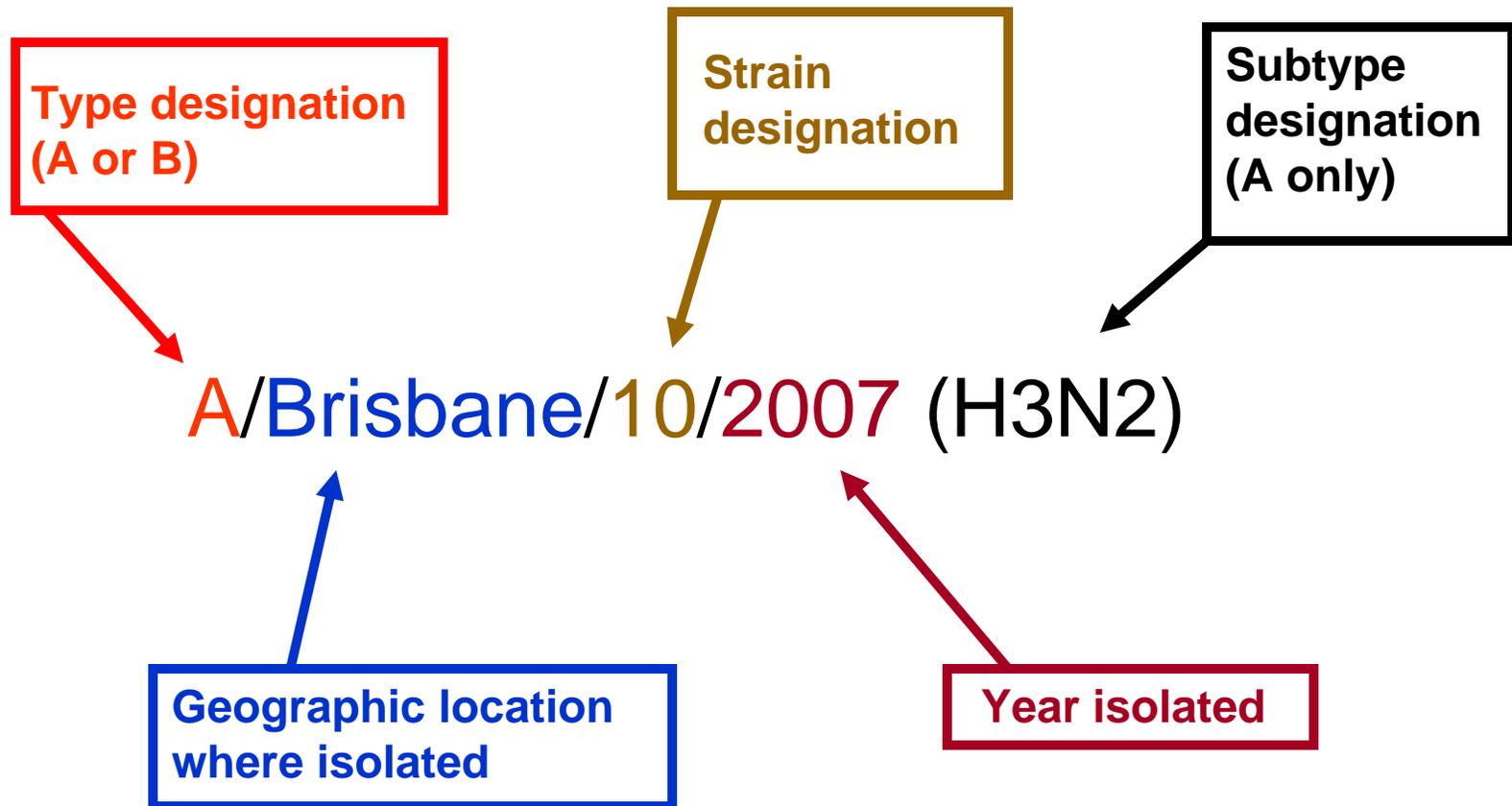


Influenza Risks - 2009

John Treanor, M.D.
Infectious Diseases Division
Department of Medicine

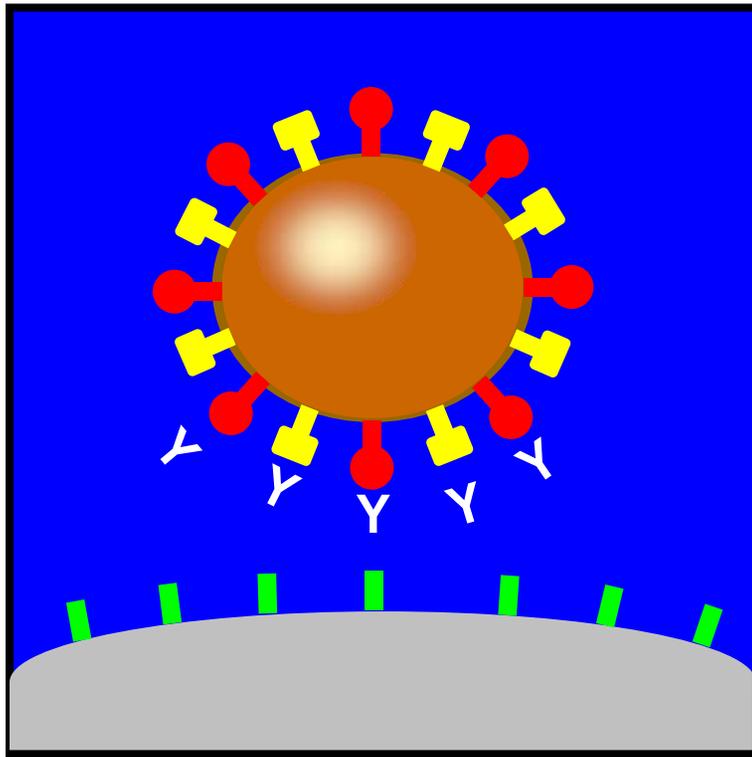
Influenza nomenclature



What unique risks does influenza pose in 2009?

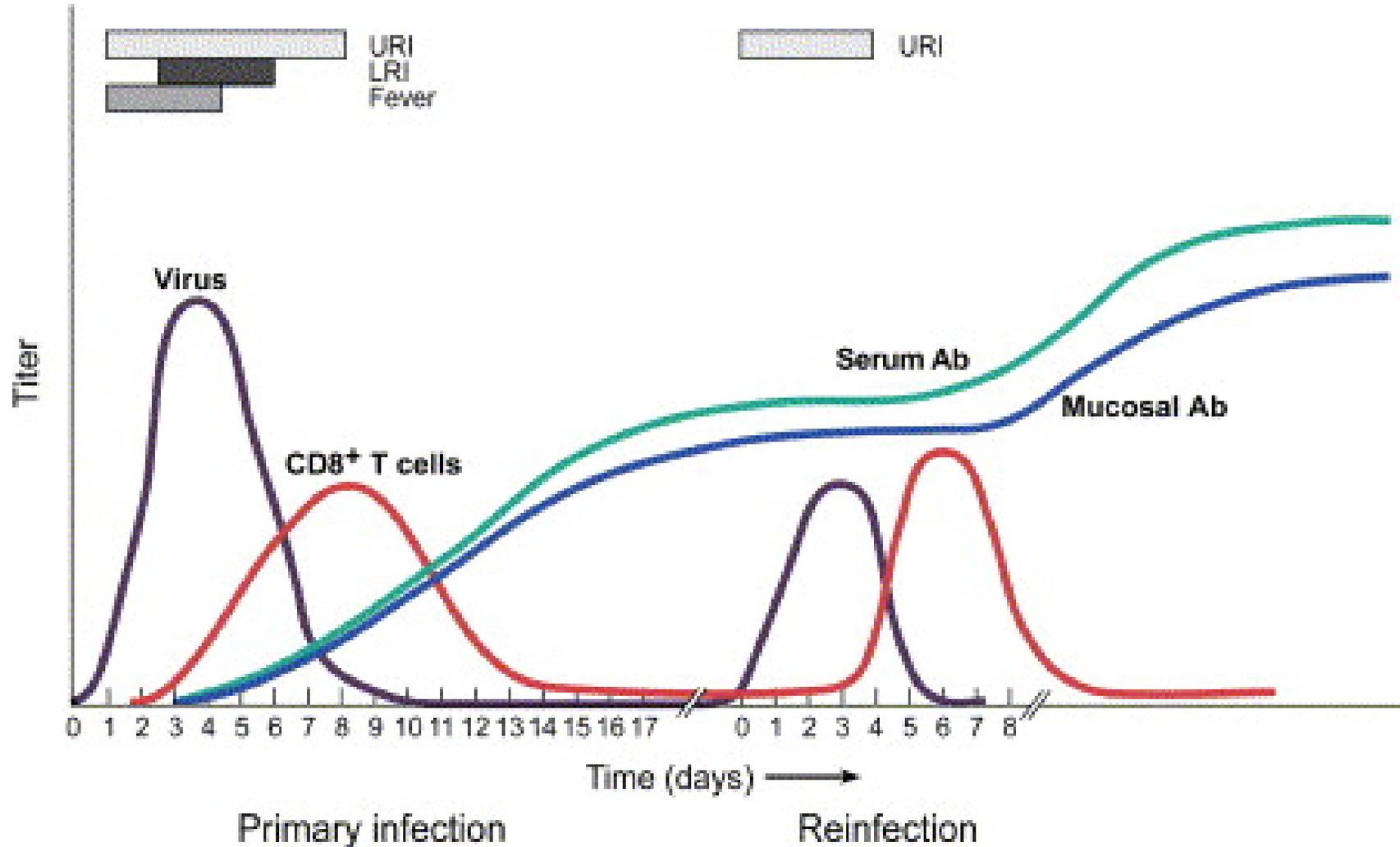
- Evolution of the antigenic structure of influenza viruses
 - Antigenic drift and vaccine mismatches
 - Distinct lineages of influenza B viruses
 - Antigenic shift and pandemic influenza
- Emergence of antiviral resistance
 - H3N2 viruses – amantadine and rimantadine
 - H1N1 viruses – oseltamivir
- Continued disease impact in young and old
 - Options for control by vaccination and antiviral therapy

Antibody against the HA and NA are the major components of influenza immunity

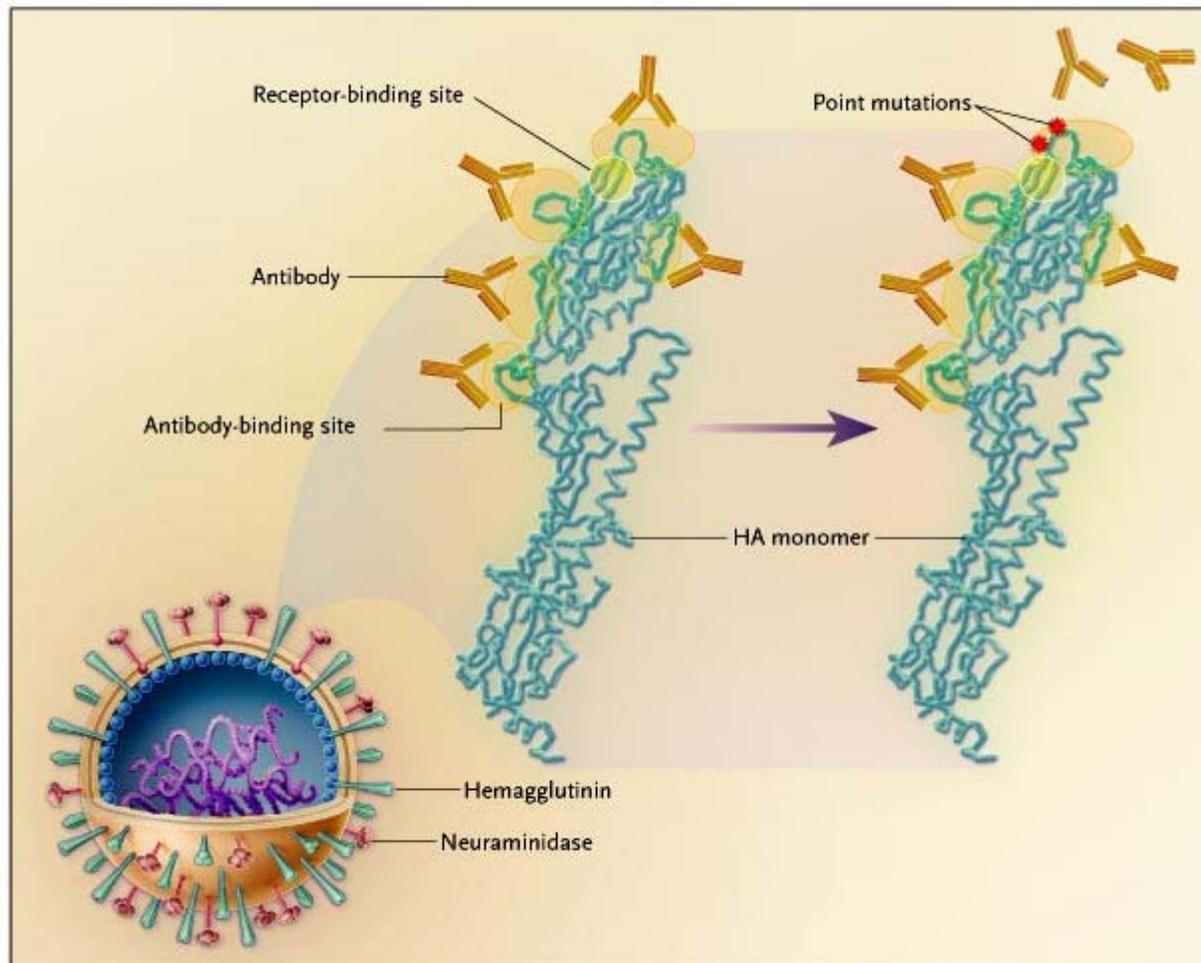


- Functions of HA antibody
 - Prevention of attachment
 - Postattachment events
- Functions of NA antibody
 - Prevention of cell spread
 - Reduced severity of illness
- Other mechanisms
 - M2 antibody
 - Cellular responses

