

Influenza surveillance and pandemic preparedness - a global challenge

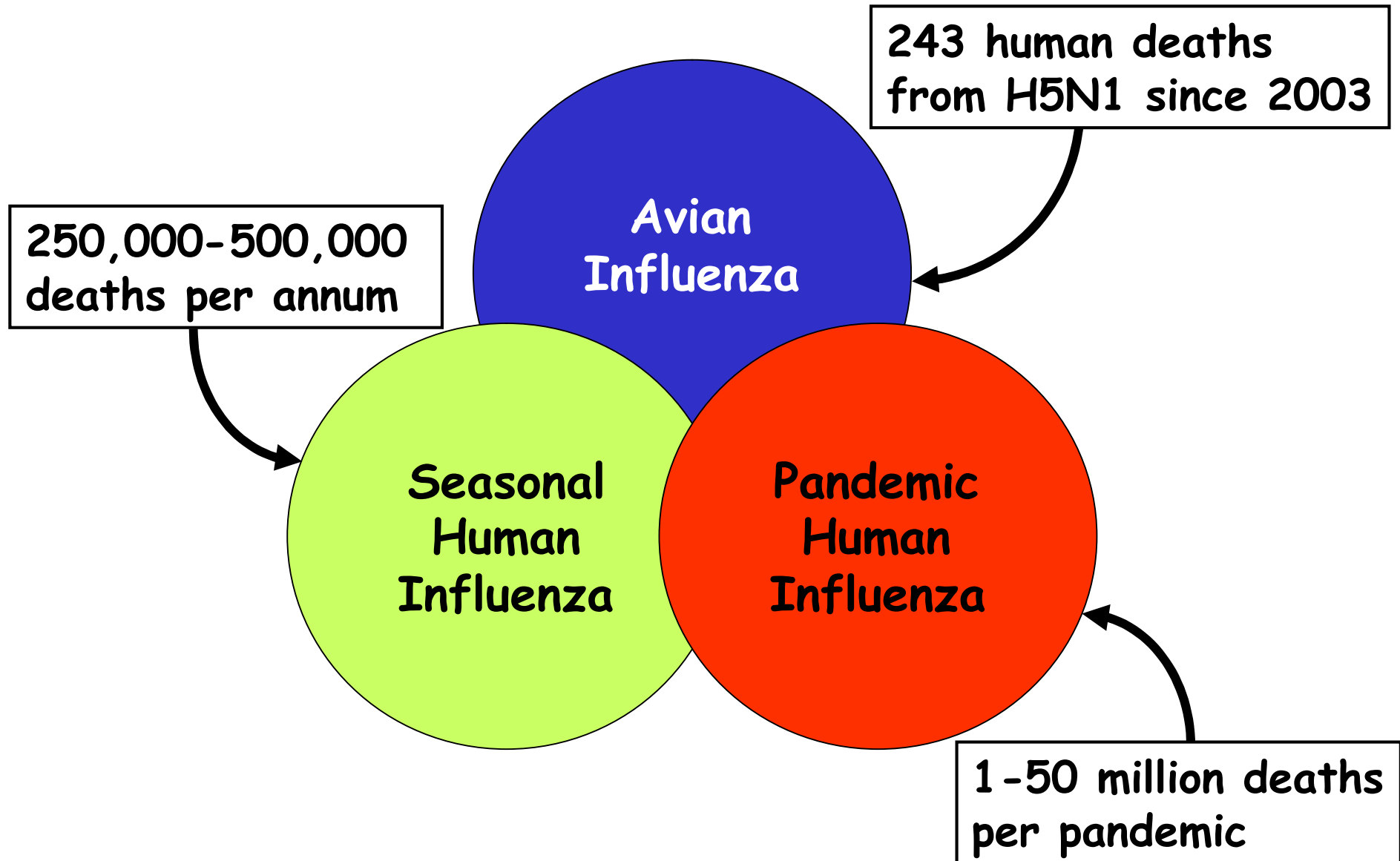
Anne Kelso

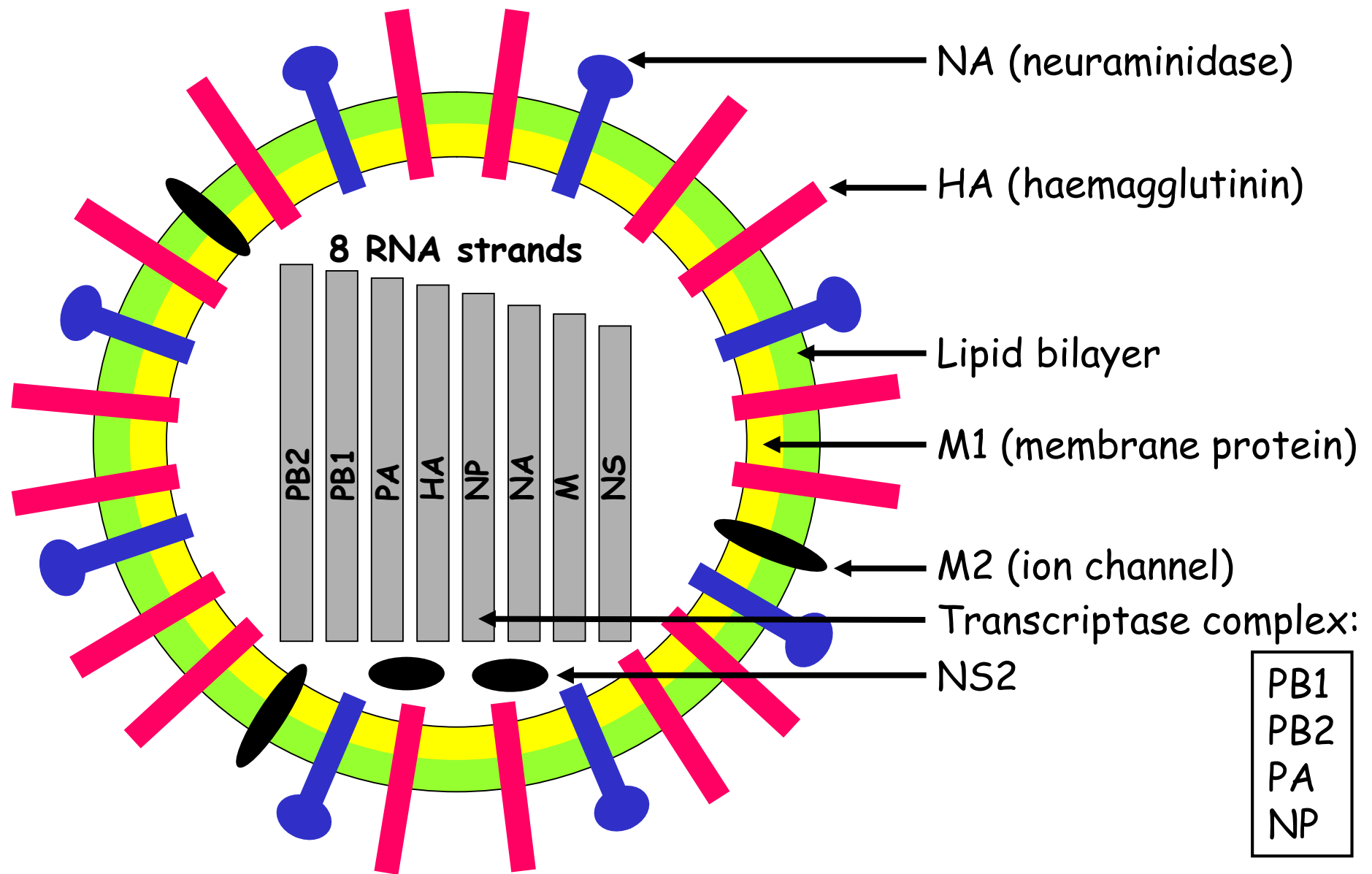


WHO Collaborating Centre for Reference and Research on Influenza
Melbourne, Australia



Three global health challenges



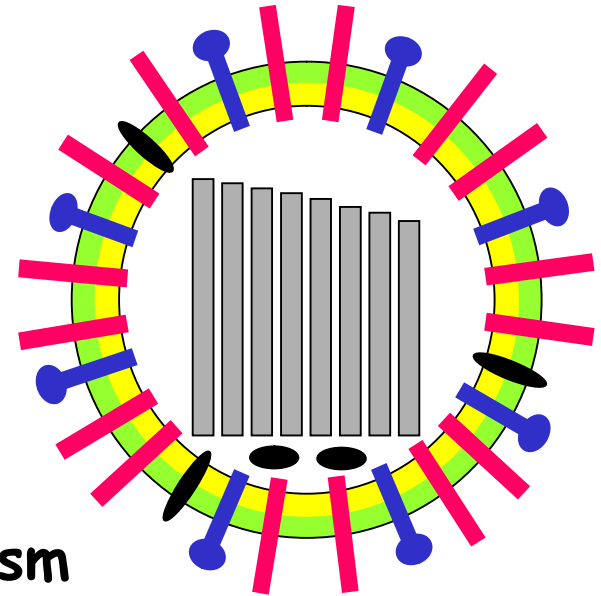


Adapted from De Jong et al, J Infect 2000

NS1 infected cell protein

Human influenza infection

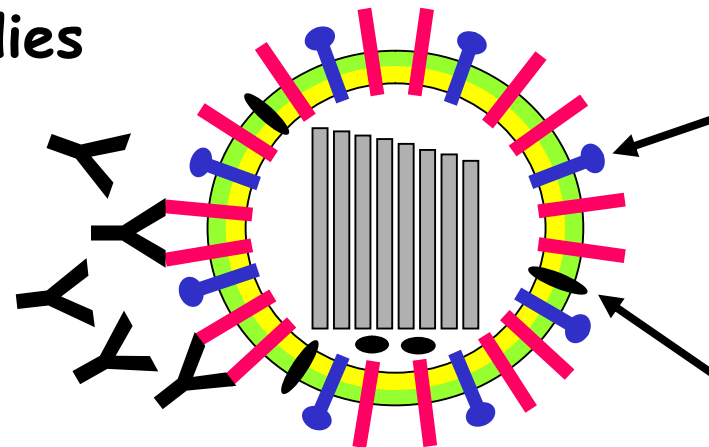
- Virus **HA** binds to sialic acid-containing receptors on epithelial cells lining respiratory tract
- Virus enters cell in a vesicle and uses **HA** and **M2** to release RNA into cytoplasm
- Virus uses **polymerase complex** and cell machinery to replicate and produce new virus particles
