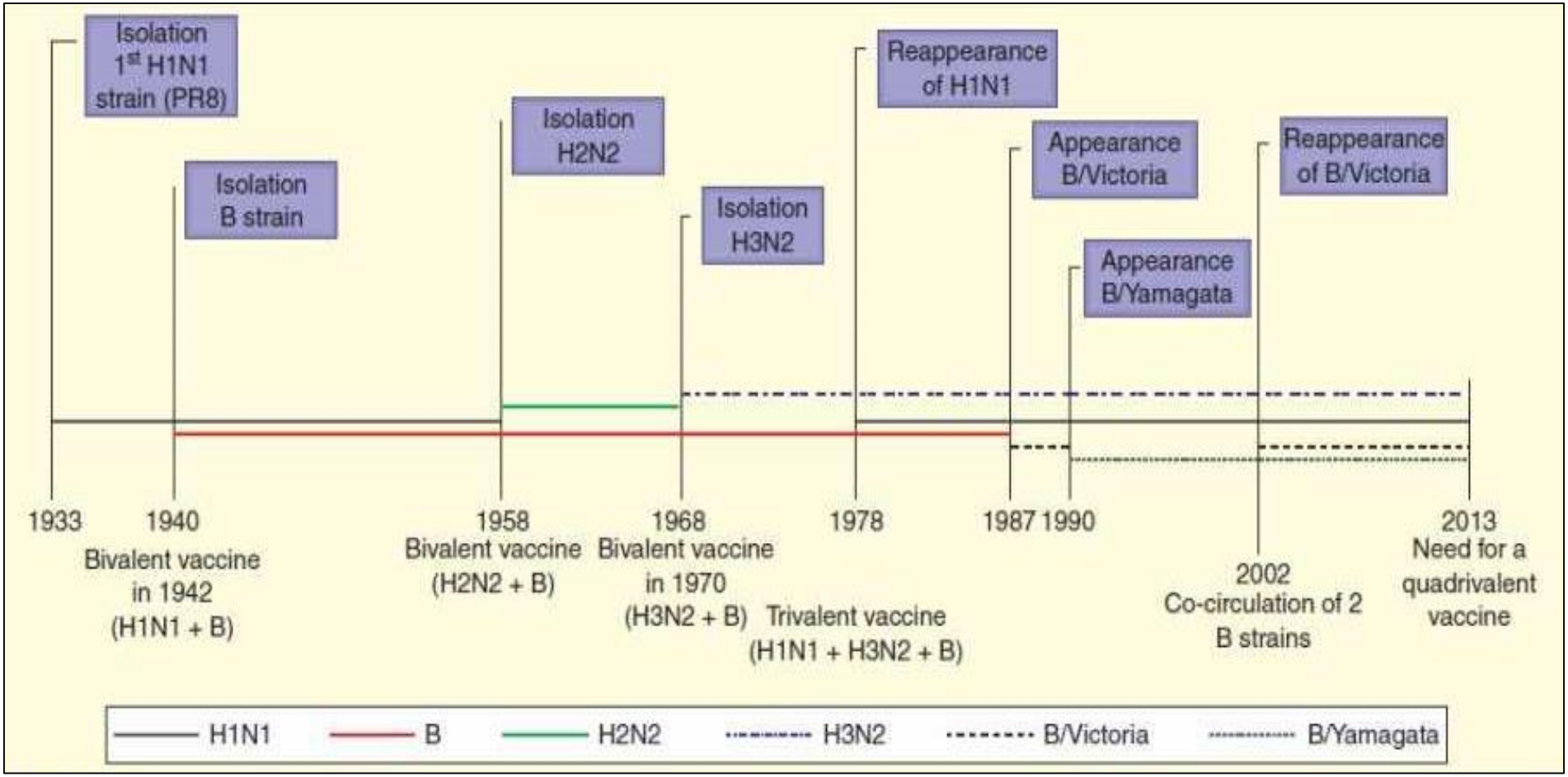
Antigenic drift of A/H3N2, A/H1N1, B/Vic and B/Yam viruses

