Respiratory Viruses

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Outline

- Influenza
  - Introduction
  - ‘Seasonal’ influenza in the tropics
  - Pandemic Influenza
  - Avian Influenza
- Other respiratory viruses
- Respiratory viruses with high mortality
- Summary

Influenza Virus

- Family: Orthomyxoviridae
- First isolated 1933
- Segmented genome
- 8 single stranded, negative sense RNA molecules
- Encodes for 10 proteins
  - Nucleoprotein (NP), Matrix (M) protein
  - Important surface glycoproteins
    - Hemagglutinin (HA)
    - Neuraminidase (NA)

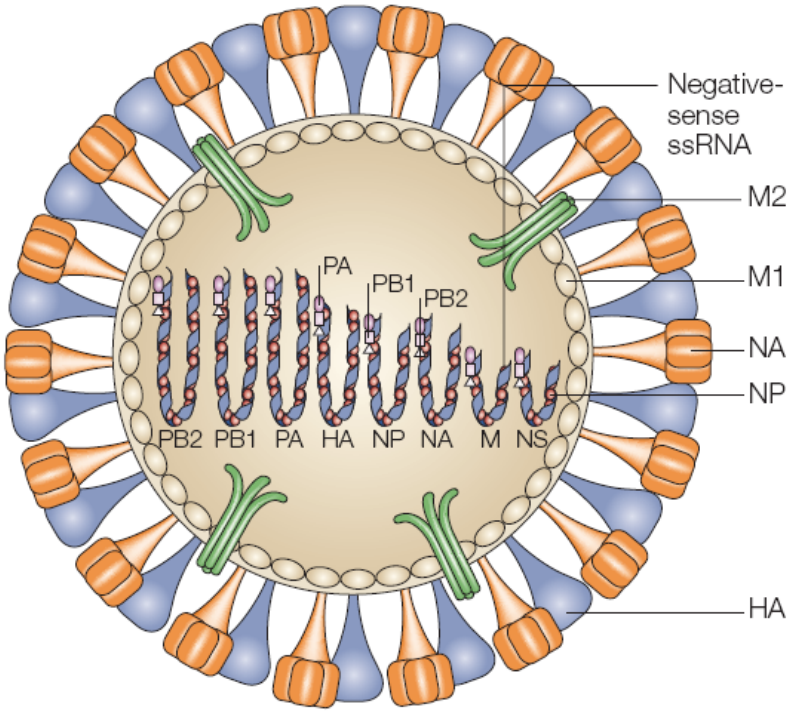


Figure 1 | **Schematic diagram of an influenza A virus virion.** Two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), and the M2 ion-channel protein are embedded in the viral envelope, which is derived from the host plasma membrane. The ribonucleoprotein complex comprises a viral RNA segment associated with the nucleoprotein (NP) and three polymerase proteins (PA, PB1 and PB2). The matrix (M1) protein is associated with both ribonucleoprotein and the viral envelope. A small amount of non-structural protein 2 is also present, but its location within the virion is unknown.

Influenza Typing

- Classified based on antigenic differences in NP and M
- Influenza A viruses have various types of HA and NA
- Influenza B viruses do NOT have shifts and major changes in HA and NA
- Example Nomenclature

Type /Host / Place / Strain #/Year (Influenza subtype)

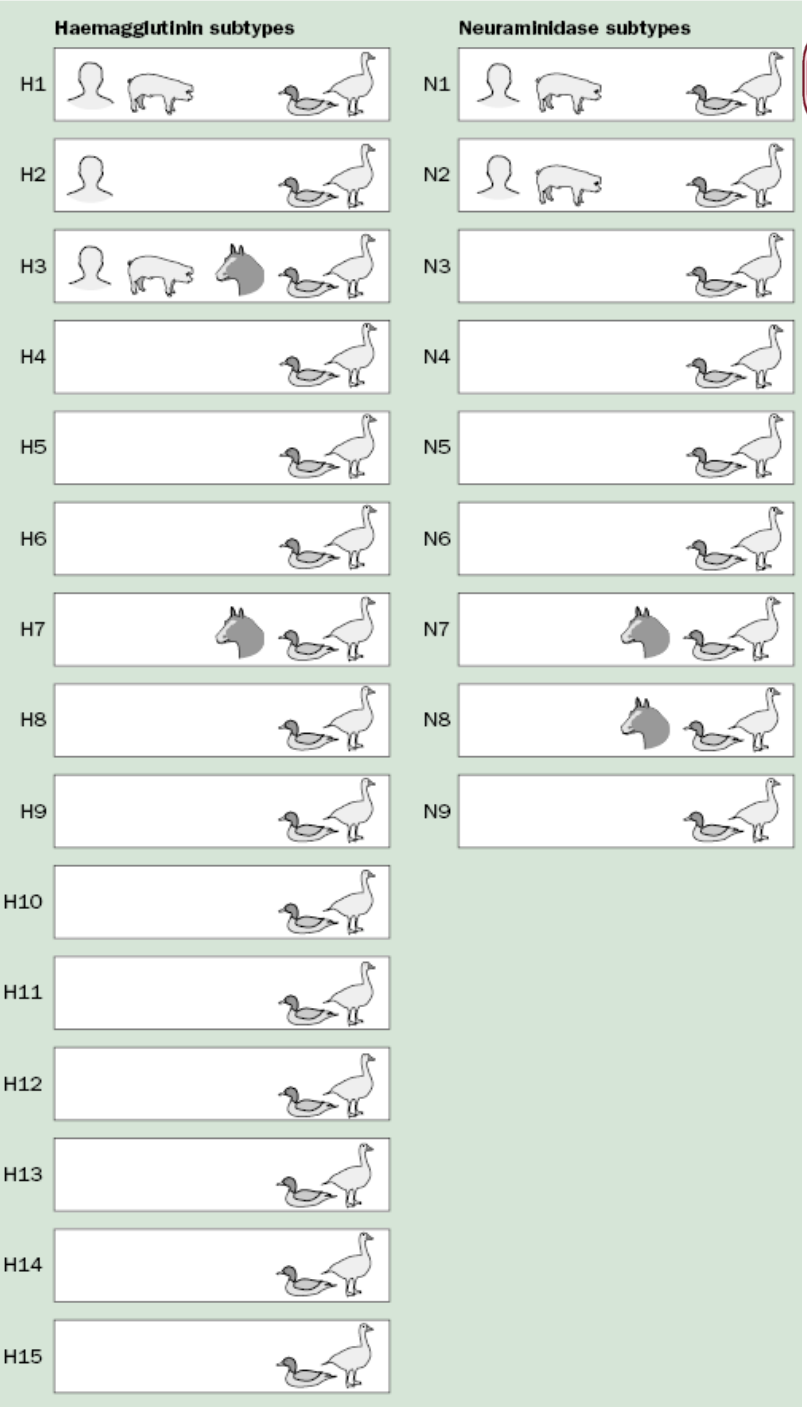
A / Duck / Vietnam/ 11 / 04 (H5N1)