- New viruses escape using **NA** to cleave sialic acid:
 - releases viruses from cell surface
 - prevents virus clumping
 - facilitates dispersion through mucus



Specific prevention and treatment of influenza

Vaccines induce host to make antibodies against HA

Antibodies stop virus from infecting cells



Antiviral drugs

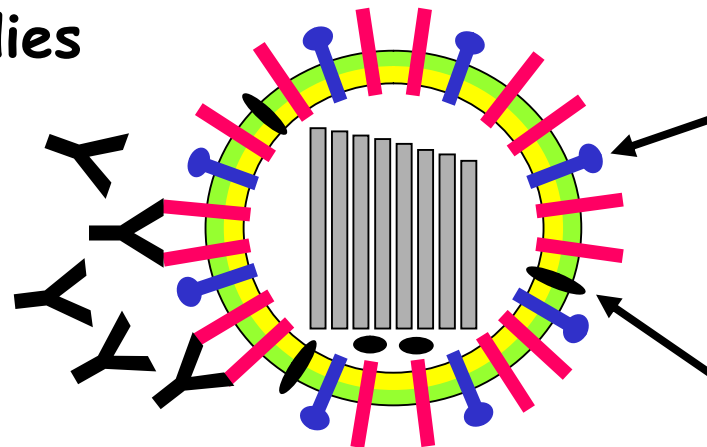
NA inhibitors block virus release from infected cell

M2 inhibitors block viral RNA release into cytoplasm of infected cell

Specific prevention and treatment of influenza

Vaccines induce host to make antibodies against HA

Antibodies stop virus from infecting cells



Antiviral drugs

NA inhibitors block virus release from infected cell

M2 inhibitors block viral RNA release into cytoplasm of infected cell

So why is influenza a problem?

