

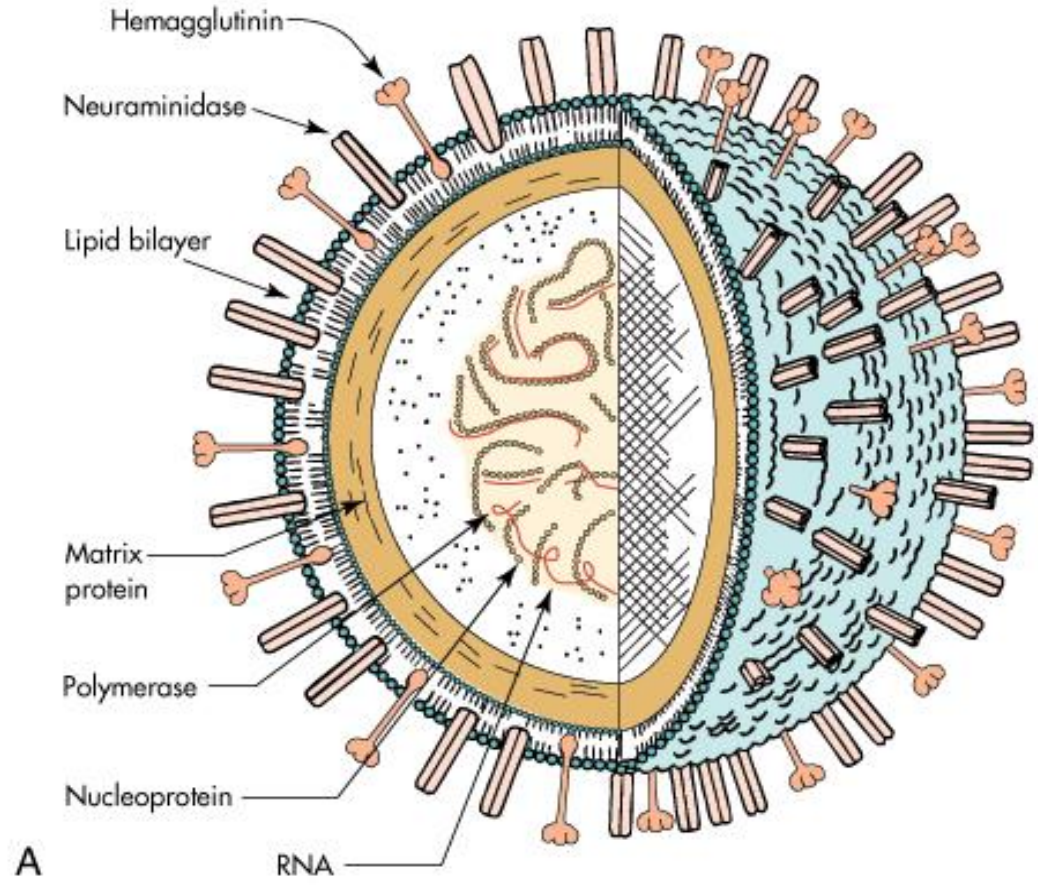
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# Chřipka

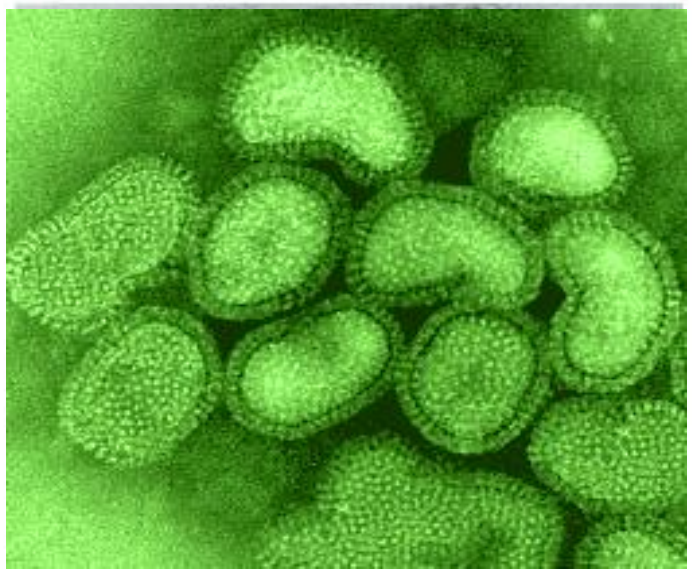
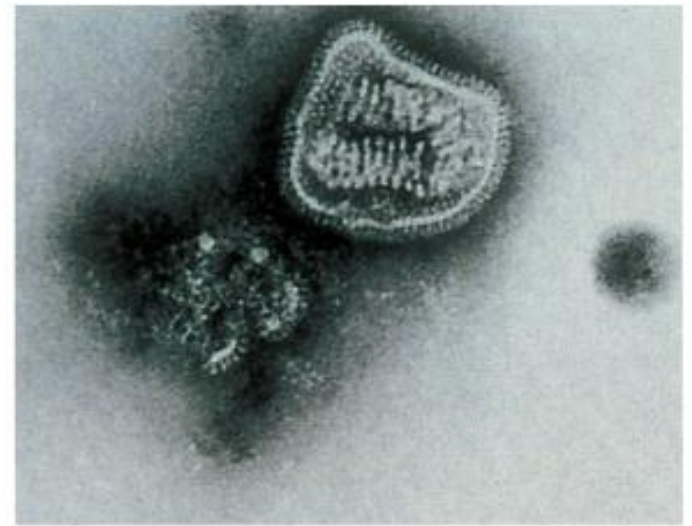
Influenza virus



# Influenza A virion

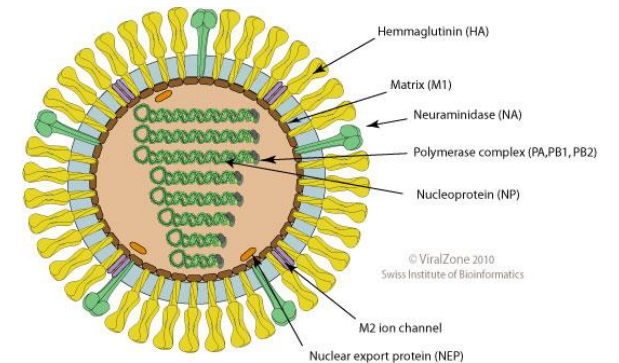


Virion diameter c.100 μm

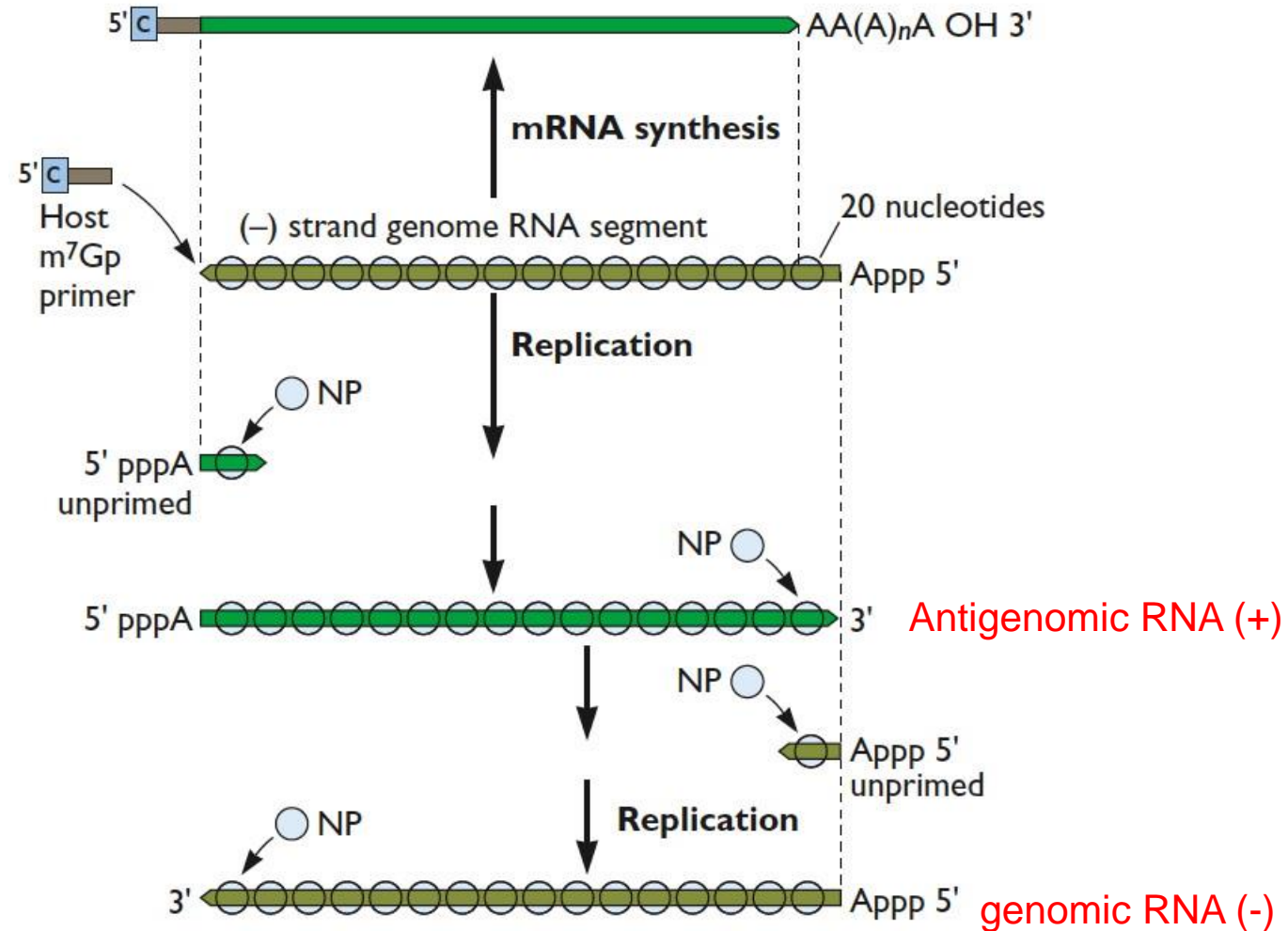


# Čel: *Orthomyxoviridae* *Influenza virus*

- hostitelé: ptáci, prase, člověk, kůň, pes a další obratlovci
- tropizmus: epitel respiračního traktu (savci), epitel intestinálního a respiračního traktu (ptáci)
- buněčné receptory: kyselina N-acetylneuraminová (kys. sialová)
- velikost 80-120 nm, obalený, segmentovaný (-)ssRNA lineární genom (13,5 kb)
- jediný (-)ssRNA virus replikující se v jádře
- 8 segmentů (velikost segmentu 890 až 2340 nt) kódujících 11 proteinů
  - u viru chřipky C pouze 7 segmentů
- každý RNA segment tvoří ribonukleoprotein (RNP komplex)
- Taxonomie: *Influenzavirus A* (člověk, prase, ptáci, kůň, netopýr, pes), B (člověk, mořští savci), C (člověk, prase), D (prase, dobytek)
- součástí virionu jsou i buněčné proteiny tubulin a cyklophilin A



# Influenza virus (transkripce a replikace)

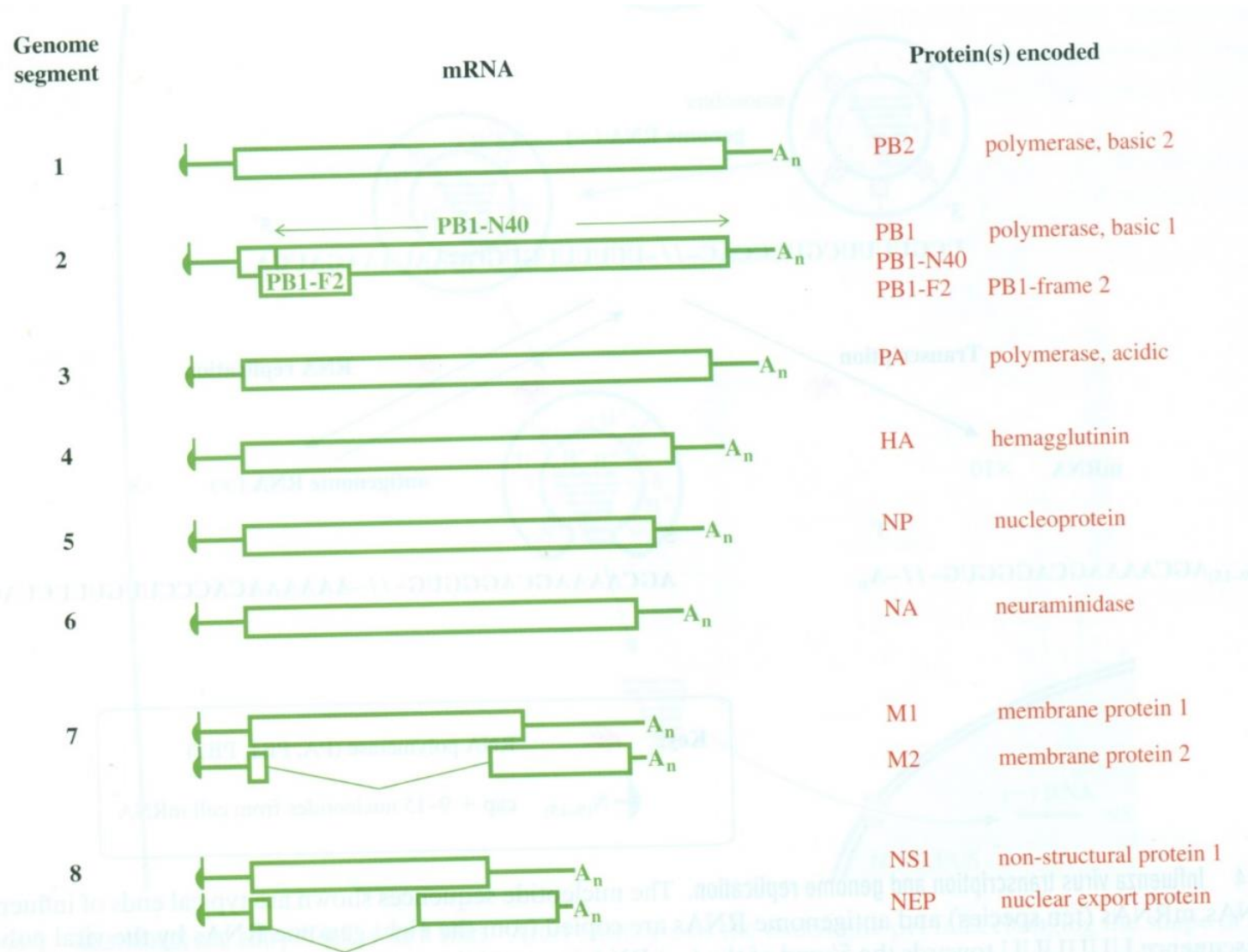


# Strategie replikace u influenza viru

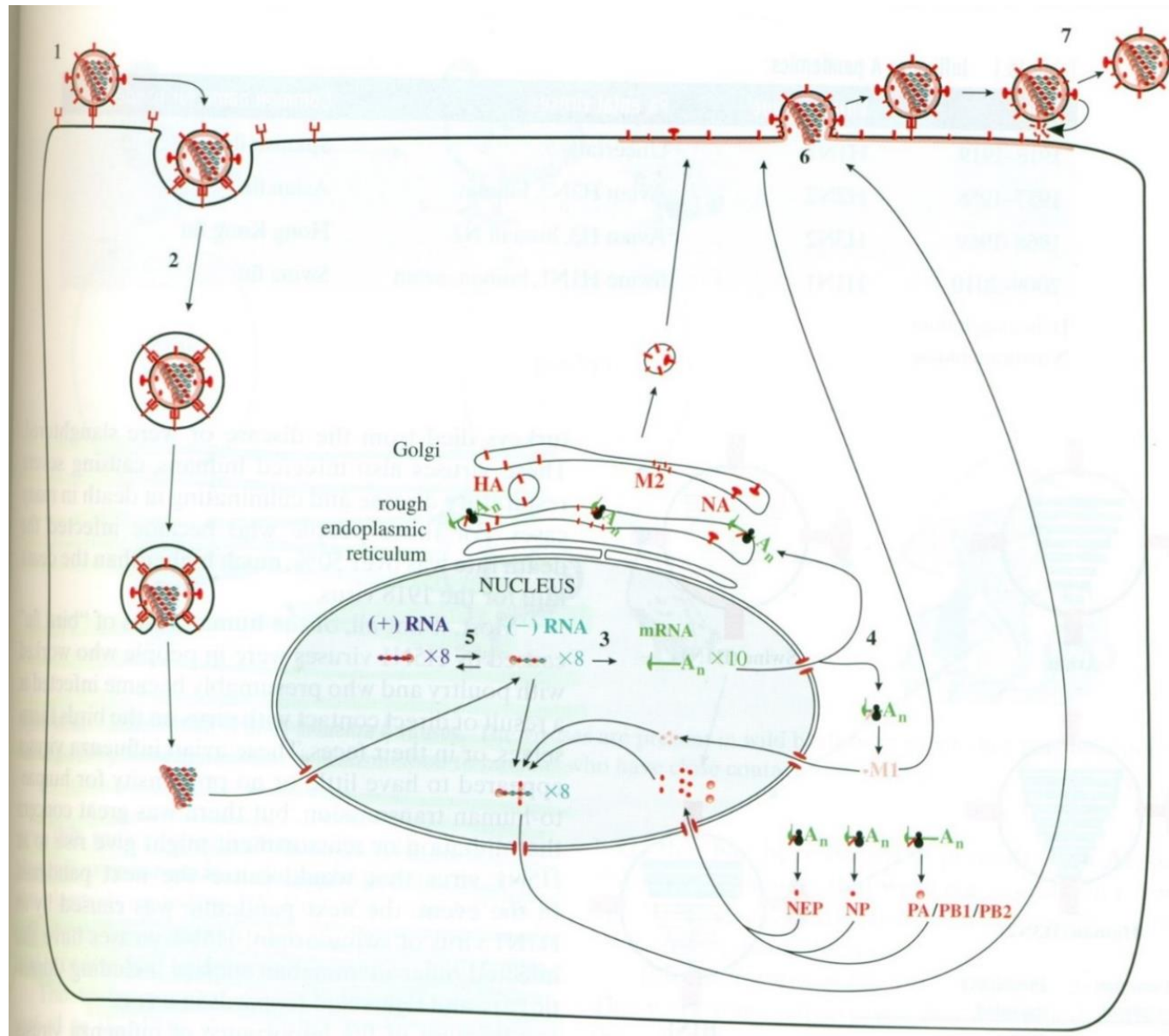
## Replikace probíhá v jádře

1. virus se spojí hemagglutininem (HA1) k receptoru kys. sialové host. buňky a spustí endocytózu
2. acidifikace uvnitř endozómu (změna konformace M2-pumpování H<sup>+</sup>, strmé snížení pH) způsobí fúzi obalu viru s membránou endozómu – RNP komplex putuje k jádru
3. **transkripce** genomických segmentů virovou RNA polymerázou produkuje mRNA
4. současně **replikace** antigenomic (+)ssRNA jako templát pro syntézu nových (-)ssRNA
5. Obalové proteiny (HA, NA, M2) jsou translatovány na ER a transportovány do GK, kde probíhají postranlační modifikace (M2 plní opačnou roli než při vstupu do buňky-pumpuje H<sup>+</sup> ven, aby nedošlo ke konformačním změnám HA komplexu)
6. zbylé proteiny jsou syntetizovány na volných ribozomech v cytoplazmě
7. sestavení viru a pučení na plazmatické membráně (RNP komplex se akumuluje pod CM, stejně jako transmembránové proteiny HA, NA, M2, **M1 protein se váže na CM, 'packaging signal' umožní integraci osmi RNA segmentů do nového virionu**)
8. po vypuštění viru přes CM je virus spojen s receptory přes HA, dokud neuraminidáza neodštěpí receptor a virus opustí buňku

# Organizace genomu viru chřipky



# Strategie replikace viru chřipky (shrnutí)



# Infekce vyvolané orthomyxoviry

Chřipka A (lidé a zvířata), B (lidé, sporadická onemocnění s lehčím průběhem), C-nezařazen, D-Pandemie člověka:

AH1N1(1918) – španělská, zemřelo až 40 mil. lidí

AH2N2 1957/58 ('asijská' chřipka,) >1 mil. lidí

AH3N2 1968/70 ('hongkongská' chřipka,) >1 mil. lidí

AH1N1 1977 ('ruská' chřipka)

všechny pandemické kmeny měly vloženy do svého genomu charakteristické úseky genomu ptačích chřipkových virů; vznikly tedy reasortací ptačích a savčích kmenů při koinfekci vnímavého hostitele (obvykle prasete jako tzv. 'mixing vessel').

