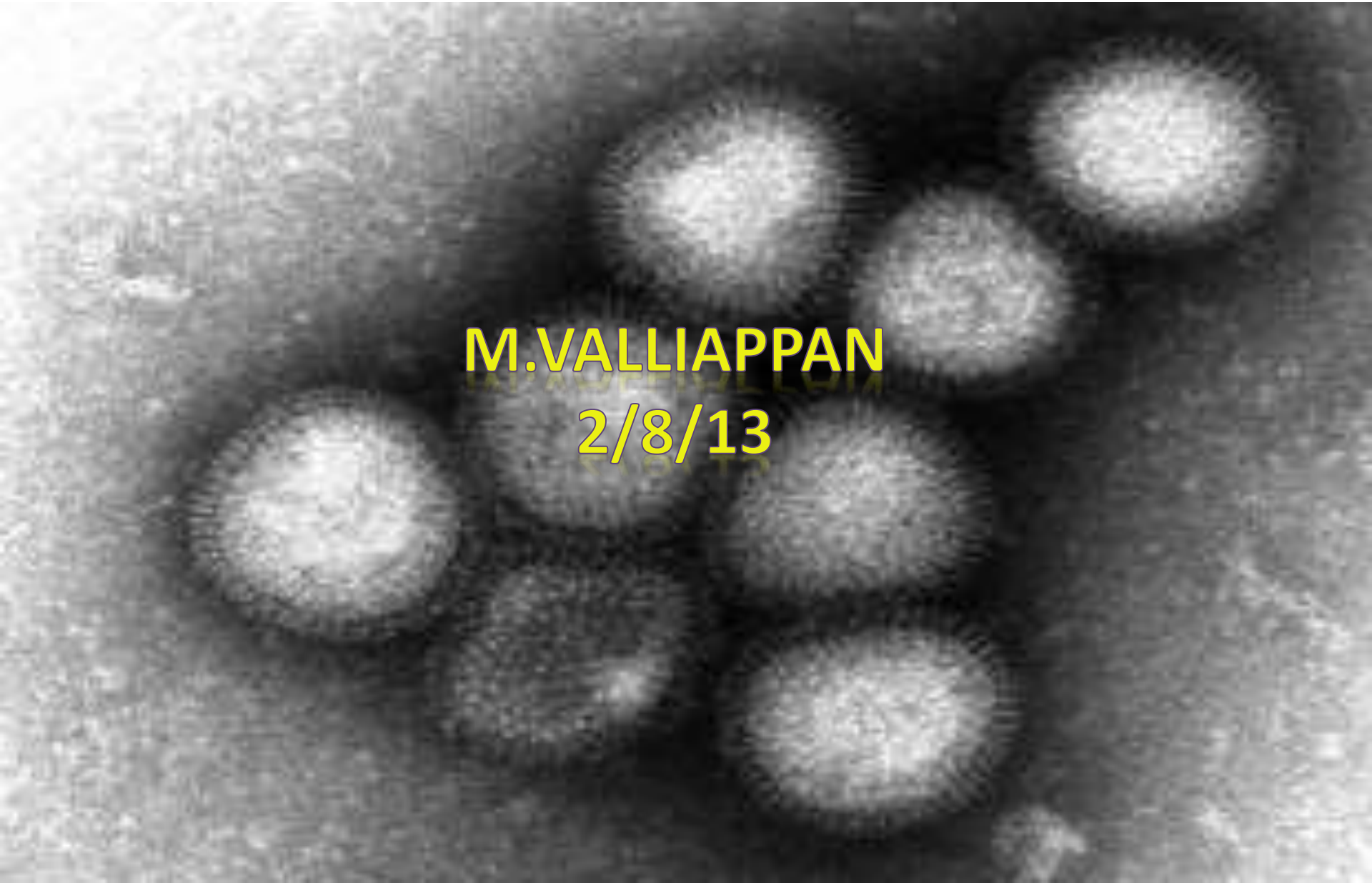
Novel Influenza viruses



- Virology
- Current viruses
- Clinical presentation
- Diagnosis
- Management – antivirals and supportive
- Vaccination
- Emergency preparedness
- Surveillance and predicting a pandemic

Influenza- disaster from heaven

- Italian word “influence” – unfavourable astrological influences

Enveloped orthomyxovirus, negative sense RNA (segmented), with 3 types, A,B,C

	Influenza A	*Influenza B*	*Influenza C*
Genetics	8 gene segments	8 gene segments	7 gene segments
Structure	10 viral proteins M2 unique	11 viral proteins NB unique	9 viral proteins HEF unique
Host range	Humans, swine, equine, avian, marine mammals*	Humans only	Humans and swine
Epidemiology	Antigenic shift and drift	Antigenic drift only; two main lineages cocirculate	Antigenic drift only; multiple variants
Clinical features	May cause large pandemics with significant mortality in young persons	Severe disease generally confined to older adults or persons at high risk; pandemics not seen	Mild disease without seasonality

Mandell's Infectious diseases

Eight RNA segments of the influenza genome and corresponding protein and function

RNA Segment	Protein	Function
PB2	Transcriptase	Cap binding
PB1	Transcriptase	Cap elongation
PA	Transcriptase	Protease activity
HA	Hemagglutinin	Anchoring to cell
NP	Nuclear protein	RNA binding and transport
NA	Neuraminidase	Release of virus
M1/M2	Matrix proteins	M1, major component of virion; M2, ion channel
NS1/NS2	Nonstructural protein	NS1, RNA transports, translation; NS2, unknown function