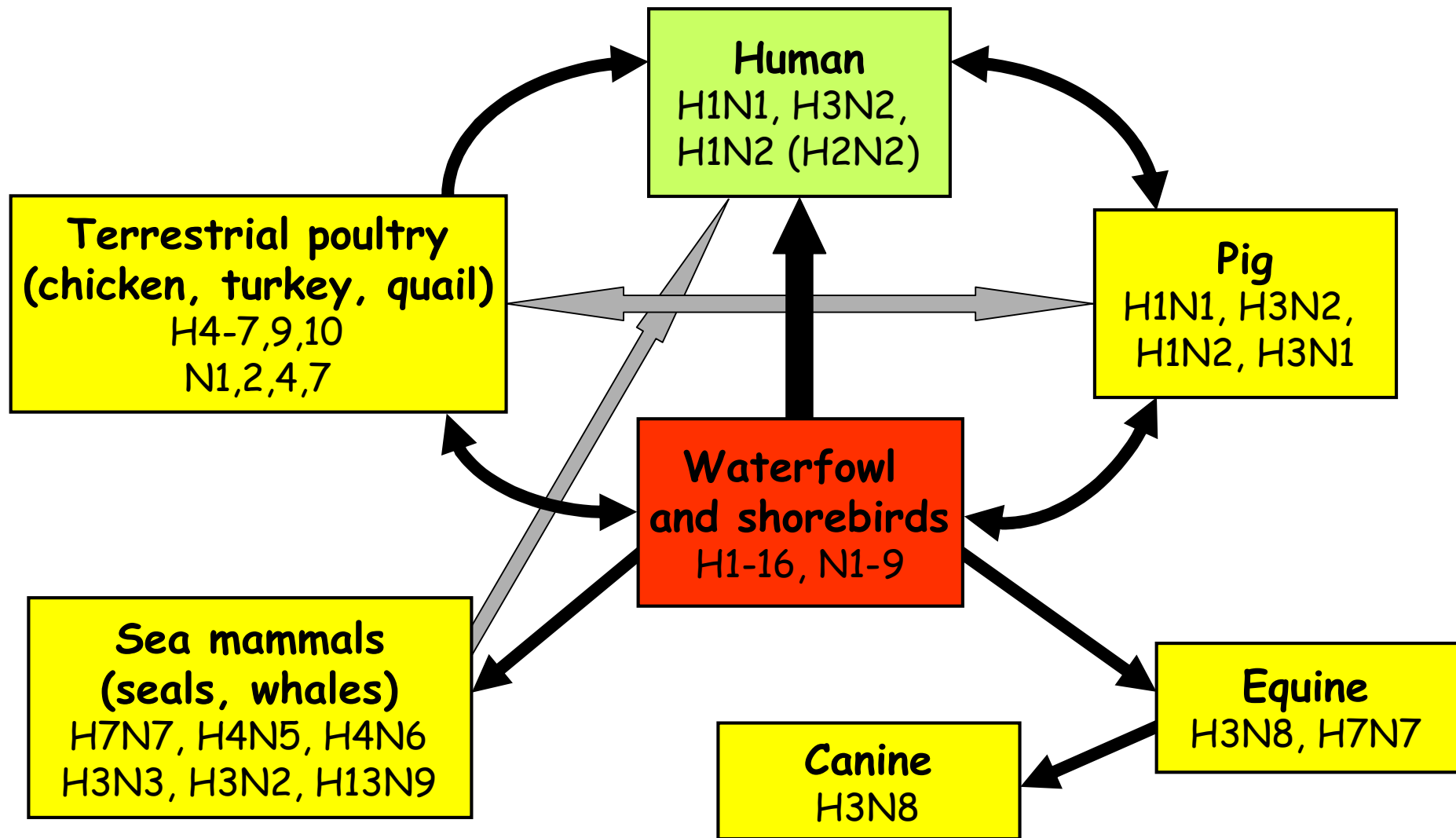
Virus variability

Three types of influenza virus infect humans

Type	Subtype	Natural host	Variability	Disease
A	H1N1 (H1N2) (H2N2) H3N2	Avian (others)	High	Most epidemics All pandemics
B	-	Human only	Moderate	Some epidemics
C	-	Human (pig)	None	Mild

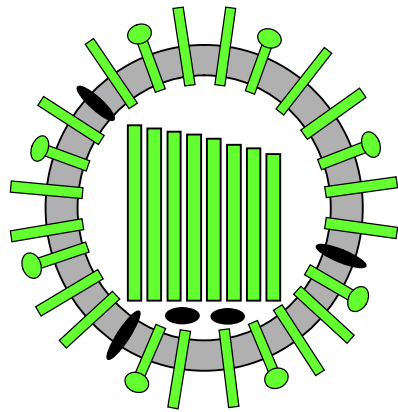
- Subtypes are named according to their HA and NA group
- The current influenza vaccine contains:
 - an A/H1N1 virus
 - an A/H3N2 virus
 - a B virus