HA and NA

- Hemagglutinin initiates infection by binding to sialic acid residue on respiratory epithelial cells

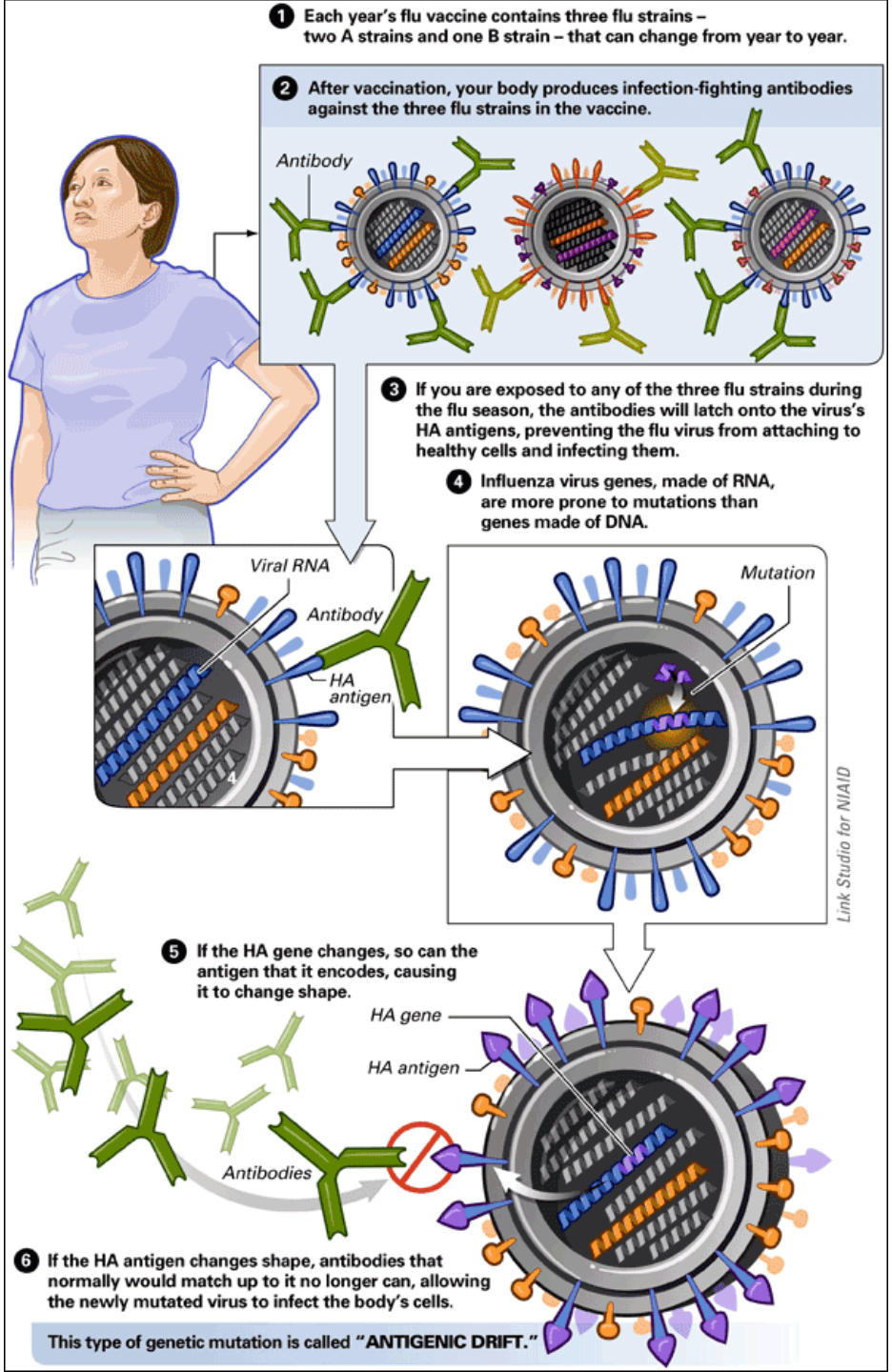
- Neuraminidase liberates new virions after viral replication and help virions stay separated

- All HA and NA in birds
- Crossing of species is limited
  - Humans
    - H1, H2, H3
    - N1, N2
  - Horses
    - H7, N7
    - H3, N8
  - Pigs
    - H1, H3
    - N1, N2



Antigenic Drift

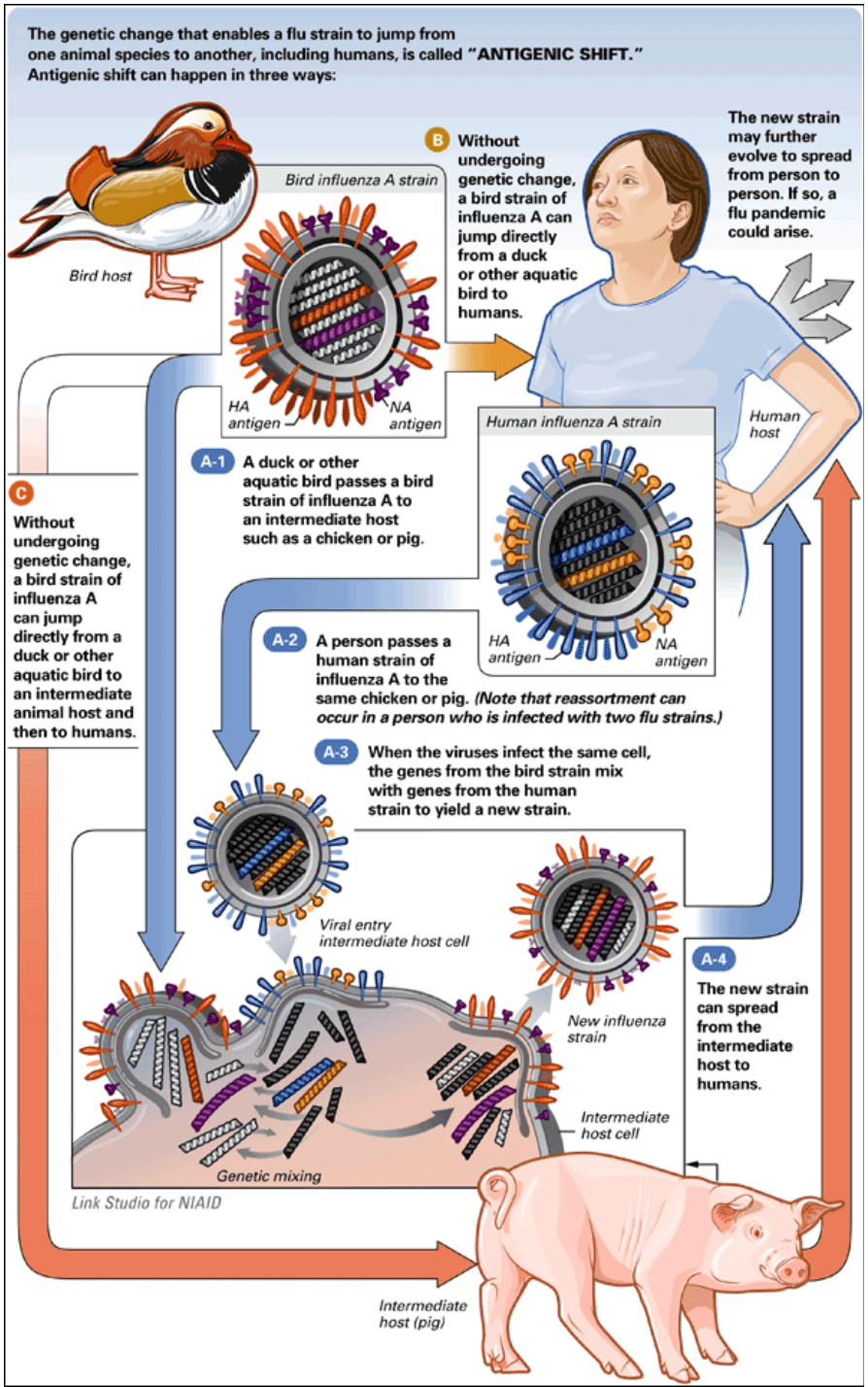
- Occurs in Influenza A and B
- Point mutations in the viral RNA genes
- Leads to production of new hemagglutinin or neuraminidase
- **Annual occurrence** to avoid host immune system
- Less severe ‘seasonal’ epidemics
- Occurs as virus spreads through a susceptible population