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



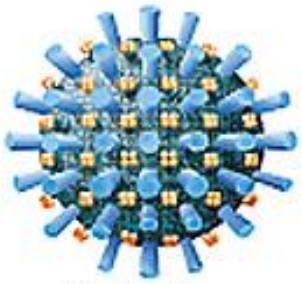
Trevor Bedford et al. eLife Sciences 2014;3:e01914

Evolution of influenza viruses and corresponding evolution of influenza vaccines



Complexity of influenza vaccines

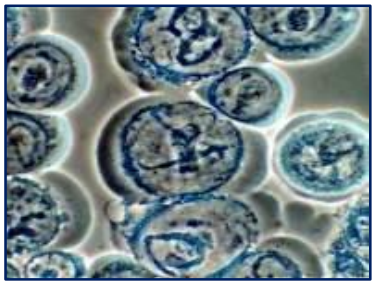
- Vaccines types:
  - Northern and Southern hemisphere seasonal vaccines
  - Pandemic influenza vaccines
  - Pre-pandemic influenza vaccines (zoonotic influenza vaccines)
- Vaccine technologies:
  - Whole virus vaccines
  - Split vaccines (sub-unit vaccine)
  - Live attenuated vaccines
  - Recombinant vaccines


Whole virus


Split virus


Subunit
(surface antigen)


Live attenuated


Recombinant VLP

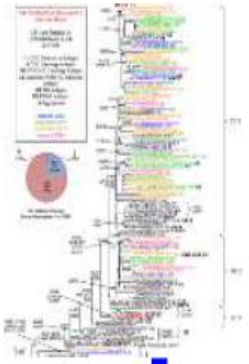
Complexity of influenza vaccines – cont.

- Vaccine manufacturing:
  - Egg-based
  - Cell-based
  - Recombinant vaccine (Virus-like particles VLP) made in recombinant baculovirus in Sf9 insect cells
- Vaccines formulations:
  - Vaccine viruses change twice/yr. NH (Feb.) and SH (Sep.) vaccines
  - TIV (H1N1+H3N2+B_{vic} or B_{yam}) and QIV (H1N1+H3N2+B_{vic}+B_{yam})
  - Monovalent pandemic vaccines (A(H1N1)pdm09)
  - Adjuvented vaccines (e.g. A(H1N1)pdm09 adjuvented vaccine)
  - High-dose seasonal vaccines for the elderly
- Vaccine application:
  - Children 6 m to 8 y old requires 2 doses (TIV, QIV or LAIV)
    6 – 35 months old (TIV half dose x 2)
  - ≥65 years (TIV or QIV regular dose or TIV high dose)
  - Attenuated vaccines (LAIV) 2 to 49 yrs.
  - Vaccination timing (prior to peak season in NH or SH)

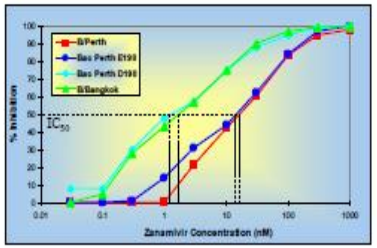
WHO influenza vaccine virus selection process

Comparative titres by haemagglutination inhibition assays

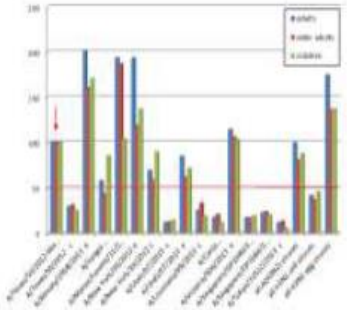
Sequence data
- mainly HA & NA
- Some others e.g. M