Interspecies transmission of influenza A virus

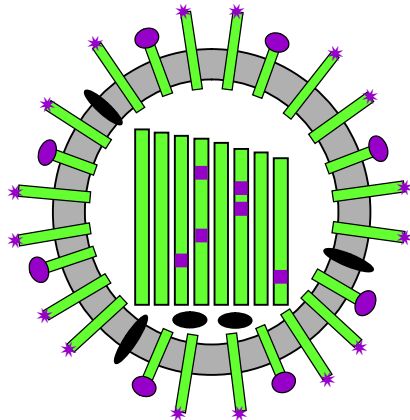


Development of new influenza A viruses

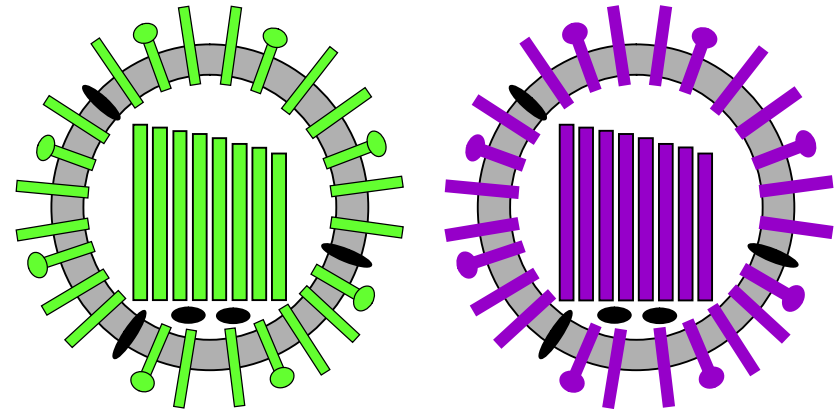
Mutation



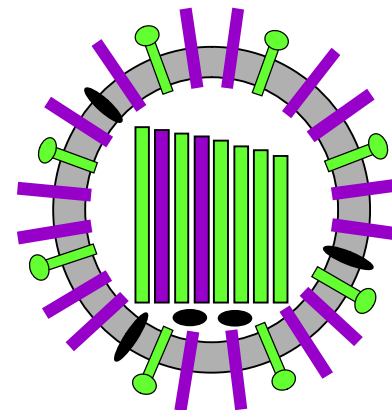
Random genetic changes, immune selected



Reassortment

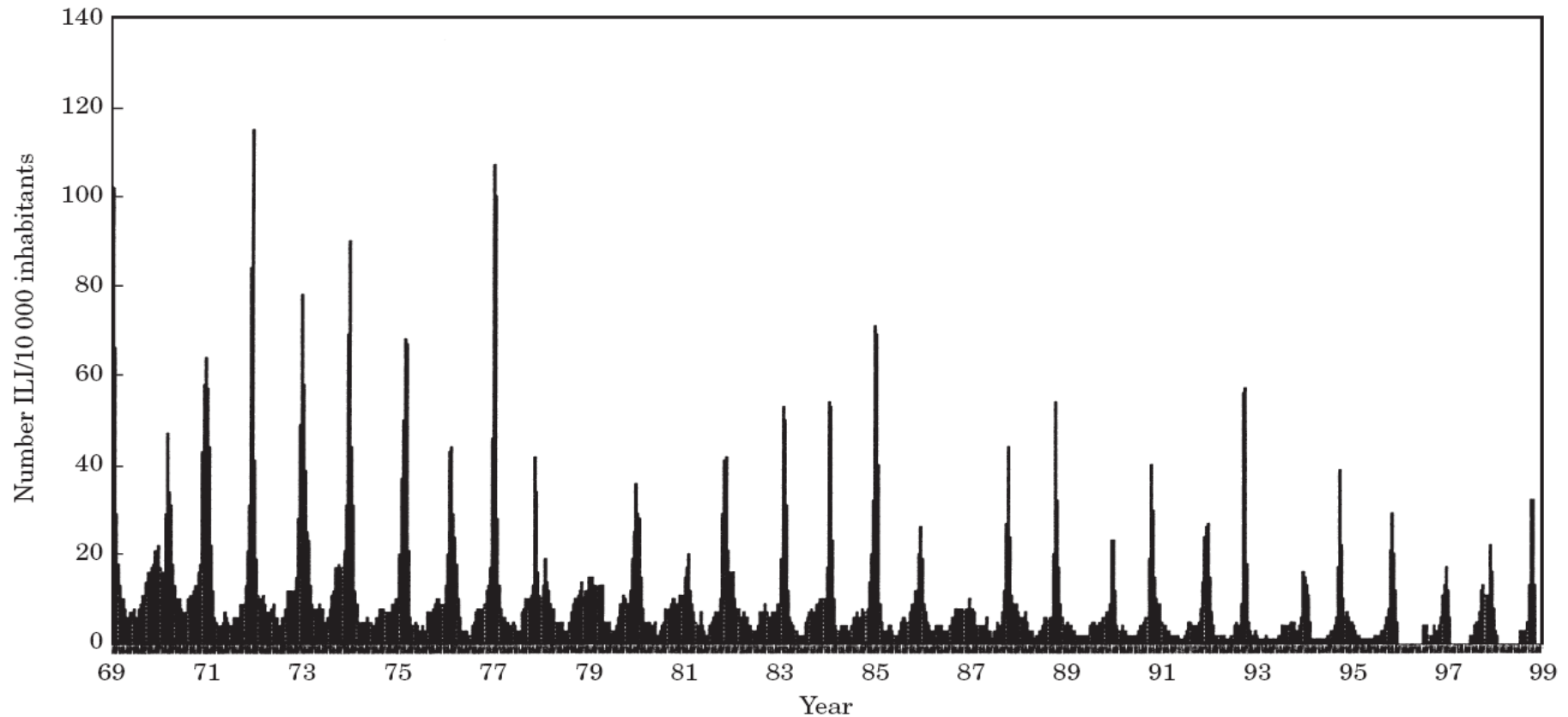


Genome shuffling when two viruses infect one cell



Seasonal influenza surveillance

Seasonality of human influenza infection



ILI per 10,000 inhabitants per week among patients presenting to general practices in The Netherlands

De Jong et al, J. Infect. (2000)

WHO Global Influenza Surveillance Network



- 124 WHO National Influenza Centres in 95 countries
- 10 WHO H5 Reference Laboratories in 7 countries
- **4 WHO Collaborating Centres for Influenza**
- 3 key reference/regulatory laboratories

National Influenza Centres
H5 Reference Laboratories
Other diagnostic laboratories

Specimens & virus isolates
Epidemiological data

Collaborating Centres
Regulatory/Reference Labs
Vaccine manufacturers

Strain analyses, sequences
Reference reagents
Vaccine recommendations
Candidate vaccine strains
Modified viruses