N Engl J Med 2009

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Resultant virus

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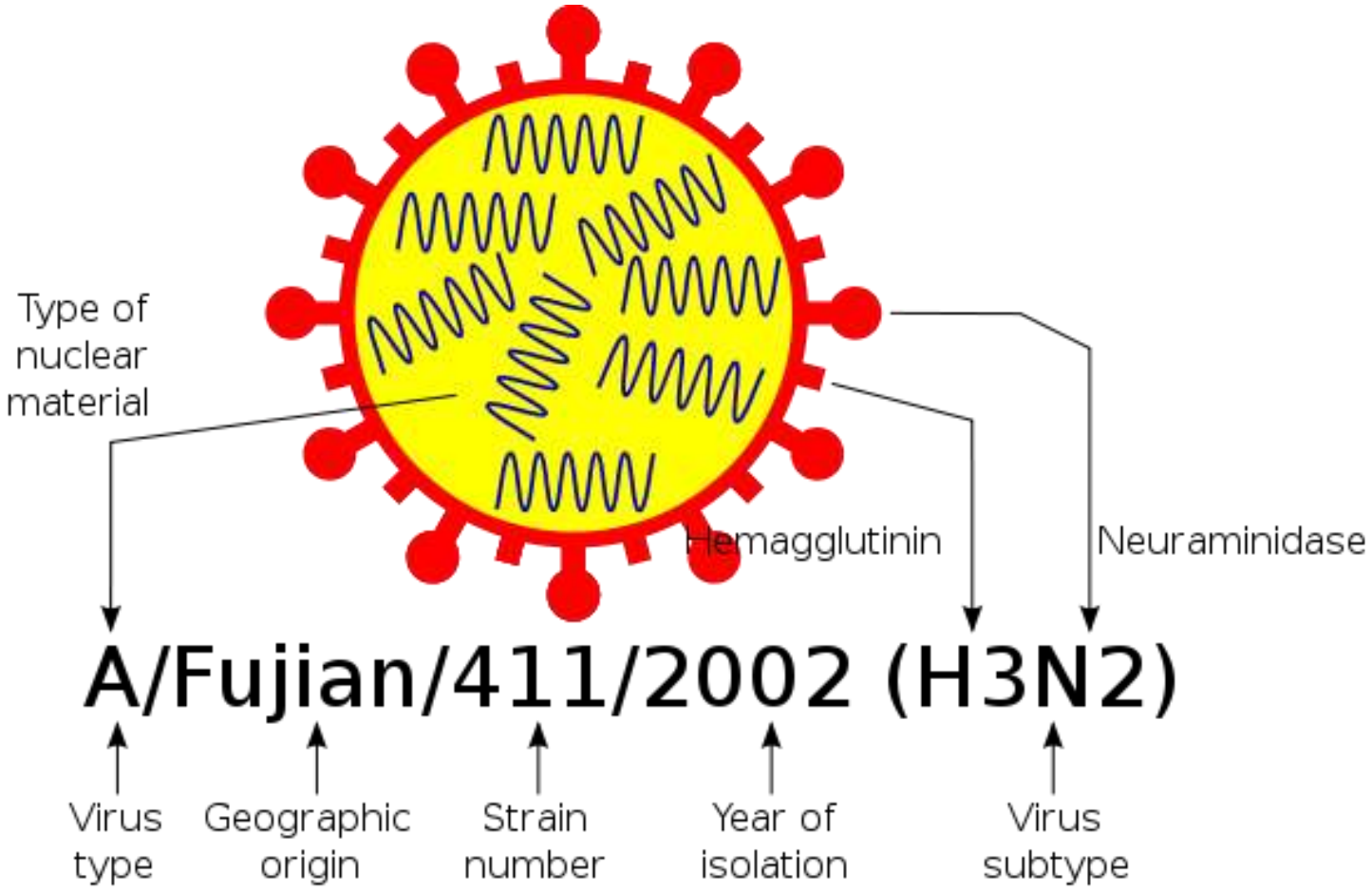
Med Clin N Am 97 (2013)

How are they named?



- Of the 16 HA subtypes, 6 have been found in human infections (H1, H2, H3, H5, H7, and H9).
- So far, only 3 subtypes of HA (H1, H2, H3) and 2 subtypes of NA (N1, N2) have caused pandemics in humans

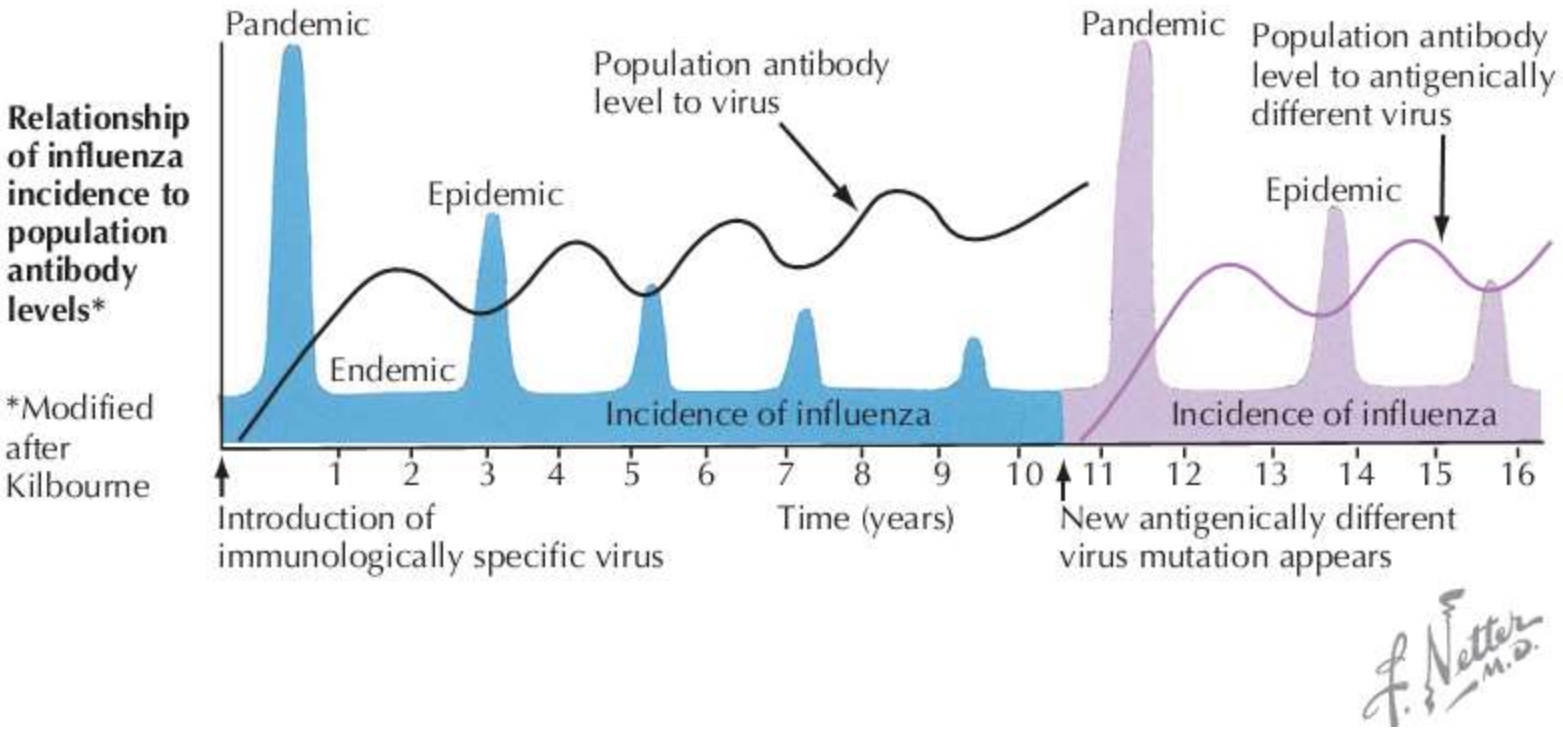
Antigenic drift

- Drift- relatively minor antigenic changes within the HA or NA of the virus
- gradual accumulation of amino acid changes in one or more of the five identified major antigenic sites on the HA molecule.
- antibody generated by exposure to previous strains does not neutralize the antigenic variant
- immunologic selection takes place, and the variant sup-plants previous strains as the predominant virus in the epidemic.