Antiviral drug resistance
- Oseltamivir
- Zanamivir
- Other compounds



Human vaccine serology



Vaccine virus selection

Other information

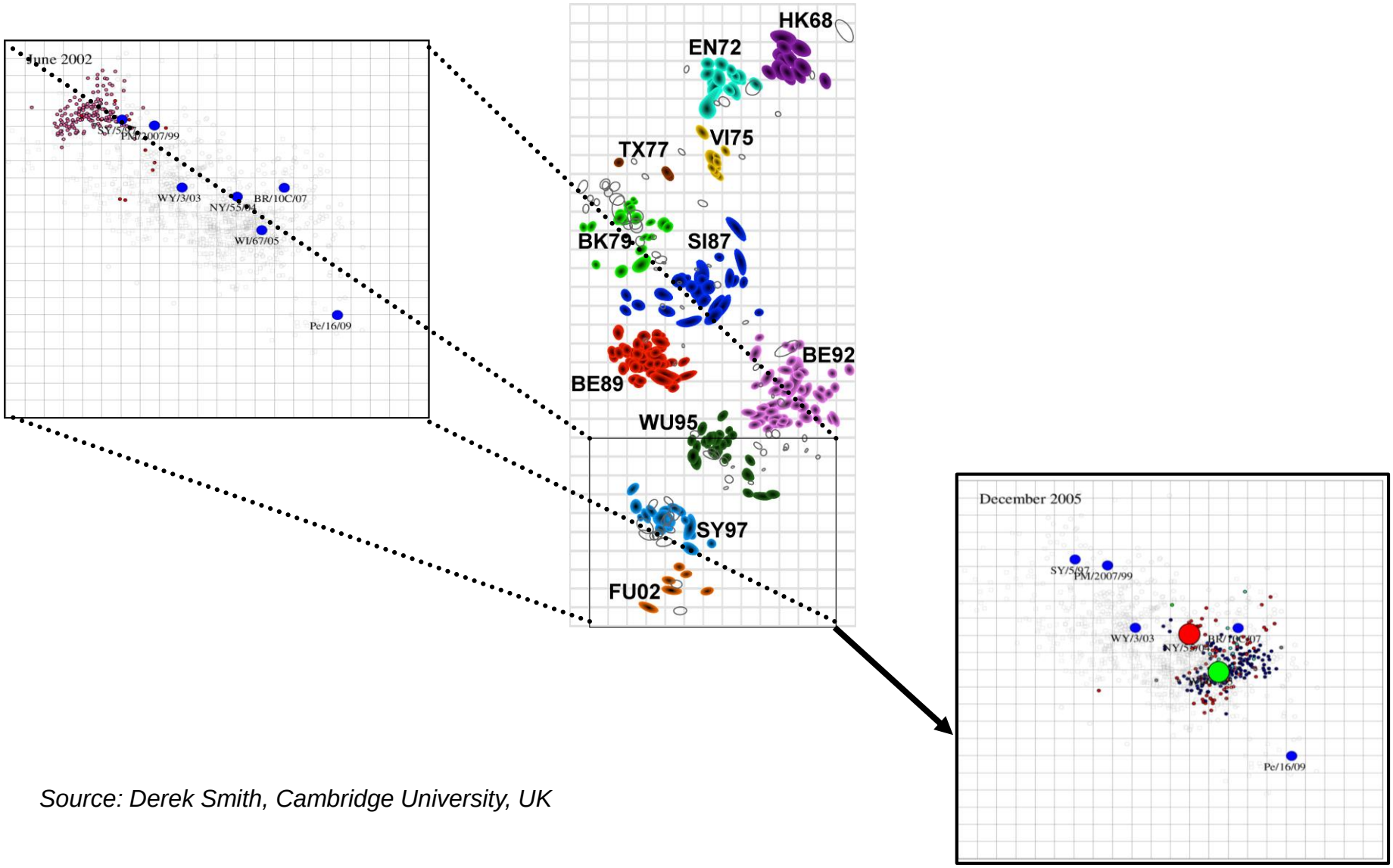
Growth in eggs & cells

Vaccine efficacy estimates

http://asvac2015.com/wp-content/uploads/2015/06/4.-PS03_Zhang_GISRS_VVS_20150611.pdf