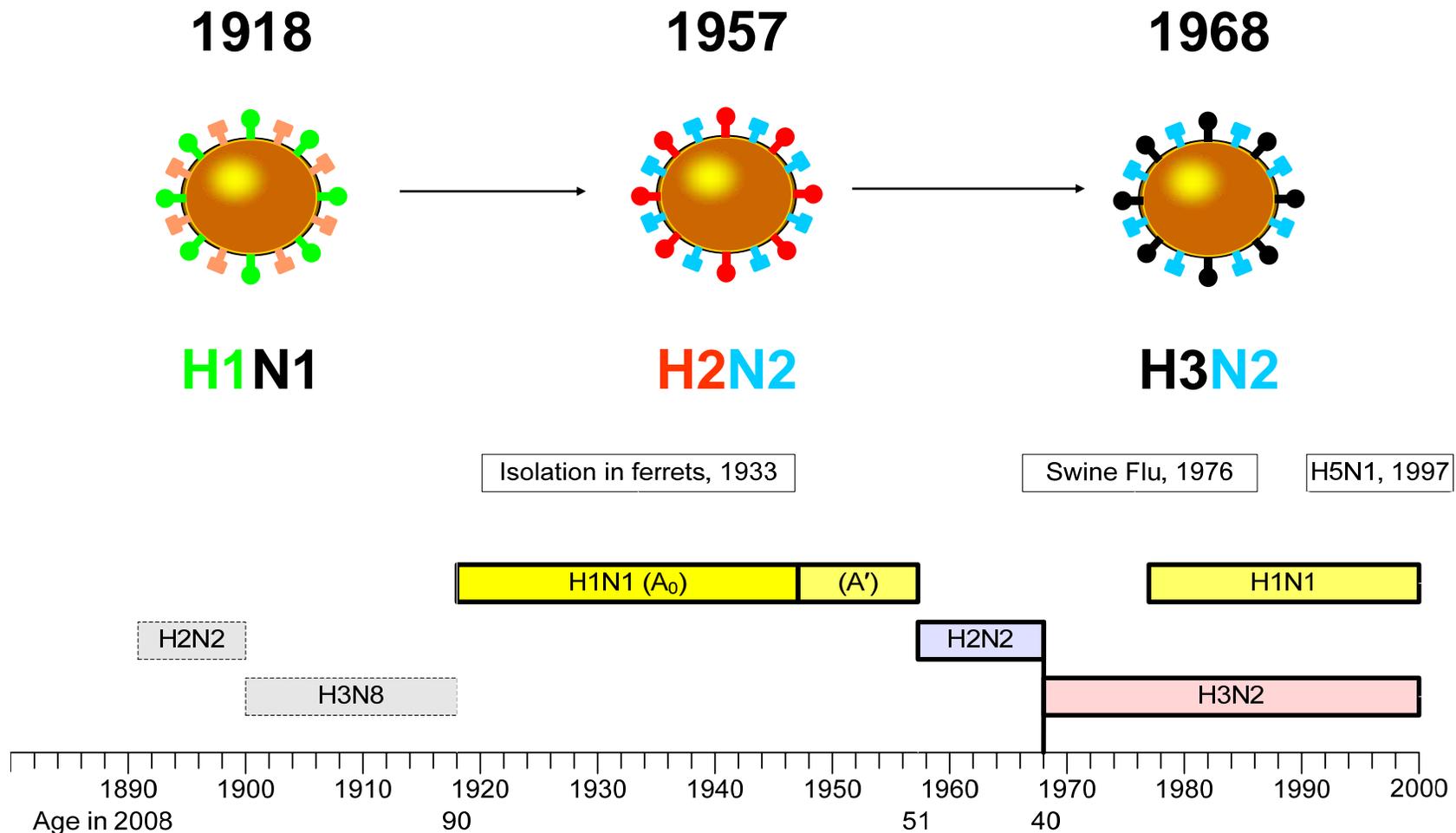
Immune response to influenza infection and reinfection



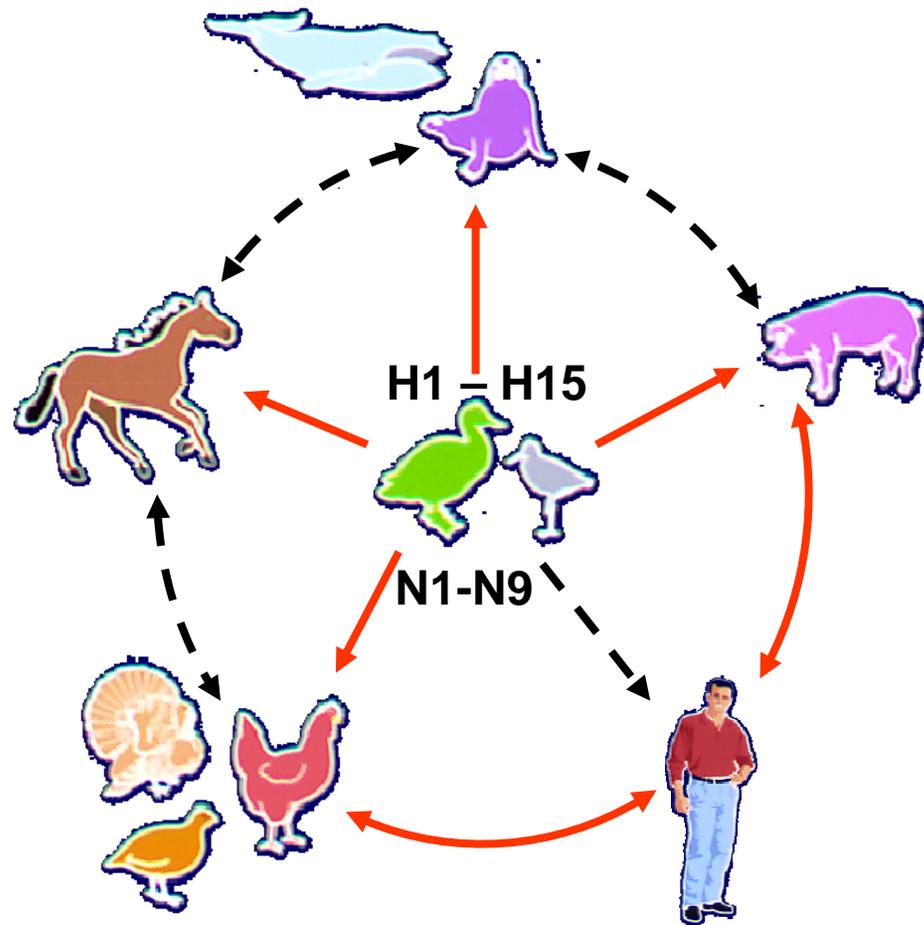
Antigenic drift – point mutations in HA antibody combining sites



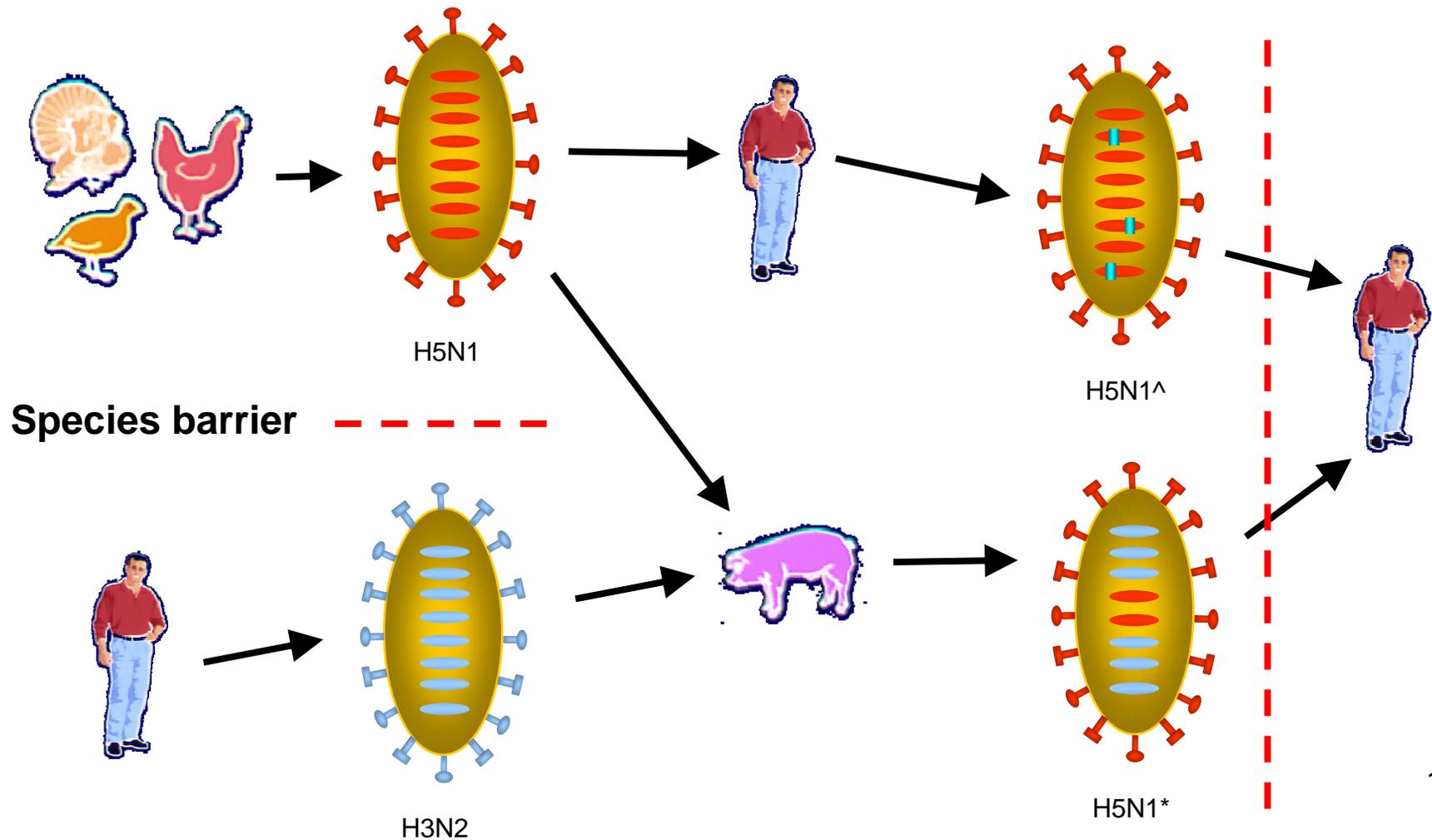
Pandemics occur when viruses with a new H or N emerge