Seasonal influenza vaccines

WHO recommendations for seasonal vaccines

Year	Month	A/H1N1	A/H3N2	B
1997	February	A/Bayern/7/95	A/Wuhan/359/95	B/Beijing/184/93
	September	A/Bayern/7/95	A/Sydney/5/97	B/Beijing/184/93
1998	February	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93
	September	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93
1999	February	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93
	September	A/New Caledonia/20/99	A/Moscow/10/99	B/Beijing/184/93
2000	February	A/New Caledonia/20/99	A/Moscow/10/99	B/Beijing/184/93
	September	A/New Caledonia/20/99	A/Moscow/10/99	B/Sichuan/379/99
2001	February	A/New Caledonia/20/99	A/Moscow/10/99	B/Sichuan/379/99
	September	A/New Caledonia/20/99	A/Moscow/10/99	B/Sichuan/379/99
2002	February	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
	September	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
2003	February	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
	September	A/New Caledonia/20/99	A/Fujian/411/2002	B/Hong Kong/330/2001
2004	February	A/New Caledonia/20/99	A/Fujian/411/2002	B/Shanghai/361/2002
	September	A/New Caledonia/20/99	A/Wellington/1/2004	B/Shanghai/361/2002
2005	February	A/New Caledonia/20/99	A/California/7/2004	B/Shanghai/361/2002
	September	A/New Caledonia/20/99	A/California/7/2004	B/Malaysia/2506/2004
2006	February	A/New Caledonia/20/99	A/Wisconsin/67/2005	B/Malaysia/2506/2004
	September	A/New Caledonia/20/99	A/Wisconsin/67/2005	B/Malaysia/2506/2004
2007	February	A/Solomon Islands/3/2006	A/Wisconsin/67/2005	B/Malaysia/2506/2004
	September	A/Solomon Islands/3/2006	A/Brisbane/10/2007	B/Florida/4/2006
2008	February	A/Brisbane/59/2007	A/Brisbane/10/2007	B/Florida/4/2006 (Bris/3/07)

Antiviral drug sensitivity

Class	Drug	Assay	A(H1N1)	A(H3N2)	B
M2 channel blockers	Amantadine	Sequence	variable	mostly resistant	n/a
	Rimantidine				
NA inhibitors	Oseltamivir	Sequence & enzyme inhibition	variable*	sensitive	sensitive
	Zanamivir		sensitive	sensitive	sensitive

* Since October 2007

Oseltamivir resistance in A(H1N1) isolates (September 2007 - 12 July 2008)

WHO Region	No. H1N1 isolates tested	No. resistant*
EURO	3019	775 (26%)
AMRO	1581	259 (16%)
WPRO	2799	145 (5%)
SEARO	13	1 (8%)
AFRO	111	23 (21%)
EMRO	12	0
Total	7535	1203 (16%)

*Measured by enzyme inhibition and/or sequencing for H274Y mutation

<http://www.who.int/csr/disease/influenza/H1N1webupdate18072008.pdf>

Where do seasonal influenza viruses come from?

The Global Circulation of Seasonal Influenza A (H3N2) Viruses

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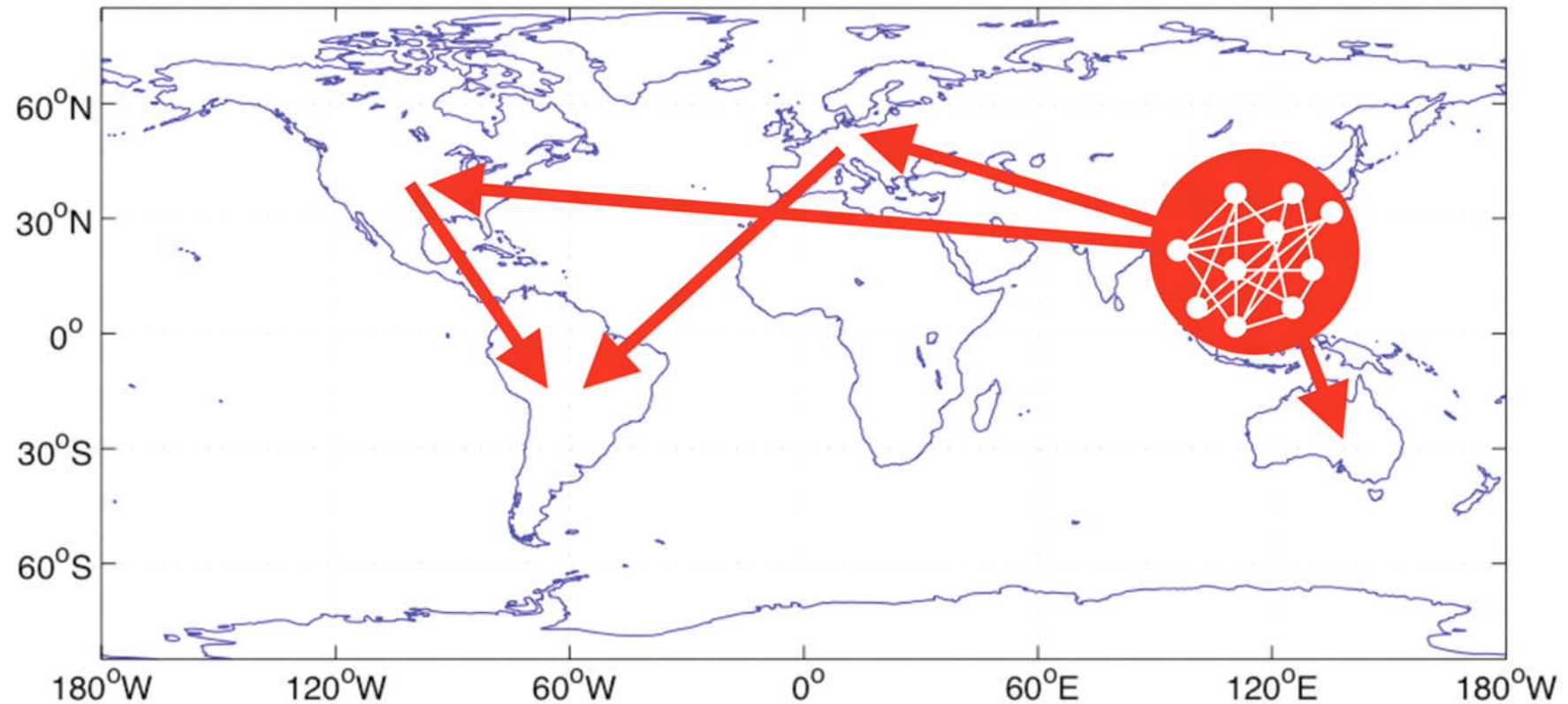
Antigenic and genetic analysis of the hemagglutinin of ~13,000 human influenza A (H3N2) viruses from six continents during 2002–2007 revealed that there was continuous circulation in east and Southeast Asia (E-SE Asia) via a region-wide network of temporally overlapping epidemics and that epidemics in the temperate regions were seeded from this network each year. Seed strains generally first reached Oceania, North America, and Europe, and later South America. This evidence suggests that once A (H3N2) viruses leave E-SE Asia, they are unlikely to contribute to long-term viral evolution. If the trends observed during this period are an accurate representation of overall patterns of spread, then the antigenic characteristics of A (H3N2) viruses outside E-SE Asia may be forecast each year based on surveillance within E-SE Asia, with consequent improvements to vaccine strain selection.