http://nieman.harvard.edu/Microsites/NiemanGuideToCoveringPandemicFlu/TheScience/HowFluVirusesChange.aspx

Antigenic Shift

- Major changes in HA and NA
- Influenza A viruses only
- **Re-assortment** of viral genetic material between viruses co-infecting the same cell
- **Pandemic strains** result from exchange of genetic material between animal and human viruses
- No protective immunity in host
- Usually more rapidly spreading and severe infection



http://nieman.harvard.edu/Microsites/NiemanGuideToCoveringPandemicFlu/TheScience/HowFluVirusesChange.aspx

Influenza in the Tropics

- Less distinct ‘seasonal’ pattern vs. temperate regions
- Year round infections
- ‘seasonal’ patterns vary by location
  - Peaks related to rainy seasons
  - Biannual peaks (rainy season and winter months)
  - Year round infection without clear peaks

Environmental Predictors of Seasonal Influenza Epidemics across Temperate and Tropical Climates

- Study conducted at 78 study sites globally
- Influenza infections peaked during low specific humidity and temperatures in areas where these values fell below threshold
- In areas with constant high humidity and temperature, influenza infections peaked in month of high precipitation

Citation: Tamerius JD, Shaman J, Alonso WJ, Bloom-Feshbach K, Uejio CK, et al. (2013) Environmental Predictors of Seasonal Influenza Epidemics across Temperate and Tropical Climates. PLoS Pathog 9(3): e1003194. doi:10.1371/journal.ppat.1003194