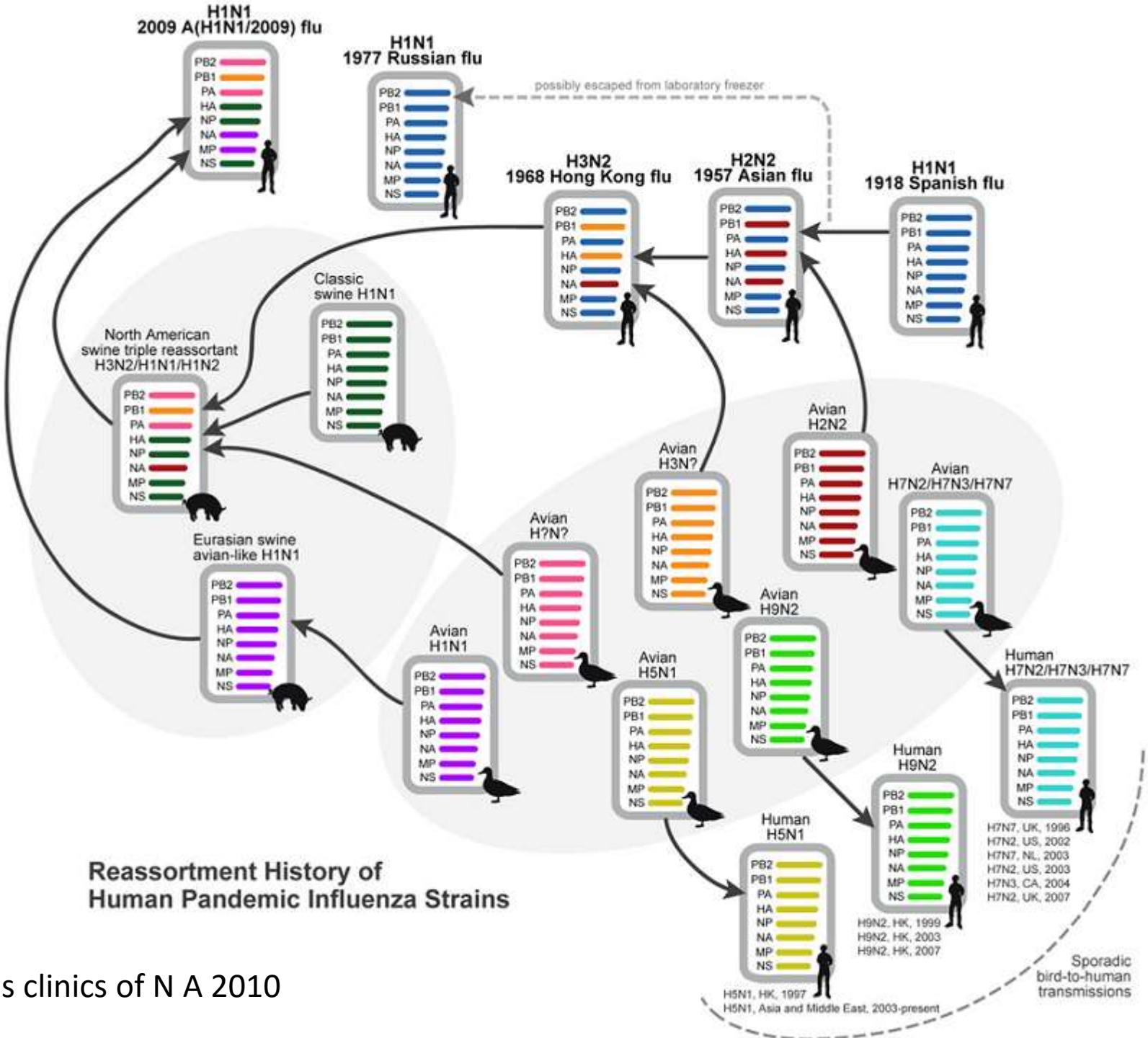
Antigenic shift

- These are “new” viruses, for which the population has no immunity
- Segmented genome, large reservoir of geetic diversity being maintained in birds

Antigenic shift & drift



Netter's infectious diseases



Inf Dis clinics of N A 2010

Current viruses

- H3N2
- H3N2 v
- H5N1
- H1N1
- H7N9
- Influenza B

WHO & CDC

Clinical features

- “On this day [July 13, 1510]…in Modena there appeared an illness that lasts three days with a great fever, & headache and then they rise…but there remains a terrible cough that lasts maybe eight days, and then little by little they recover and do not perish.”
- Tommasino de’ Bianchi - Chroniclers of the 1510 influenza pandemic

Lancet 2010

When to suspect influenza?

- ILI (influenza like illness)
- Unvaccinated
- Geographical location & season

Case definitions

- Influenza like illness- fever 100 F, 37.8 c, with cough or sore throat in the absence of a known cause other than influenza
- an ILI with laboratory-confirmed H1N1 influenza A virus detection by real-time reverse transcriptase (rRT)-PCR or culture.

CDC . USA

Unique features

Influenza Subtype	Clinical features
H7 viruses	Conjunctivitis
H9 viruses	Mild influenza like illness
H5 viruses (e.g. Avian H5N1)	Severe disease (respiratory) High mortality.
Seasonal influenza	Mild disease – complications in elderly, children, immunosuppressed, pregnant women, comorbid illness
SOIV (H1N1)	Similar to seasonal. Diarrhoea & vomiting more frequent

Diagnostic tests

Diagnostic tests for influenza

Method	Approximate Test Time	Sensitivity	Specificity
1. RT-PCR	Hours	High	Very high
2. Immunofluorescence (direct or indirect antibody staining)	Hours	Moderately high	High
3. Rapid influenza diagnostic tests	<30 min	Low to moderately high	High
4. Viral isolation (standard culture or shell vial culture)	Days	Moderately high	Highest

Clin Infect Dis 2009

In patients presenting less than 48 hours after the onset of cough and fever in influenza season, empirical treatment is more cost-effective than approaches involving testing

Arch Intern Med 2000

when clinical suspicion for influenza is high and especially if the patient is quite ill, hospitalized, or at high risk for complications of influenza (eg,an immunocompromized or frail elderly patient) RIDTs should be avoided, because of low sensitivity.