Epidemiologie: sezónní charakter, epidemie (více jak 2000 nemocných na 100 000 obyvatel), v ČR podlehe chřipce 2000-3000 osob ročně

5-15% akutních infekcí hor. cest dýchacích, avšak až 80% komplikací

Patogenita: určována povrchovými antigeny:

**Hemagglutininy H (18 subtypů)** – vazba na povrch vnímavých buněk hor. cest dýchacích (H1, H2 a H3 u lidí)

**Neuraminidáza N (11 subtypů)** - umožňuje vniknutí viru do cytoplazmy a po syntéze nových virionů také opuštění hostitelské buňky

Antigenní drift – drobná změna ve struktuře některých povrchových antigenů, kombinace H a N zůstává shodná (sezónní charakter)

Antigenní shift – úplná změna antigenu H nebo N nebo obou – nepromořená populace-pandemie, interval asi 20 let



# Infekce vyvolané orthomyxoviry

**Přenos:** kapénkově (vysoce nakažlivé onemocnění)

**Inkubační doba:** od vniknutí do organismu k prvním příznakům trvá 24 až 48 hodin (nakažený člověk je zdrojem infekce ještě před vznikem prvních příznaků)

**Klinický obraz:** náhlý začátek - vysoká horečka (i přes 40°C, zimnice, bolest hlavy, svalů a kloubů), bolestivý suchý kašel, nechutenství, u malých dětí zvracení, průjem, někdy febrilní křeče

**Komplikace:** primární virová pneumonie (při srdečním onemocnění), bakteriální superinfekce pneumokoky nebo hemofily (záněty středouší u dětí nebo obličejových dutin u dospělých, bakteriální pneumonie), myokarditida

Rizika: osoby starší 65 let (s chronickým onemocněním), gravidní ženy, imunokompromitovaní lidé

**Prevence:**

- (1) Vakcinace – inaktivovaná trivakcína (2 subtypy chřipky A a 1 subtyp chřipky B), každoročně, složení se mění na základě cirkulujících kmenů, obvykle 1 dávka
- (2) Hygiena – mytí rukou, výměna kapesníků, izolace pacienta

# Infekce vyvolané orthomyxoviry

**Diagnostika:** izolace viru na TK nebo kuřecích embryích (výtěr z nasofaryngu), určení kmenů (HIT), sérologie (KFR, HIT), RT-PCR

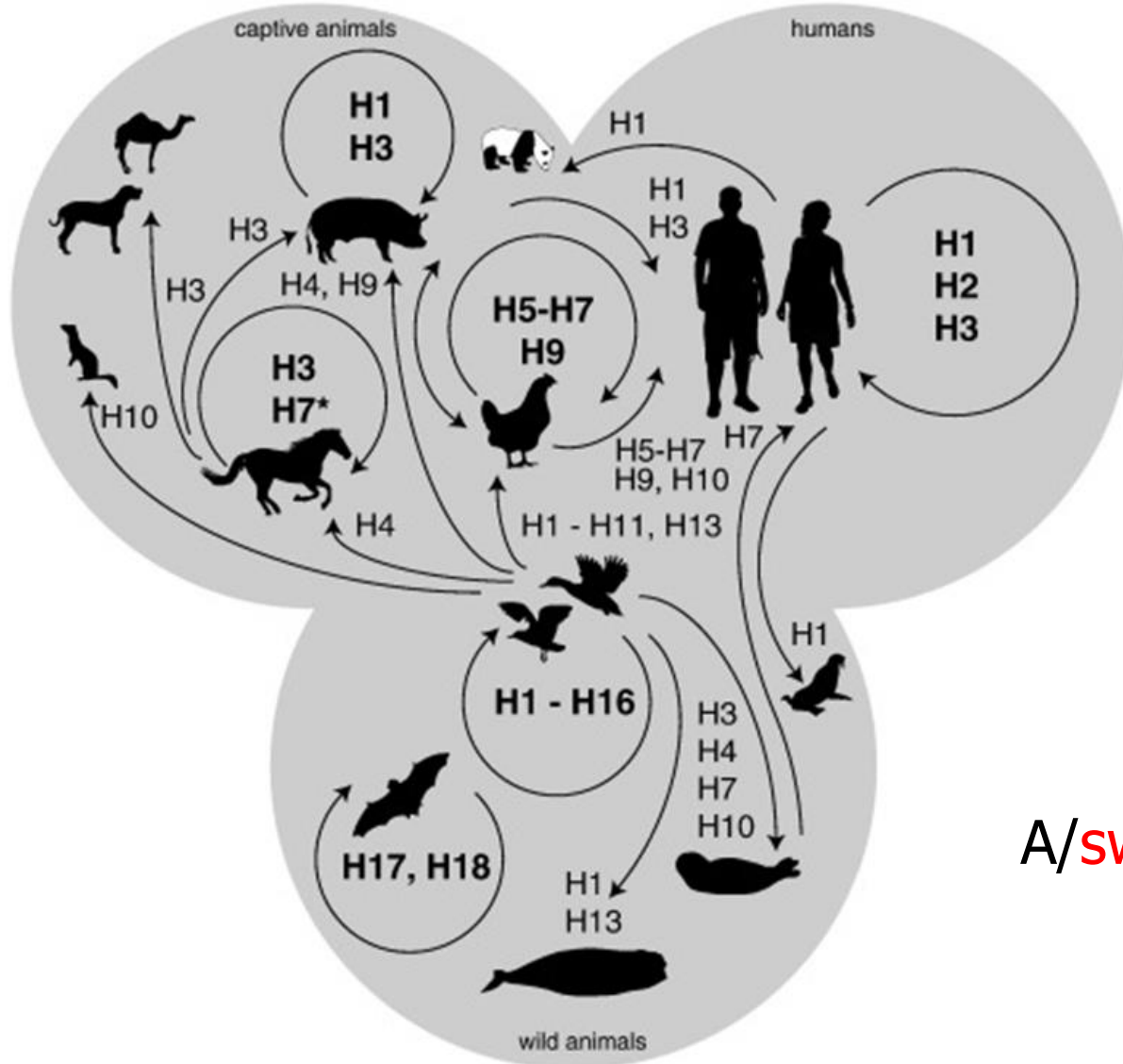
**Léčba:** symptomatická (paracetamol, antitusika)

Antivirotika (léčba/profylaxe): léčba nejpozději do dvou dnů od počátku onemocnění

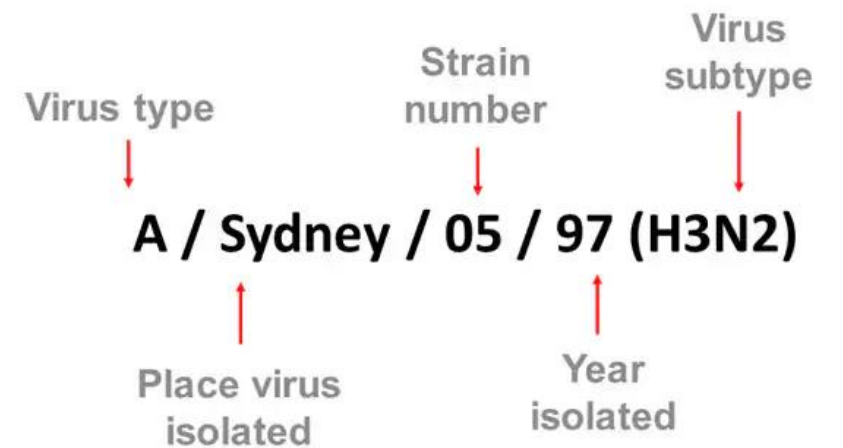
- (1) Blokátory proteinového kanálku M chřipkového viru A- zástava replikace virů
- (2) Inhibitory neuraminidázy – znemožňují virům opustit hostitelskou buňku (zanamivir-Relenza/inhalátor/dospělí; Oseltamivir-Tamiflu/tobolky/děti)

Národní protipandemický plán – organizační opatření, jak postupovat v případě vzniku chřipkové pandemie (pandemická vakcína, zásoba antivirotik a jejich distribuce)

# Hostitelé chřipky ve vztahu k hemaglutininu

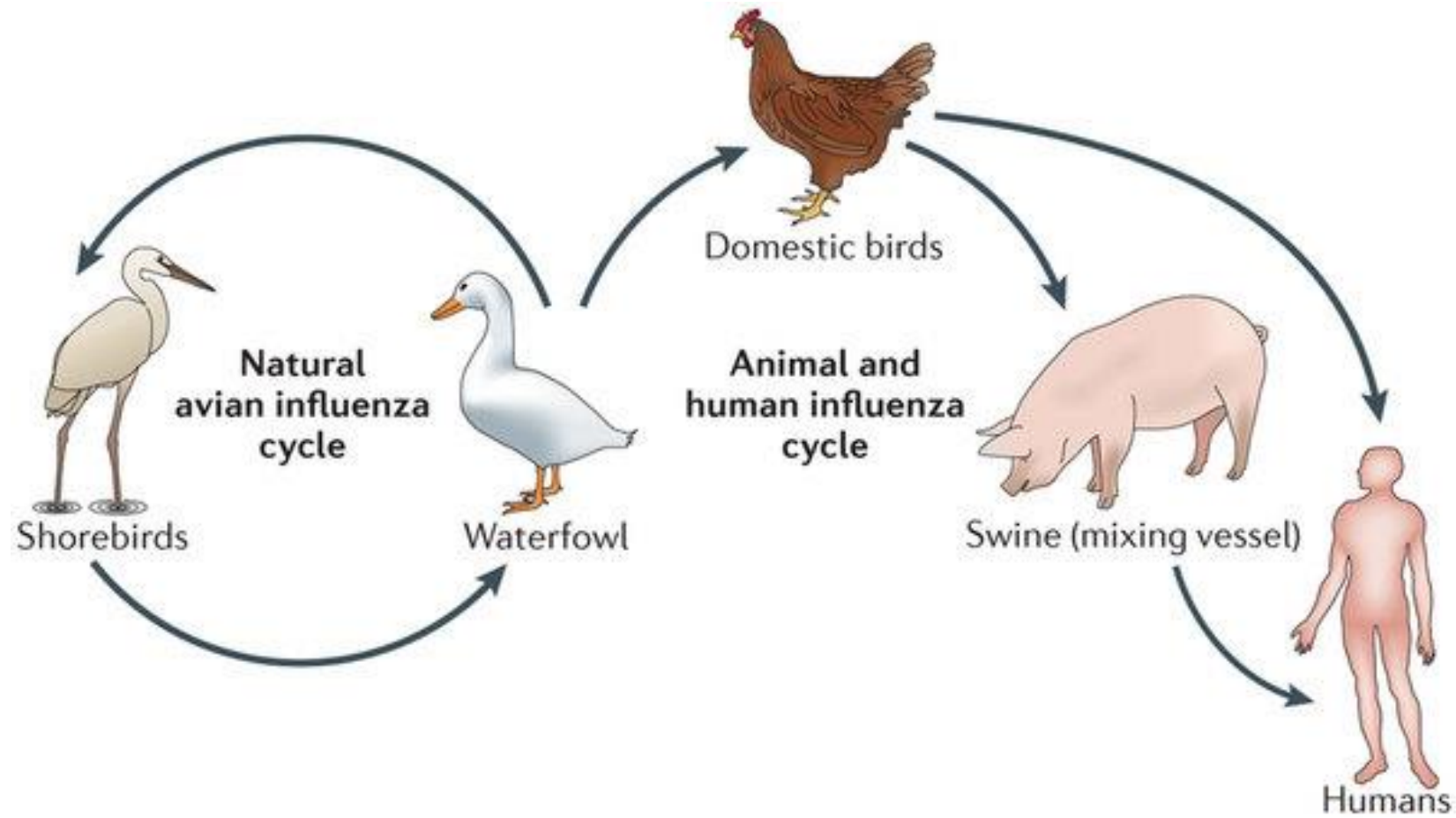


Understanding the naming of flu viruses

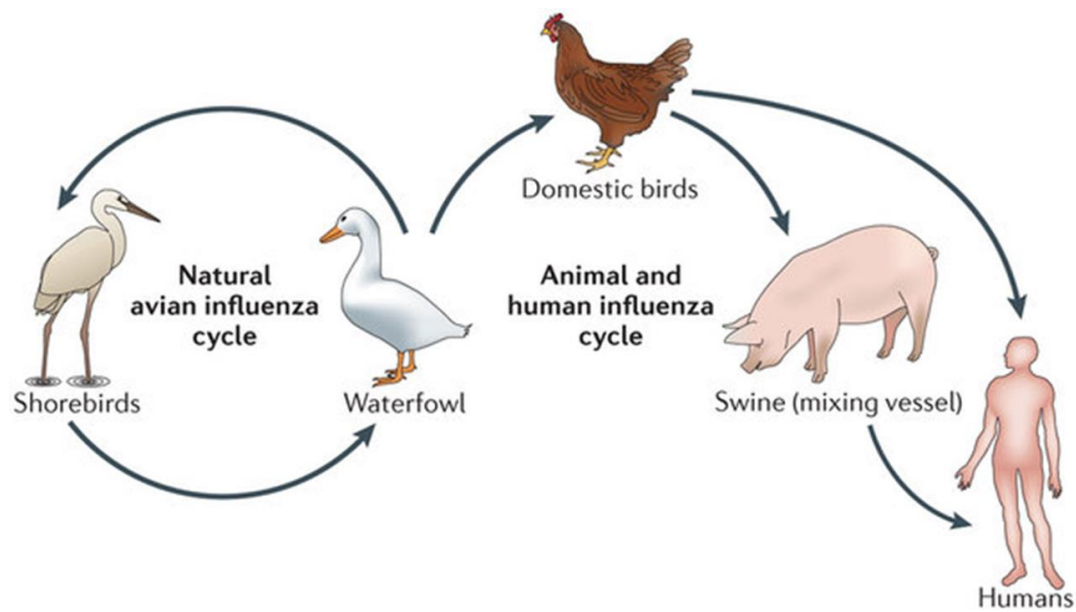


A/**swine**/South Dakota/152B/2009 (H1N2)

# Cirkulace chřipky u obratlovců



# Cirkulace chřipky u obratlovců

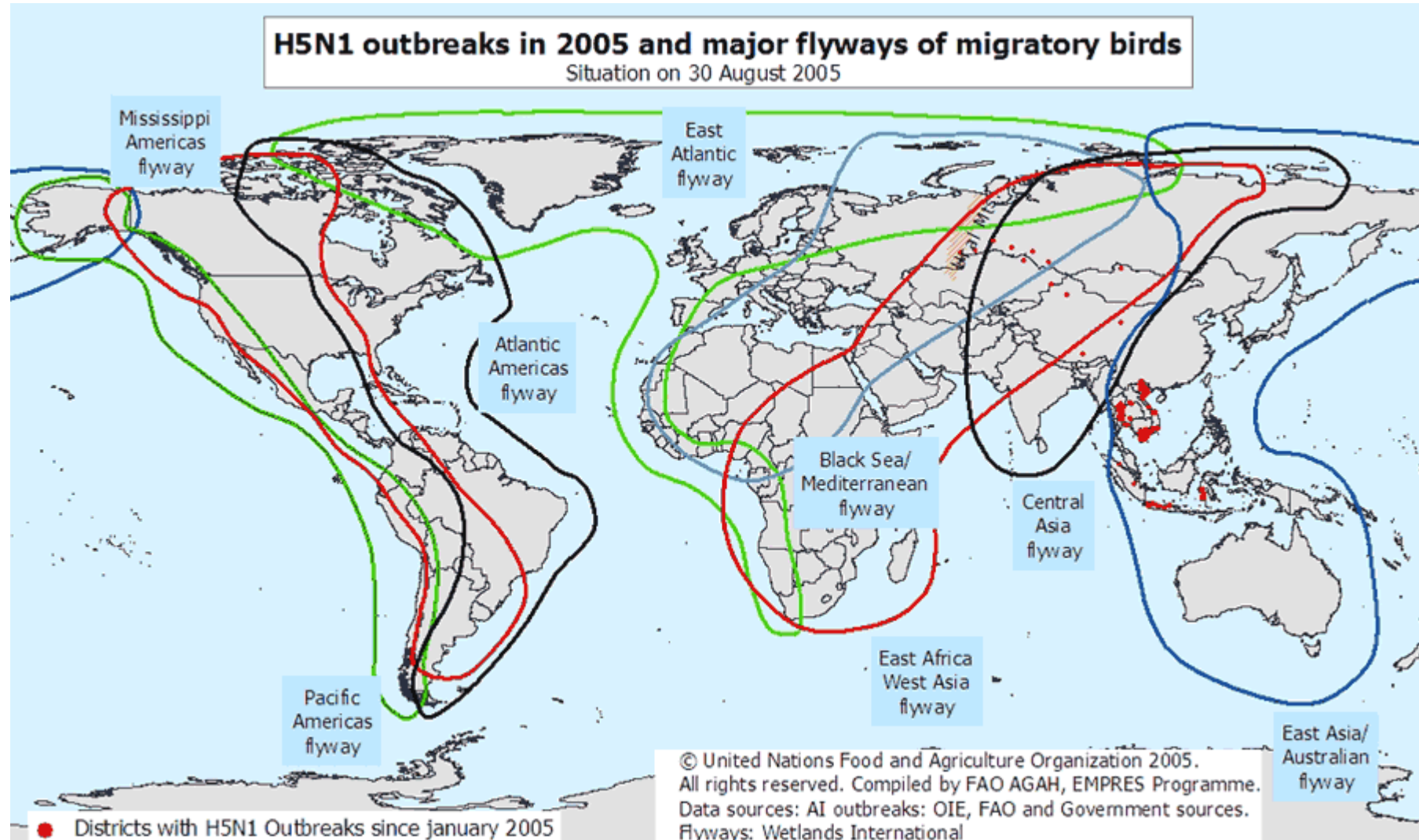


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Mixing vessel

# Role of migratory birds in spread of H5N1



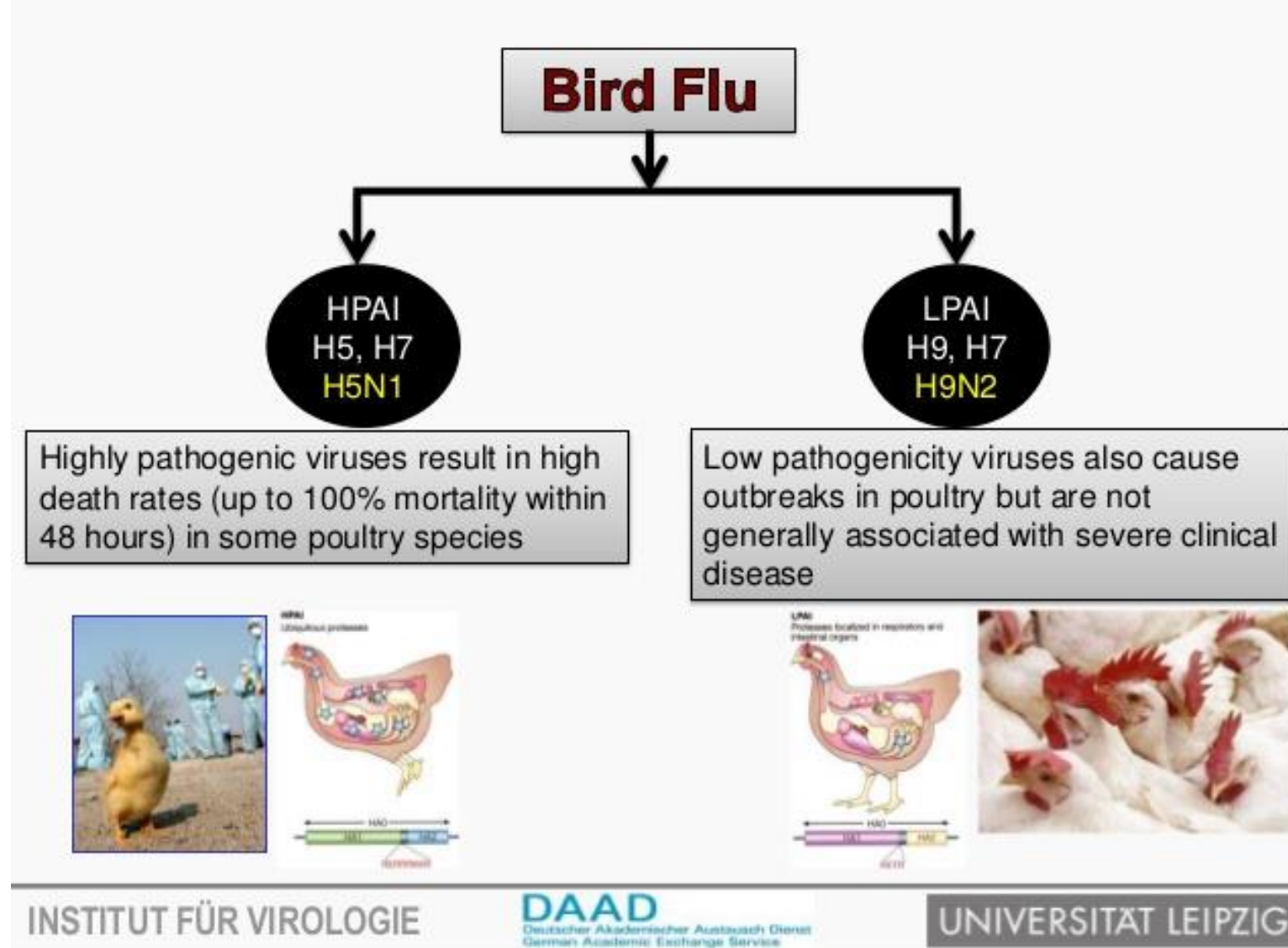
# Live animal (wet) markets



Dlouhodobé epidemické a pandemické riziko představuje úzký kontakt lidí s drůbeží, prasaty a dalšími obratlovci v jihovýchodní Asii (společné příbytky, kontakt mezi ptáky a prasaty).