Potential HA and NA subtypes responsible for pandemics

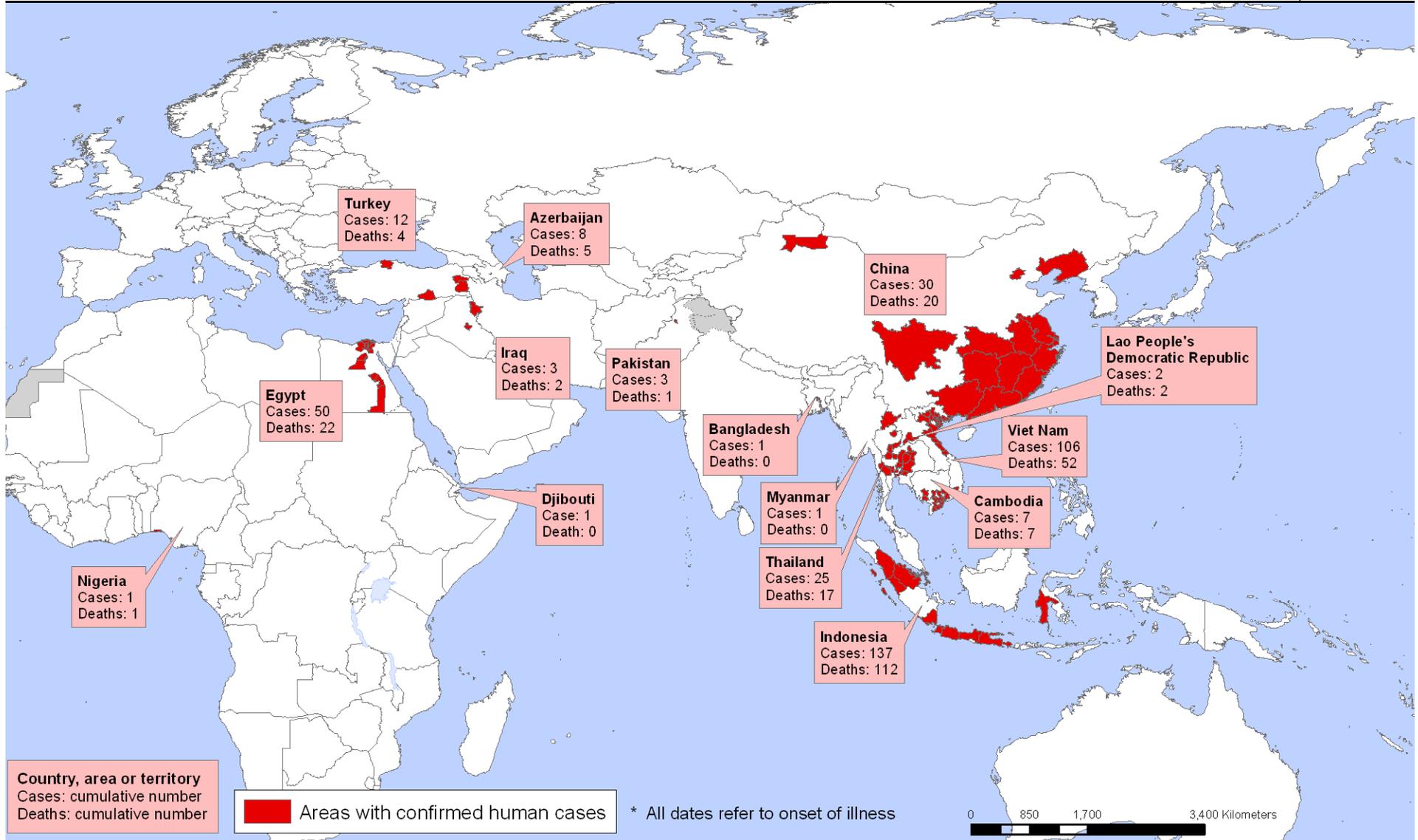


Two routes to a pandemic



Areas with confirmed human cases of H5N1 avian influenza since 2003 *

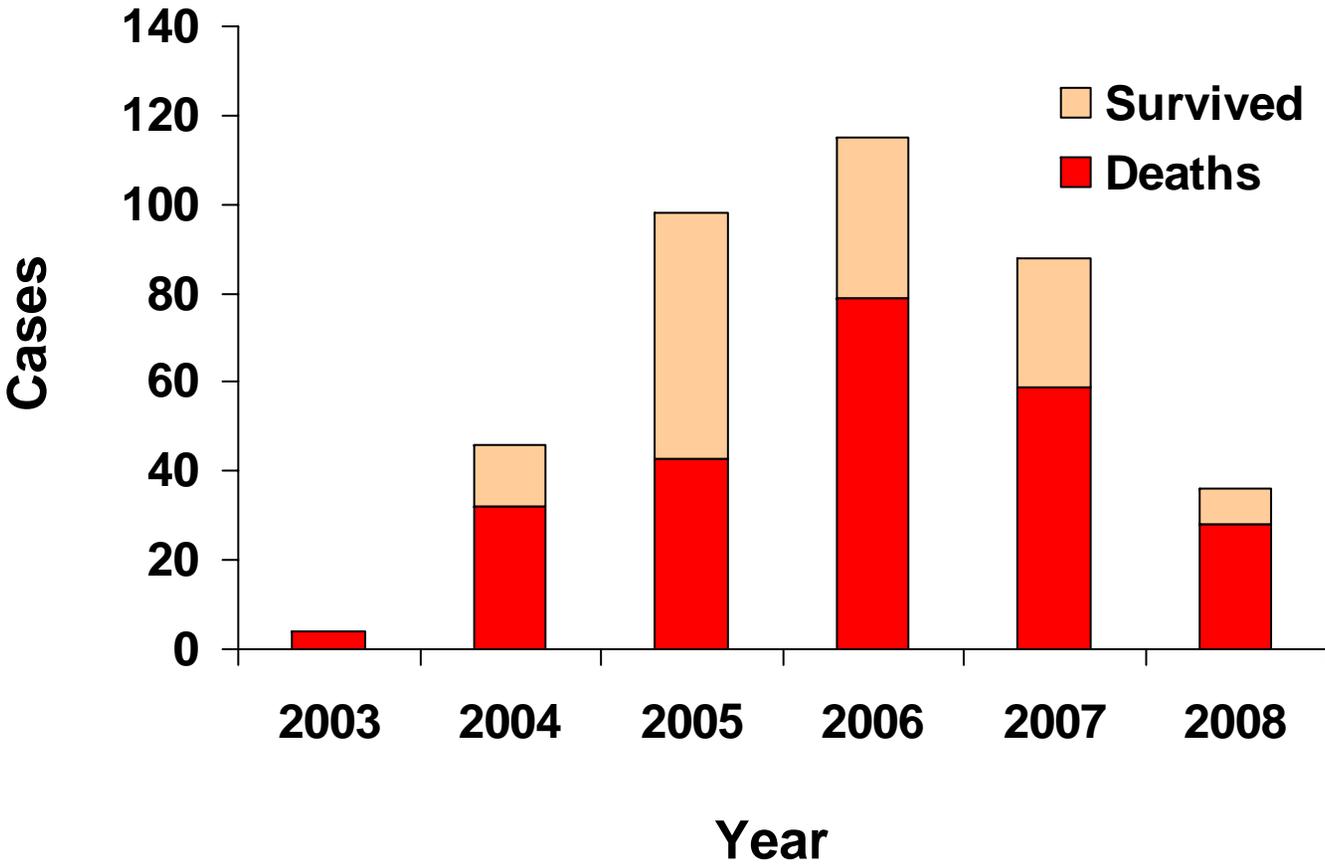
Status as of 10 September 2008
Latest available update



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2008. All rights reserved

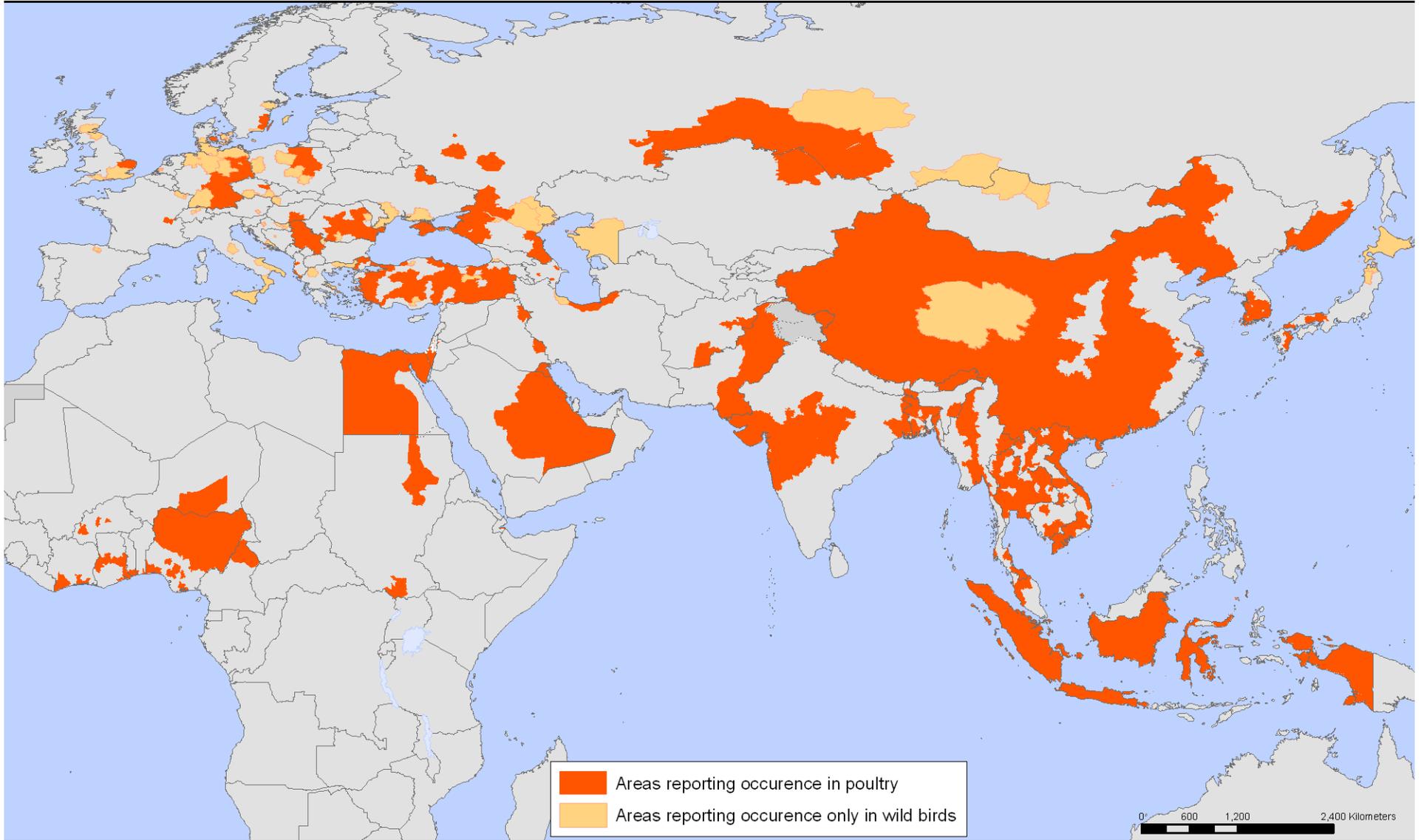
Data Source: WHO
Map Production: Public Health Information and Geographic Information System (GIS)
World Health Organization

Confirmed Human H5N1



Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds since 2003

Status as of 15 September 2008
Latest available update



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The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

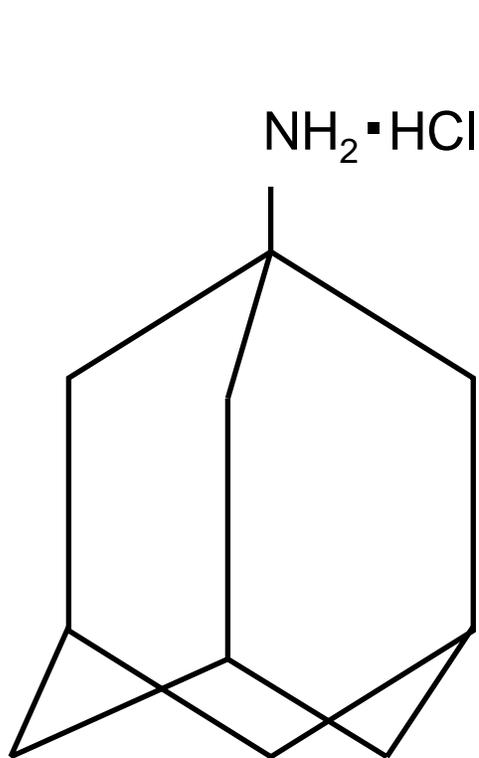
Data Source: World Organisation for Animal Health (OIE) and national governments

Map Production: Public Health Information and Geographic Information Systems (GIS), World Health Organization