Influenza A (H3N2) virus is currently the major cause of human influenza morbidity and mortality worldwide. On average, influenza viruses infect 5 to 15% of the global population, resulting in ~500,000 deaths annually (*1*). Despite substantial progress in many areas of influenza research, questions such as when and to what extent the virus will change antigenically, and to what extent viruses spread globally, remain unanswered. A fundamental issue behind these questions is whether epidemics are the con-

sequence of low-level persistence of viruses from the previous epidemic or whether they are seeded from epidemics in other regions and, if so, from where (*2–8*).

Addressing these issues of local persistence and global spread is vitally important for designing optimal surveillance and control strategies. If epidemics were regularly seeded from an outside region and if the source region of seed strains could be identified, it may be possible to forecast which variants would appear in epidemics in seeded

Schematic of the dominant seeding hierarchy of seasonal A(H3N2) viruses



Russell et al. Science 320:340-346 (2008)

Global aviation network



10

25000

Hufnagel et al. Proc. Natl. Acad. Sci. USA 101: 15124-15129 (2004)

Reasons for influenza A virus variability

- Supply of new influenza viruses from other hosts and places
- Virus mutation and mixing due to segmented ssRNA genome
 - Immune or drug selection of variants, or co-selection with fitness-enhancing mutations
 - Existing immunity following infection or vaccination becomes ineffective
 - Seasonal influenza vaccine must be updated regularly to remain protective
 - New antiviral drugs may be required



The slaughter starts: Turkey carcasses are carried away in Suffolk, the centre of Britain's poultry industry

Daily Mail, 14 November 2007



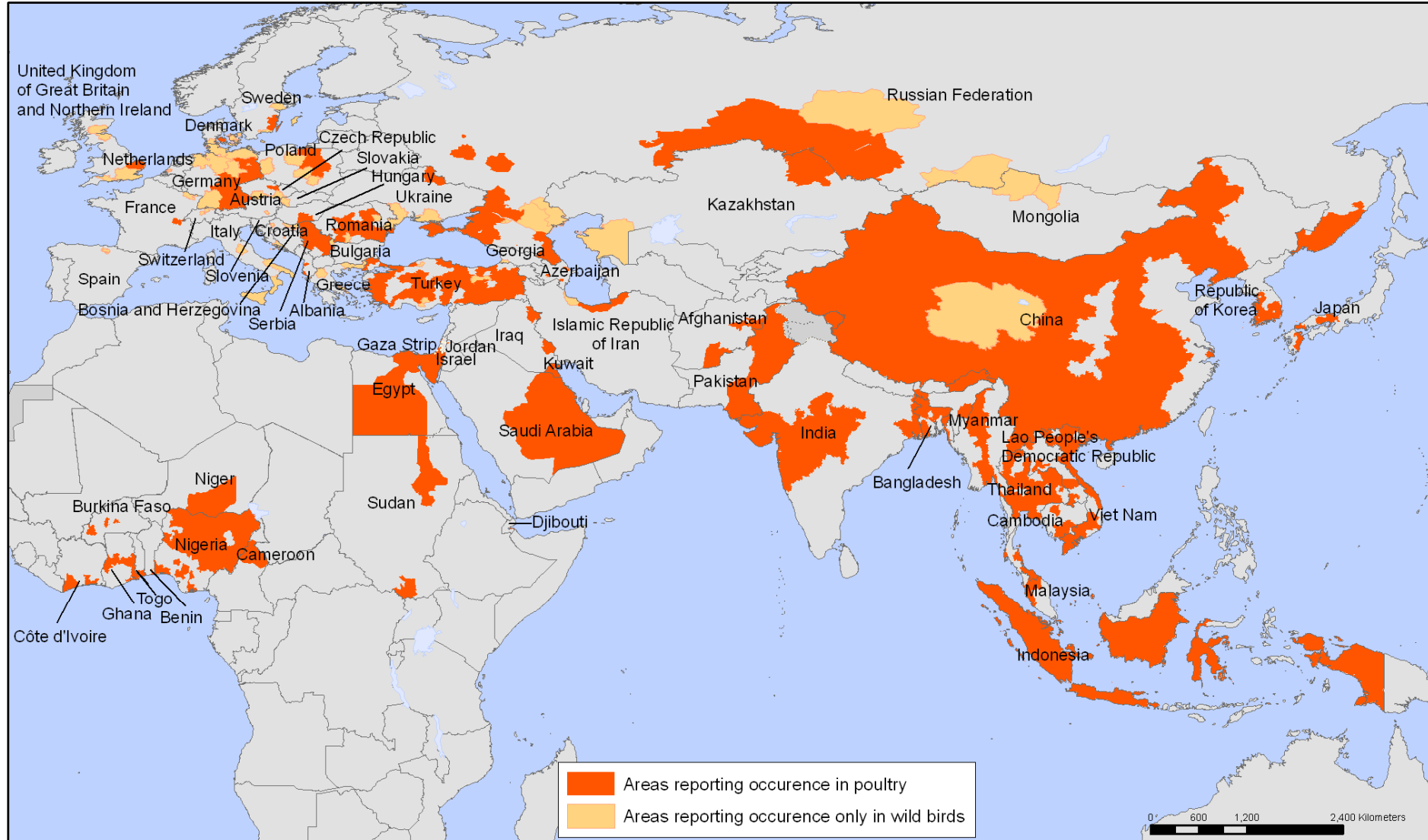
Dumped: Turkey carcasses are loaded into a lorry on Redgrave Park Farm