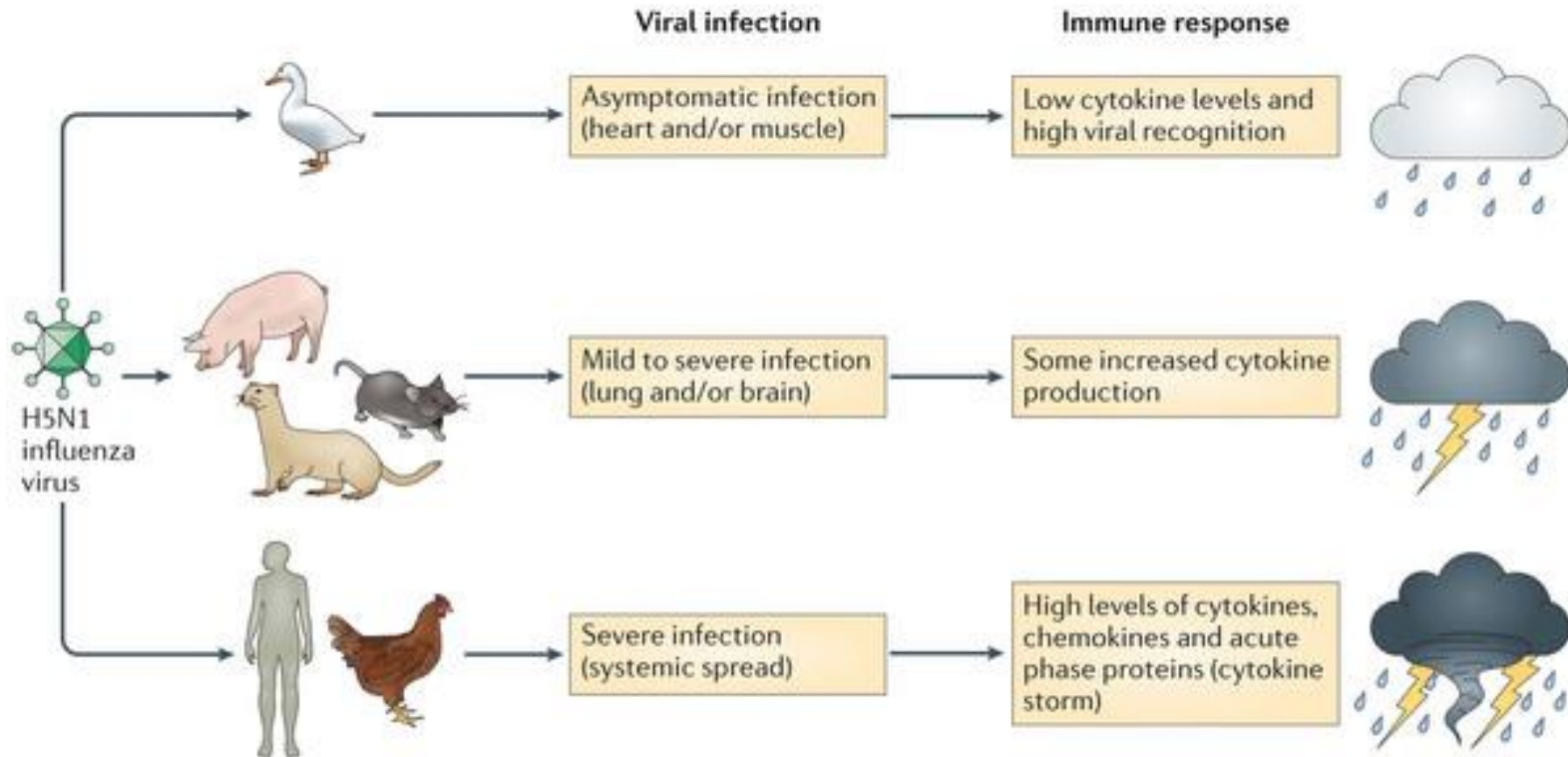


# High pathogenic and low pathogenic bird influenza

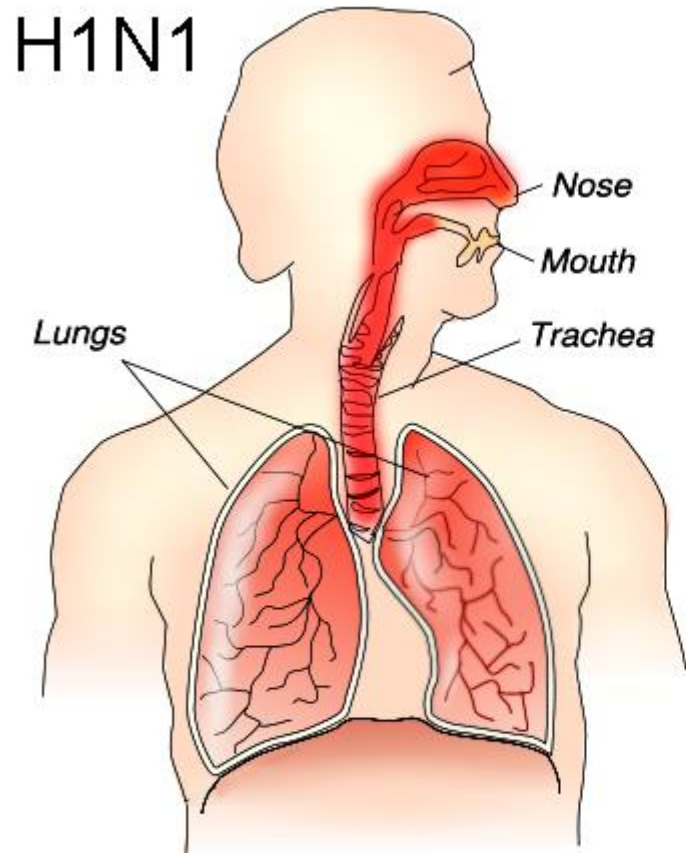




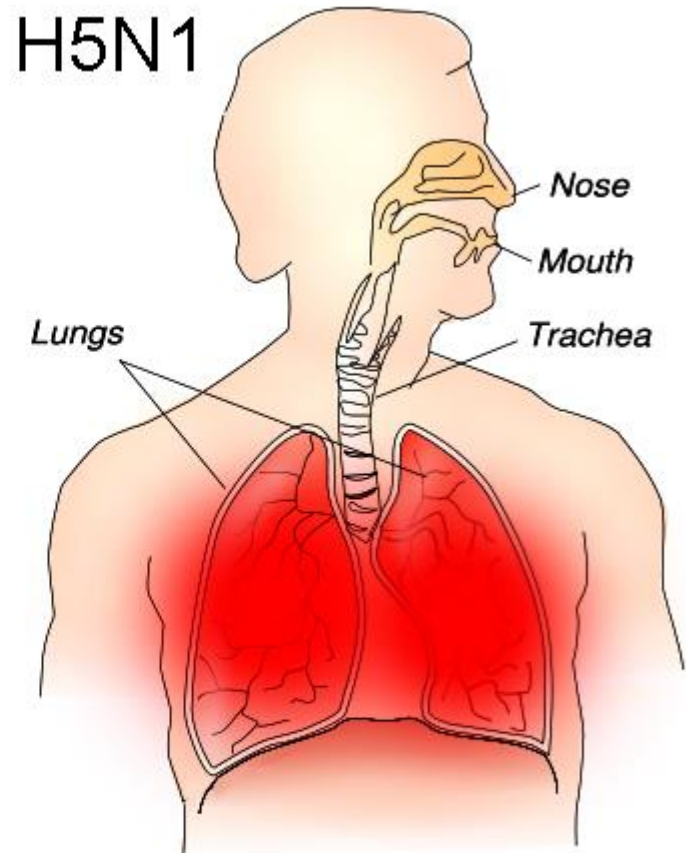
# Response of immune system to H5N1 infection



## Rozdíl v klinické manifestaci u H1N1 a H5N1



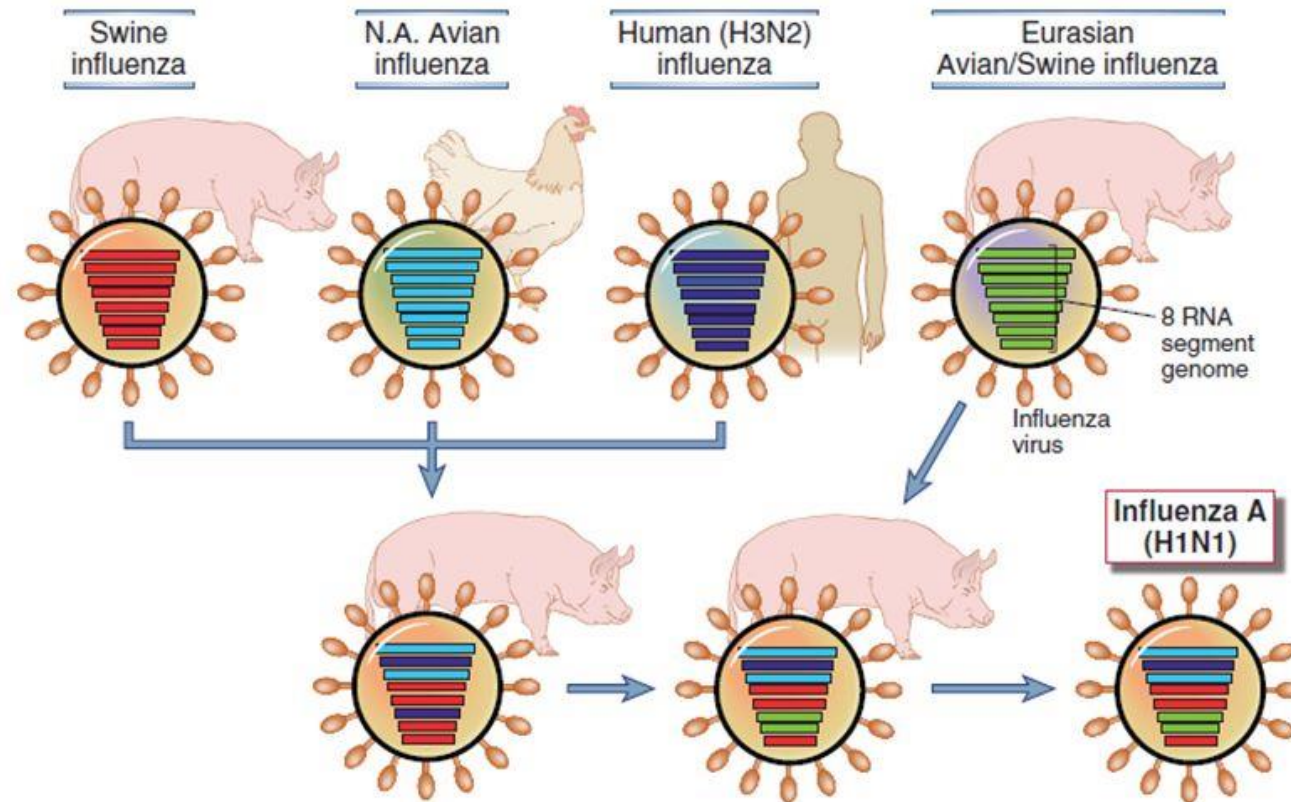
Easily spread  
Rarely fatal



Spreads slowly  
Often fatal

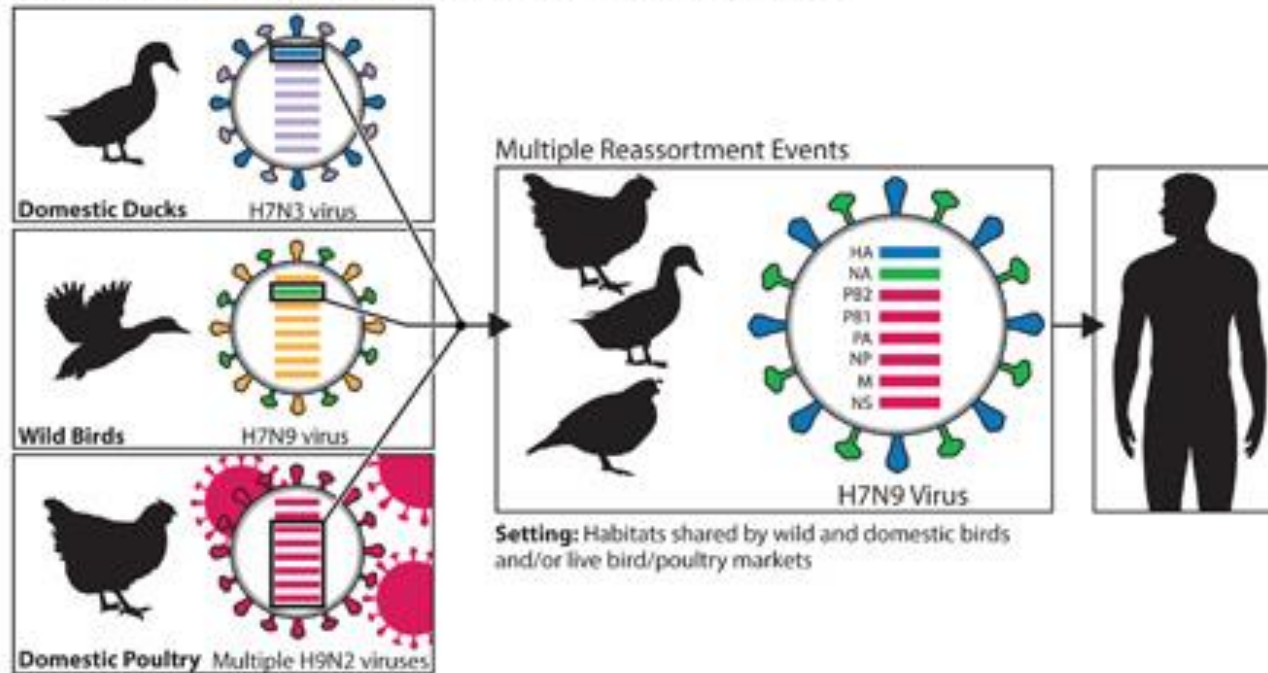
# Evolution of H1N1 (2009)

**Generation of new influenza virus strains by genetic recombination (antigenic shift)**



# Evolution of H7N9 (2013)

## Genetic Evolution of H7N9 Virus in China, 2013



The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks, its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.



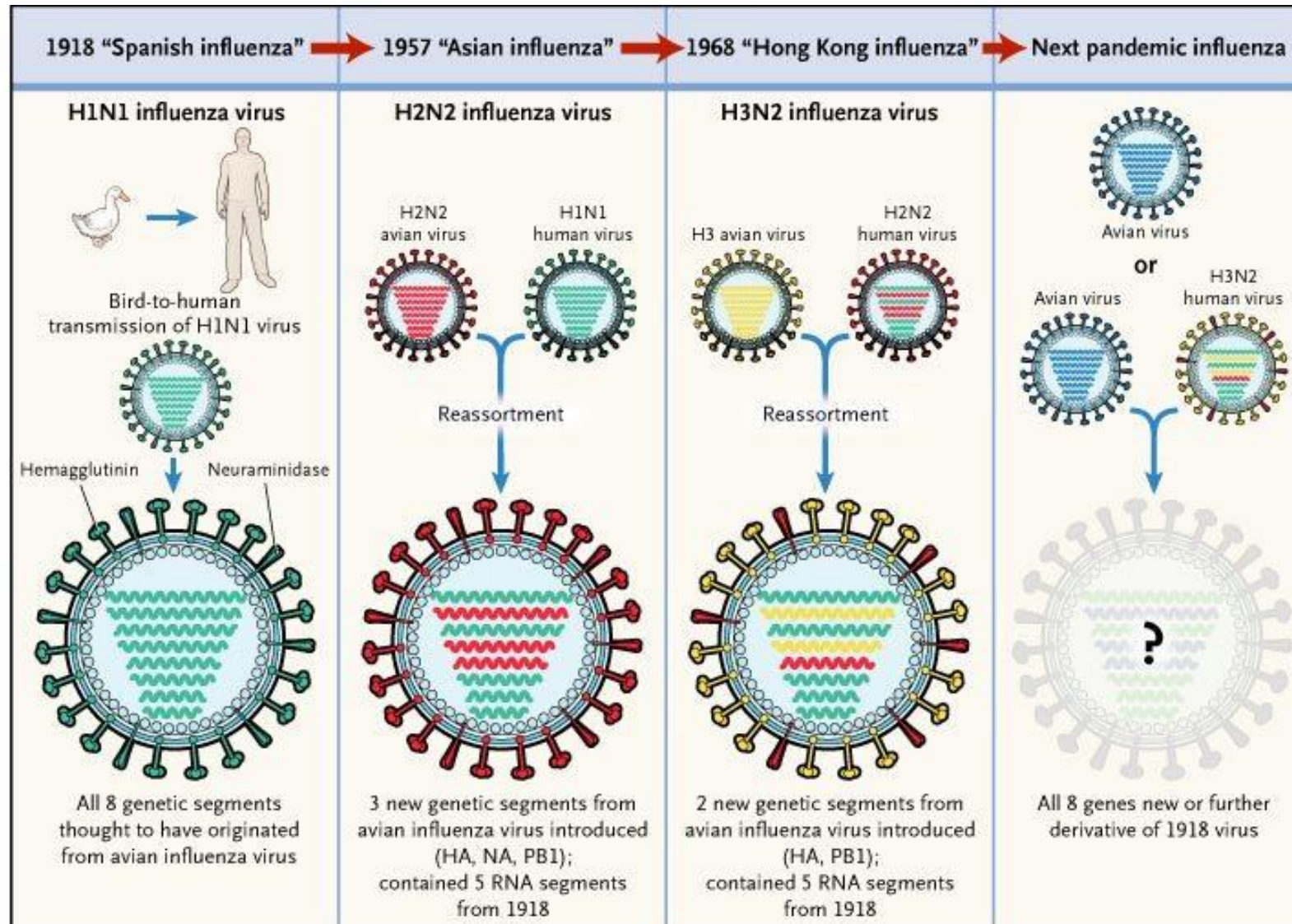
Centers for Disease  
Control and Prevention  
National Center for Immunization  
and Respiratory Diseases

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# Precautions (safety measures): H7N9, hospital, China