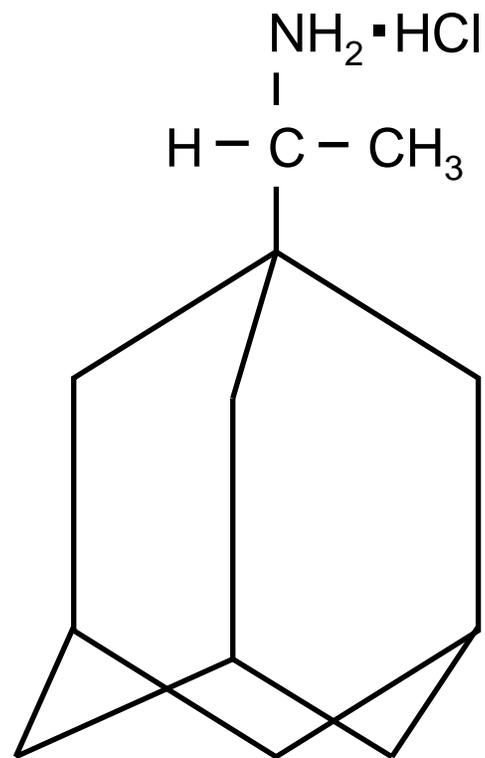
Antiviral Agents for Influenza

- M2 inhibitors
 - Amantadine
 - Rimantadine
- Neuraminidase inhibitors (NIs)
 - Zanamivir
 - Oseltamivir
 - Peramivir
- Other agents in development

Amantadine and Rimantadine



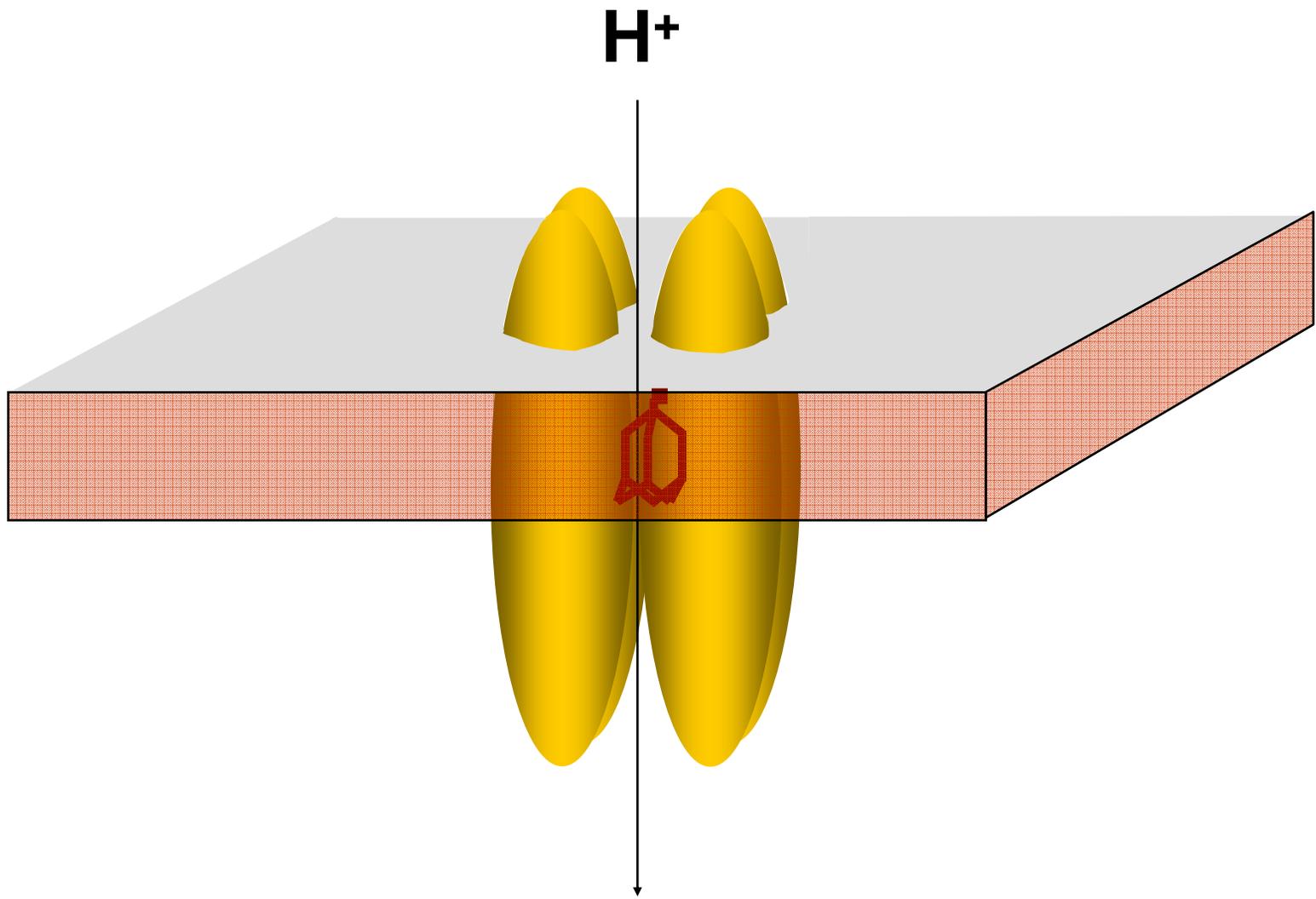
AMANTADINE



RIMANTADINE

Amantadine and Rimantadine

- Inhibit function of the viral M2 protein
- Orally bioavailable
- Well tolerated, CNS toxicity A>R
- Effective in prophylaxis and therapy of influenza A in adults
 - Reductions in duration of symptoms
 - More rapid return to normal activities
 - Reductions in fever
 - Variable effects on virus shedding

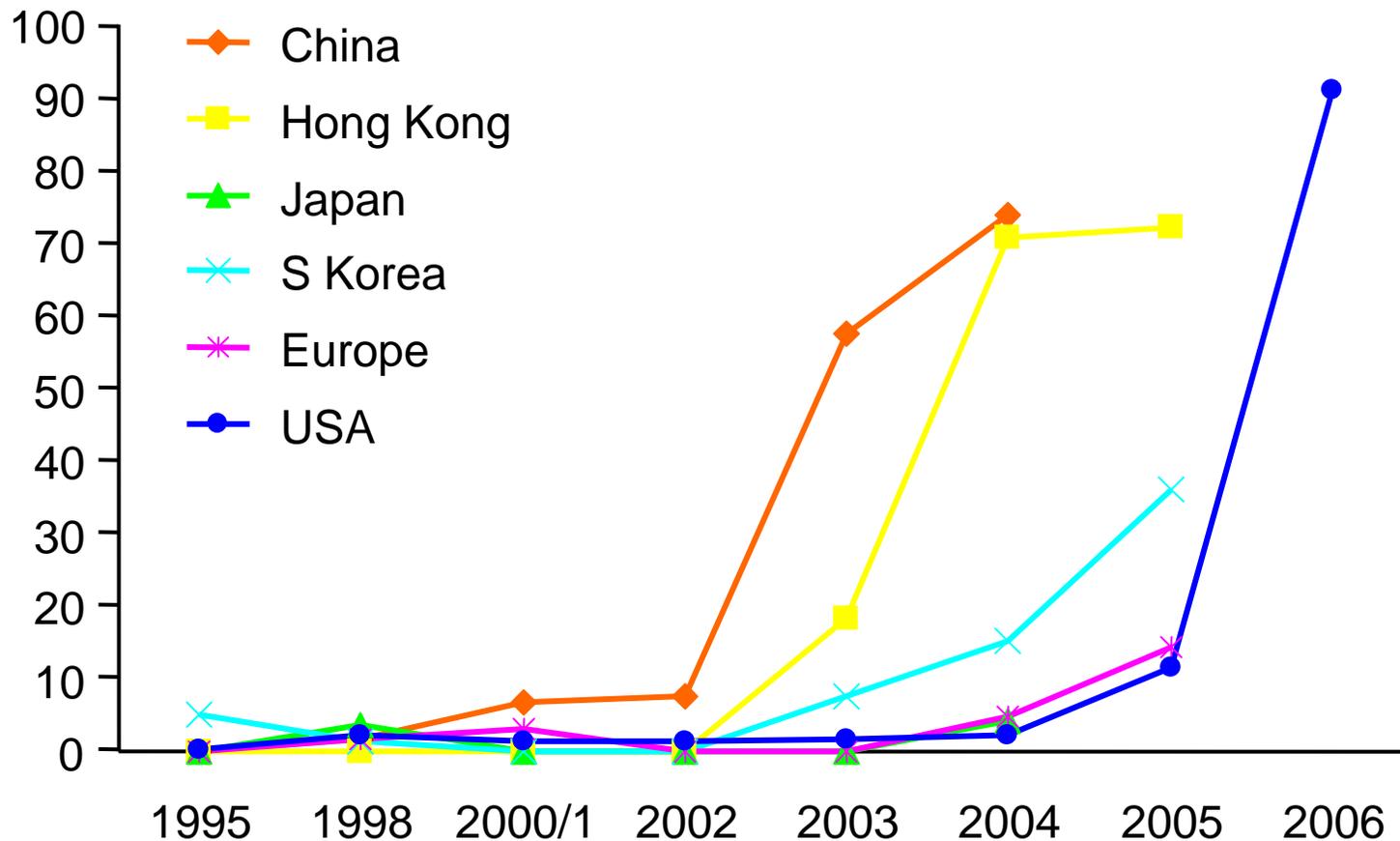


Amantadine/Rimantadine Resistance



- Single amino acid change in transmembrane portion of M2
- Genetically stable, fully virulent in animals
- Transmitted to, and causes disease in, susceptible contacts
 - Family studies
 - Institutions
- May be reduced by combination with vaccine

Antiviral Resistance to M2 Inhibitors in Community Isolates of A/H3N2 1995-2005



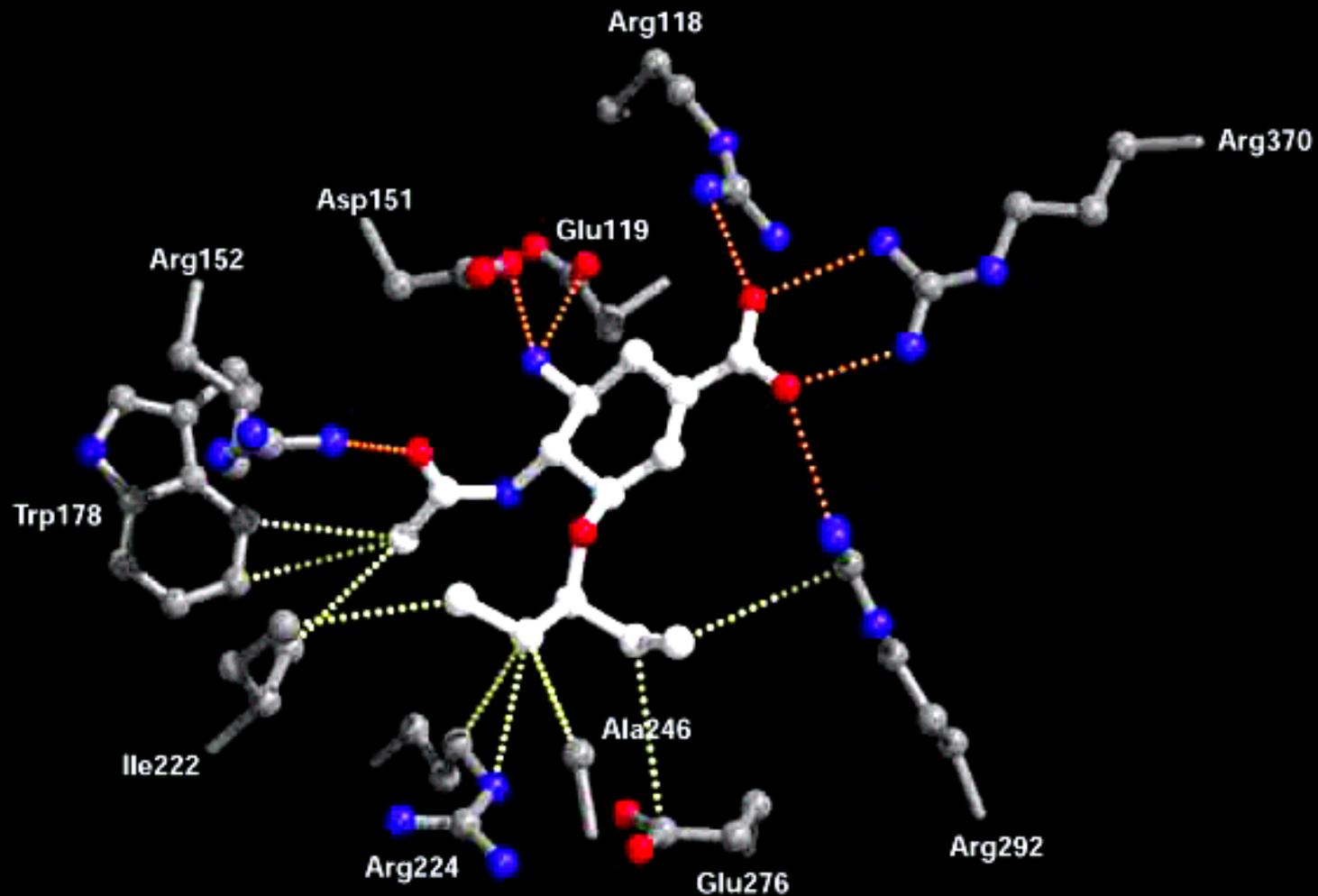
Bright R et al. *Lancet*. 2005;366:1175-1181.