Med clinics of NA 2013

Pandemic

- the emergence and global spread of a new influenza A subtype to which the population has little or no immunity
- spreads rapidly from human to human
- cause great numbers of hospitalizations and deaths

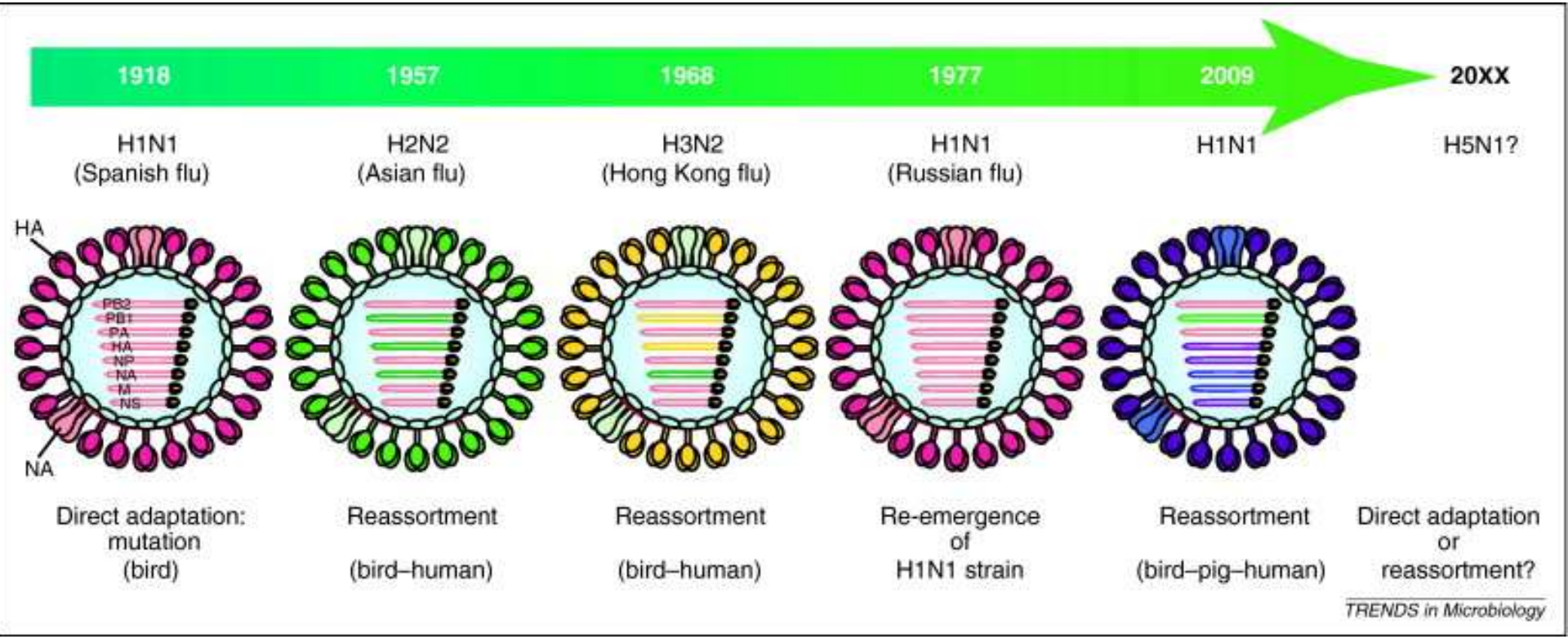
Phase 1	No viruses circulating among animals have been reported to cause infections in humans
Phase 2	An animal influenza virus has been confirmed to have caused infection in humans and is therefore considered a potential pandemic threat
Phase 3	Small clusters of disease in people have not resulted in human-to-human transmission sufficient to sustain community-level outbreaks
Phase 4	Human-to-human transmission able to cause community-level outbreaks has been verified
Phase 5	Human-to-human spread of the virus into at least 2 countries in 1 WHO region
Phase 6	Human-to-human spread of the virus into at least 1 other country in a different WHO region in addition to phase 5 criteria

World Health Organization

How does a pandemic begin?

- Increase in number of influenza like illness in children,
- Illness in adults
- Illness in vulnerable population & severe disease. High mortality & secondary attack rates upto 50%.
- Waves of disease outbreaks continue

Pandemics so far



Mexico March 2009

- Triple reassortment, north american swine & Eurasian swine
- Adults were distinctly spared > 60 yrs, probably due to cross reactivity resulting from infection by antigenically related virus

N Engl J Med 2012

Risk Factor	Examples and Comments
Age <5 yr	Increased risk especially for children <2 yr of age; highest hospitalization rates among children <1 yr
Pregnancy	Risk of hospitalization increased by a factor of 4 to 7, as compared with age-matched nonpregnant women, with highest risk in third trimester
Chronic cardiovascular condition	Congestive heart failure or atherosclerotic disease; hypertension not shown to be an independent risk factor
Chronic lung disorder	Asthma or COPD, cystic fibrosis
Metabolic disorder	Diabetes
Neurologic condition	Neuromuscular, neurocognitive, or seizure disorder
Immunosuppression	Associated with HIV infection, organ transplantation, receipt of chemotherapy or corticosteroids, or malnutrition
Morbid obesity†	Suggested but not yet proved to be an independent risk factor for complications requiring hospitalization or ICU admission and possibly for death
Hemoglobinopathy	Sickle cell anemia
Chronic renal disease	Renal dialysis or transplantation
Chronic hepatic disease	Cirrhosis
Long history of smoking	Suggested but not yet proved to be an independent risk factor
Long-term aspirin therapy in children	Risk of Reye's syndrome; drugs containing salicylates should be avoided in children with influenza
Age ≥65 yr	Highest case fatality rate but lowest rate of infection