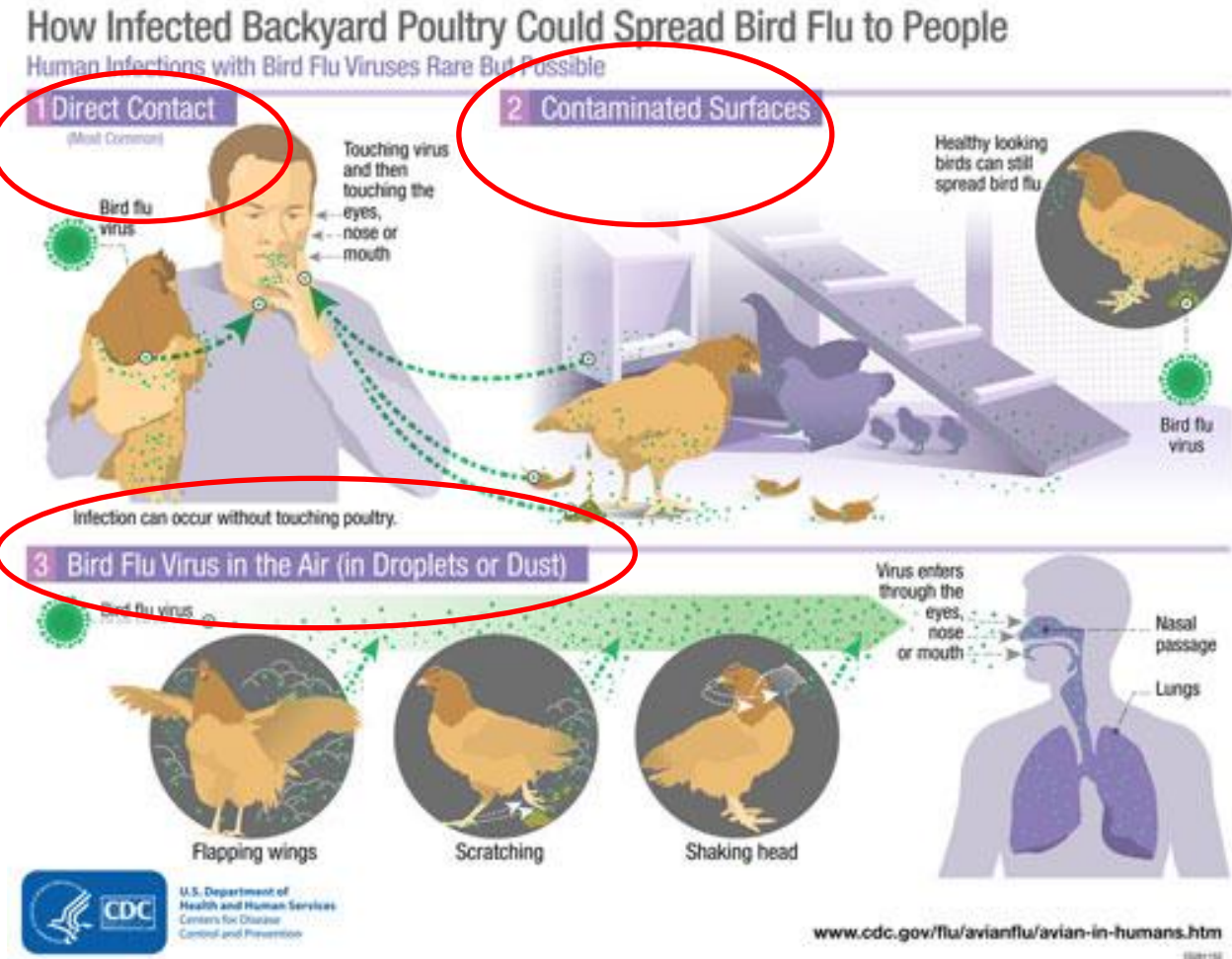
# Influenza pandemics (history)



# Výskyt H9N2, H7N7, H5N6



# Source of infection





# Preventive measures: 'culling'



# Chřipka H1N1: porovnání pandemických kmenů

**1918: španělská chřipka**

**2009: mexická (prasečí) chřipka**

1918: 50 mil. obětí

2009: 18 tis. obětí (přes 70 zemí)

Zdroj H1N1 (1918): formalínem fixovaná plicní tkáň, oběť chřipky (Aljašský permafrost) - reverzní genetika

Společné: mladí zdraví lidé ('cytokine storm')

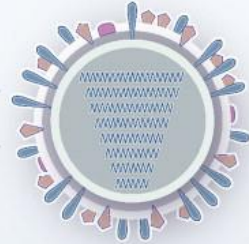
Rozdíl: H1N1 (2009) – gastrointestinální diskomfort a zvracení u 40% případů

Genetický rozdíl/změny v AMK: hemagglutinin, neuraminidáza a polymeráza (PB1, PB2 proteiny)

- výrazně přispěli k významné virulenci španělské chřipky
- HA (1918) se efektivněji váže na alfa2-6-glykan receptor kys. sialové než jiné pandemické kmeny- vazebná kapacita HA k receptoru kys. sialové je klíčové z hlediska patogenity
- efektivní kooperace mezi povrchovými HA a NA
- PB1 (1918) - vyšší transkripční aktivita

# Molecular determinants of H5N1 pathogenesis *in vivo*

## SELECTED MOLECULAR DETERMINANTS OF H5N1 PATHOGENESIS *IN VIVO*



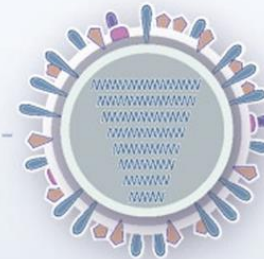
Complementary changes within RNP proteins		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Point mutations</b> (Li et al, 2011)	Mutations located in/ around binding area of PB2 (position 63) and PB1 (position 677) associated with reduced virulence <i>in vivo</i>	
<b>Point mutations</b> (Manz et al, 2011)	Disruption of protein-protein interaction site between PA (position 706) and PB1 (position 8) essential for polymerase complex formation associated with reduced virulence <i>in vivo</i>	
<b>Importin-<math>\alpha</math> isoform binding specificity</b> (Gabriel et al, 2011)	Avian influenza viruses depend on importin- $\alpha 3$ for nuclear import	Adaptive mutations in PB2 and NP which lead to enhanced binding of importin- $\alpha 7$ associated with mammalian adaptation and increased pathogenicity

PB1-F2 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Length</b> (Zamarin et al, 2006)	Absence or truncation of protein associated with reduced virulence <i>in vivo</i>	Intact protein associated with heightened virulence <i>in vivo</i>
<b>Point mutation</b> (Conenello et al, 2007 and 2011)	Asparagine at position 66 associated with reduced virulence and induction of host responses <i>in vivo</i>	Serine at position 66 associated with increased virulence and antiviral response <i>in vivo</i>

PB2 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Point mutation</b> (Hatta et al, 2001; Shinya et al, 2004; Hatta et al, 2007; Fornek et al, 2009)	Glutamic acid at position 627 associated with less efficient viral replication in mammalian species and reduced replication at 33°C	Lysine at position 627 associated with enhanced polymerase activity, mammalian host adaptation, and increased virulence <i>in vivo</i>
<b>Point mutation</b> (Li et al, 2005; Steel et al, 2009)		Asparagine at position 701 associated with mammalian host adaptation and increase virulence <i>in vivo</i>
<b>Point mutation</b> (Yamada et al, 2010)		A basic amino acid at position 591 (arginine or lysine) associated with efficient replication and increased virulence <i>in vivo</i>
<b>Point mutation</b> (Zhou et al, 2011)		Glycine at position 158 associated with increased virulence <i>in vivo</i>

PB1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Point mutations</b> (Xu et al, 2012)	Leucine at positions 473 and 588 associated with decreased polymerase activity and replication efficiency	Valine and proline at positions 473 and 588 associated with increased polymerase activity
<b>Point mutations</b> (Hulse-Post et al, 2007)	Histidine at position 436 associated with decreased replication efficiency and virulence <i>in vivo</i>	

NP protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Point mutation</b> (Kim et al, 2010)		Lysine at position 357 associated with increased virulence <i>in vivo</i> (requires 627K present in PB2)



NA protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Stalk length</b> (Matsuoka et al, 2009)		Shortened NA stalk (deletion at positions 49-68) associated with enhanced virulence <i>in vivo</i>

NS1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>PDZ ligand domain</b> (Jackson et al, 2008)		Presence of PDZ domain binding motif (position 222-5) associated with increased virulence <i>in vivo</i>
<b>Point mutation</b> (Jiao et al, 2008)		Serine at position 42 associated with increased virulence <i>in vivo</i>

<b>eIF4G1 binding domain</b> (Seo et al, 2002; Zhou et al, 2010)	Truncation of eIF4G1 binding domain (position 81-113) results in attenuated phenotype <i>in vivo</i>	
<b>CPSF30 binding site</b> (Spesock et al, 2011)		Phenylalanine at position 103 and methionine at position 106 results in greater stability of CPSF30 binding, leading to enhanced replication and virulence <i>in vivo</i>

M1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>Point mutations</b> (Fan et al, 2009)		Aspartic acid and alanine at positions 30 and 215 associated with increased virulence <i>in vivo</i>

HA protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
<b>HA cleavage motif sequence</b> (Horimoto and Kawaoka, 1994)	Single arginine residue at cleavage site generally restricts HA0 cleavage to occur outside the respiratory tract	Polybasic amino acids at cleavage site (positions 323-330) allows HA0 cleavage to occur outside the respiratory tract

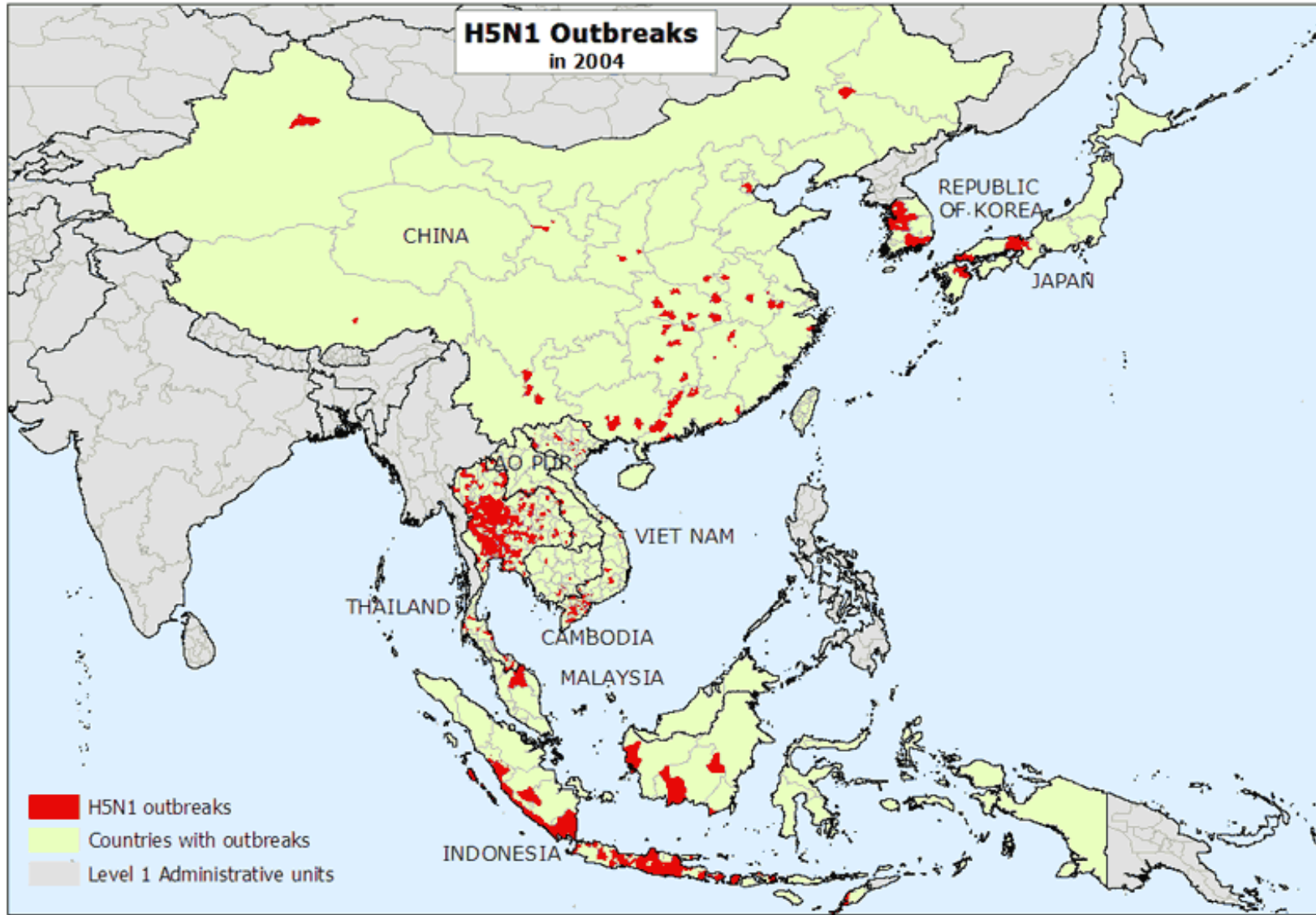
<b>HA fusion peptide pocket</b> (Reed et al, 2009; Kromm et al, 2011)		Isoleucine at position 58 of HA2 associated with decreased pH of fusion and increased HA stability associated with increased infectivity and replication efficiency <i>in vivo</i>
<b>Point mutation</b> (Manz et al, 2010)	Glutamic acid at position 222 associated with restricted replication to respiratory tract tissues and reduced binding affinity	Lysine at position 222 associated with extrapulmonary spread <i>in vivo</i>

<b>HA glycosylation</b> (Matsuoka et al, 2009; Wang et al, 2010)	Carbohydrate moieties proximal to HA cleavage site may limit access of proteases, additional glycosylation sites on HA associated with decreased virulence <i>in vivo</i>	Absence of glycosylation sites may result in greater access of proteases to cleavage site, resulting in broader cell tropism, removal of glycosylation site at position 158 associated with efficient virus replication <i>in vivo</i>
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<b>Receptor binding preference</b> (Maines et al, 2011; Herfst et al, 2012)	H5N1 viruses with enhanced binding to $\alpha 2-6$ linked sialic acids exhibit reduced virulence <i>in vivo</i>	Viruses with an $\alpha 2-3$ linked sialic acid binding preference
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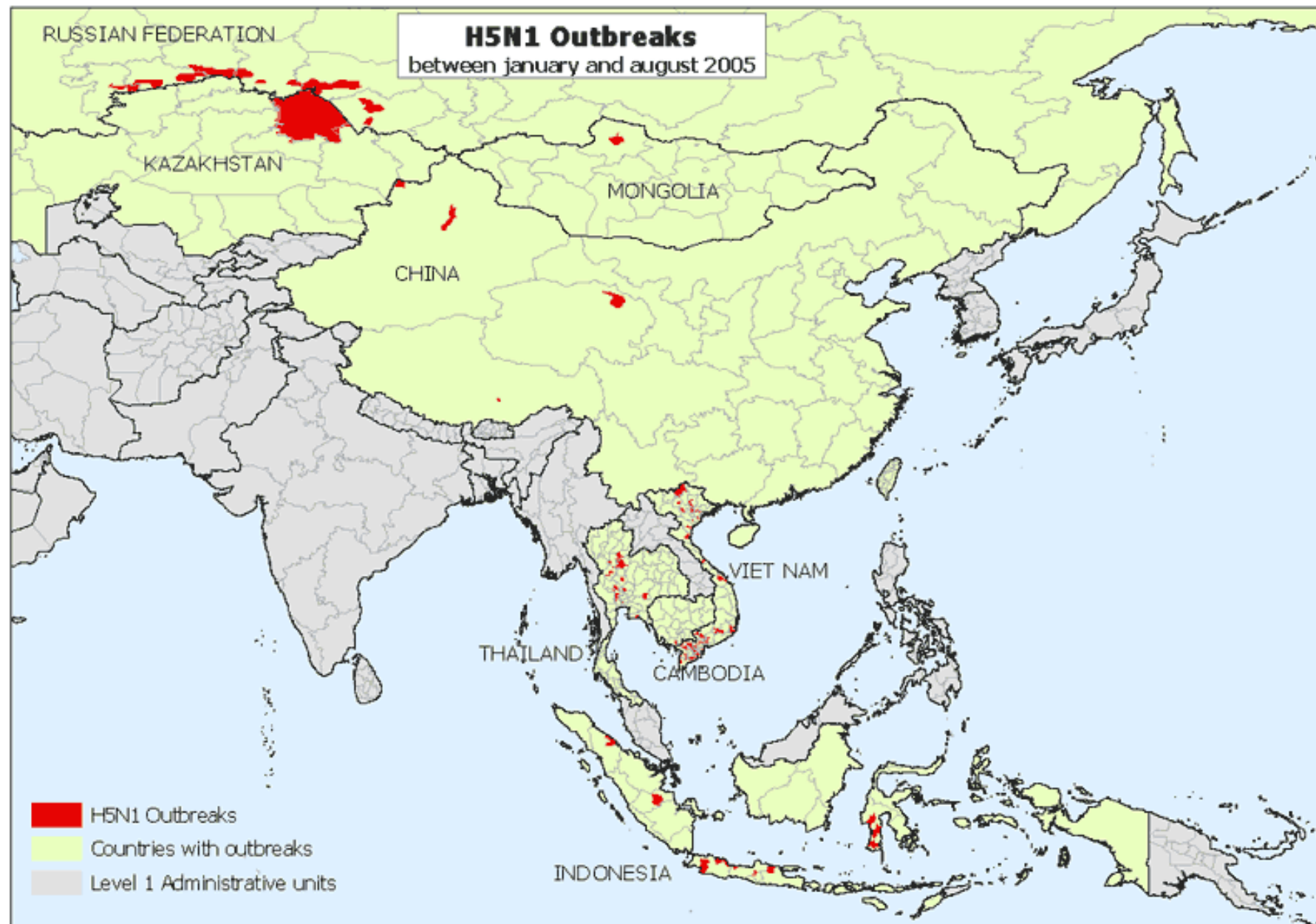
# HPAI klinické projevy





This map represents the districts or provinces that experienced outbreaks of H5N1 type of Avian Influenza between January and December 2004. The original data have been collected and aggregated at the most detailed administrative level and for the units available for each country.