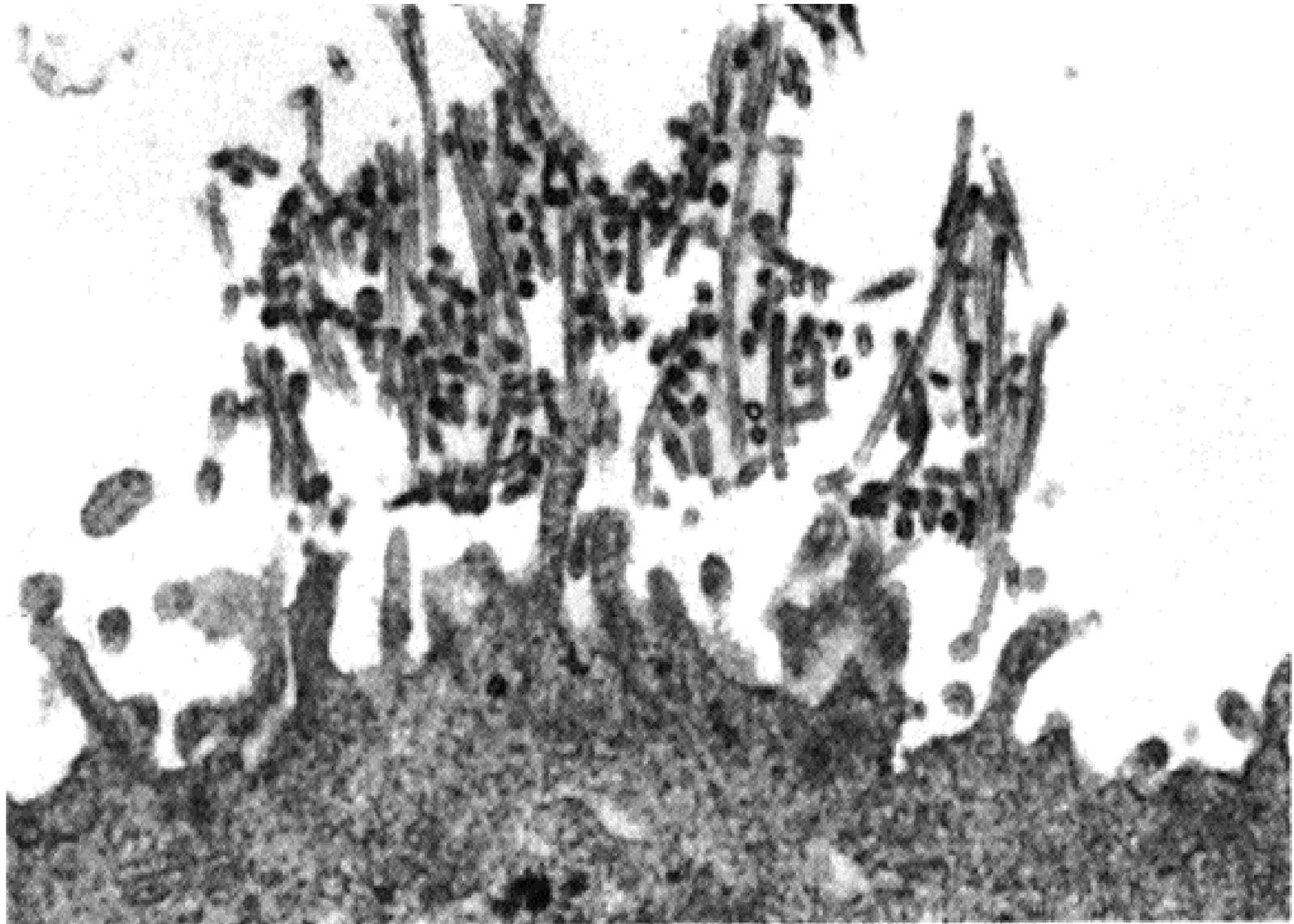
Bright R et al. *JAMA*. 2006;295:891-894.

Neuraminidase Inhibitors (NIs)

- Active in vitro and in animal models against both influenza A and B viruses
- Active against neuraminidases of all influenza A viruses tested (N1-N9)
- Zanamivir: oral inhaler, no appreciable systemic absorption, GI elimination
- Oseltamivir: oral ethylester prodrug, converted in liver to active form, eliminated by tubular secretion (probenecid inhibits), does not cross blood-brain barrier
- Peramivir: IV, long half-life, experimental

Oseltamivir Carboxylate in Active Site of NA



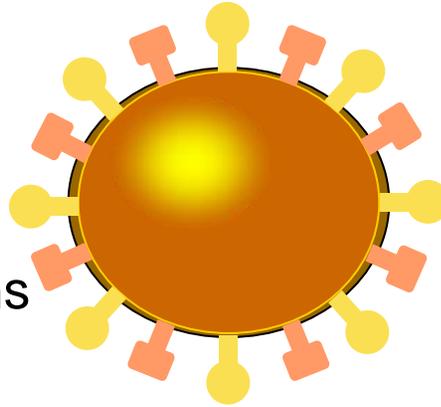


Activity of NIs Against Clinical Isolates of Influenza Viruses

	IC ₅₀ (nM) by Chemiluminescent Assay		
	Zanamivir	Oseltamivir	Peramivir
<u>H3N2 viruses</u>			
A/Victoria/2/95	1.60 (0.85-2.93)	0.67 (0.52-0.78)	0.56 (0.33-0.72)
A/Sydney/5/97	3.23 (1.44-4.76)	1.48 (0.82-1.97)	0.82 (0.62-1.09)
H3N2 isolates (n=38)	2.09 (1.15-4.22)	0.73 (0.32-1.66)	0.60 (0.30-0.93)
<u>H1N1 viruses</u>			
A/Beijing/262/95	0.65 (0.52-0.81)	1.53 (0.97-2.07)	0.41 (0.29-0.58)
H1N1 isolates (n=4)	1.14 (0.94-1.32)	0.90 (0.71-1.31)	0.27 (0.13-0.39)
<u>Influenza B viruses</u>			
B/Harbin/07/94	5.94 (2.69-9.53)	10.01 (6.10-12.80)	1.38 (0.97-1.66)
B isolates (n=23)	4.15 (2.19-6.34)	11.53 (4.93-18.59)	0.87 (0.52-1.36)

Clinical effects of NIs

- Therapy (within 48 hrs of sx onset)
 - Adults:
 - Approximately 30% reduction in duration of illness
 - Reduced rates of influenza complications including hospitalizations
 - Children
 - Reduced duration of fever
 - Reduced rates of otitis media and other physician diagnosed complications
- Prophylaxis
 - Reduced cumulative incidence in seasonal prophylaxis of adults and elders (additive with vaccine)
 - Reduced secondary attack rates in family prophylaxis and outbreak control in nursing homes

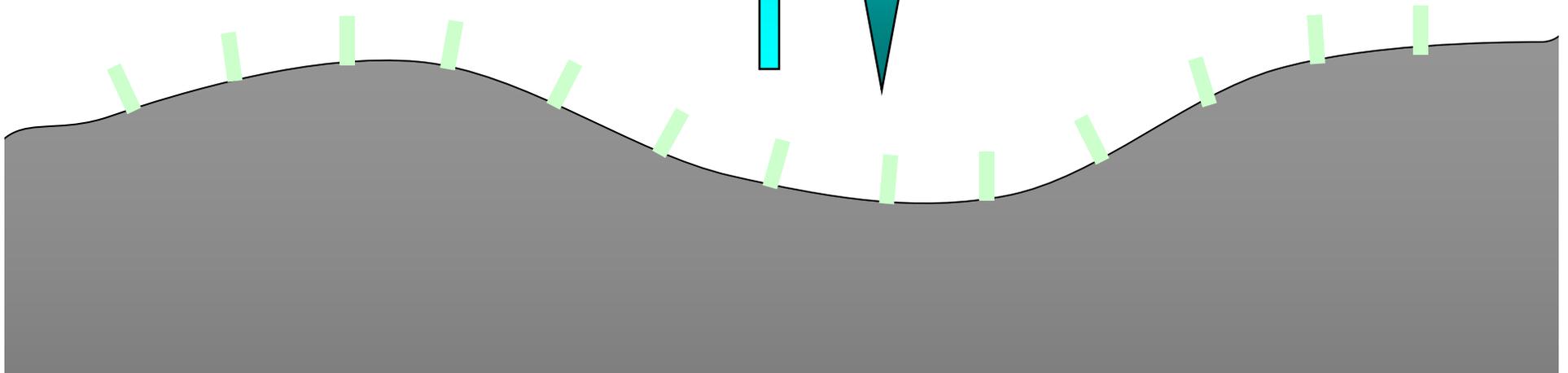


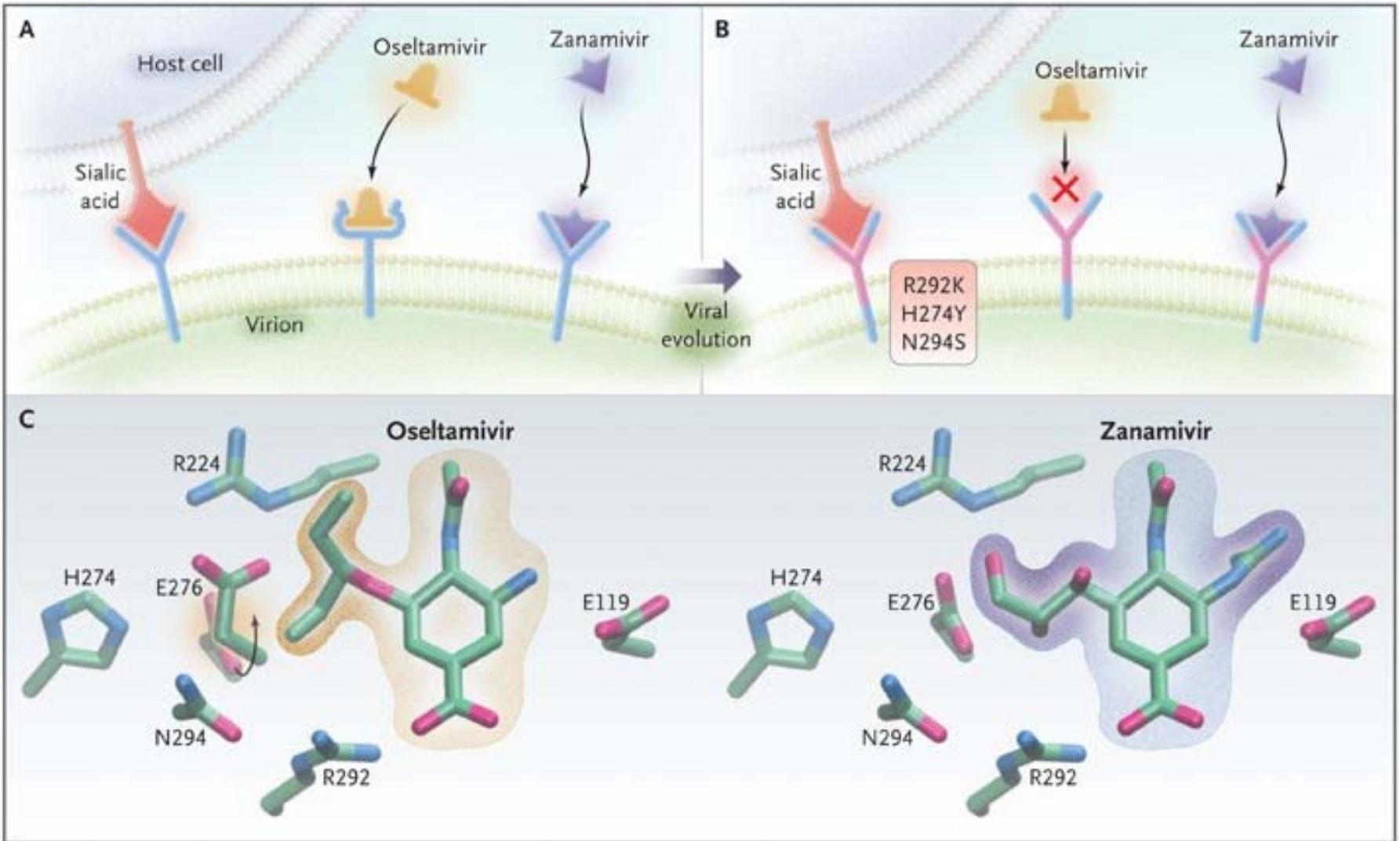
Neuraminidase mutations

- framework mutations
- catalytic site
- NA specific
 - E119V (N2)
 - R292K (N2)
 - H274Y (N1)
 - D198N (B)
- Specific for drug