Antigenic Cartography - evolution of antigenic drift

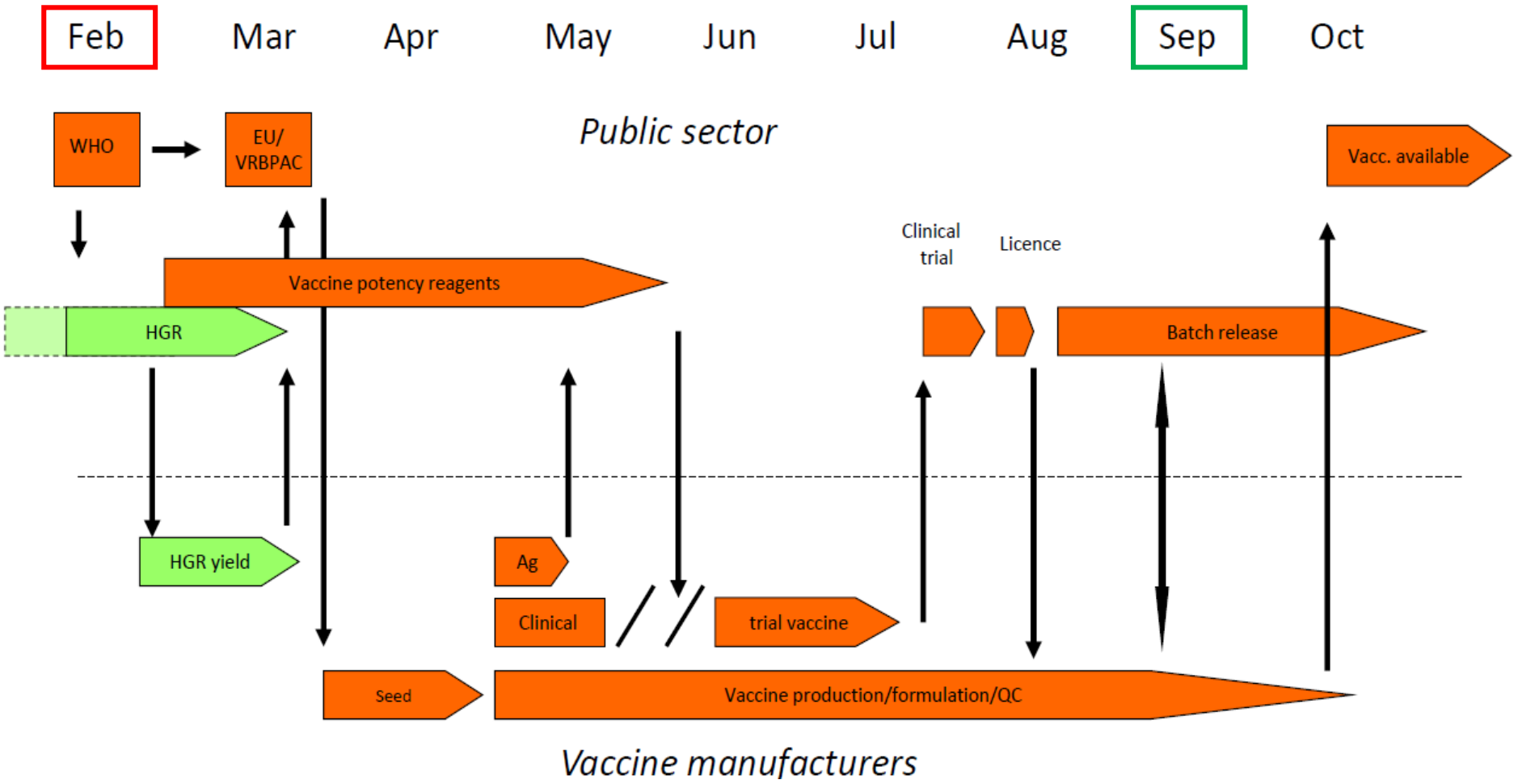
(H3N2) Fujian - California cluster transition