N Engl J Med 2013

China March 2013

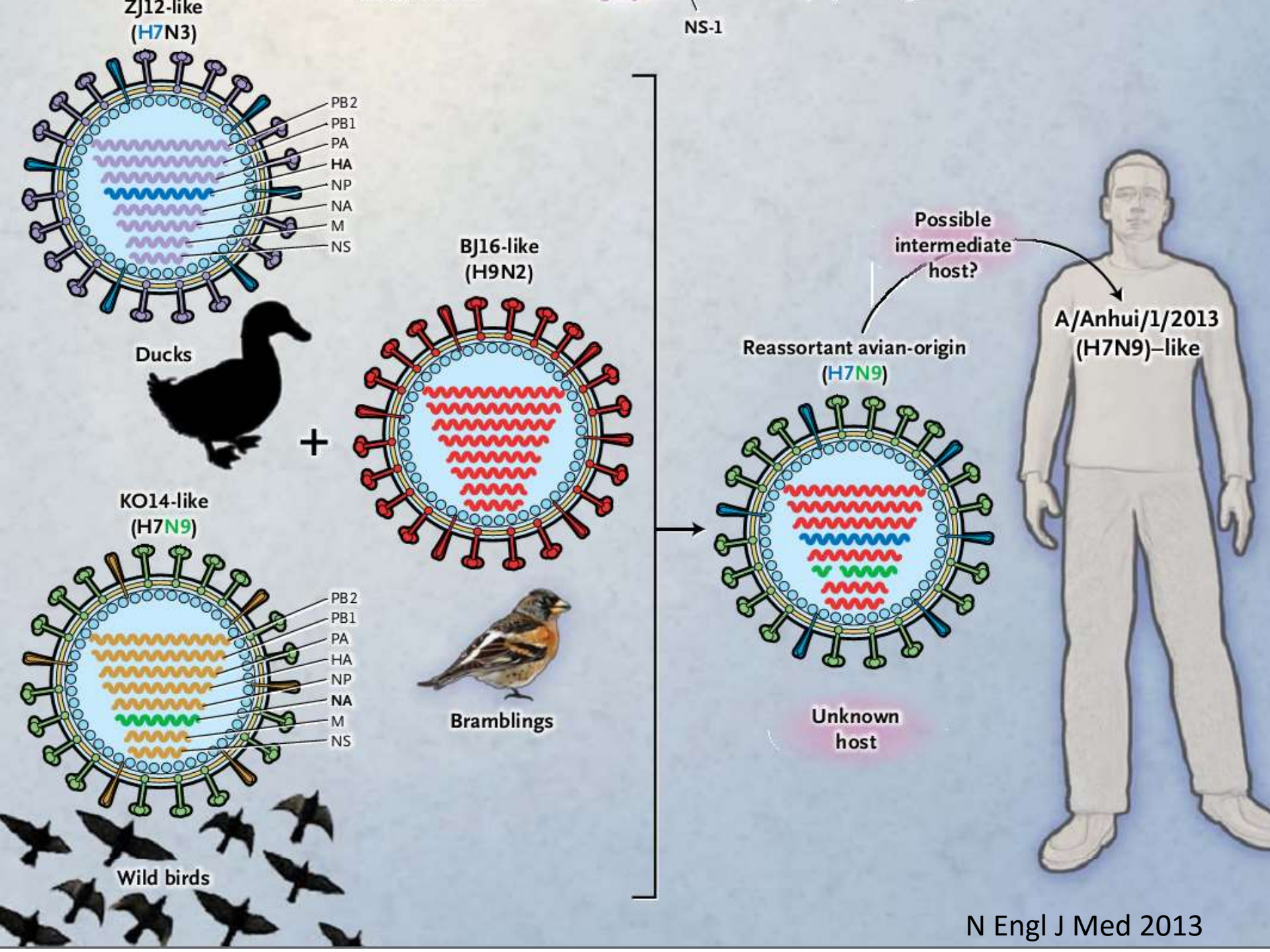
- Three patients admitted with Influenza like illness progressing to ARDS. PCR from clinical specimen positive for Influenza A (neg for B, other respiratory viruses)
- However it was “unsubtypable”… not the routine subtypes in circulation.(H1N1,H3N2,H5N1)
- Does it herald **the beginning of a pandemic**!!??

Return Of the Avians!!!

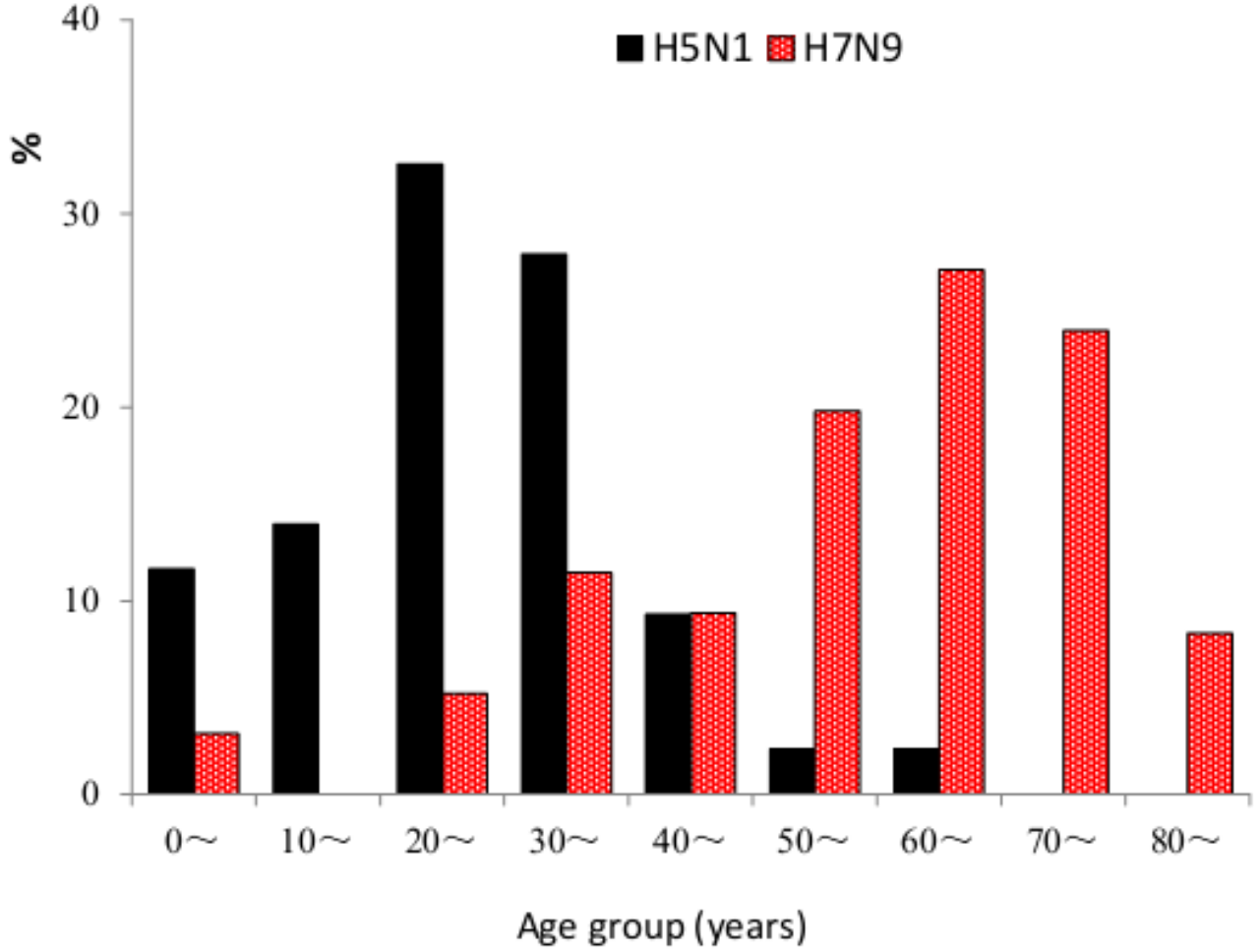
REAL TIME PCR & SEQUENCE ANALYSIS REVEALED **A NEW AVIAN STRAIN**

PREVIOUSLY UNRECOGNISED, FROM **VARIOUS POTENIAL PARENTAL STRAINS**

WHO.MAY 2013



N Engl J Med 2013



Urban elderly males were much affected , among the 101 cases

China mission report. 2013

H7N9

Characteristics	Percentage of patients
ICU admission	76.6%
≥65 years	42.3%
Underlying medical condition	61.3%
mortality	27%
lymphocytopenia	88.3%
Exposure to poultry	55.5

The only risk factor, to be associated with progression to ARDS, was preexisting comorbidities

N Engl J Med 2013

Why are we worried?