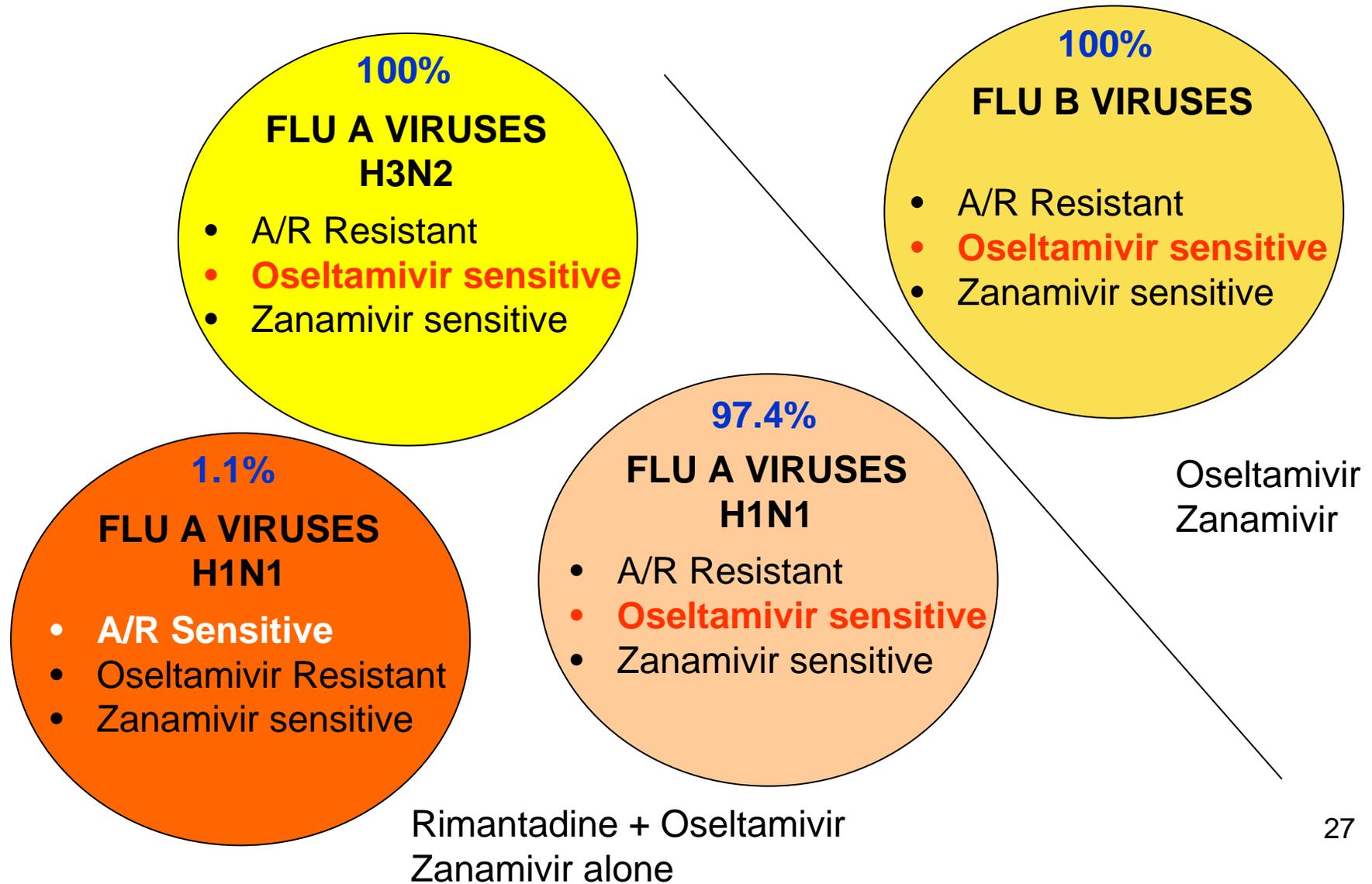
Hemagglutinin mutations

- receptor binding
- glycosylation sites
- changes in cell surface
- result in cross resistance





The world of influenza viruses



Guidance for antiviral therapy

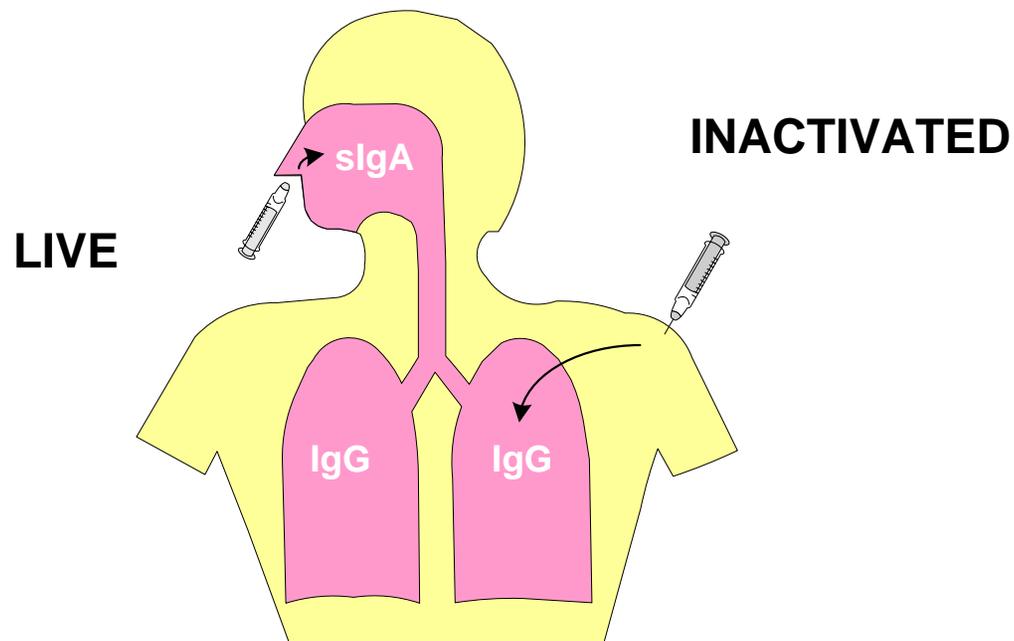
- Focus antiviral use on early therapy or prophylaxis (contact, outbreak) of high risk or severely ill patients
- Use community surveillance and/or rapid testing where available
 - Influenza B: oseltamivir or zanamivir*
 - Influenza A (H1N1): rimantadine or zanamivir*
 - Influenza A (H3N2): oseltamivir or zanamivir*
 - Influenza A (unknown subtype): zanamivir* or rimantadine + oseltamivir

* Patients 7 or older who can comply with diskhaler device

Influenza rapid detection tests

	Differentiates A and B?	CLIA Waiver?
3M Rapid Detection (3M)		
Directigen Flu A (Becton-Dickinson)		
Directigen Flu A+B (Becton-Dickinson)	✓	
Directigen EZ flu A+B (Becton-Dickinson)	✓	
BinaxNOW Influenza A&B (Inverness)	✓	✓
OSOM Influenza A&B (Genzyme)	✓	
QuickVue Influenza Test (Quidel)		✓
QuickVue Influenza A+B (Quidel)	✓	✓
SAS FluAlert (SA Scientific)	✓	
TRU FLU (Meridian Bioscience)	✓	
EXPECT Flu A&B (Remel)	✓	

Two Types of Flu Vaccine: Live and Inactivated



Trivalent Vaccine =
One H1N1 virus
One H3N2 virus
One B virus

Influenza Vaccines Licensed for Use in Different Age Groups—United States, 2007–2008 Season

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Mercury Content (µg/dose)	Age Group
TIV	Fluzone	Sanofi Pasteur	0.25-mL prefilled syringe	0	6–35 mo
			0.5-mL prefilled syringe	0	36 mo
			0.5-mL vial	0	36 mo
			5.0-mL multidose vial	25	6 mo
TIV	Fluvirin	Novartis	0.5-mL prefilled syringe	<1.0	4 y
TIV	Fluvirin	Novartis	5.0-mL multidose vial	24.5	4 y
TIV	Fluarix	GlaxoSmithKline	0.5-mL prefilled syringe	<1.25	18 y
TIV	FluLaval	GlaxoSmithKline	5.0-mL multidose vial	25	18 y
TIV	Afluria	CSL Limited	0.5-mL prefilled syringe	0	18 y
			5-mL multidose vial	24.5	
LAIV	FluMist	MedImmune	0.2-mL sprayer	0	2–49 y

Comparing TIV and CAIV-T

	TIV	CAIV-T
Administration	Intramuscular	Intranasal
Immune response	Serum antibodies	Mucosal immunity
Formulation	Inactivated	Live attenuated
Efficacy children	~30–70%	70%–90%
Efficacy adults	70%–90%	70%–90%
Efficacy elders	Low	Unknown
Safety	Sore arm	Runny nose
Growth medium	Chick embryos	Chick cells
Indication	Any person ≥ 6 mo	Healthy persons ≥ 2 –49 y

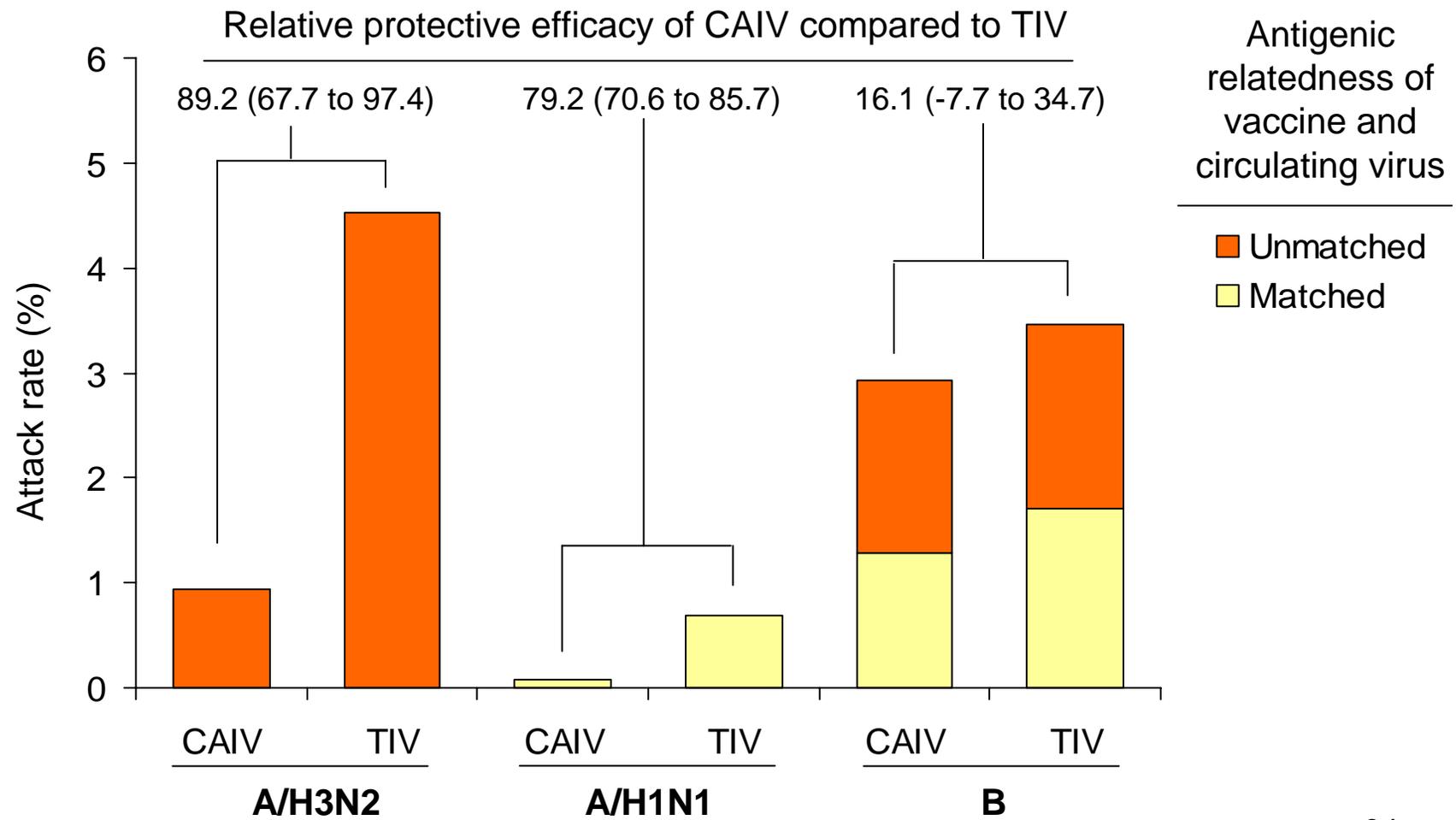
TIV is highly efficacious in healthy adults