One more for the slaughter: Masked technicians take part in the cull

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

Status as of 14 April 2008
Latest available update



World Health Organization

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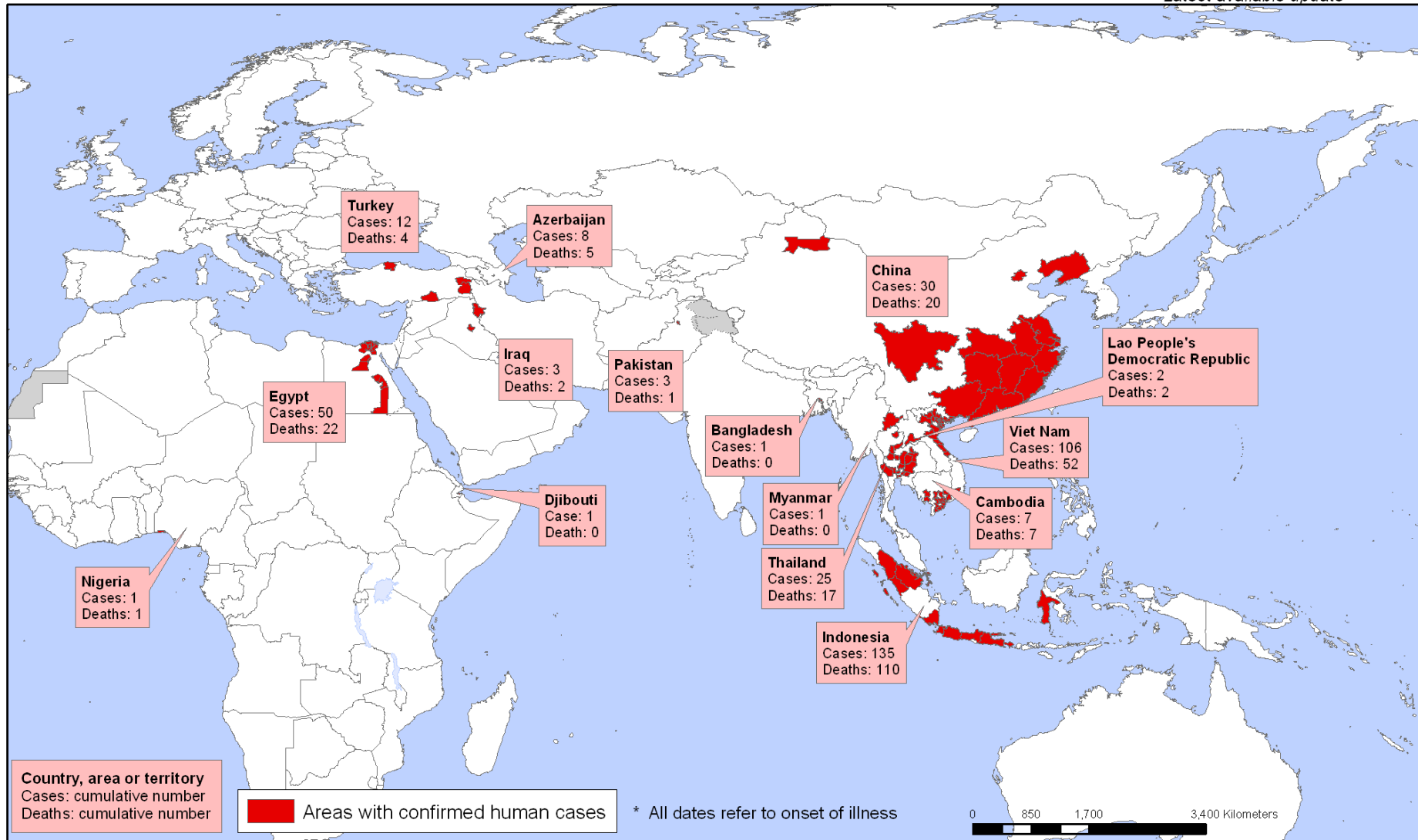
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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 Mapping and GIS
World Health Organization

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

Status as of 19 June 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.