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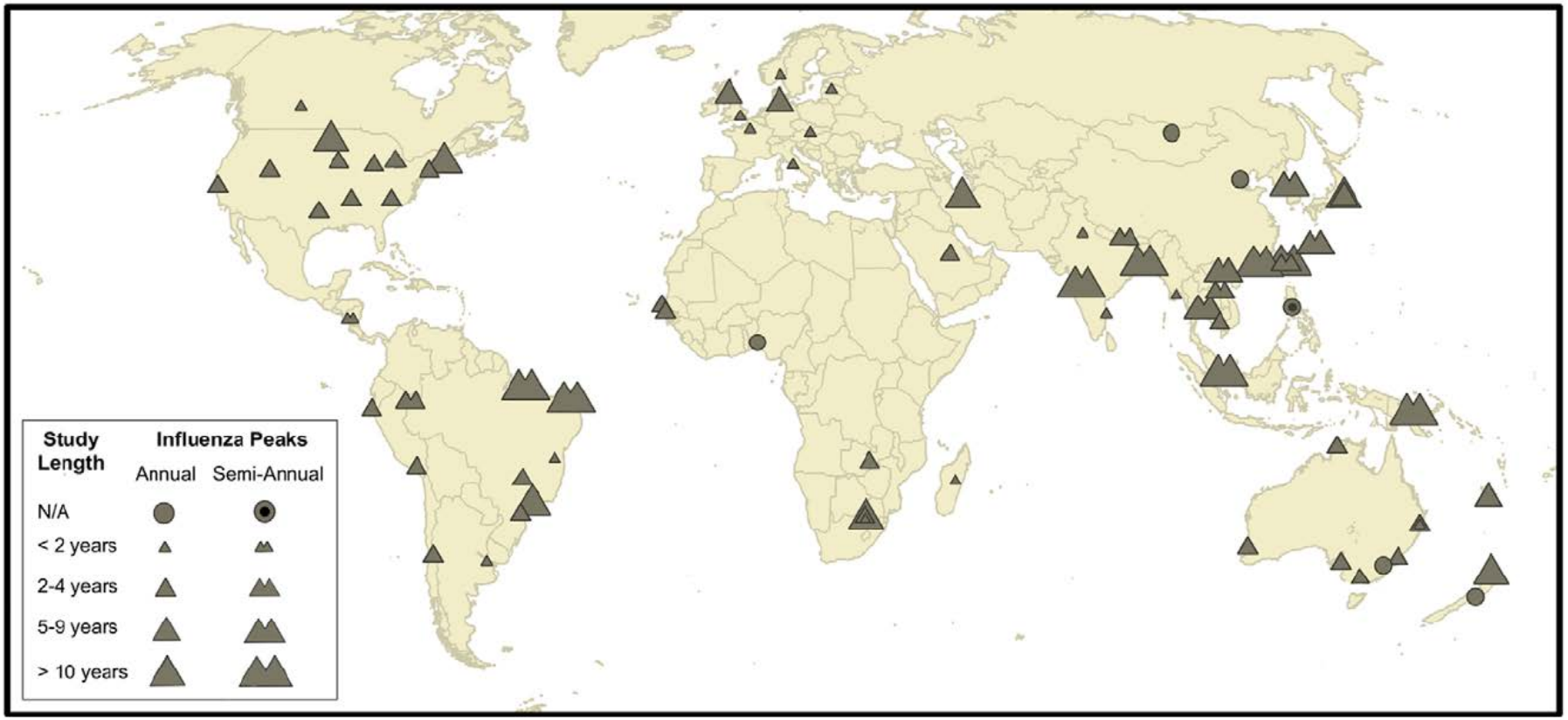
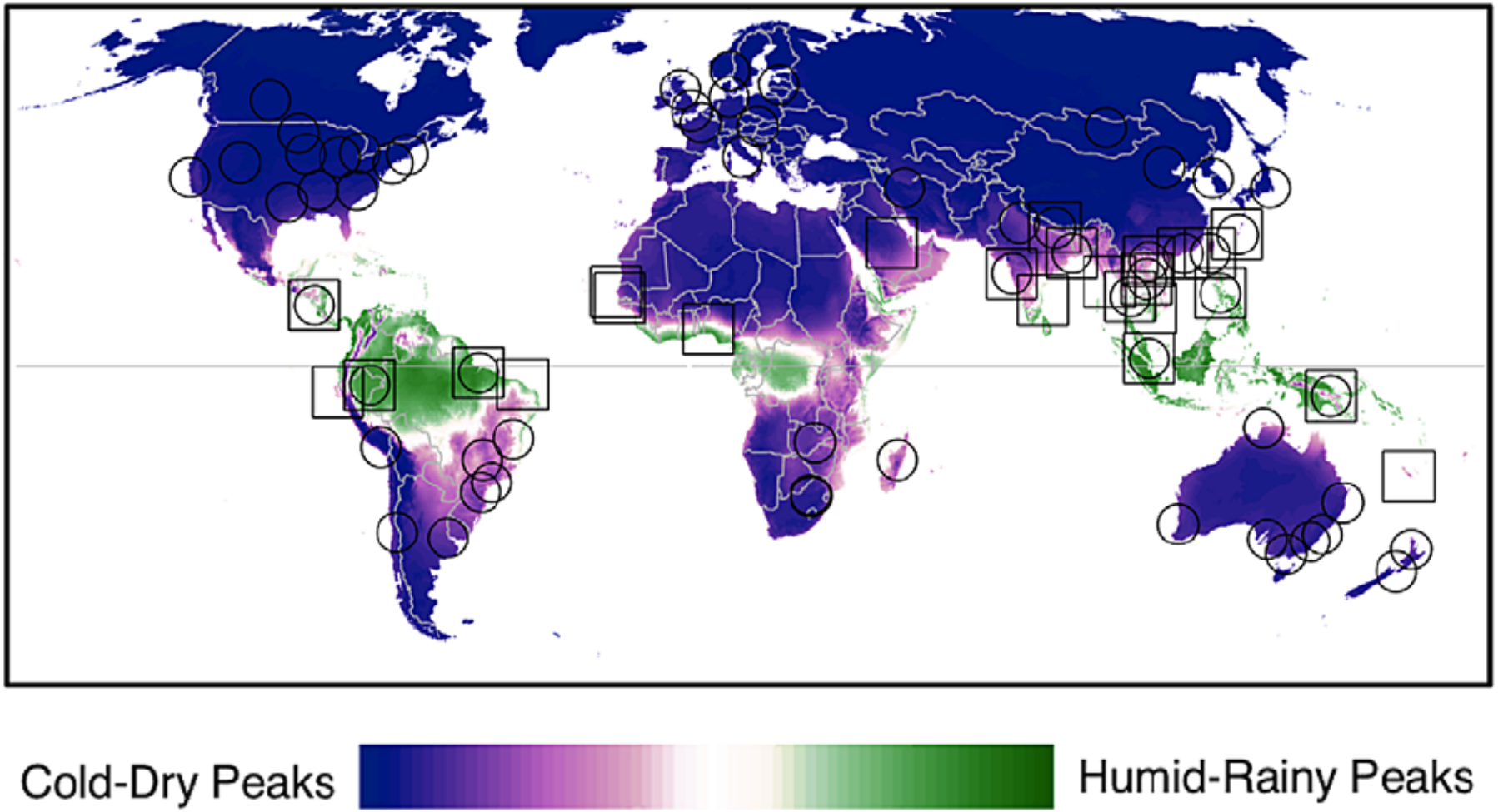
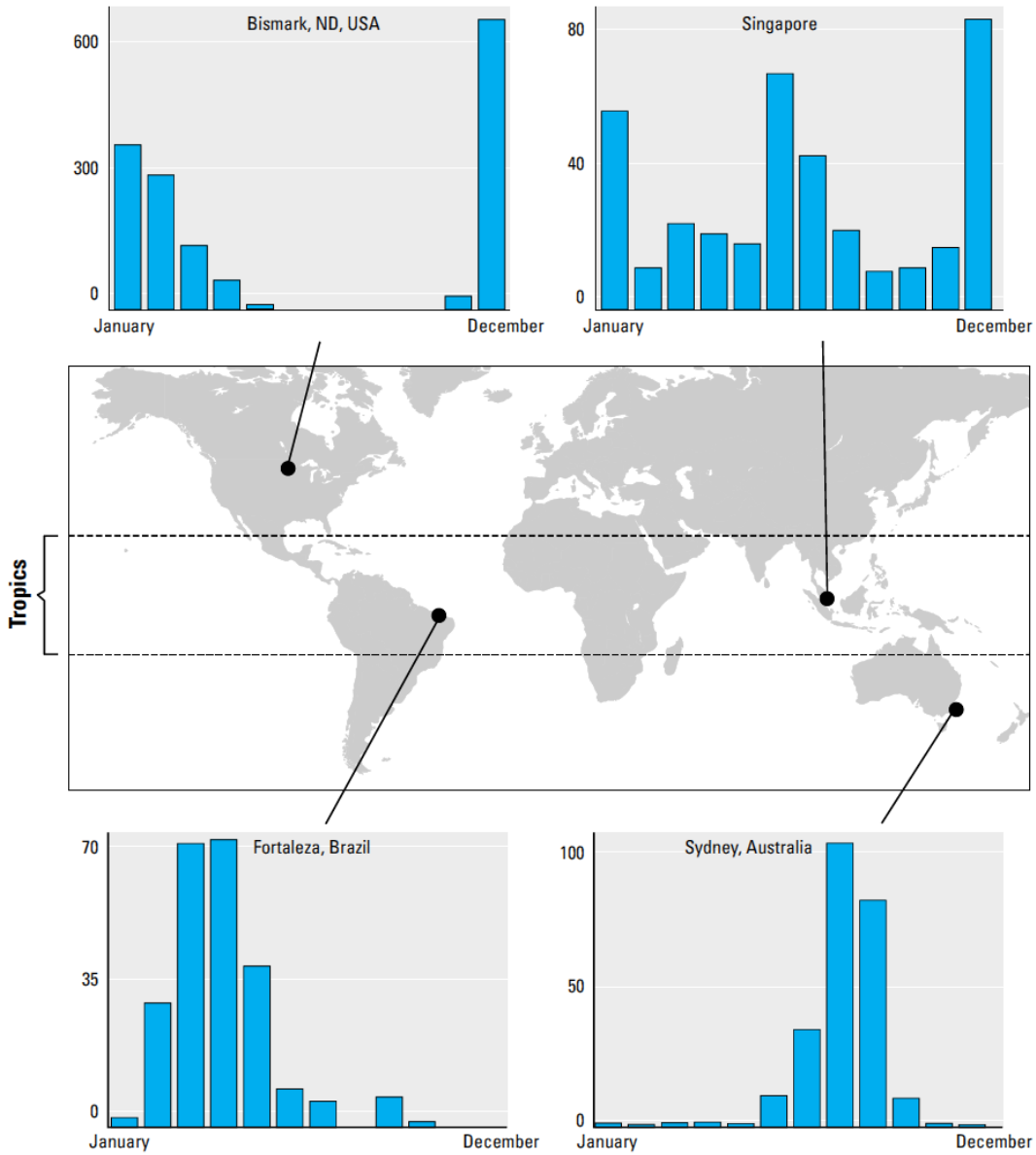
Influenza in the tropics