Source: Derek Smith, Cambridge University, UK

Influenza vaccines production

Seasonal vaccine cycle (NH)



http://asvac2015.com/wp-content/uploads/2015/06/4.-PS03_Zhang_GISRS_VVS_20150611.pdf

Global Influenza Vaccine Market Leaders

1 **Who**: Sanofi/Sanofi Pasteur MSD **What**: Fluzone/Vaxigrip **Estimated sales:** $1.343 billion	SANOFI
2 **Who**: GlaxoSmithKline ($GSK) **What:** FluLaval/Fluviral **Estimated sales:** $375 million	gsk
3 **Who**: Novartis **What**: Fluvirin **Estimated sales**: $359 million	NOVARTIS
4 **Who**: Abbott Laboratories **What**: Influvac **Estimated sales**: $188 million	
5 **Who**: AstraZeneca ($AZN) **What**: FluMist **Estimated sales:** $162 million	AstraZeneca
6 **Who**: Mitsubishi Tanabe Pharma **What**: BIKEN HA **Estimated sales**: $108 million	Mitsubishi Tanabe Pharma
7 **Who**: Novartis **What**: OptaFlu **Estimated sales**: $71 million	NOVARTIS
8 **Who**: Johnson & Johnson ($JNJ) **What**: Inflexal V **Estimated sales**: $35 million	Johnson&Johnson
9 **Who**: Sinovac Biotech ($SVA) **What**: Anflu **Estimated sales**: $10 million	sinovac
10 **Who**: Laboratorios Farmacéuticos ROVI **What**: Levrison **Estimated sales**: $3 million	ROVI

Estimated $2.6 billion industry

WHO recommendations for influenza vaccination (2012)

5 recommended groups for countries using or considering introduction of seasonal influenza vaccination:

- Pregnant women (highest priority group)
- 4 other priority groups (in no order of priority) are:
  - Health-care workers;
  - Children under 5 (particularly 6-23 months);
  - Elderly
  - Persons with underlying health conditions

WHO recommendations for influenza vaccination (2012)

- Countries with existing influenza vaccination programmes targeting any of these groups (e.g. vaccinating the elderly to meet WHA 56.19 resolution of 75% coverage by 2010) should continue to do so and should consider incorporating immunization of pregnant women into such programmes
- Countries should decide individually how they would prioritize and develop coverage goals for these risk groups based on burden of disease, cost-effectiveness, feasibility and other appropriate considerations.

Global mapping of pandemic vaccine production capacity

Global pandemic influenza vaccine production capacity is still **insufficient**

- Annual vaccine production: ~ 850 million doses
- Estimated annual vaccine production capacity (2015): 1.7 billion doses

WHO strategies to increase production capacity include:

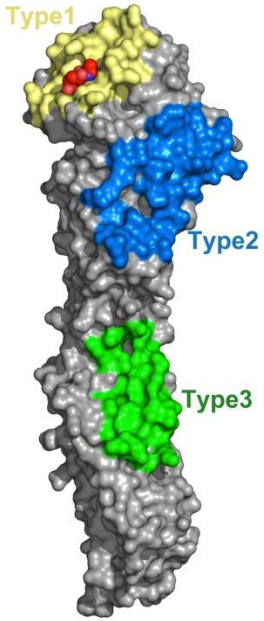
- Shifting to higher yielding technologies including live attenuated vaccine and use of adjuvants
- Building (and maintaining) new capacity

What's next?
Broadly Protective Influenza Vaccine?