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Map Production: Public Health Information and GIS
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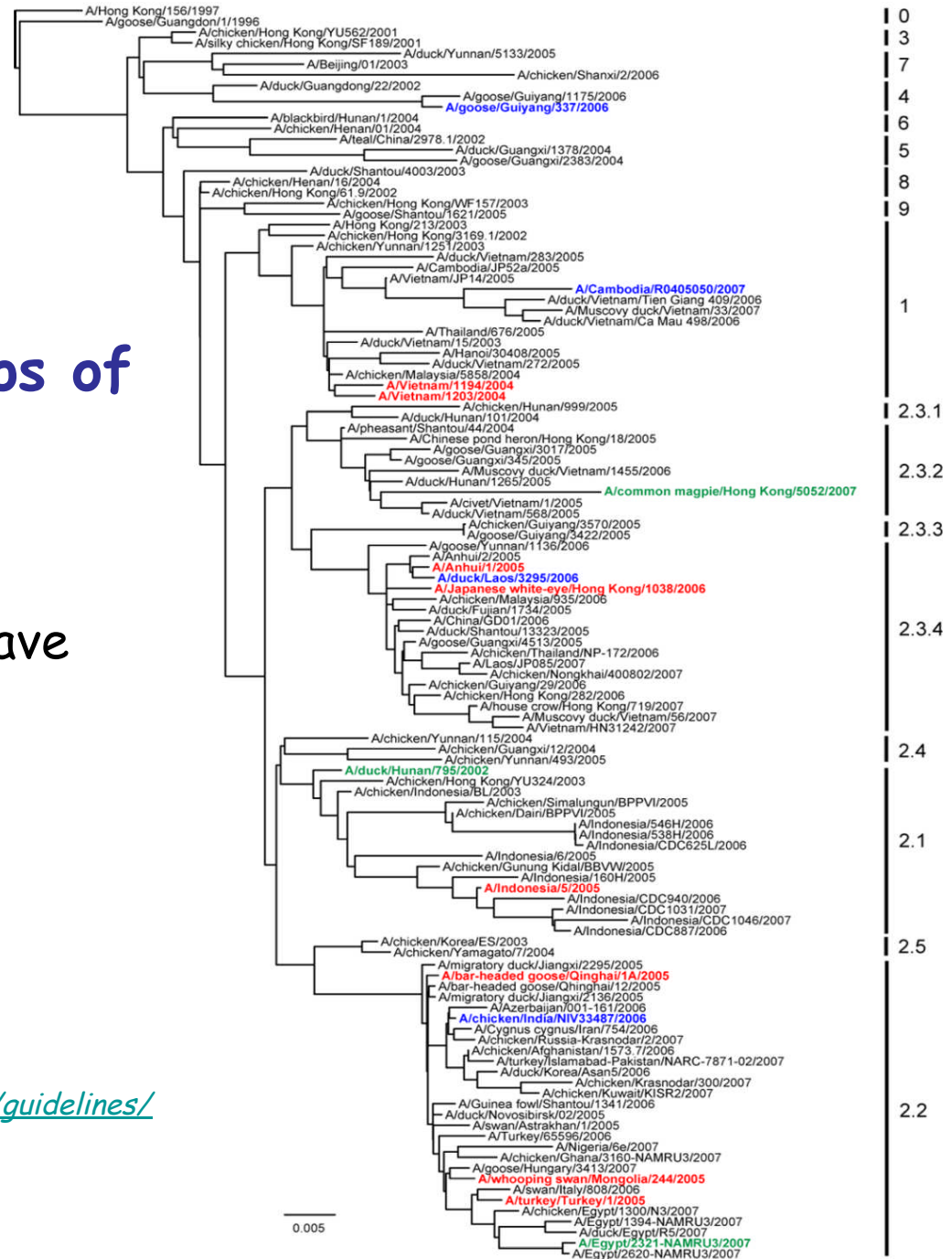
Properties of avian H5N1 influenza virus

- Shed by (sub-clinically) infected ducks
- 80-100% mortality in domestic poultry
- Probably originated in China \leq 1996, now antigenically divergent into multiple clades and subclades
- A million infected animals for every infected human
- Spread mainly through poultry trade, less via migratory birds
- ~60% mortality in humans (243 deaths/385 cases)
- Transmission to humans by close contact with infected birds
- Several family clusters but human-to-human transmission not yet sustained

Phylogenetic relationships of H5N1 virus HA genes

Clade 0, 1, 2 and 7 viruses have infected humans

http://www.who.int/csr/disease/avian_influenza/guidelines/H5VaccineVirusUpdate20080214.pdf



Will avian H5N1 give rise to a pandemic?

Characteristics of a pandemic influenza virus

- It spreads easily from person to person
- It spreads globally
- It causes severe disease
- People are not protected by their existing immunity to other influenza viruses
- Epidemiology can differ from seasonal influenza
- It might be:
 - a mutated form of a known animal influenza virus
 - a reassortant of animal and human viruses
 - an unknown influenza virus

Origins of previous pandemic influenza A viruses

Pandemic	Subtype	Origin	Pathogenicity
1918	H1N1	Avian - mutation?	High?
1957	H2N2	Avian/human reassortment	Low
1968	H3N2	Avian/human reassortment	Low

H3N2 is still circulating as an adapted human virus

H1N1 was replaced by H2N2 in 1957 then reappeared in Russian influenza epidemic of 1977-8 and continues to circulate

Reassortment in human influenza A viruses

<i>Gene</i>	1918	1957	1968
HA	H1	H2	H3
NA	N1	N2	N2
M1			
M2			
NS1			
NS2			
PB1			
PB2			
PA			
NP			
Status	Still circulating	Apparently extinct	Still circulating

Requirements for emergence of a new pandemic influenza virus

- New HA (and NA) to which humans are not immune
- Switch of HA specificity from $\alpha 2,3$ to $\alpha 2,6$ linked sialic acid
- Balanced HA and NA activities
- Efficient viral replication in upper respiratory tract (33°C) required for droplet transmission between humans (PB2?)
- Increased virulence (PB1)? Excess host cytokines?
- Ability to elicit sneezing?

Requirements for emergence of a new pandemic influenza virus from H5N1

- New HA (and NA) to which humans are not immune
H5N1
- Switch of HA specificity from $\alpha 2,3$ to $\alpha 2,6$ linked sialic acid
H5N1 prefers $\alpha 2,3$ linkage
- Balanced HA and NA activities
H5N2 is functional
- Efficient viral replication in upper respiratory tract (33°C)
required for droplet transmission between humans (PB2?)
H5N1 replicates inefficiently in mouse URT

Chen, Davis, Zhou, Cox & Donis. Genetic compatibility and virulence of reassortants derived from contemporary avian H5N1 and human H3N2 influenza A viruses. PLoS Pathogens 4 (2008)

Summary

- The problem with the influenza virus is its variability, especially its potential for sudden major change.
- Seasonal influenza is a serious illness which the WHO addresses by global monitoring and vaccine updating.
- An influenza pandemic remains a significant risk, from avian H5N1 virus and other animal influenza viruses.
- Technical advances in surveillance and the design of vaccines (and antivirals) will contribute to effective prevention and control of pandemic influenza.

WHO Collaborating Centre for Reference and Research on Influenza

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Thank you



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