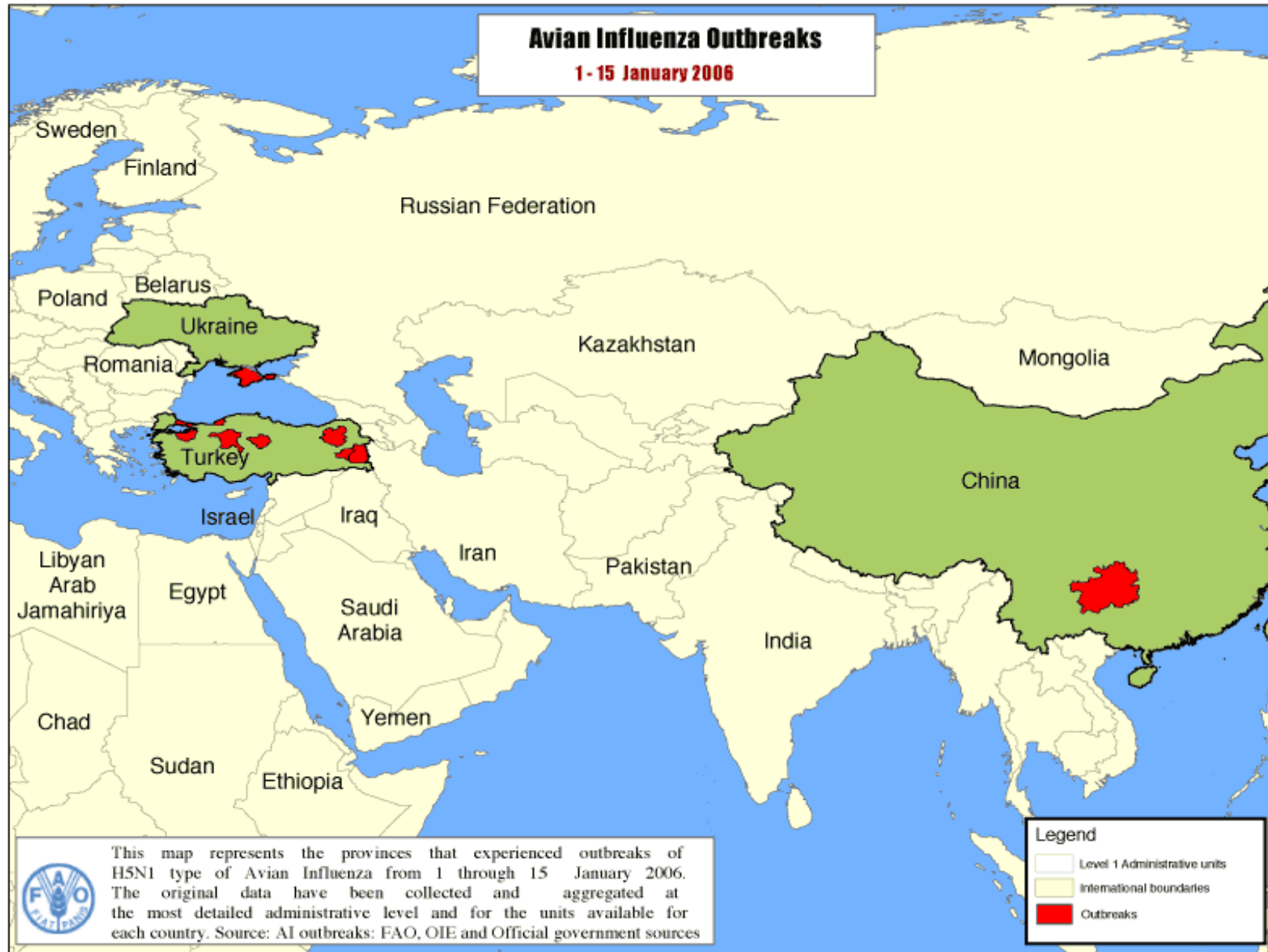
Data source: OIE, FAO and Government sources



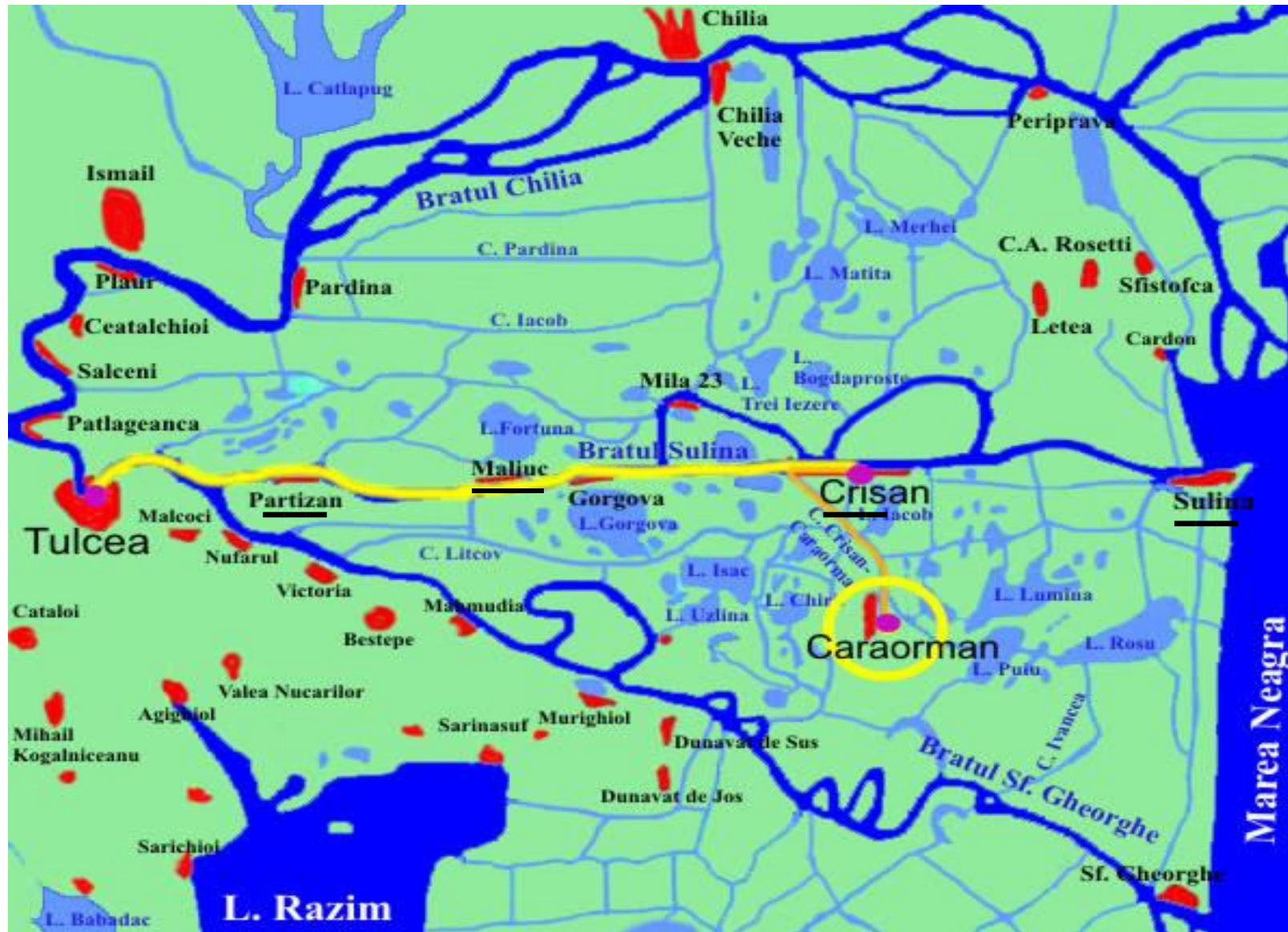
This map represents the districts or provinces that experienced outbreaks of H5N1 type of Avian Influenza since January 2005 (map updated to 31 August 2005). The original data have been collected and aggregated at the most detailed administrative level and for the units available for each country.

Data source: OIE, FAO and Government sources

# HPAI, January 2006



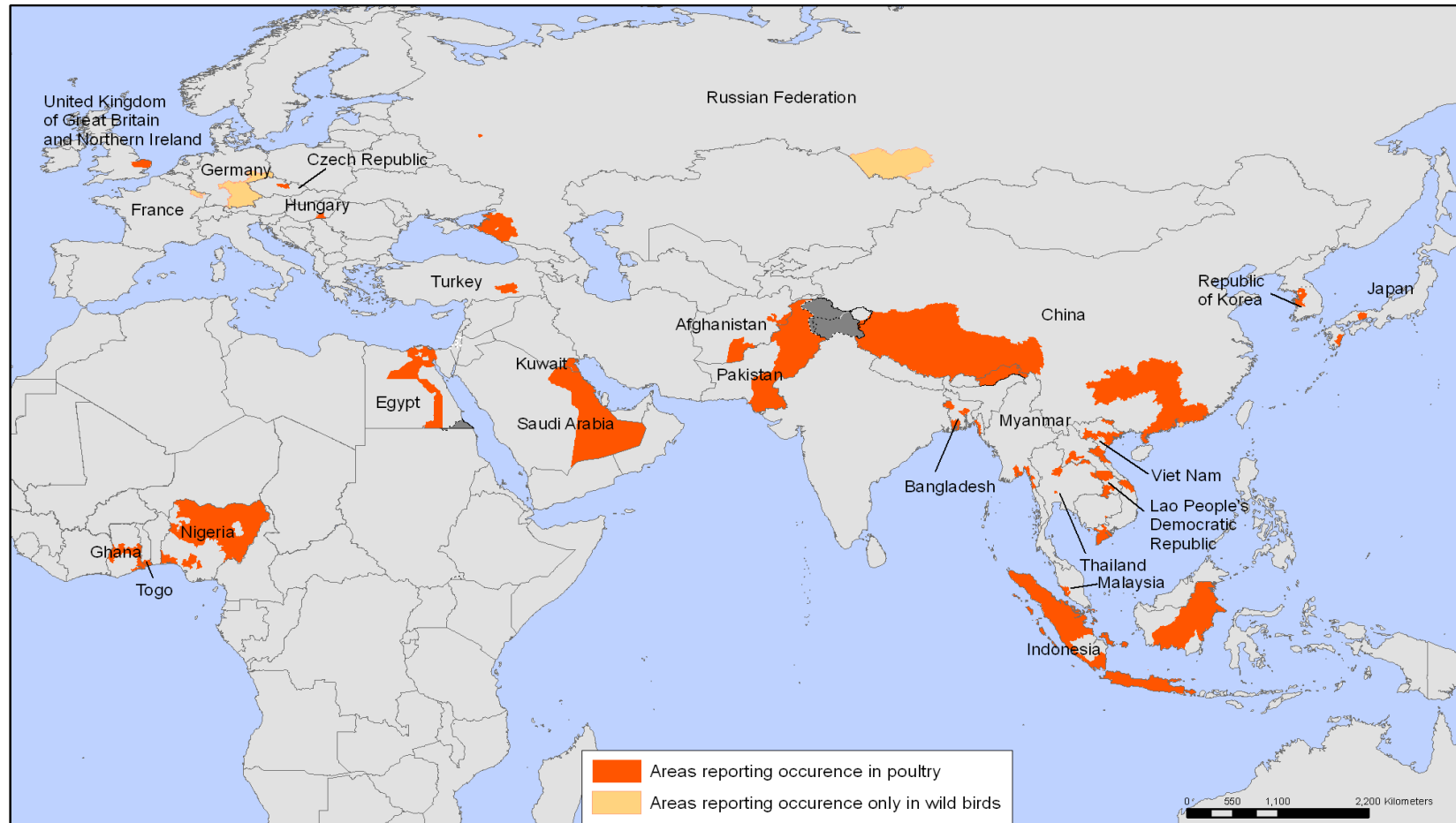
# HPAI v Dunajské deltě, říjen 2005





# H5N1, leden až červen 2007

Areas reporting confirmed occurrence of H5N1 avian influenza in poultry and wild birds between January and June 2007



# První případ HPAI H5N1 v Česku: labuť v Hluboké n.Vlt., 27. březen 2006



# Summary of the H5N1 spread chronology (as of 31 January 2006)

- Since 1996: HPAI H5N1 virus circulates in SE. Asia
- Since late 2003: circulation greatly activated in that area
- April-May 2005: Qinghai + Xinjiang provinces, N.China
- July 2005: Novosibirsk region, Asian Russia
- July to August 2005: Kazakhstan, Tibet, Mongolia
- August 2005: Altai, Kurgan, Omsk, Tyumen regions, Asian Russia, and Chelyabinsk region in southern Ural (at the limits of Europe)
- October 2005: Turkey, Romania, Croatia, European Russia, Crimea
- 
- November 2005: Kuwait
- January 2006: Cyprus, Iraq, Saudi Arabia

# HPAI risk for humans: live poultry markets



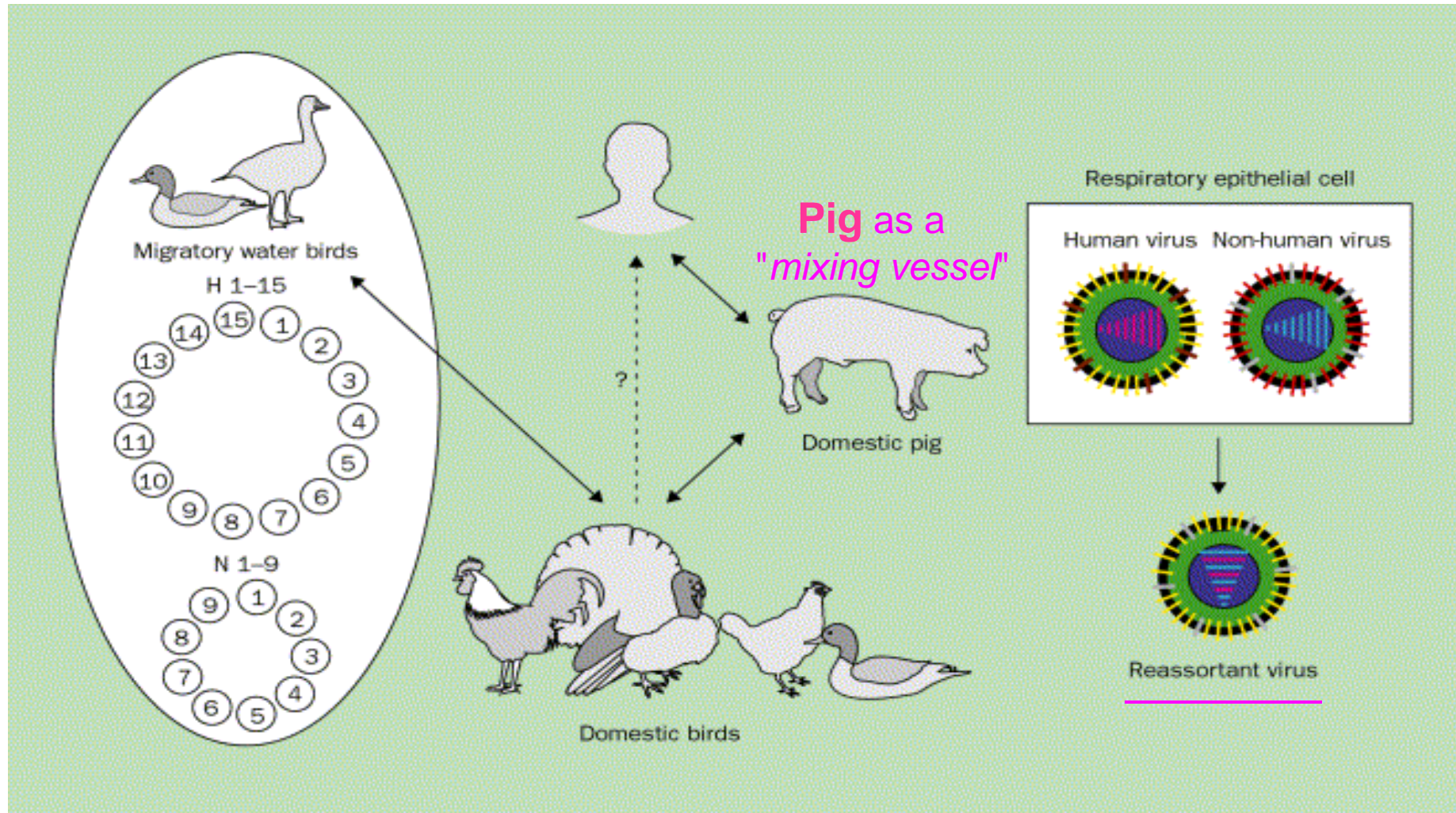
Long Bien Market, Hanoi, Vietnam 2002



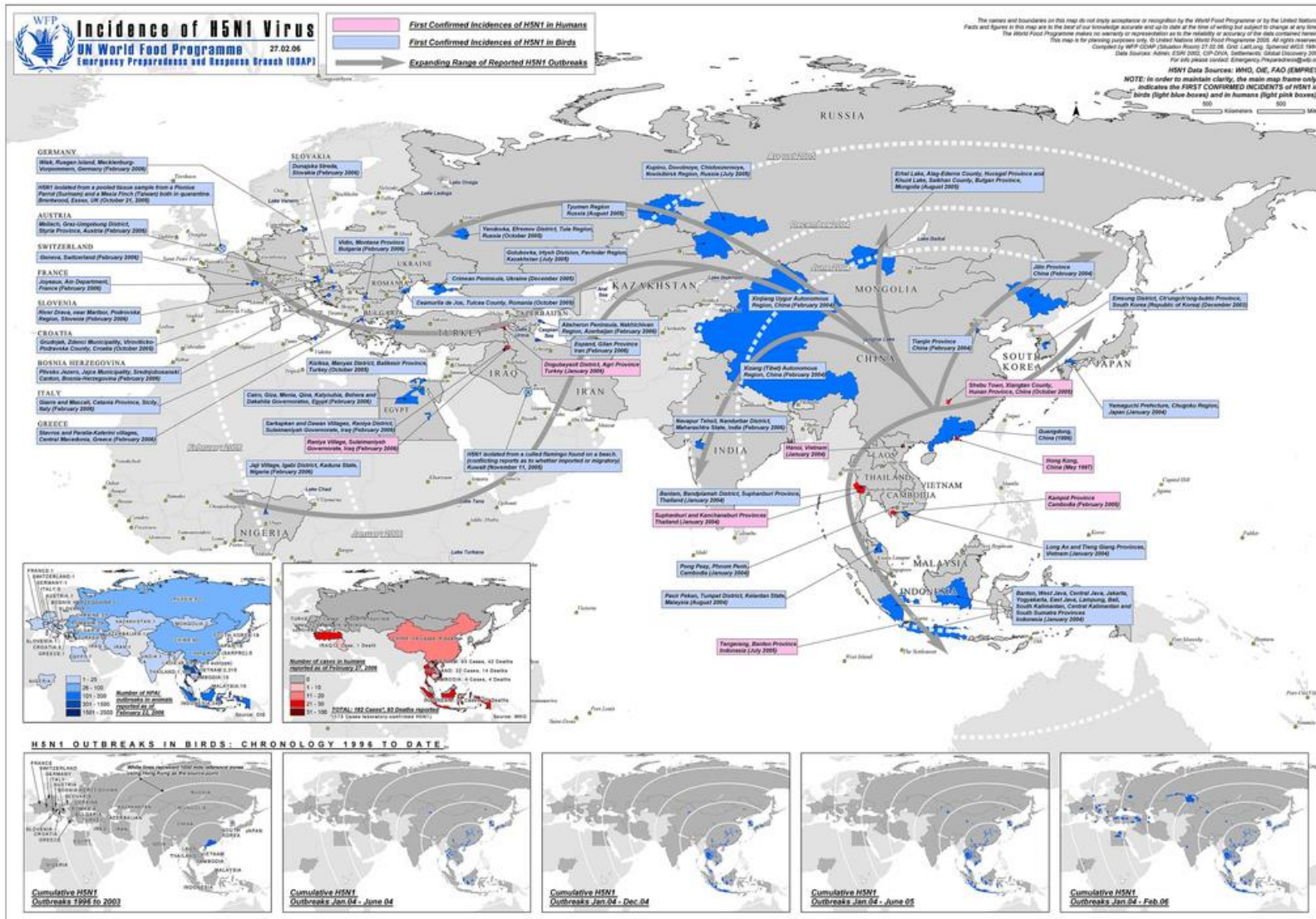
T. Uyeki (CDC)

# Origin of pandemic influenza

(Nicholson et al. 2003)