- Humans not exposed to H7, hence susceptible
- Genome analysis suggests, mammalian adaptation possible, hence the fear of human to human transmission
- Low pathogenicity in birds make it difficult to recognize. (unlike the 1918 swine flu, which caused severe disease in pigs as well as humans)

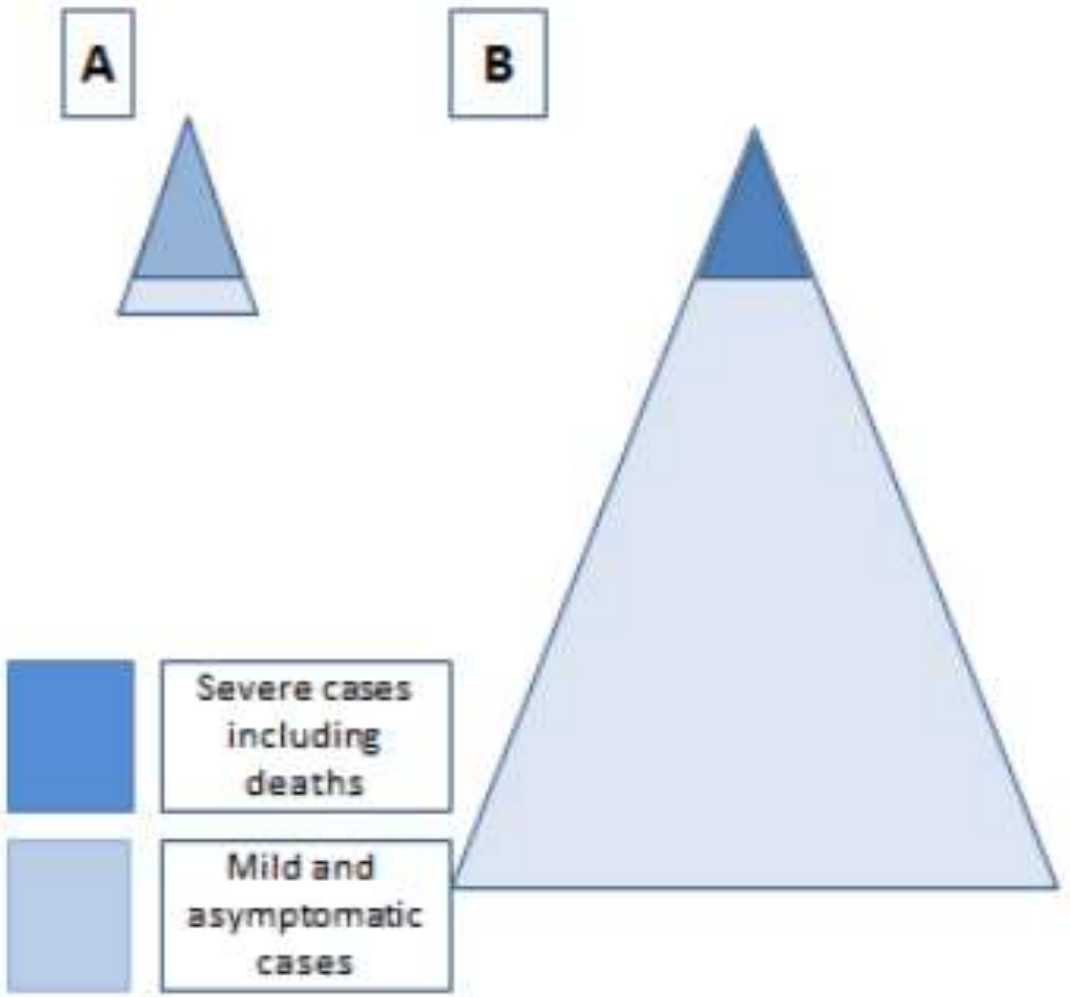
Why are we worried?

- H7N9 viruses were not detected in animals before
- Just days after the human outbreak was announced, the China Ministry of Agriculture reported detection of avian influenza H7N9 of low pathogenicity (LPAI) in avian species in the city of Shanghai

Two possible scenarios consistent with the current observed human epidemiology of the A(H7N9) cases

A The observed A(H7N9) cases are a high proportion of all cases and there are few mild or asymptomatic cases

B The observed severe A(H7N9) cases are only a proportion of all the cases and there are many mild or asymptomatic cases



China mission report. 2013

Swine Origin Influenza virus

- Outbreaks in humans by variants
- A hybrid of pandemic H1N1 (2009) & H3N2 – **H3N2 v**
- The current H3N2 Vaccine does not offer protection
- Swine to human transmission
- Causing localized outbreaks

- Spreads more readily from animals to humans
- No clear evidence of human-human transmission so far

Avian influenza

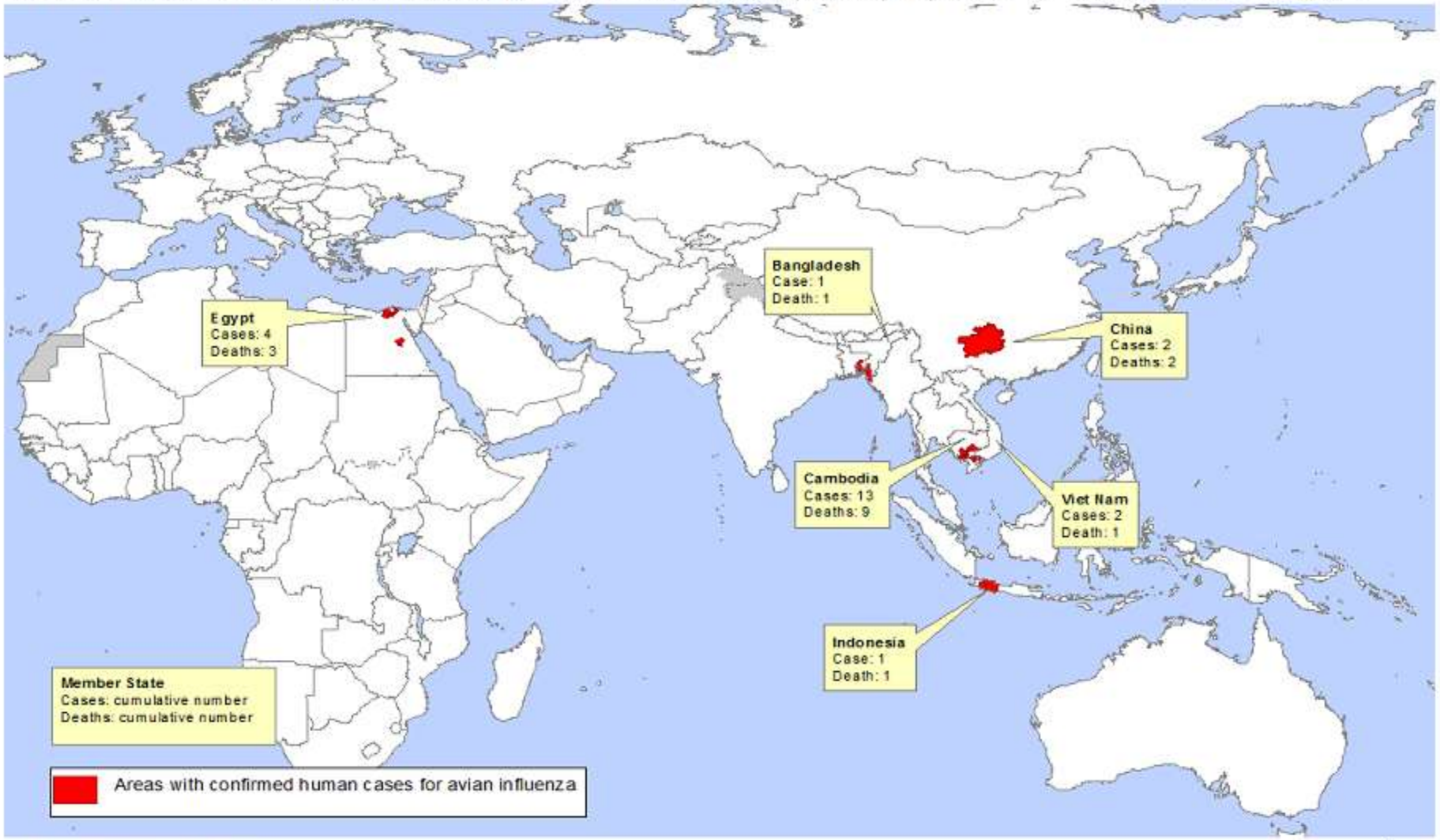
- High pathogenic avian influenza (HPAI) – H5N1
- Low pathogenic avian influenza (LPAI) – H9N2, H7N7, H7N2, H7N3