Influenza in the tropics



Rainy season = influenza peak



Tamerius et al.
Environ Health Perspect
2011

Multiple Factors Impact Influenza Epidemics

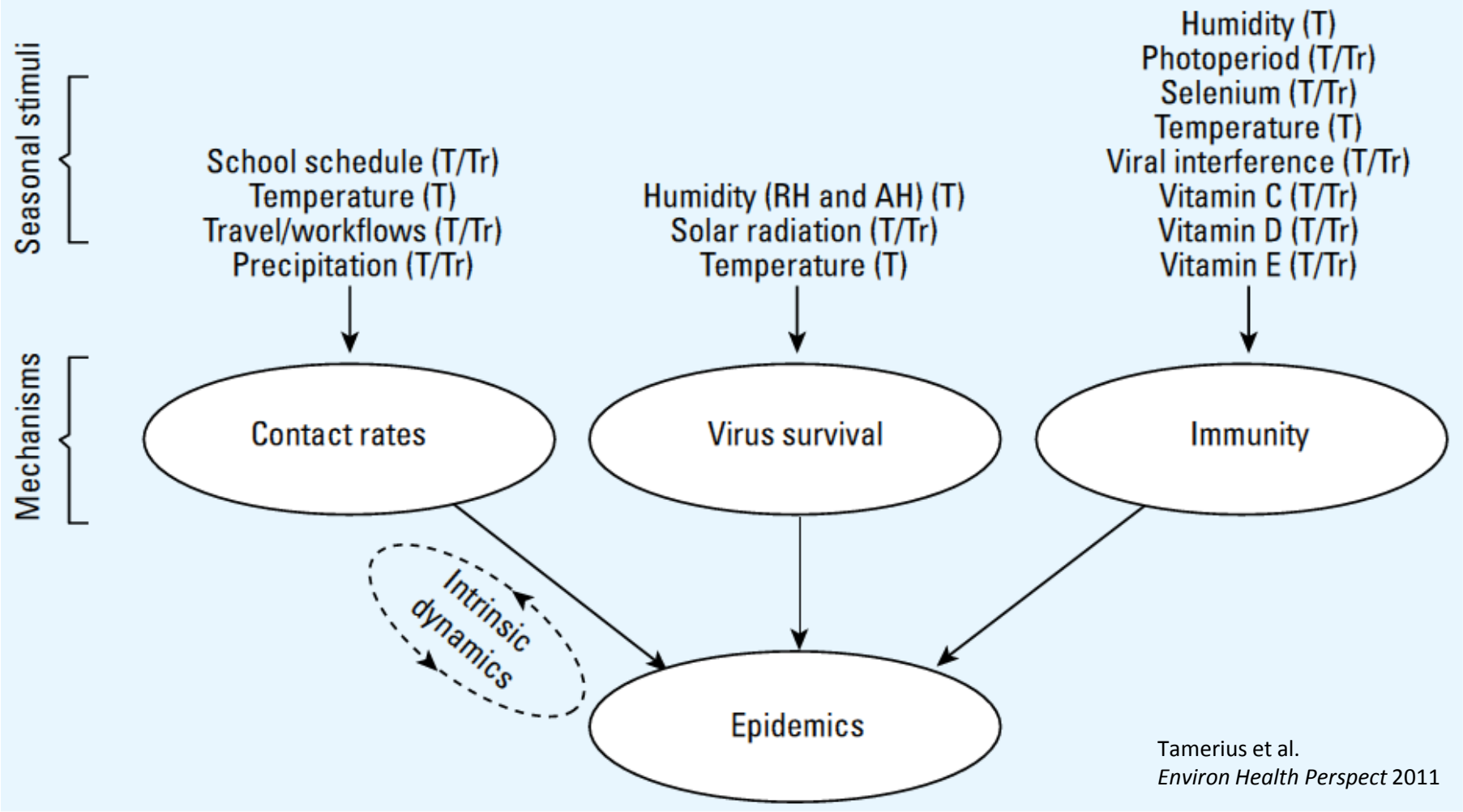


Figure 2. Putative relationship and causal connections among key seasonal stimuli, mediating mechanisms, and influenza epidemics. The notation adjacent to each seasonal stimulus indicates whether it potentially explains influenza seasonality in the tropics (Tr), temperate regions (T), or both (T/Tr). The diagram also includes a component depicting the effects of intrinsic dynamics.

Seasonal Influenza Vaccine

- Surveillance at 130 influenza centers in 101 countries
- WHO centers (Atlanta, London, Melbourne, Tokyo, Beijing)
- Meetings and decision for inclusion:
  - September for Southern hemisphere's vaccine
  - February for Northern hemisphere's vaccine
- WHO recommended 2013-2014 vaccine:
  - An A/California/7/2009 (H1N1) pdm09-like virus
  - An A(H3N2) virus similar to A/Victoria/361/2001
    - CDC: A/Texas/50/2012
  - A B/Massachusetts/2/2012-like virus
  - A B/Brisbane/60/2008-like virus **
- Identify strain to be used, growing virus strain, quality control, production, sale, distribution, administration
- TAKES TIME (at least 6 months) and MISMATCHES OCCUR