Year	Vaccine	Epidemic	Attack rate (%)		Efficacy (%)
			C	V	
1959-1960	A/Jap/57 (H2N2)	A/Jap/57 (H2N2)	1.5	0.1	94
1965-1966	A/Jap/57 (H2N2)	A/AA/65 (H2N2)	1.7	0.4	76*
1968-1969	A/AA/67 (H2N2)	A/HK/68 (H3N2)	6.5	4.2	35**
1971-1972	A/HK/68 (H3N2)	A/HK/68 (H3N2)	2.0	0.2	90
1972-1973	A/HK/68 (H3N2)	A/Eng/72 (H3N2)	4.6	1.8	61*
1973-1974	A/Eng/72 (H3N2)	A/PC/73 H3N2)	2.4	0.6	75*

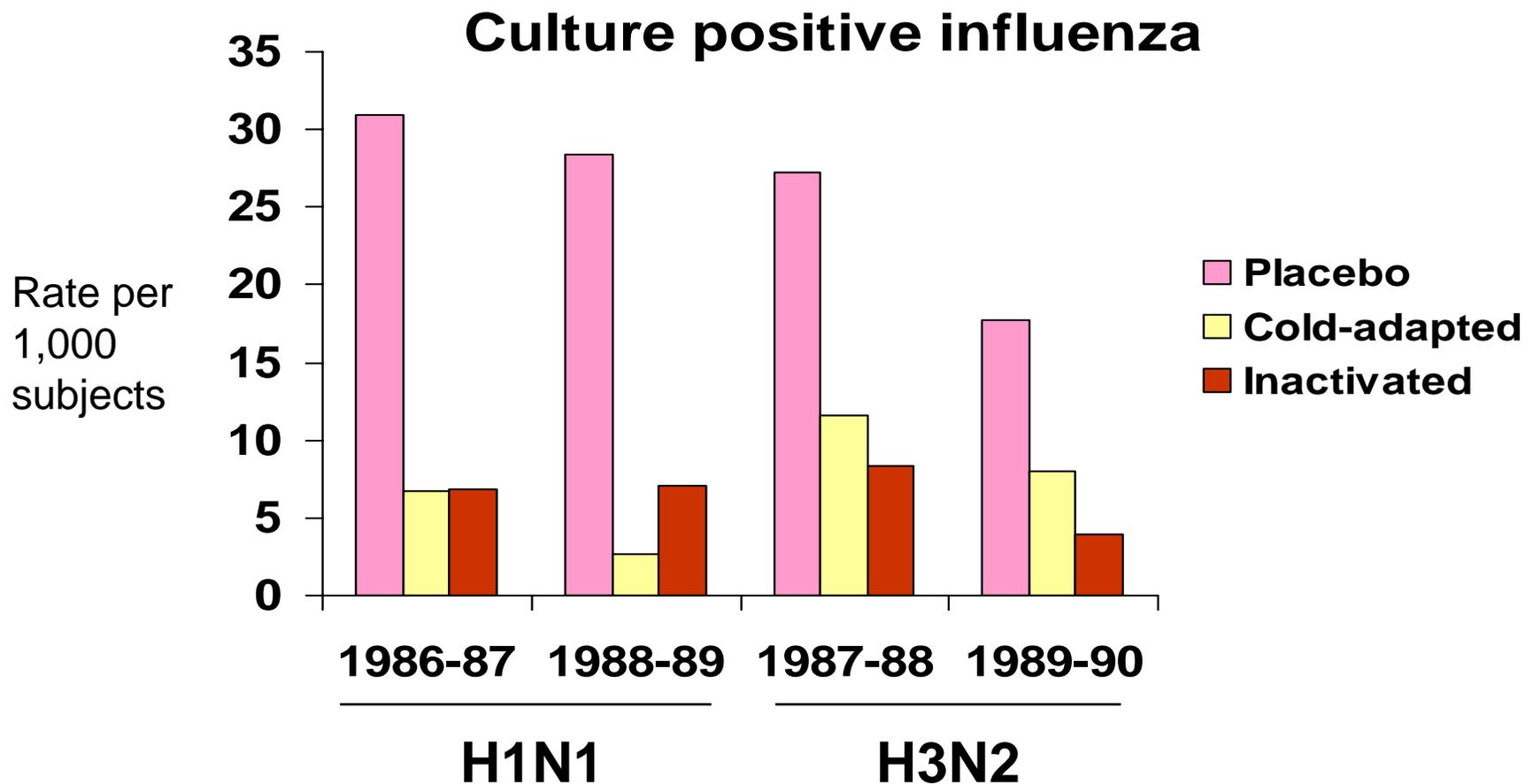
* Drift

** Shift

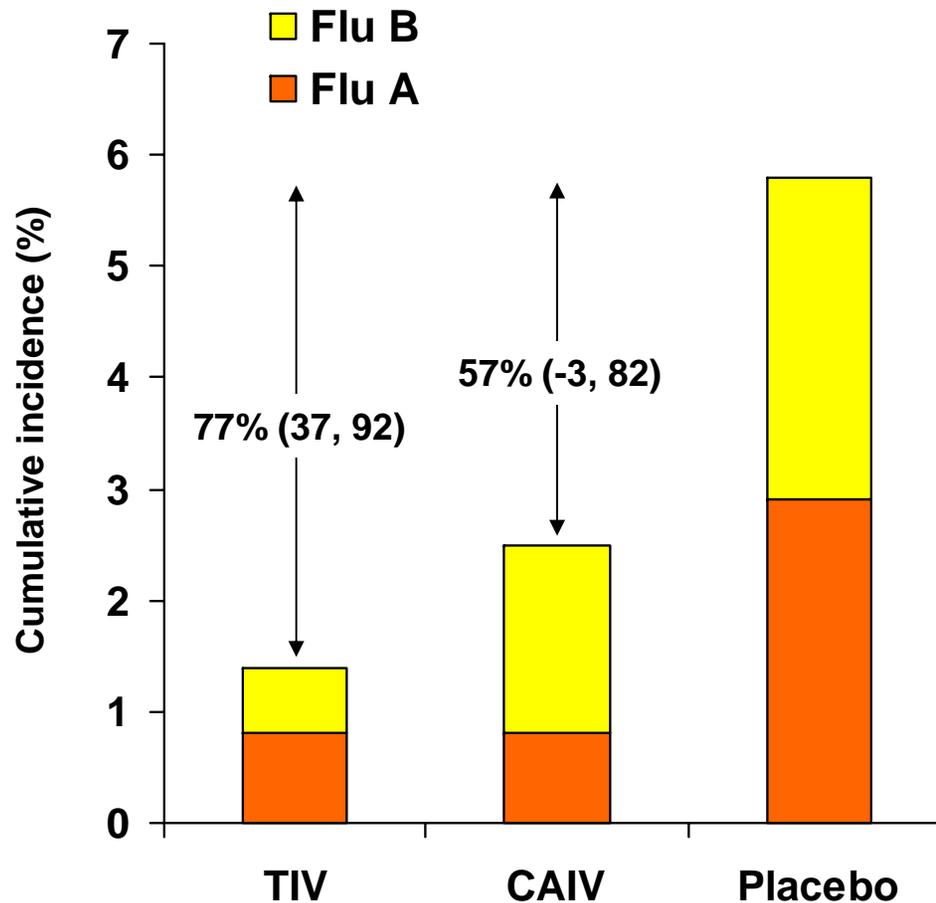
Live vaccine is especially efficacious in unprimed, immunologically naïve subjects



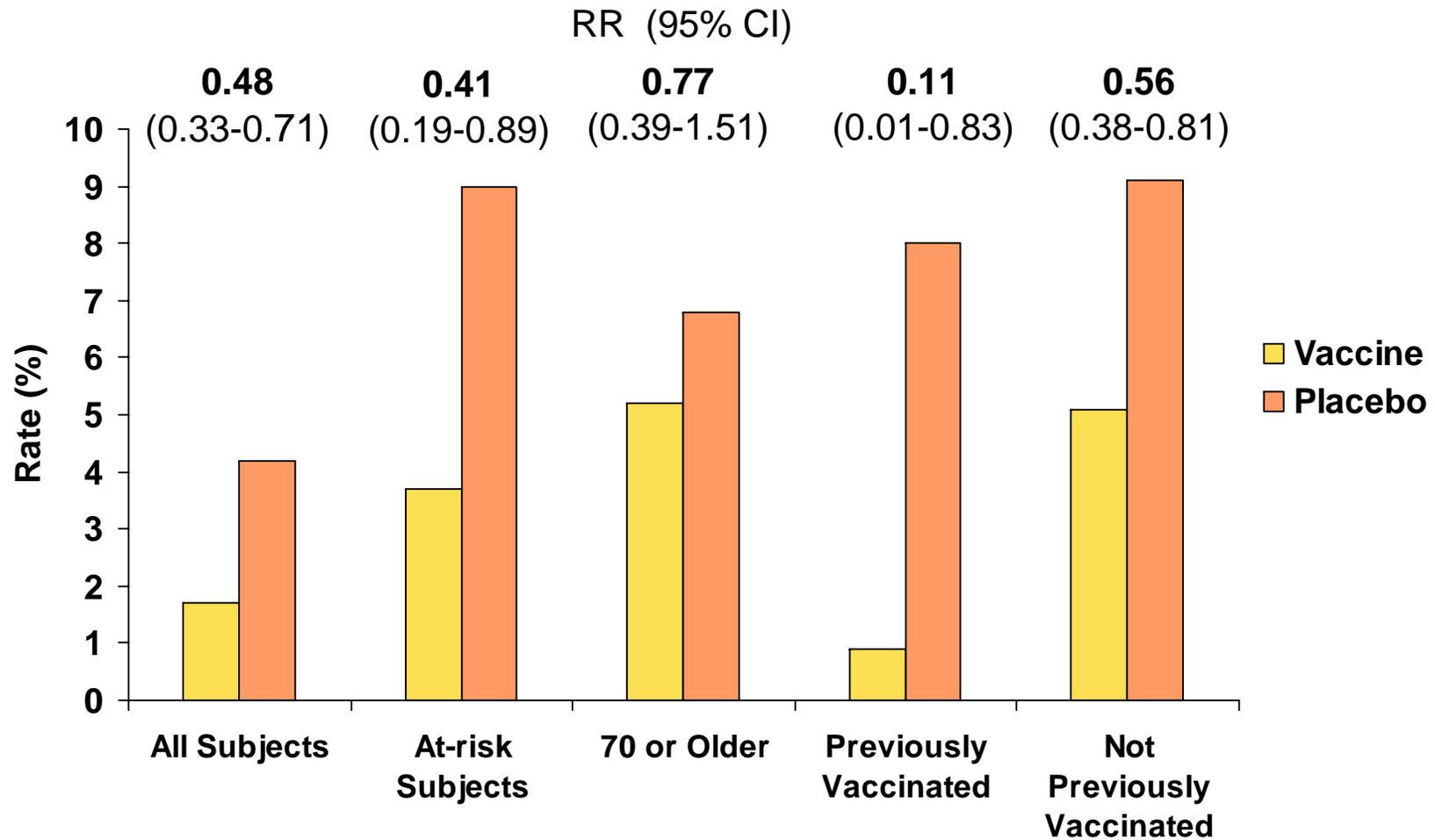
Live vaccine provides protection against flu in healthy adults



Live vaccine may be less efficacious than inactivated vaccine in adults



Inactivated vaccine is poorly effective in the elderly (probably)



US - Basic Vaccine Strategy

- Reduce disease impact by vaccinating those at high risk
- Reduce transmission of influenza to high-risk patients by vaccinating contacts