Avian influenza

- H5N1, Hongkong 1997, chicken to humans for first time. 6 of 18 died, high mortality of 30%

Science 1998

- Eradicated from HongKong after a mass cull of poultry, but continued to circulate asymptomatically amongst birds in southern China,
- reemerged in 2002 to 2003 & has been causing ongoing sporadic human infection & disease, with a high mortality (close to 60%) till present



Current status of Avian influenza.WHO

Influenza B

- Two distinct lineages only
- Seal is the only known interspecies
- Intrinsic resistance to all adamantanes

Osterhaus AD, et al. Science (New York, NY). 2000;288(5468):1051-3.

Prevention

- Immuno prophylaxis
- Chemo prophylaxis
- Non pharmacologic interventions during an epidemic

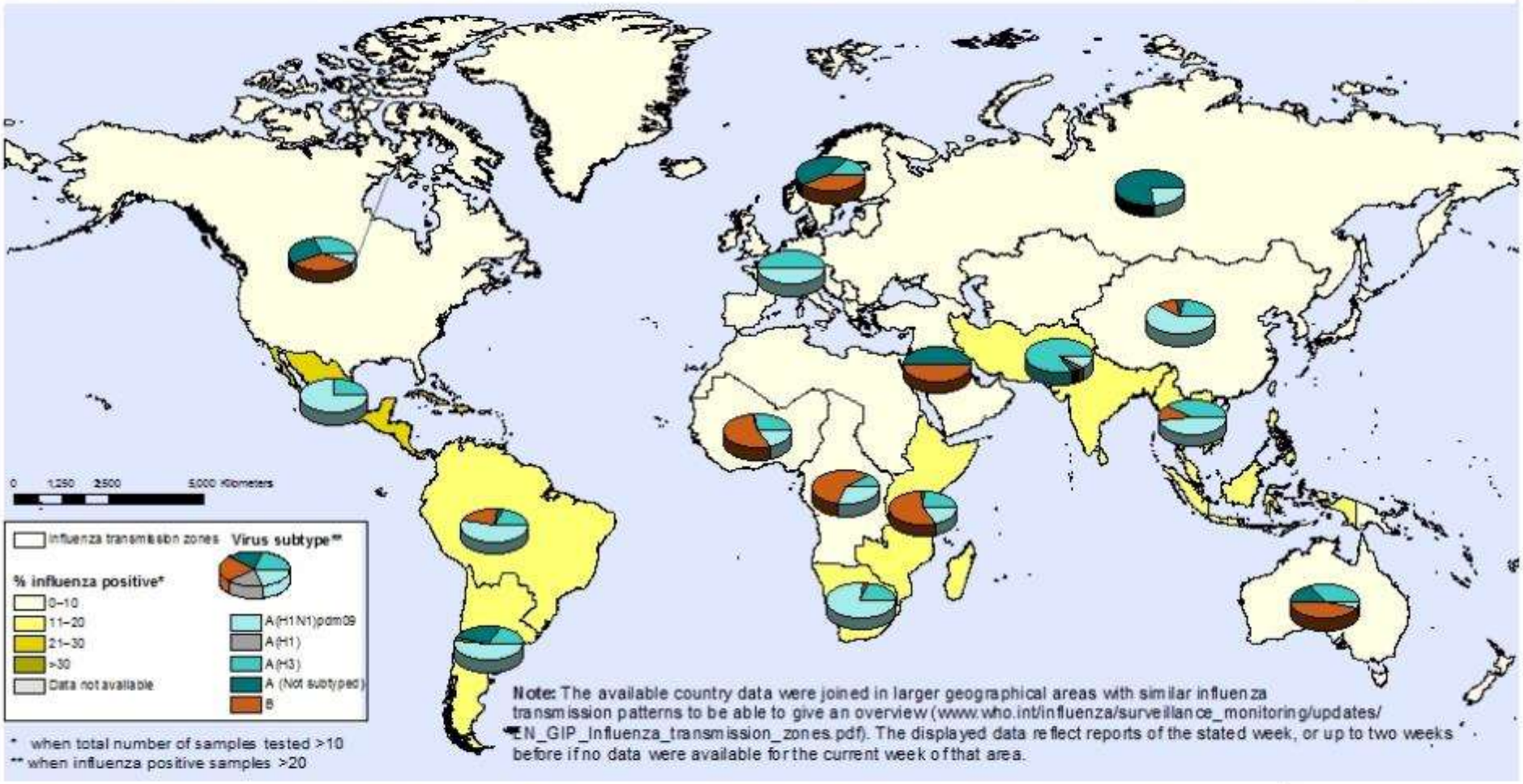
Vaccine

- Challenges – HA 16, NA 9,
- A large numbers of aquatic birds as their reservoir
- Antigenic drifts & shifts

- Hence there is a need for annual surveillance & vaccination accordingly.

Percentage of respiratory specimens that tested positive for influenza
By influenza transmission zone

Status as of week 27
30 June - 06 July 2013



Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf). The displayed data reflect reports of the stated week, or up to two weeks before if no data were available for the current week of that area.

* when total number of samples tested >10
** when influenza positive samples >20

Data Source: WHO/GIP, data in HQ as of 16 July 2013.
Data used are from FluNet (www.who.int/flunet), 12.00 UTC snapshot, from WHO regional offices and/or ministry of health websites.