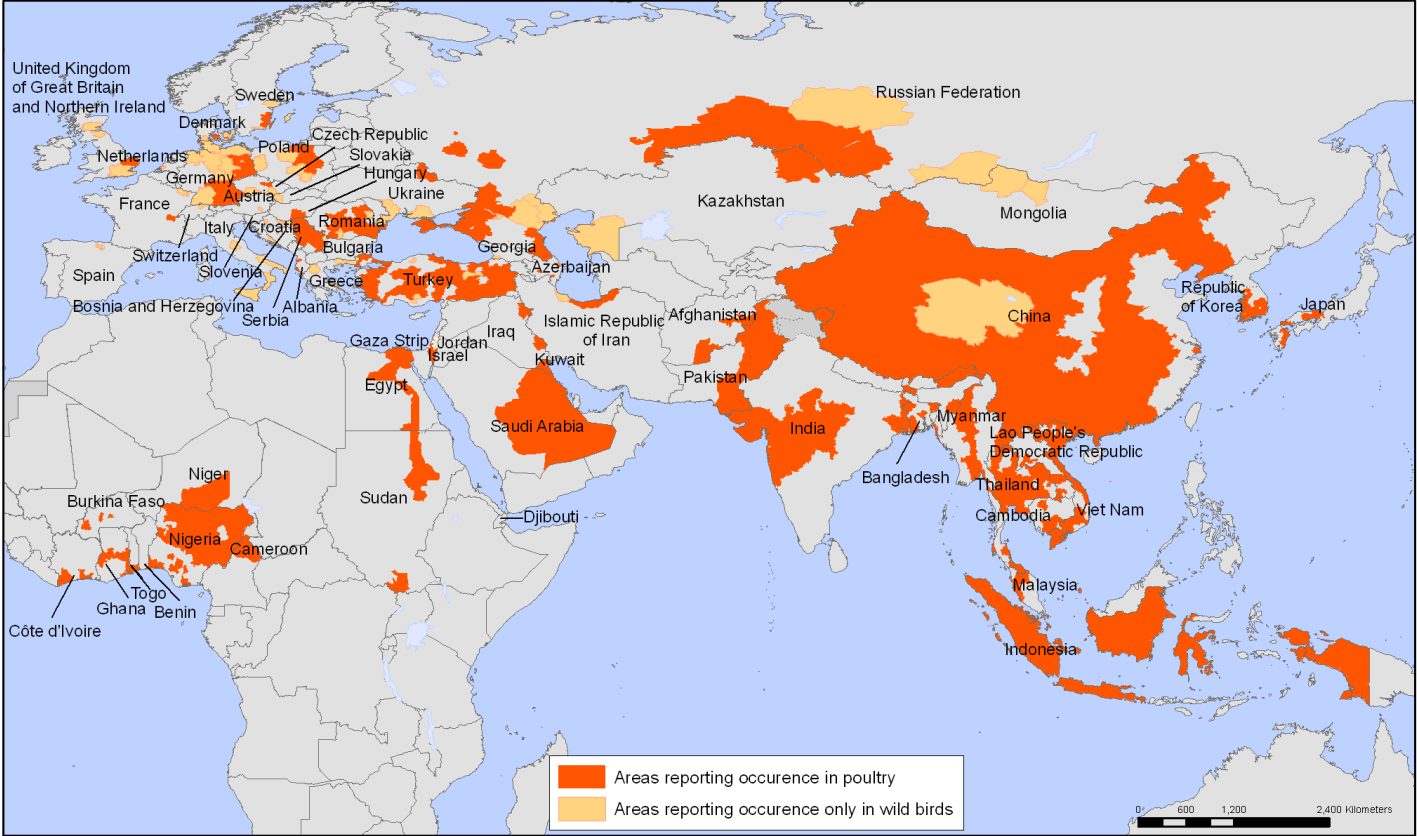
# Worldwide circulation of H5N1



# Cirkulace H5N1

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

Status as of 18 January 2008  
Latest available update

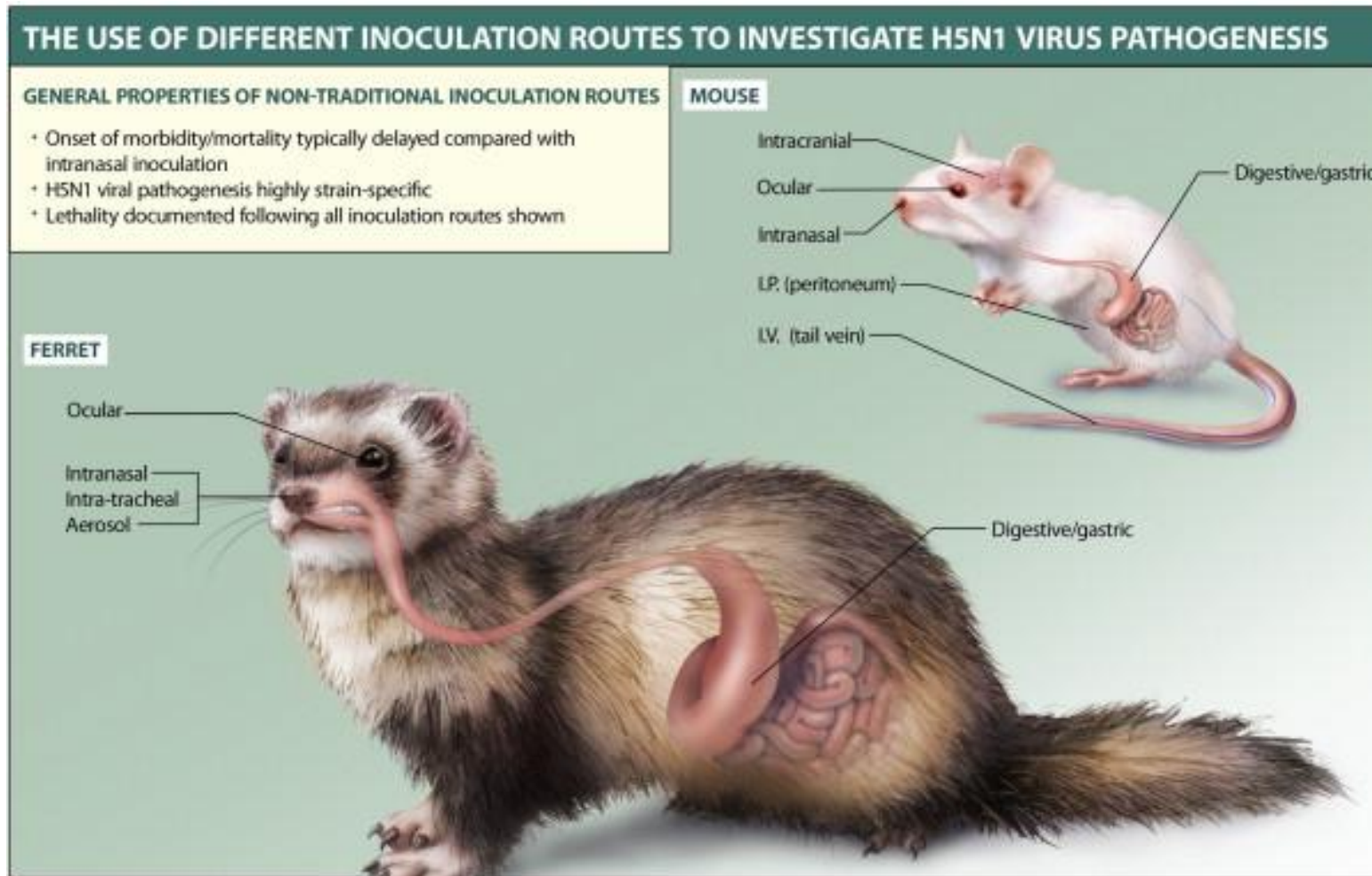


 **World Health Organization**  
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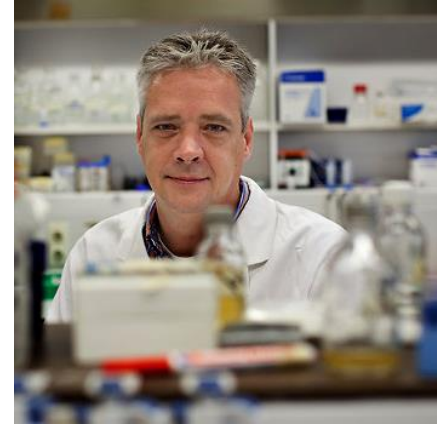
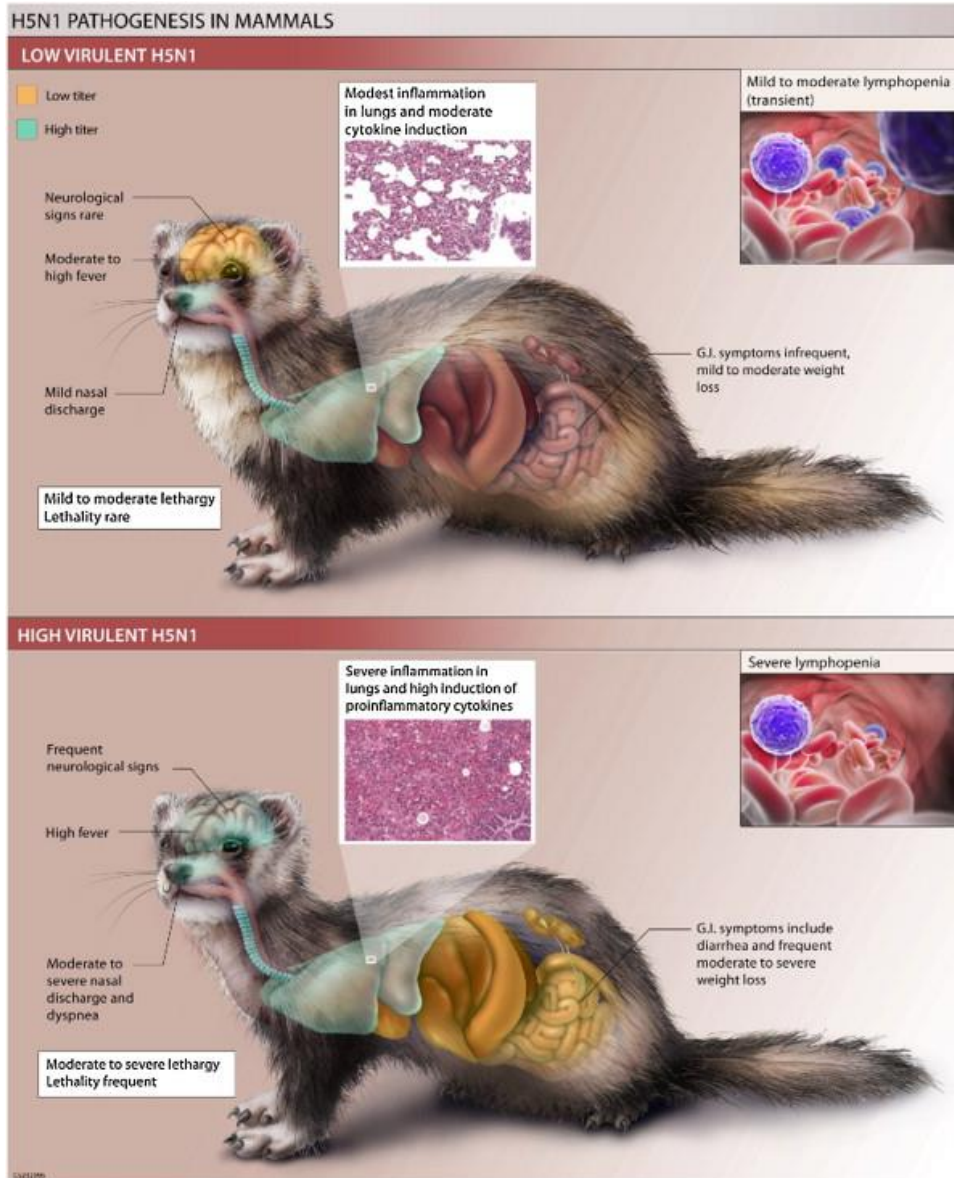
Data Source: World Organisation for Animal Health (OIE) and national governments  
Map Production: Public Health Mapping and GIS  
World Health Organization

# Animal model for experimental infection of influenza viruses



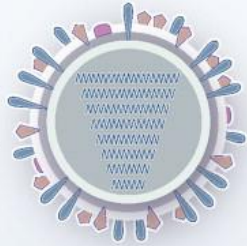


# H5N1 in experimental model



# Molecular determinants of H5N1 pathogenesis *in vivo*

SELECTED MOLECULAR DETERMINANTS OF H5N1 PATHOGENESIS IN VIVO



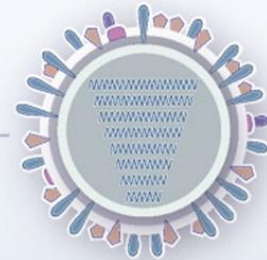
Complementary changes within RNP proteins		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Point mutations (Li et al, 2011)	Mutations located in/ around binding area of PB2 (position 63) and PB1 (position 677) associated with reduced virulence <i>in vivo</i>	
Point mutations (Manz et al, 2011)	Disruption of protein-protein interaction site between PA (position 706) and PB1 (position 8) essential for polymerase complex formation associated with reduced virulence <i>in vivo</i>	
Importin- $\alpha$ isoform binding specificity (Gabriel et al, 2011)	Avian influenza viruses depend on importin $\alpha 3$ for nuclear import	Adaptive mutations in PB2 and NP which lead to enhanced binding of importin- $\alpha 7$ associated with mammalian adaptation and increased pathogenicity

PB1-F2 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Length (Zamarin et al, 2006)	Absence or truncation of protein associated with reduced virulence <i>in vivo</i>	Intact protein associated with heightened virulence <i>in vivo</i>
Point mutation (Cosenello et al, 2007 and 2011)	Asparagine at position 66 associated with reduced virulence and induction of host responses <i>in vivo</i>	Serine at position 66 associated with increased virulence and antiviral response <i>in vivo</i>

NP protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Point mutation (Kim et al, 2010)		Lysine at position 357 associated with increased virulence <i>in vivo</i> (requires 627K present in PB2)

PB2 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Point mutation (Halla et al, 2001; Shinya et al, 2004; Halla et al, 2007; Fornek et al, 2009)	Glutamic acid at position 627 associated with less efficient viral replication in mammalian species and reduced replication at 33°C	Lysine at position 627 associated with enhanced polymerase activity, mammalian host adaptation, and increased virulence <i>in vivo</i>
Point mutation (Li et al, 2005; Steel et al 2009)		Asparagine at position 701 associated with mammalian host adaptation and increase virulence <i>in vivo</i>
Point mutation (Yamada et al, 2010)		A basic amino acid at position 591 (arginine or lysine) associated with efficient replication and increased virulence <i>in vivo</i>
Point mutation (Zhou et al, 2011)		Glycine at position 158 associated with increased virulence <i>in vivo</i>

PB1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Point mutations (Xu et al, 2012)	Leucine at positions 473 and 598 associated with decreased polymerase activity and replication efficiency	Valine and proline at positions 473 and 598 associated with increased polymerase activity
Point mutations (Hulse-Post et al, 2007)		Histidine at position 436 associated with decreased replication efficiency and virulence <i>in vivo</i>



NA protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Stalk length (Matsuoka et al, 2009)		Shortened NA stalk (deletion at positions 49-68) associated with enhanced virulence <i>in vivo</i>

NS1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
PDZ ligand domain (Jackson et al, 2008)		Presence of PDZ domain binding motif (position 222-5) associated with increased virulence <i>in vivo</i>
Point mutation (Jiao et al, 2008)		Serine at position 42 associated with increased virulence <i>in vivo</i>
eIF4GI binding domain (Seo et al, 2002; Zhou et al, 2010)	Truncation of eIF4GI binding domain (position 81-113) results in attenuated phenotype <i>in vivo</i>	

M1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
CPSF30 binding site (Spesock et al, 2011)		Phenylalanine at position 103 and methionine at position 106 results in greater stability of CPSF30 binding, leading to enhanced replication and virulence <i>in vivo</i>

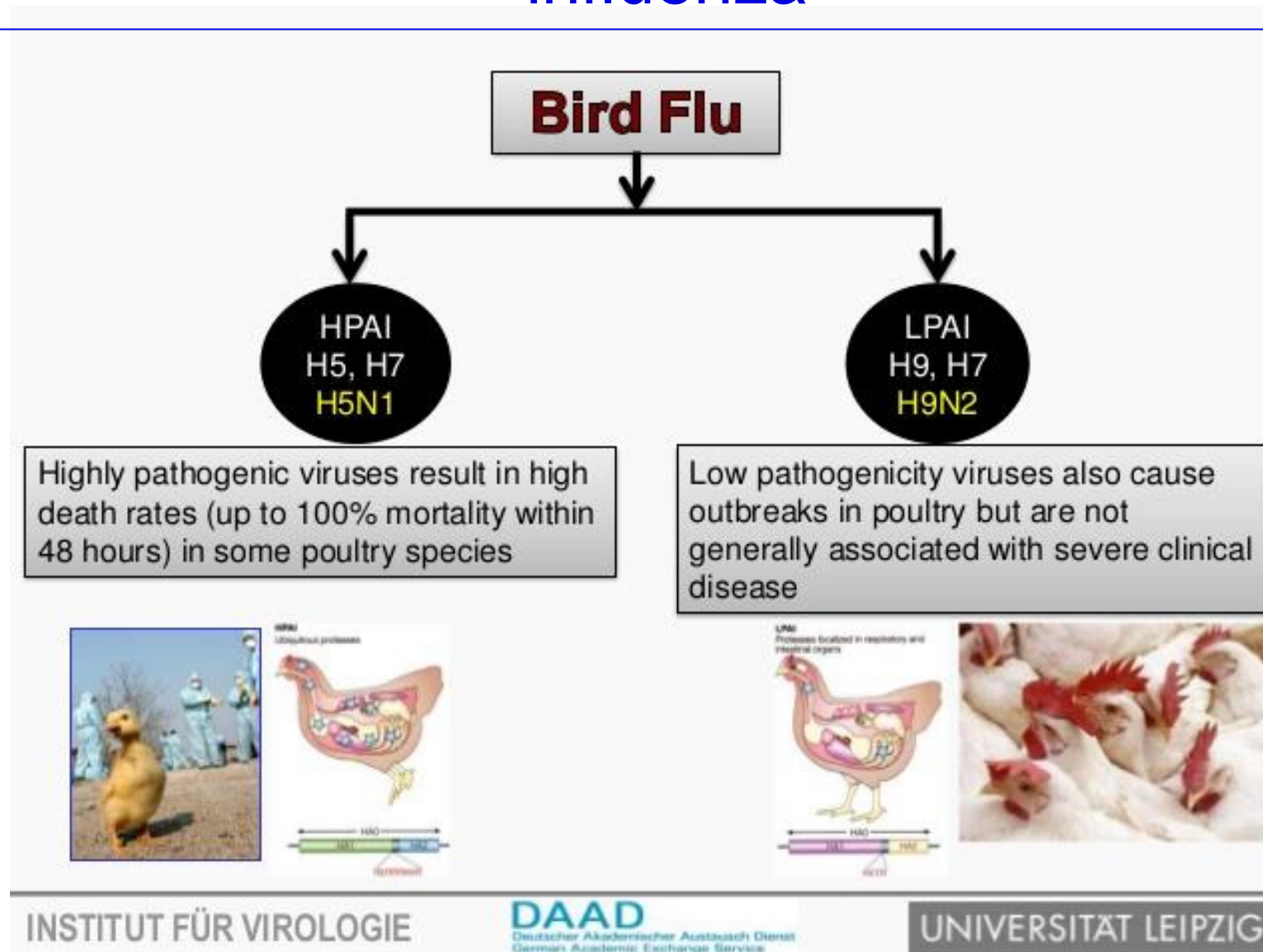
M1 protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
Point mutations (Fan et al, 2009)		Aspartic acid and alanine at positions 30 and 215 associated with increased virulence <i>in vivo</i>

HA protein		
Viral or host component	Less virulent <i>in vivo</i>	More virulent <i>in vivo</i>
HA cleavage motif sequence (Horimoto and Kawaoka, 1994)	Single arginine residue at cleavage site generally restricts HA0 cleavage to respiratory tract tissues	Polybasic amino acids at cleavage site (positions 323-330) allows HA0 cleavage to occur outside the respiratory tract
HA fusion peptide pocket (Reed et al, 2009; Kronn et al, 2011)		Isoleucine at position 58 of HA2 associated with decreased pH of fusion and increased HA stability associated with increased infectivity and replication efficiency <i>in vivo</i>
Point mutation (Manz et al, 2010)	Glutamic acid at position 222 associated with restricted replication to respiratory tract tissues and reduced binding affinity	Lysine at position 222 associated with extrapulmonary spread <i>in vivo</i>
HA glycosylation (Matsuoka et al, 2009; Wang et al, 2010)	Carbohydrate moieties proximal to HA cleavage site may limit access of proteases, additional glycosylation sites on HA associated with decreased virulence <i>in vivo</i>	Absence of glycosylation sites may result in greater access of proteases to cleavage site, resulting in broader cell tropism; removal of glycosylation site at position 158 associated with efficient virus replication <i>in vivo</i>
Receptor binding preference (Maines et al, 2011; Horst et al, 2012)	H5N1 viruses with enhanced binding to $\alpha 2-6$ linked sialic acids exhibit reduced virulence <i>in vivo</i>	Viruses with an $\alpha 2-3$ linked sialic acid binding preference