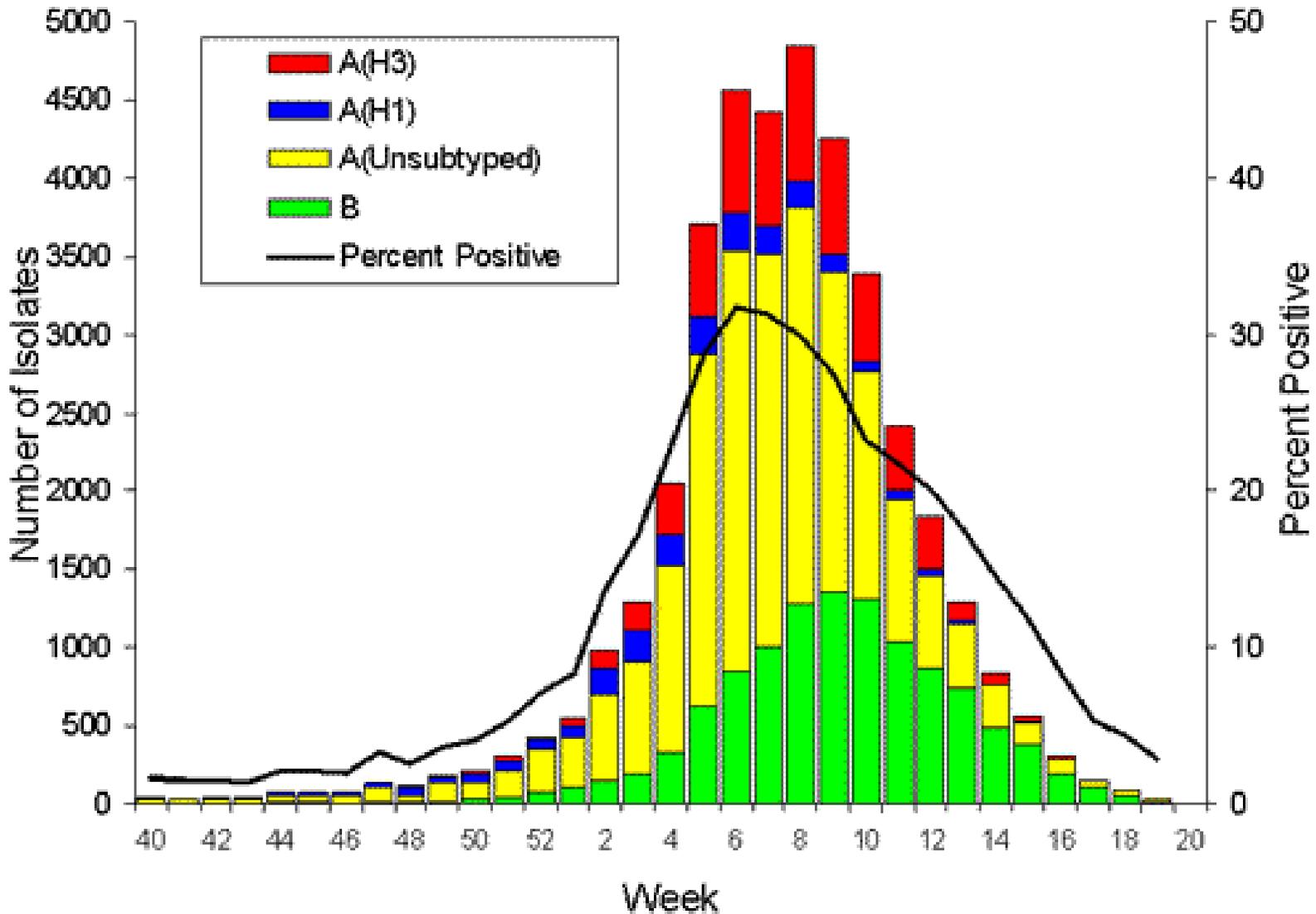
Reduce disease impact by vaccinating those at high risk

- Condition based
 - Chronic cardiopulmonary conditions (not hypertension)
 - Chronic renal disease, Diabetes,
 - HIV, Pregnancy
- Age based
 - Adults ≥ 50)
 - Children ≤ 5
 - Children <18 when feasible

Reduce transmission to high-risk patients by vaccinating contacts

- Residents of chronic care facilities that house high-risk persons
- Health-care workers
- Other employees
- Persons providing home care
- Household contacts
 - Especially, contacts (including out of household caregivers) of < 6-month-olds

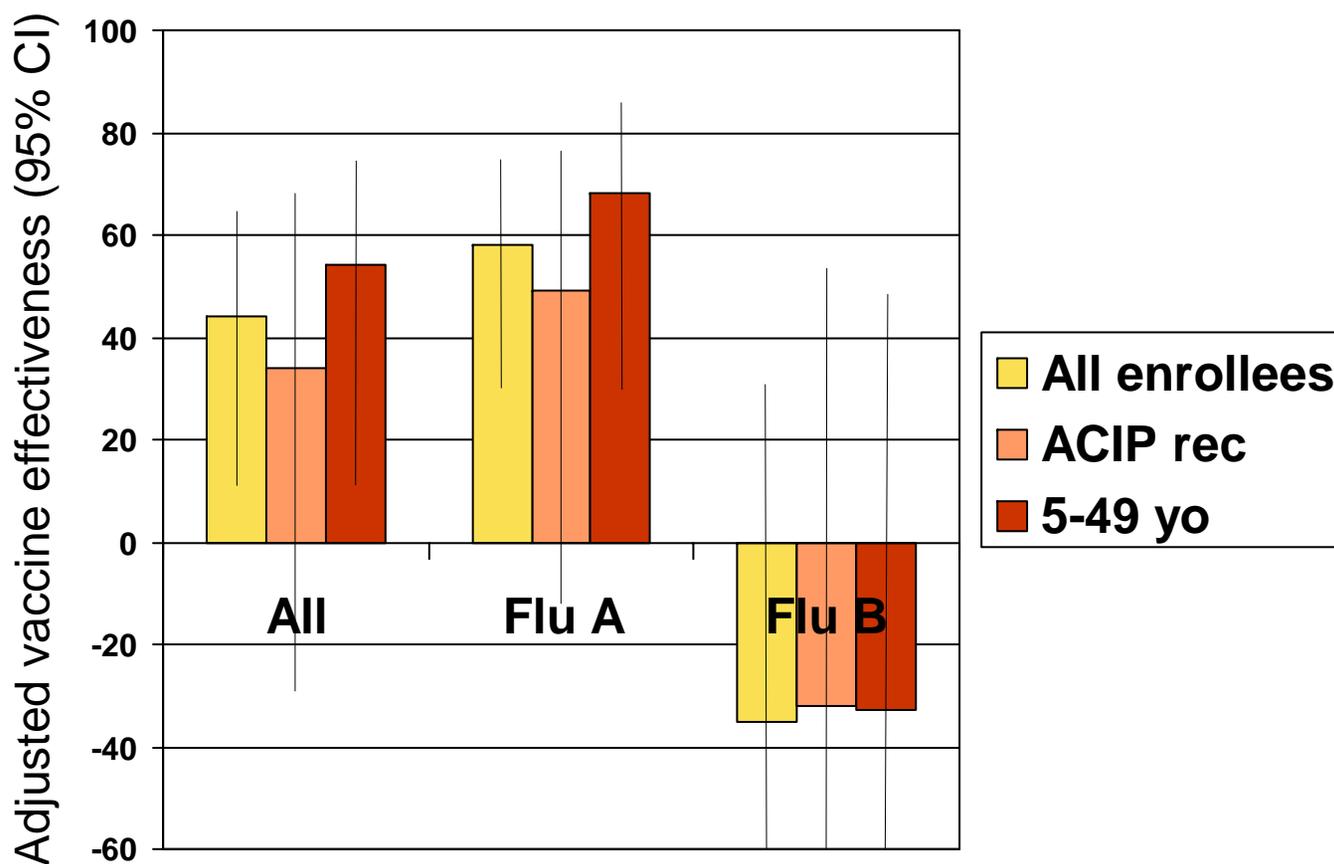
U.S. WHO/NREVSS Collaborating Laboratories National Summary, 2007-08



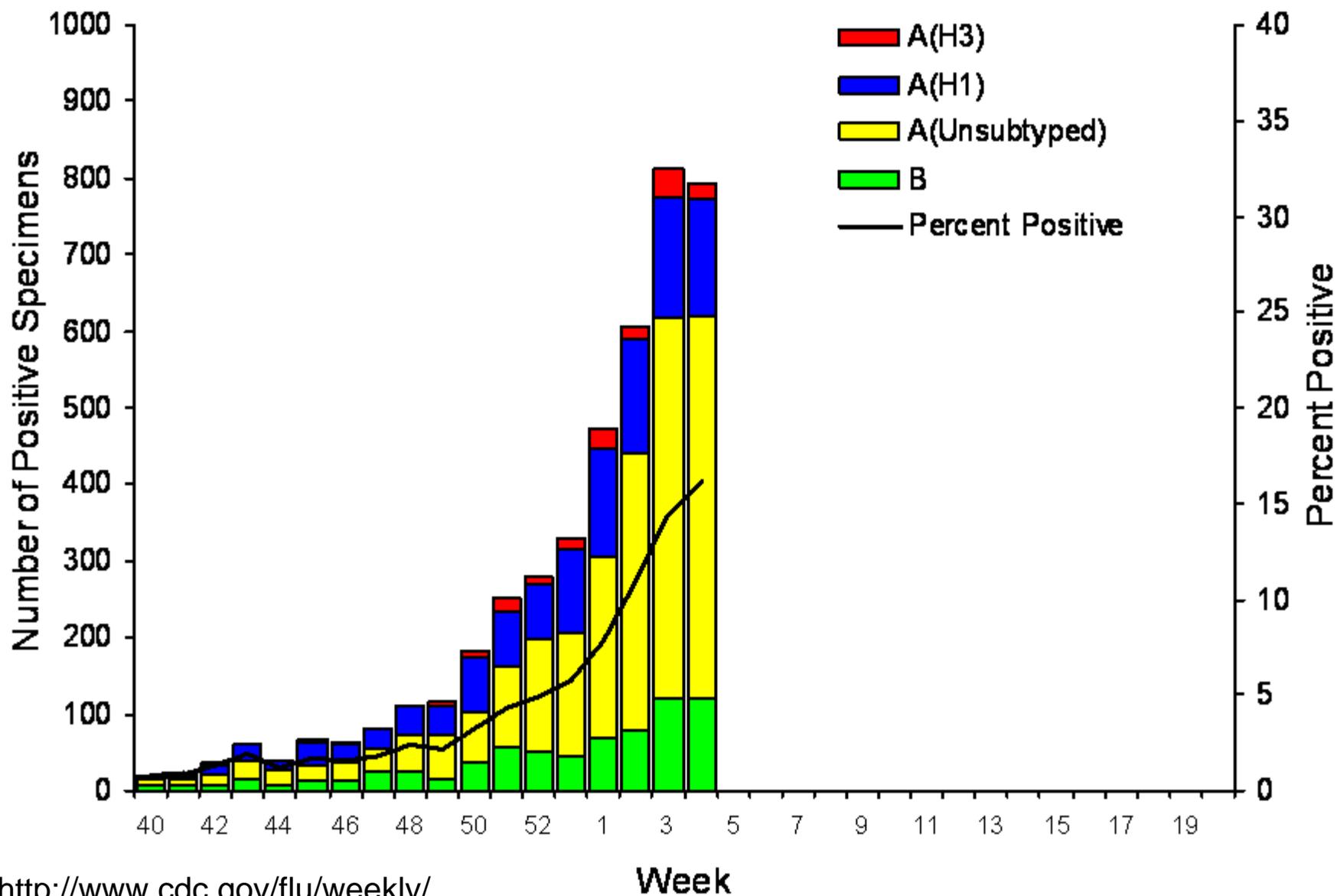
Characterization of influenza viruses 2007-2008 season

- H1N1 Viruses
 - 267/395 (68%) similar to vaccine strain (A/Solomon Islands/06)
 - 108/395 (27%) similar to A/Brisbane/59/07
- H3N2 viruses
 - 59/280 (21%) similar to vaccine strain (A/Wisconsin/67/05)
 - 182/280 (65%) A/Brisbane/10/2007
- Influenza B
 - 8/272 (3%) Victoria (vaccine) lineage
 - 264/272 (97%) Yamagata lineage (92% B/Florida/04/06)

Estimates of flu vaccine effectiveness 2007-2008 season



Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2008-09



Conclusions

- Seasonal influenza remains an important public health threat
- Optimal methods of control have yet to be determined
 - Resistance is compromising current antiviral approaches
 - Continued antigenic variation is compromising vaccine effectiveness, although magnitude of problem is unclear
 - Some populations are not well protected, and better vaccines are needed
 - Herd immunity may play an important role
- Continued, but difficult to quantify, risk of pandemic influenza