World Health Organization

Vaccine for 2012-2013

- An A/California/7/2009 (H1N1)-like virus (against 2009 pandemic H1N1 influenza)
- An A/Victoria/361/2011 (H3N2)-like virus
- A B/Wisconsin/1/2010-like virus

WHO

Vaccines

- Triple inactivated vaccine (TIV)
- Live attenuated influenza vaccine (LAIV)

	LAIV	TIV
administration	Intra nasal	intramuscular
organisms	Influenza A,B(2,1)	Influenza A,B(2,1)
Age group	2-49 yrs	≥6 months

- For elderly, high dose triple inactivated vaccine, (intradermal) is available
- Effective in 50 to 80 % cases, based on the population studied

Newer vaccines

- **Adjuvants** – aluminium salts & saponin based ICSOMATRIX adjuvants have been tried.
- Increase immunogenecity
- Stimulates multiple arms of immune system
- Reduces the dose of the inactivated virus required for seroconversion

Brown LE. Vaccine. 2010;28(50):8043-5.

Universal vaccine

- Antibody-mediated protection directed against the influenza HA protein is generally strain-specific because the dominant epitopes on the globular head of the HA that are the target of the antibody response are under immune pressure to drift.
- Target antigens under evaluation include – H1, M1,M2e,NP,NA

Subbarao K, Matsuoka Y. Trends in microbiology. 2013;21(7):350-8.

Chemoprophylaxis

- Not a substitute for vaccines
- Indicated for
  - High risk-within 2 wks of vaccination
  - Unvaccinated
  - Vaccine contraindicated
- Neuraminidase inhibitors are used.

Non Pharmacologic Interventions

- Face mask
- Hand hygiene, with alcohol based hand sanitizers
- Cough etiquettes
- Closure of schools, avoid crowding
- Education about influenza
- Early reporting

Am J of Inf Control. 2010

Predicting a pandemic?

- Increased knowledge of the basic biology and ecology underlying host–switching events is required
- In 2007 -2008 the possibility of H5N1 acquiring human-human transmission & a potential pandemic was considered,..
- However, 2009 pandemic was again caused by H1N1 (triple reassorted)

JAMA 2008

Predicting a pandemic?

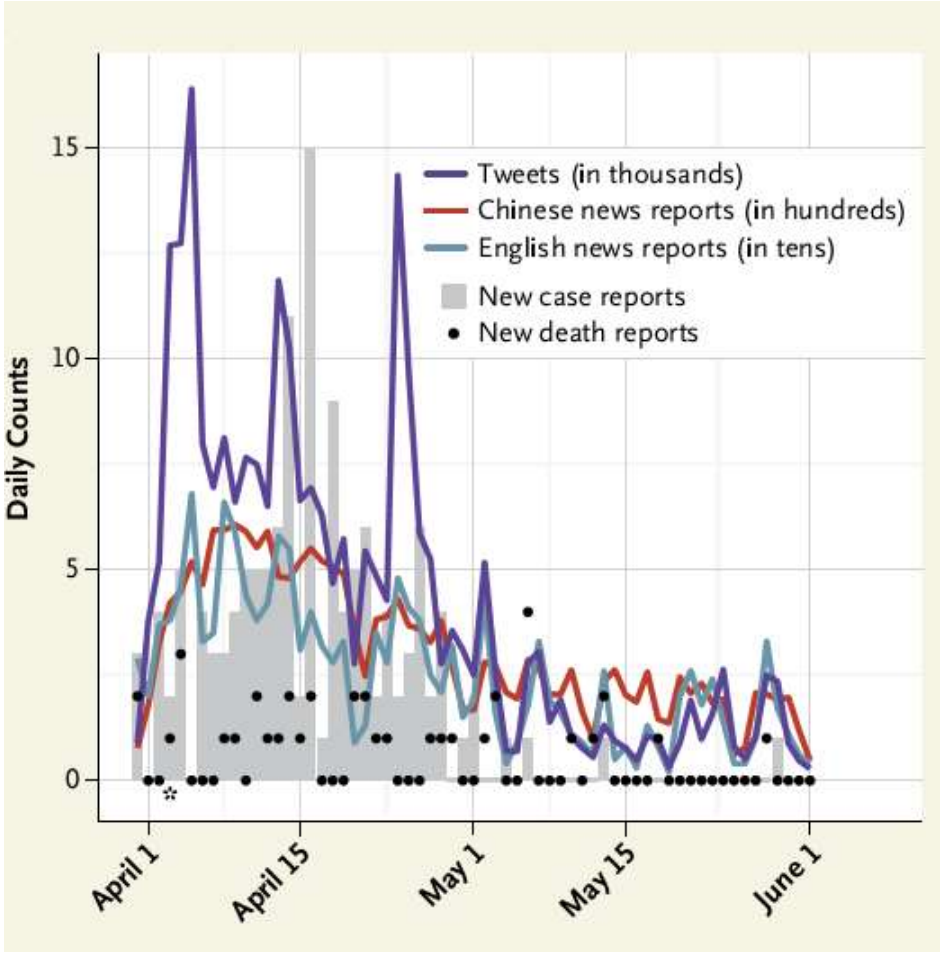
- Expect the Unexpected
- Pandemic prevention & control strategies must be planned accordingly

Preparedness & Response

- Surveillance
- Lab support – national institute of virology, Pune
- Hospital facilities & domiciliary rx
- Oseltamivir Rx & prophylaxis
- Drug & vaccine development and stockpiling
- Entry & exit screening
- Quarantine & isolation

Gov Of India

Digital Epidemiology



Salathe M, et al. The New England journal of medicine. 2013;369(5):401-4.

Lessons from SARS, extrapolated

- Nosocomial spread to health care workers caring for the critically ill
- vulnerability of health care facilities in an air-borne epidemic, and the necessity of establishing stringent infection control measures and crisis management protocols.
- The rapidity of spread, globally

Lessons from SARS-mechanical ventilation & ICU

- Elective & early intubation
- Low tidal volume ventilation
- Avoid aerosol generating procedures
- Negative pressure rooms wherever possible
- Adapting general hospitals for critical care, advance planning & conducting preparedness exercise.

The controversies!!!

“Tamiflu”-how safe is it?

- . A review of unpublished regulatory information from trials of neuraminidase inhibitors …. Still not completed by reviewers of cochrane collobarative. Since Roche has failed to provide the true details, for the past 3 yrs.
- BMJ has launched Open data campaign, to release full clinical trial reports

An ideal culture plate!- China

- Lots of birds, Live poultry markets
- Lots of humans
- An ideal climate!
- Good platform for genetic reassortment

Controversies again

- A team of scientists in China has created hybrid viruses by mixing genes from H5N1 and the H1N1 strain behind the 2009 swine flu pandemic, and showed that some of the hybrids can spread through the air between guinea pigs

Science 2013

- Chinese scientist, claim it to be an effort towards understanding influenza,…and prevent its spreads

- ‘Appalling irresponsibility': Senior scientists attack Chinese researchers for creating new strains of influenza virus in veterinary laboratory - The INDEPENDENT (UK) 2013