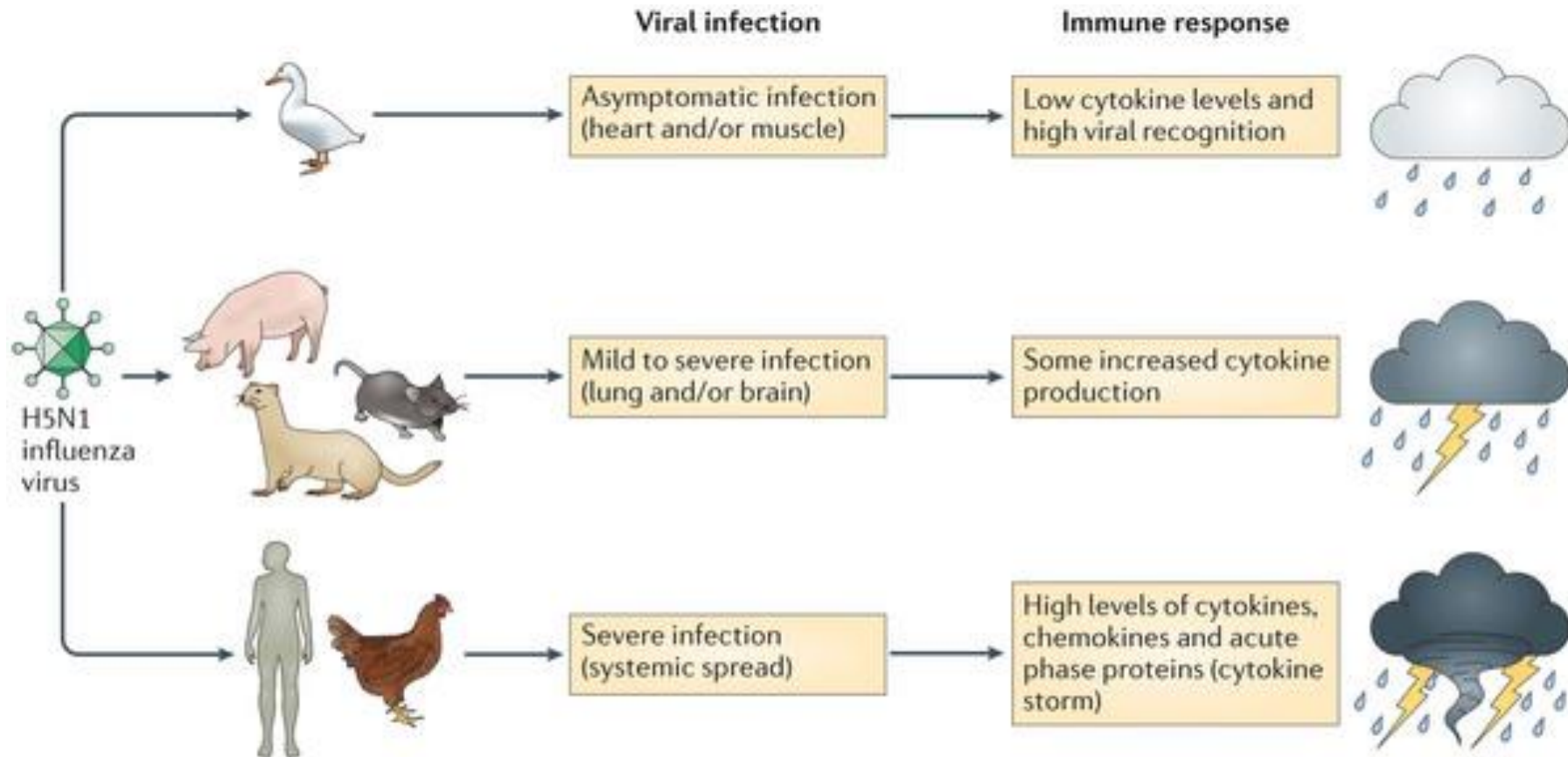
# Live bird (poultry) markets



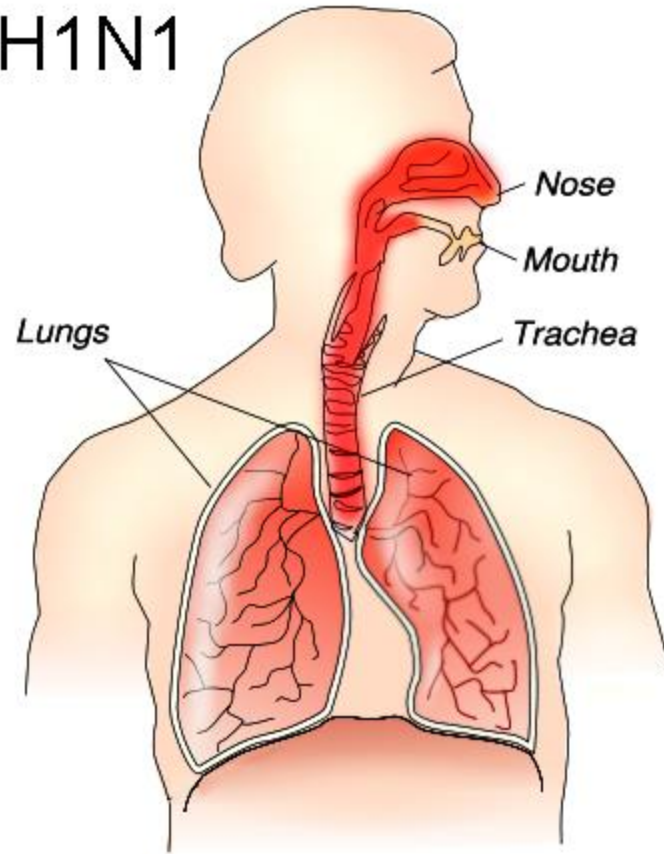
# High pathogenic and low pathogenic bird influenza



# Response of immune system to H5N1 infection

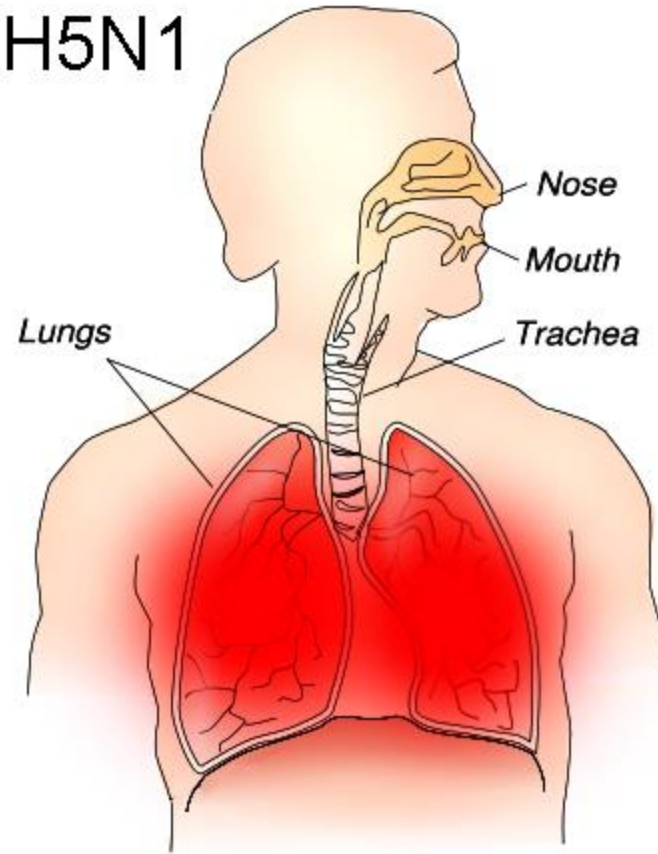


H1N1



Easily spread  
Rarely fatal

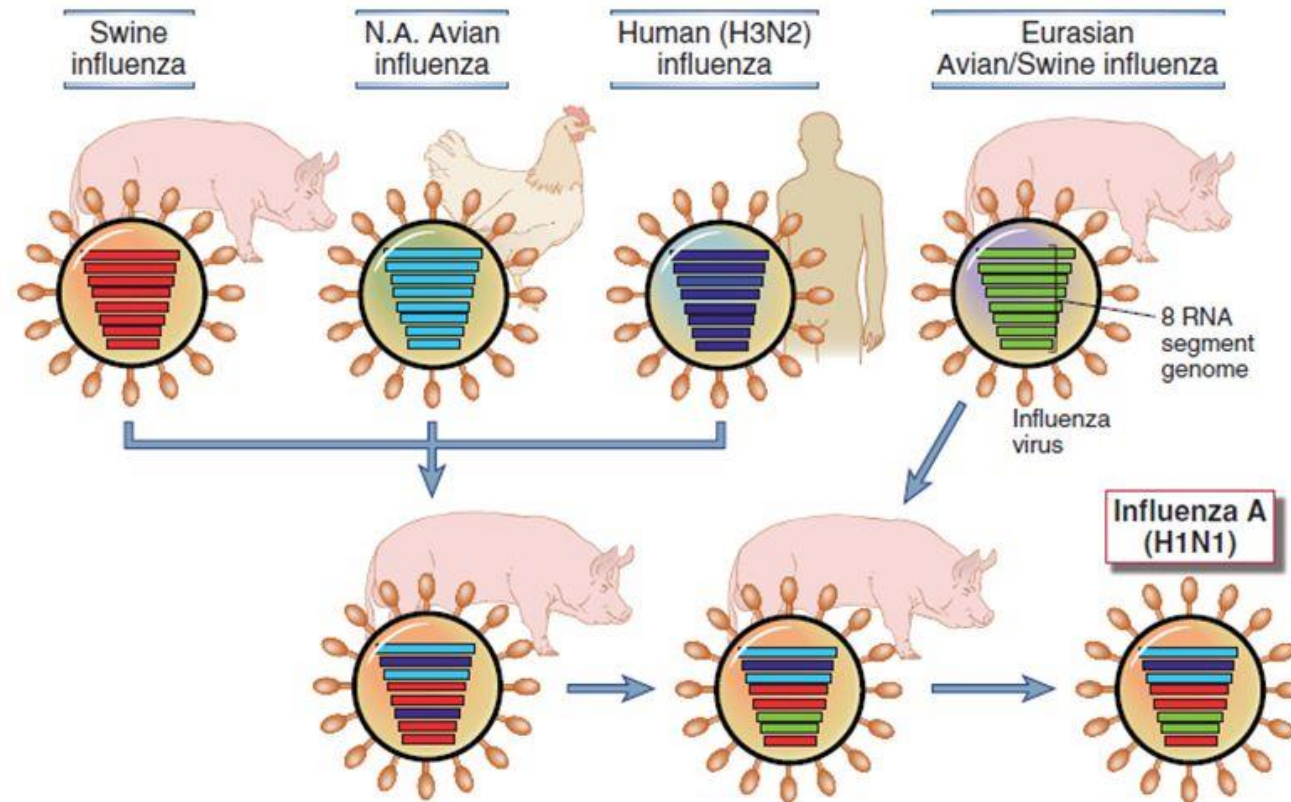
H5N1



Spreads slowly  
Often fatal

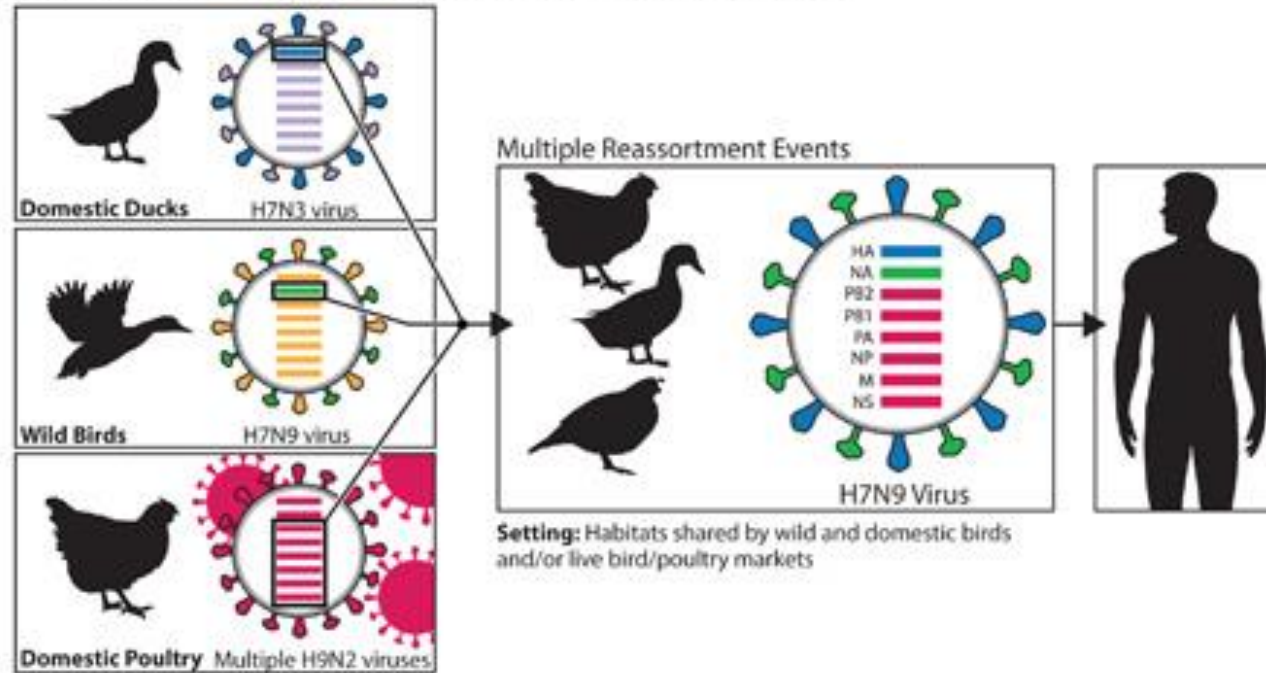
# Evolution of H1N1 (2009)

**Generation of new influenza virus strains by genetic recombination (antigenic shift)**



# Evolution of H7N9 (2013)

## Genetic Evolution of H7N9 Virus in China, 2013



The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Experts think multiple reassortment events led to the creation of the H7N9 virus. These events may have occurred in habitats shared by wild and domestic birds and/or in live bird/poultry markets, where different species of birds are bought and sold for food. As the above diagram shows, the H7N9 virus likely obtained its HA (hemagglutinin) gene from domestic ducks, its NA (neuraminidase) gene from wild birds, and its six remaining genes from multiple related H9N2 influenza viruses in domestic poultry.

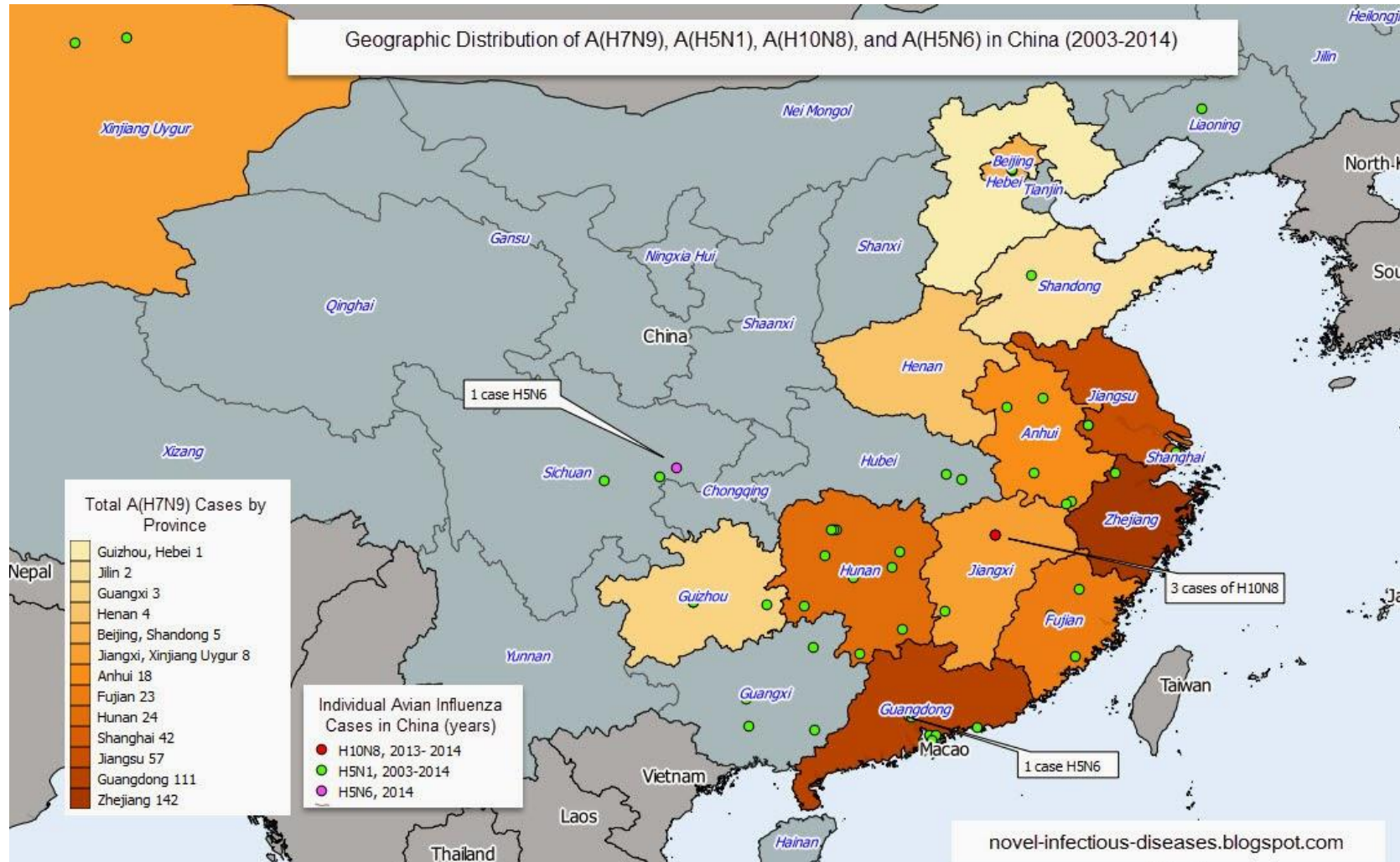


Centers for Disease  
Control and Prevention  
National Center for Immunization  
and Respiratory Diseases