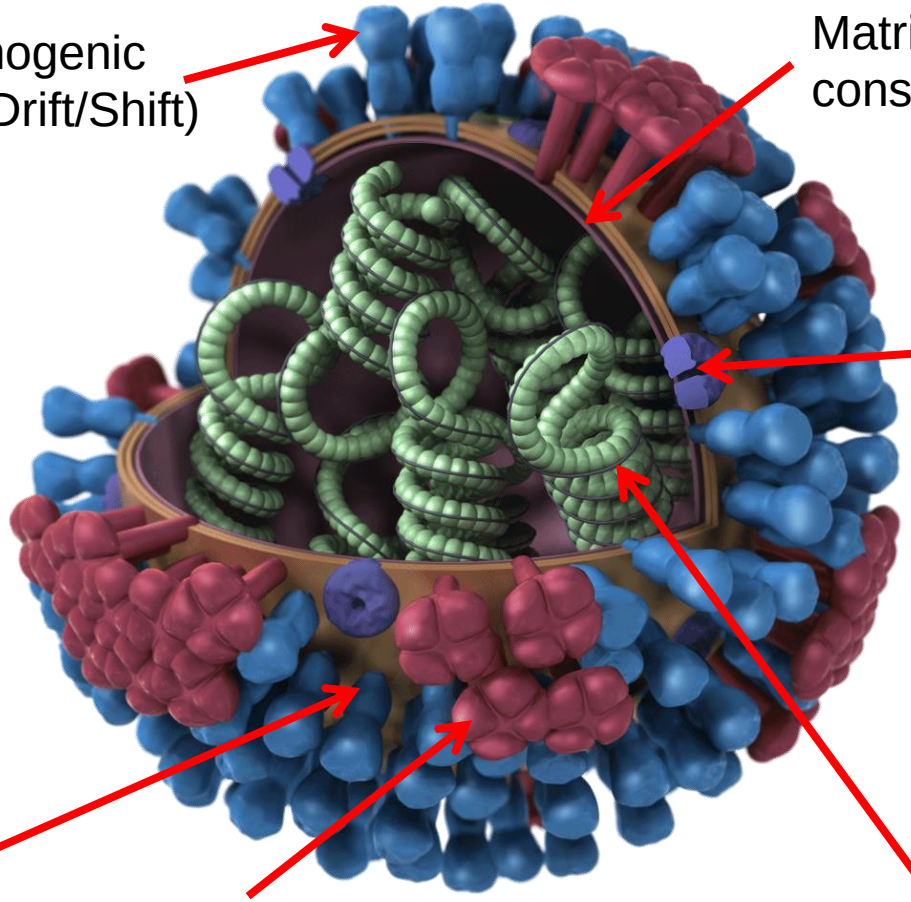
- Immunity from natural viral infection does not protect against distant antigenic variants
- Vaccine-mediated immunity must afford greater protection across antigenic variants within a subtype and across subtypes than natural immunity
- "Universal "Influenza Vaccine - would induce protection against antigenic drift and (ideally) antigenic shift
  - Extend protection of each vaccine to 5-10 years (drift/seasonal)
  - Extend protection to several subtypes (shift/pandemic)
  - Truly "universal": One vaccine for all influenza viruses

Potential Vaccine Targets to Conserved Regions of the Influenza Virus

HA - surface, immunogenic but highly variable (Drift/Shift)



Matrix: internal, highly conserved, induces CMI



M2e: surface, immunogenic, more conserved, Ab-mediated protection

HA stalk, highly conserved, platform/format unknown

NA: surface, immunogenic, variable (Drift/Shift)

NP: internal, highly conserved, induces CMI, reduce disease severity?