Vaccine Efficacy

	Population (dates)	Patients randomly allocated to receive TIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (18–64 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	728	75% (42 to 90)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1205	16% (–171 to 70)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Beran et al (2009)[26]	Healthy adults aged 18–64 years (2005–06)	6203	22% (–49 to 59)	Type A: similar H3N2 and H1N1; type B: lineage mismatch
Beran et al (2009)[27]	Healthy adults aged 18–64 years (2006–07)	7652	62% (46 to 73)	Type A: similar H3N2; type B: lineage mismatch
Monto et al (2009)[28]	Healthy adults aged 18–49 years (2007–08)	1139	68% (46 to 81)	Type A: drifted H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2005–06)	3514	50%† (14 to 71)	Type A: similar H3N2; type B: lineage mismatch
Jackson et al (2010)[21]	Healthy adults aged 18–49 years (2006–07)	4144	50%† (–3 to 75)	Type A: similar H3N2; type B: mixed lineage
Frey et al (2010)[29]	Healthy adults aged 18–49 years (2007–08)	7576	63% (one-sided 97·5% lower limit of 47%)	Type A: mixed strains; type B: lineage mismatch
Madhi et al (2011)[30]	Adults aged 18–55 years with HIV infection (2008–09)	506	76% (9 to 96)	Type A: drifted H1N1; type B: not reported
Children (6–24 months)				
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (1999–2000)	411	66% (34 to 82)	Type A: similar H3N2 and H1N1; type B: not reported
Hoberman et al (2003)[31]	Healthy children aged 6–24 months (2000–01)	375	–7% (–247 to 67)	Type A: similar H3N2 and H1N1; type B: lineage match

No studies were available for adults aged 65 years or older or children aged 2–17 years. *One other study by Loeb and colleagues[43] met inclusion criteria and contained data for all age groups. †Our calculation.

Table 2: **Randomised controlled trials of trivalent inactivated vaccine (TIV) meeting inclusion criteria***

Lancet Infect Dis 2012; 12:36-44

Vaccine Efficacy

	Population (dates)	Patients randomly allocated to receive LAIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Adults (≥60 years)				
De Villiers et al (2010)[37]	Community-dwelling ambulatory adults aged ≥60 years (2001–02)	3242	Overall 42% (21 to 57); 31% (–3 to 53) for patients aged 60–69 years; 57% (29 to 75) for patients aged ≥70 years	Type A: similar H3N2; type B: lineage match
Adults (18–49 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	725	48% (–7 to 74)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1191	8% (–194 to 67)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Monto et al (2009)[28]*	Healthy adults aged 18–49 years (2007–08)	1138	36% (0 to 59)	Type A: drifted H3N2; type B: lineage mismatch
Children (6 months–7 years)				
Belshe et al (1998)[32]	Healthy children aged 15–71 months (1996–97)	1602	93% (88 to 96)	Type A: similar H3N2; type B: lineage match
Belshe et al (2000)[33]	Healthy children aged 26–85 months (1997–98)	1358	87% (78 to 93)	Type A: drifted H3N2; type B: not reported (1 isolate)
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2000–01)	1784	84% (74 to 90)	Type A: similar H3N2 and H1N1; type B: lineage match
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2001–02)	1119	85% (78 to 90)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Bracco Neto et al (2009)[38]	Healthy children aged 6–<36 months (2000–01)	1886	72% (62 to 80)	Majority of strains were similar (not reported by type)
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2000–01)	3174	68% (59 to 75)	Type A: similar H3N2 and H1N1; type B: lineage match
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2001–02)	2947	57% (30 to 74)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Lum et al (2010)[36]	Healthy children aged 11–<24 months (2002–03)	1233	64% (40 to 79)	Type A: similar H1N1 and mixed H3N2; type B: mixed lineage

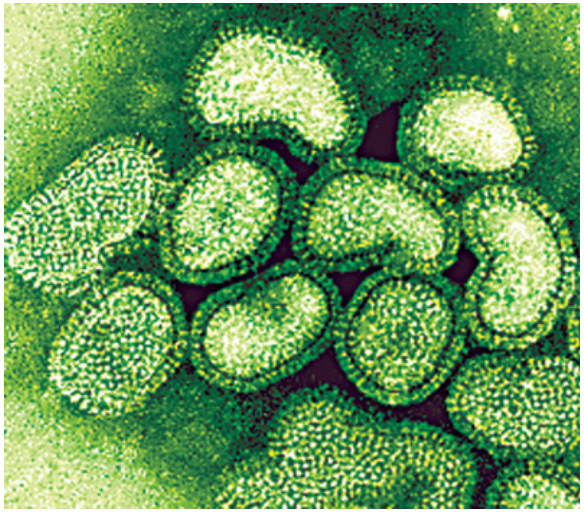
No studies were available for adults aged 50–59 years or children aged 8–17 years. *Authors reported culture, RT-PCR, and RT-PCR/culture; we report RT-PCR/culture results.

Table 3: **Randomised controlled trials of live attenuated influenza vaccine (LAIV) meeting inclusion criteria**

Lancet Infect Dis 2012; 12:36-44

Pandemic Influenza

- Influenza A virus introduction
  - Novel HA gene
  - No ‘herd’ immunity
  - Ability to spread efficiently among humans
- Pandemics of 20th century
  - All originated from avian influenza viruses
  - Intervals of 11-39 years
  - 1918 (H1N1: Spanish)
  - 1957 (H2N2: Asian)
  - 1968 (H3N2: Hong Kong)
  - 2009 (H1N1: US, Mexico)
- Pseudo- and Abortive pandemics
  - 1947 (H1N1: Japan/Korea/New Jersey)
  - 1976 (H1N1: New Jersey)
  - 1977 (H1N1: Soviet Union)



WHO Pandemic Influenza Phases

- Phases 1-3: Mostly animal infections
- Phase 4: Human-human transmission
- Phase 5-6: Pandemic, widespread human infection
- Post Peak: possibility of recurrence
- Post Pandemic: Seasonal

Pandemic Influenza

- Severe influenza syndrome
  - Fever, cough, fatigue, shortness of breath
  - Abdominal pain, diarrhea, vomiting
  - No conjunctivitis
- CXR
  - Bilateral infiltration, lobar collapse, focal consolidation
- Complications
  - Acute respiratory distress, renal failure, bacterial superinfection

1918 Influenza Pandemic

- 1/3 of the world's population (500m) infected / ill
- Case fatality rates of >2.5%
- 50-100m deaths
- 3 waves: spring/summer, summer/fall, winter
- Unclear source of pandemic virus, limited capabilities