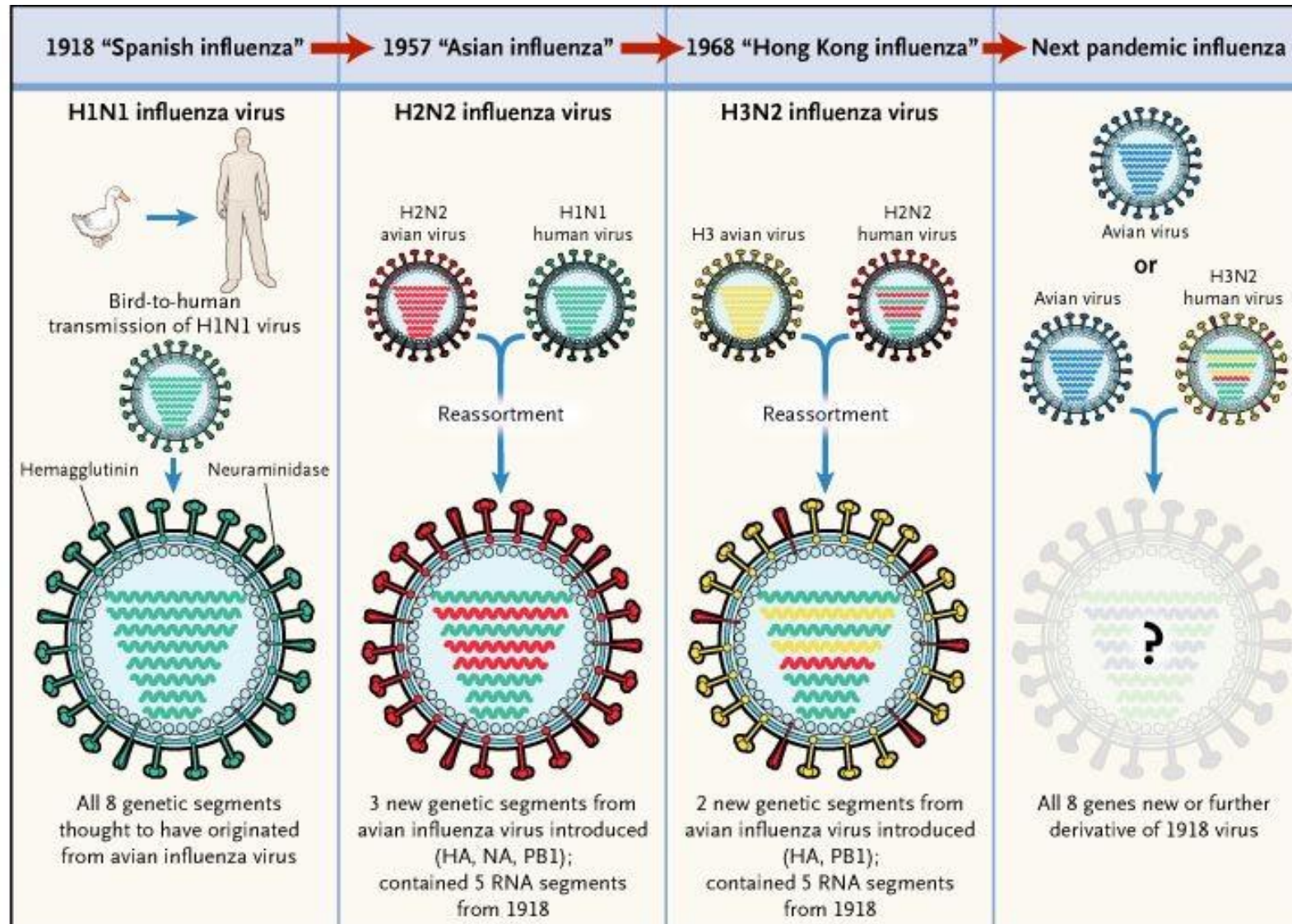
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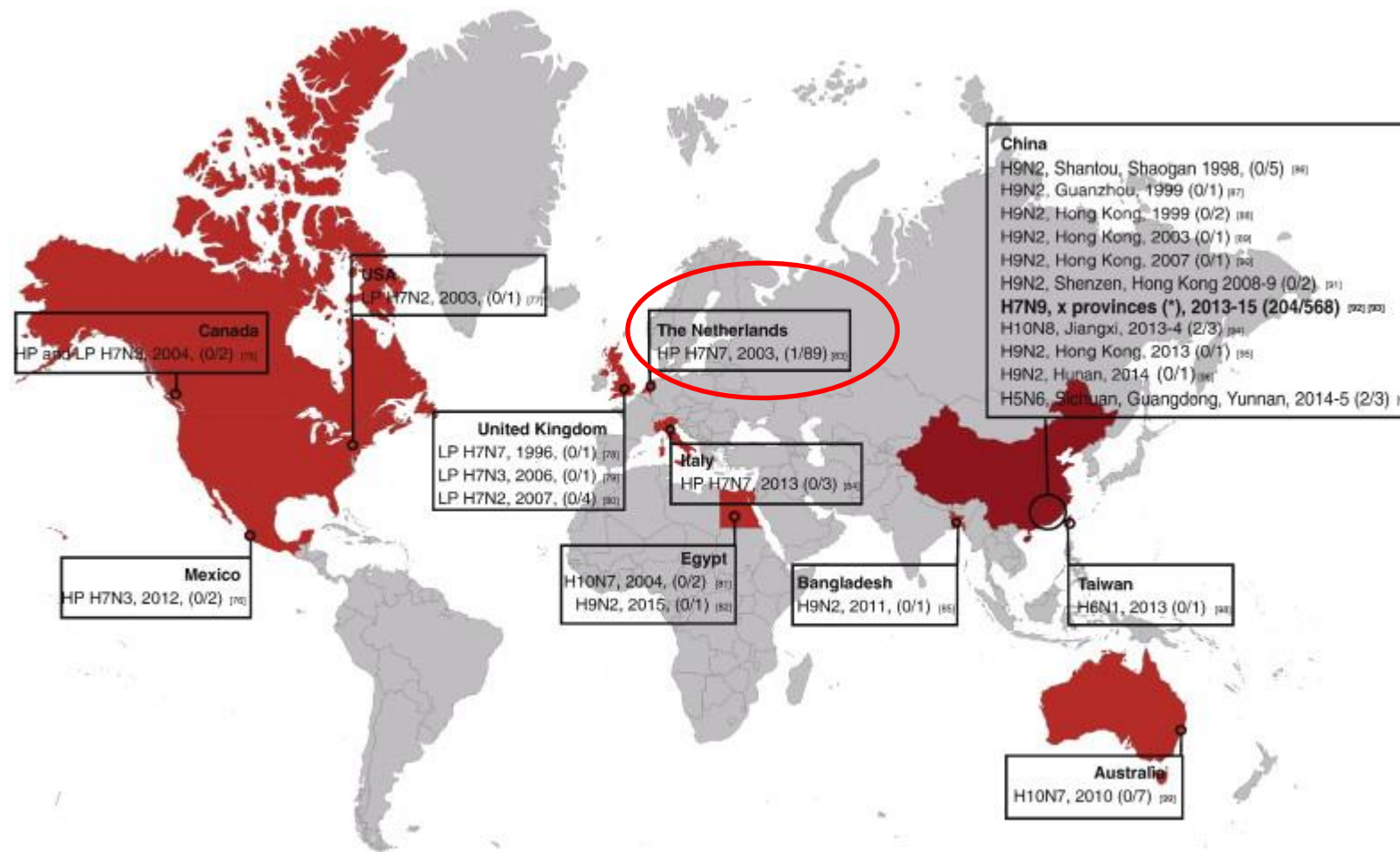
# Geographic localization of H7N9, H5N1, H10N8, H5N6



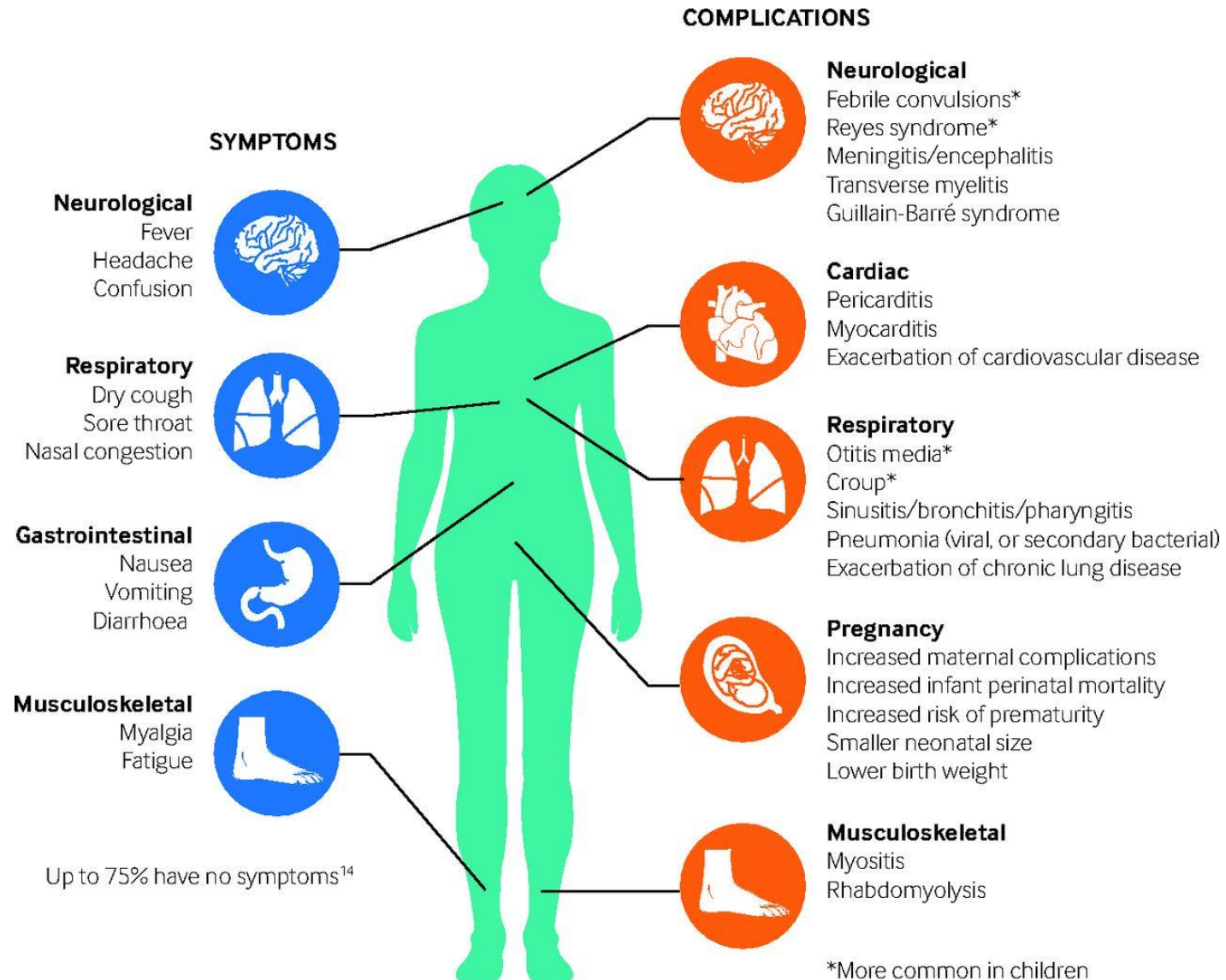
# Influenza pandemics



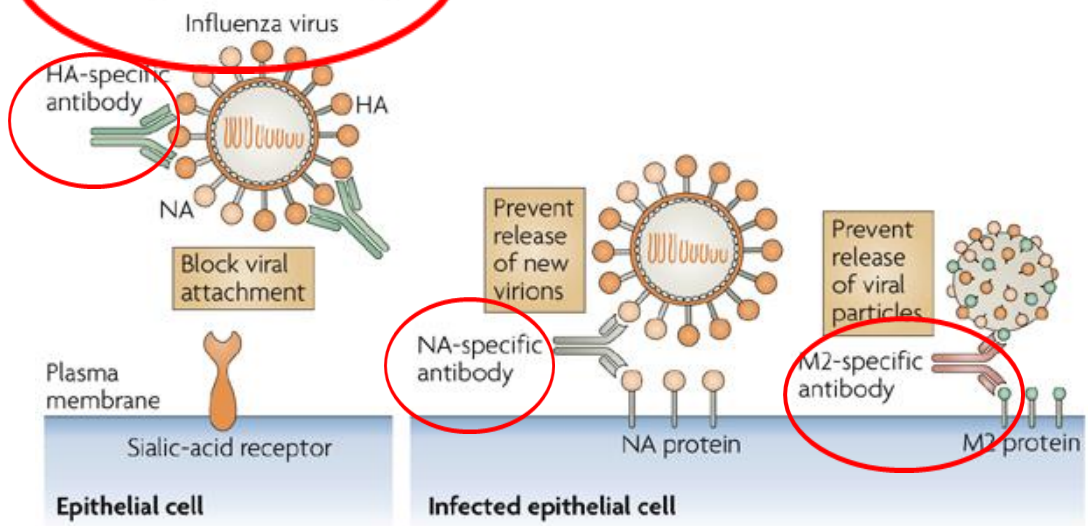
# Výskyt H9N2, H7N7, H5N6



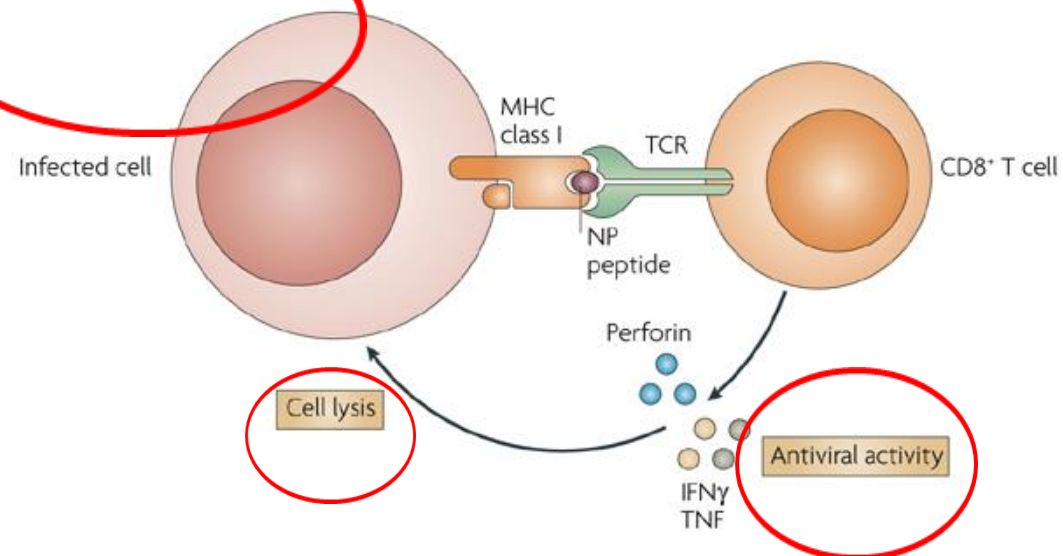
# Main symptoms and complications of flue



**a Antibody-mediated immunity**



**b Cell-mediated immunity**



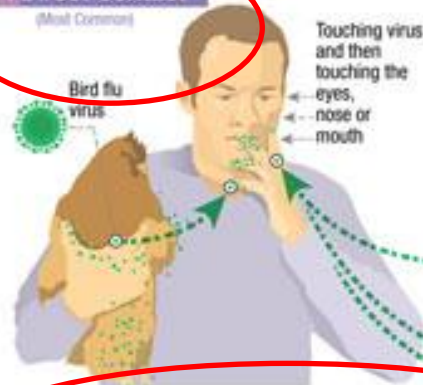
# Source of infection

## How Infected Backyard Poultry Could Spread Bird Flu to People

Human Infections with Bird Flu Viruses Rare But Possible

### 1 Direct Contact

(Most Common)

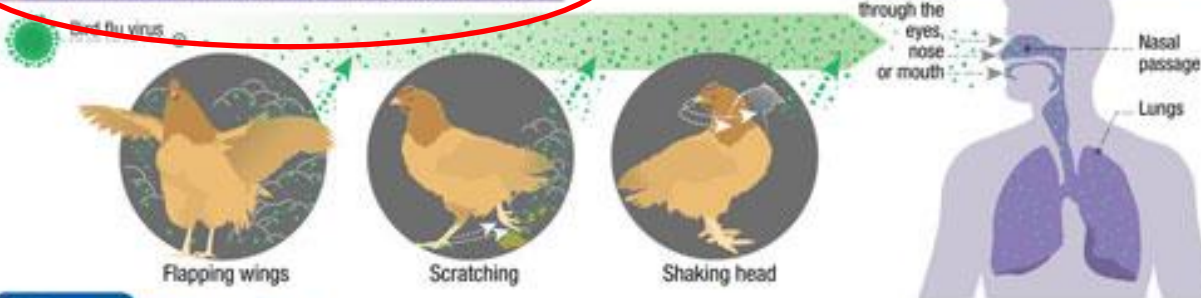


### 2 Contaminated Surfaces



Infection can occur without touching poultry.

### 3 Bird Flu Virus in the Air (in Droplets or Dust)

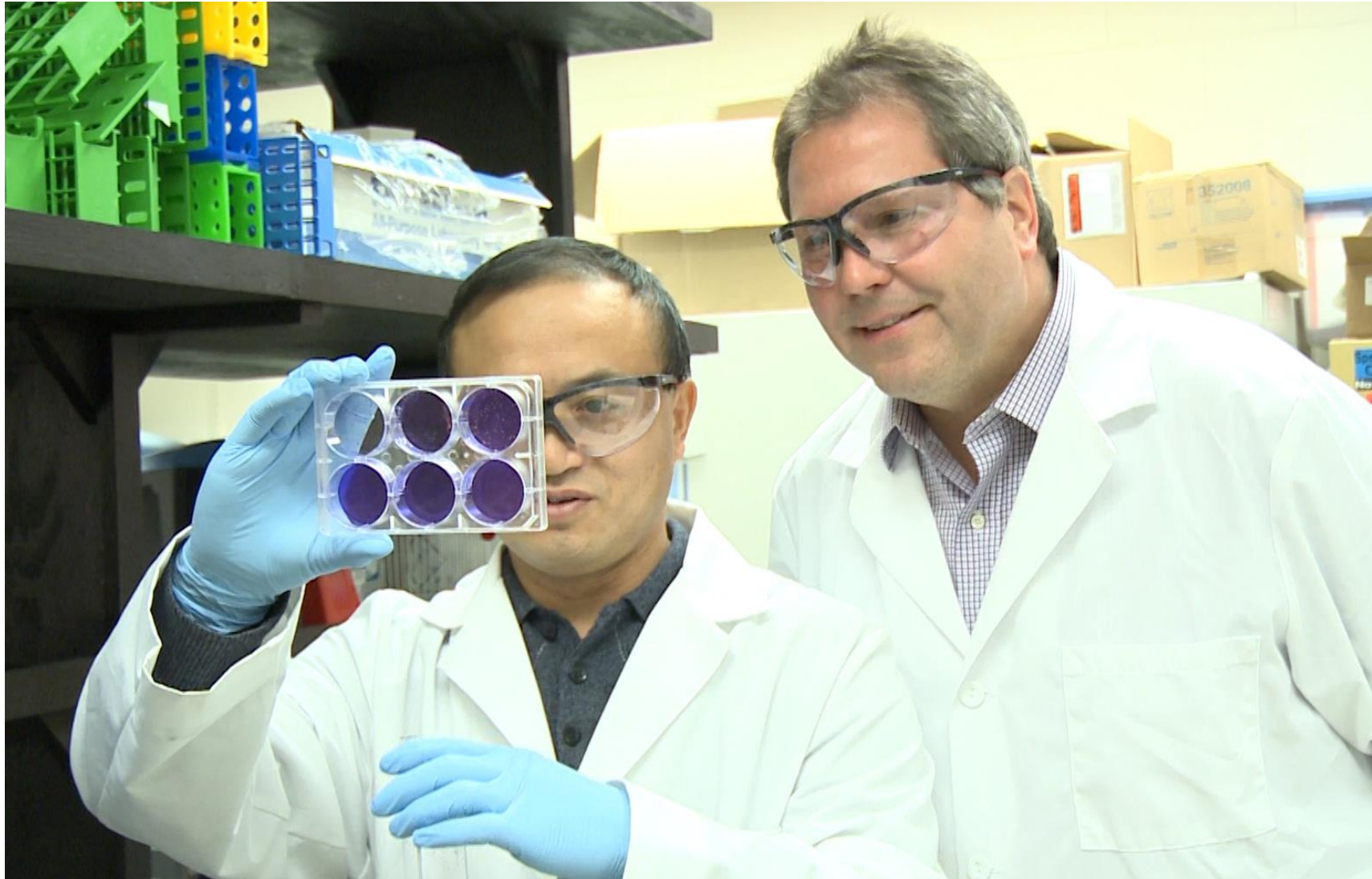


U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

[www.cdc.gov/flu/avianflu/avian-in-humans.htm](http://www.cdc.gov/flu/avianflu/avian-in-humans.htm)

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# Laboratory diagnostics



# Distribuce chřipkových virů v Evropě

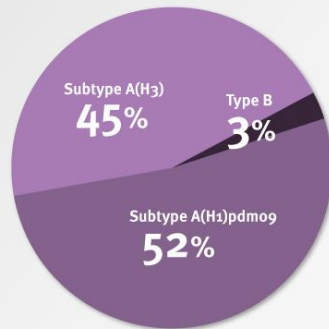
## Influenza in Europe

Week 18 (28 April – 04 May 2014)



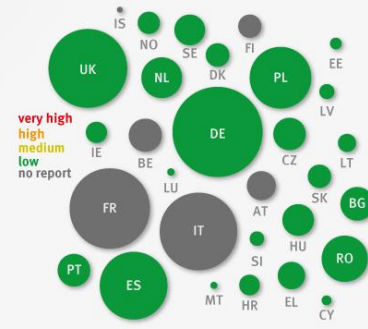
### Viruses circulating in 2013–2014

Only subtyped viruses are included



### Influenza intensity in week 18

based on sentinel reports of influenza-like illness and/or acute respiratory infections in European countries



Bubble size is indicative of country population

### Influenza trend

based on the percentage of sentinel specimens found positive, by week



## Influenza in Europe

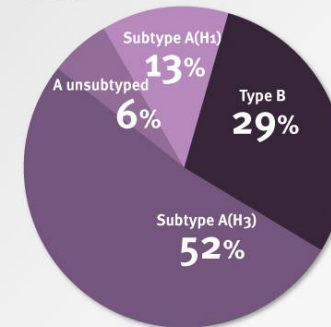
Data from EU and EEA countries for the 2014–15 season

Week 16 (13–19 April 2015)



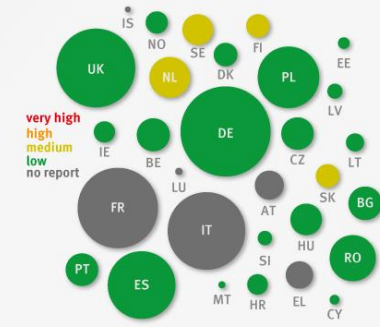
### Influenza viruses circulating in 2014–2015

Only sentinel specimens are included



### Influenza intensity in week 16

based on sentinel reports of influenza-like illness and/or acute respiratory infections



Bubble size is indicative of country population

### Influenza trend

based on the percentage of sentinel specimens found positive, by week