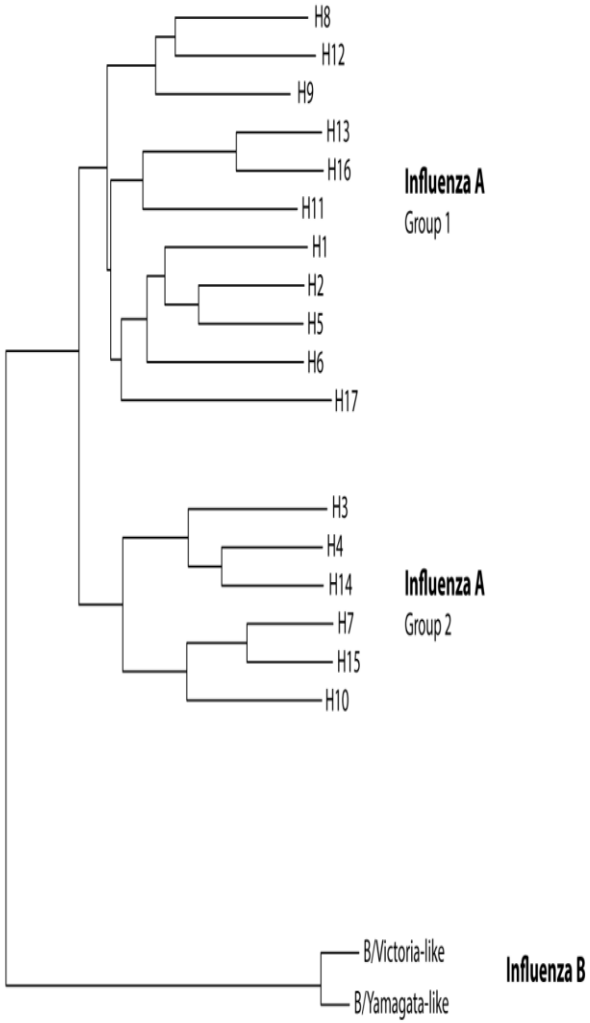
Universal Influenza Vaccines

- *The Ideal situation*:

  A single vaccine that would provide lifelong protection against any subtype of influenza A and both lineages of influenza B

- Is it achievable? Not immediately.

- *A practical outcome*: A vaccine that will provide protection for several seasons before reformulation
  - Surveillance would remain important
  - No need to re-formulate annually
  - Reduce vaccine “mismatches”
  - Potential to reduce production and administration costs
  - Potential surge capacity for rapid scale up/change over
  - Reduce the potential for vaccine shortages
  - Year around production → increase global vaccine supply



Current efforts to develop universal vaccines

- BiondVax Pharmaceuticals Ltd.
  - Proprietary conserved/common epitopes
- Codagenix Inc.
  - LAIV using Synthetic Attenuated Virus Engineering (SAVE)
- Dynavax
  - TLR-based
- Generex and Immune Targeting
  - Peptide/T-cell vaccines
- Inovio
  - DNA vaccine
- Molecular Express Inc.
  - Lipid vesicle conjugatable adjuvant
- NIAID Intramural
  - Ferritin nanoparticles
  - DNA prime-boost
- MSSM
  - Chimeric HAs
- Sanofi/UPMC
- TechnoVax
  - VLP

BiondVax Pharmaceuticals Ltd.

CODAGENIX INC.

DYNAVAX TECHNOLOGIES

ANTIGEN EXPRESS, INC.

IMMUNE TARGETING SYSTEMS

inovio

Molecular Express, Inc.

NIH

MSSM

SANOFI PASTEUR

UPMC LIFE CHANGING MEDICINE

TechnoVax the gold standard in vaccine technology

Challenges for universal influenza vaccine

- Safety
- New carriers, vectors, fusion proteins, substrates, adjuvants
- Scalability
- Formulation and potency determination
  - Standardizing and stabilizing the protein
  - Each new substrate may require new, specialized release assays
- Complicated/uncertain regulatory pathways
- Funding

New vaccine development is a time-consuming and expensive process

Thank you for you attention.

Questions?
Comments?

First Shots Best Shot