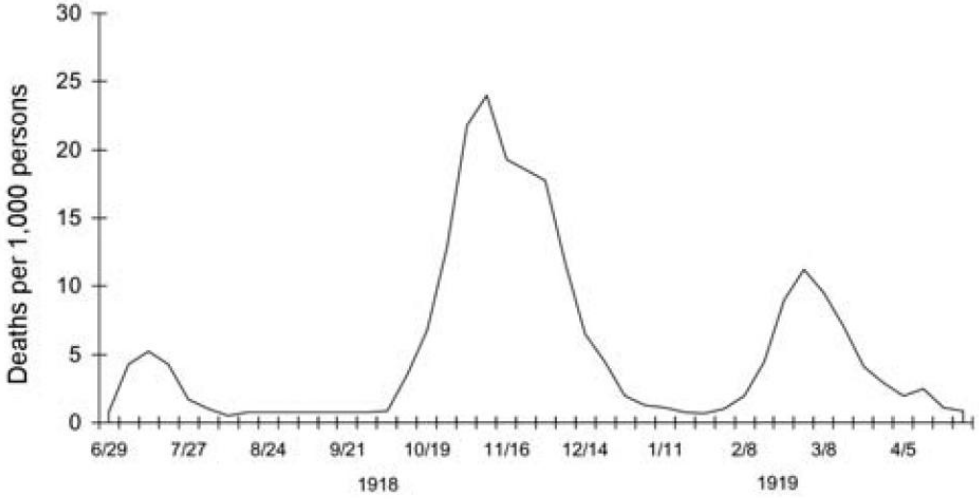


Figure 1. Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919 (*21*).

2009 H1N1 Pandemic

- ‘Swine flu’ first reported March 2009 in Mexico
- High human to human transmission, WHO pandemic level declared 6 June 2009
- Influenza A virus
  - Reassortment of 2 swine, one human strain, one avian strains
- Incubation: 1-4 days; viral shedding peak: 2-3 day into illness
- Secondary attack rate: 14-19%
- Viral shedding peaks first 2-3 days of illness
- Estimated death and impact varies by method
  - Actual deaths vs. laboratory confirmed
  - Average global H1N1 related fatality estimate: 201,200
  - CDC US H1N1 related fatality estimate: 12,470
- Less severe than 1918 H1N1 pandemic
- Immunity: natural infection, immunization, preexisting immunity from remote infection with related strain

2009 H1N1 Pandemic

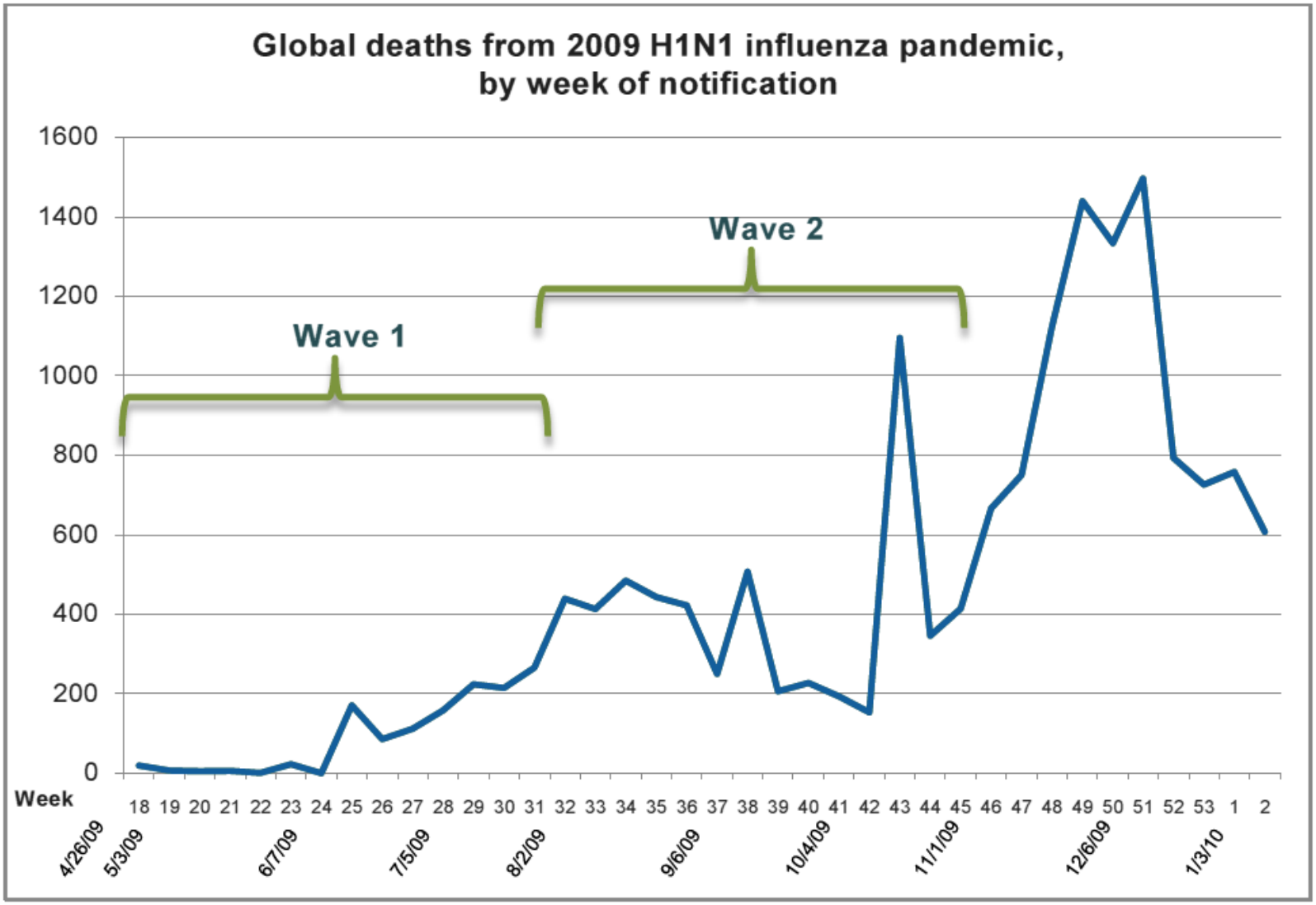


Figure 1: Global deaths from the 2009 H1N1 influenza pandemic, by week (Data Source: ECDC, 2010)

2009 H1N1 Pandemic

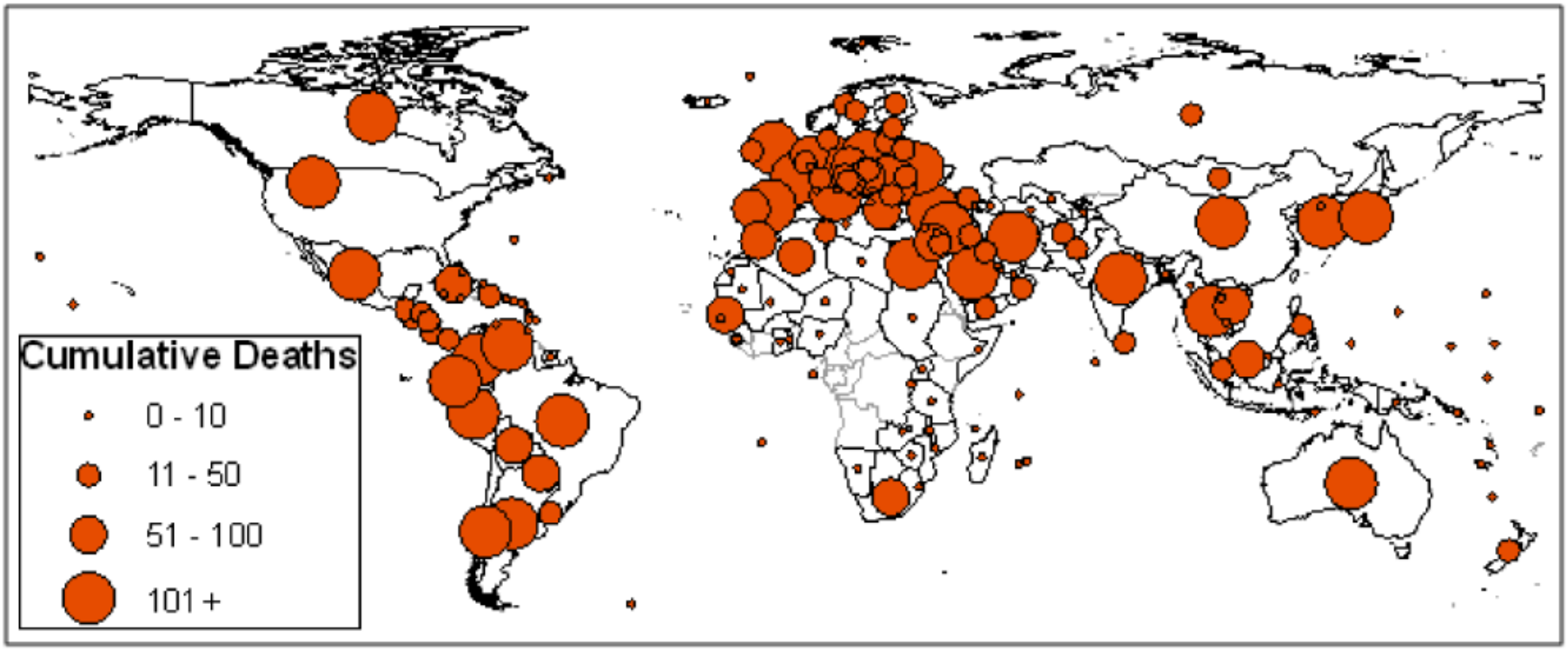


Figure 2: Map of cumulative global deaths from the 2009 H1N1 influenza pandemic, as of February 2010 (Data source: ECDC, 2010)

2009 H1N1 Pandemic

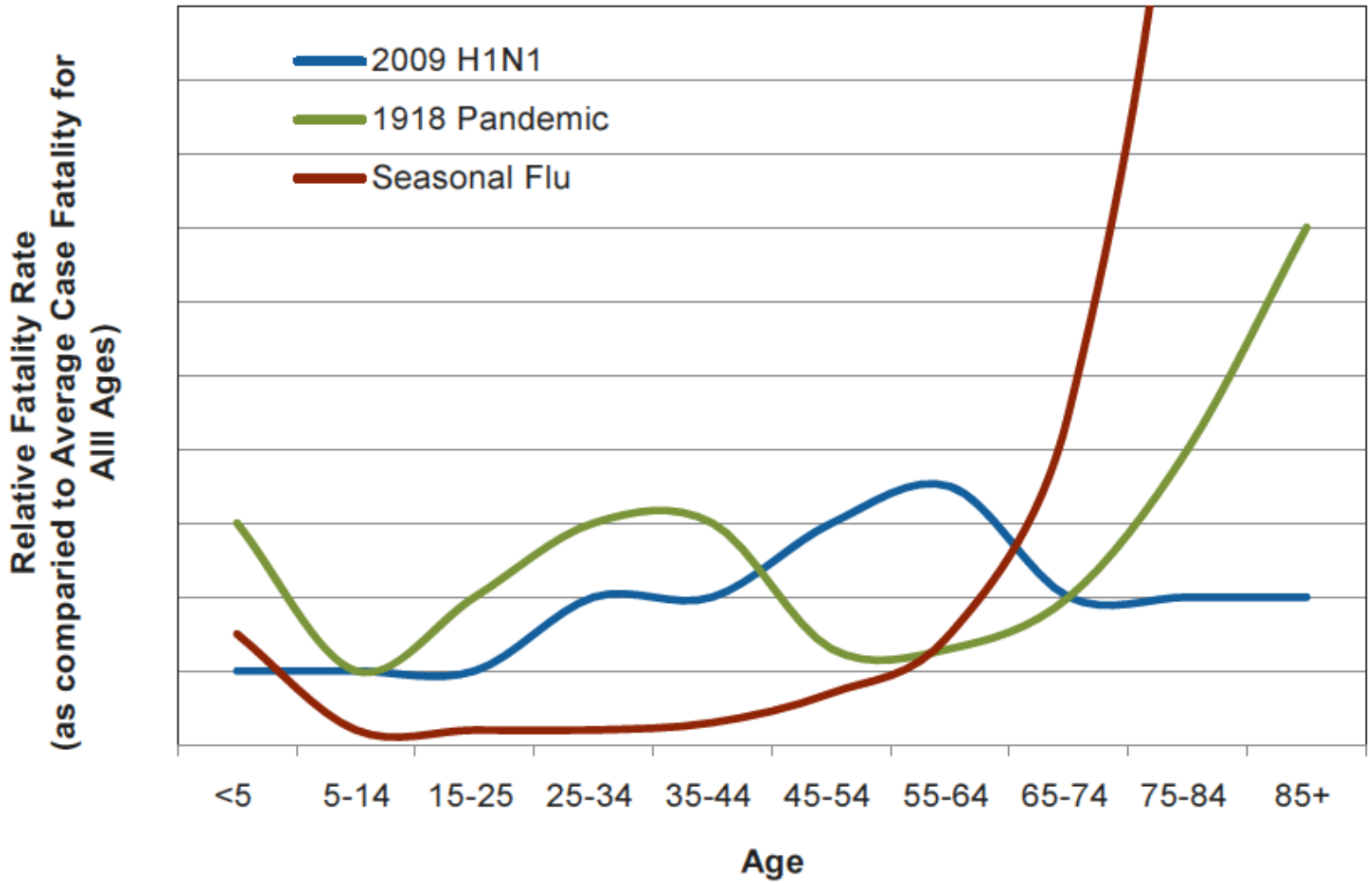


Figure 3: Age distribution of influenza mortality: comparing seasonal flu to the 1918 and 2009 pandemics

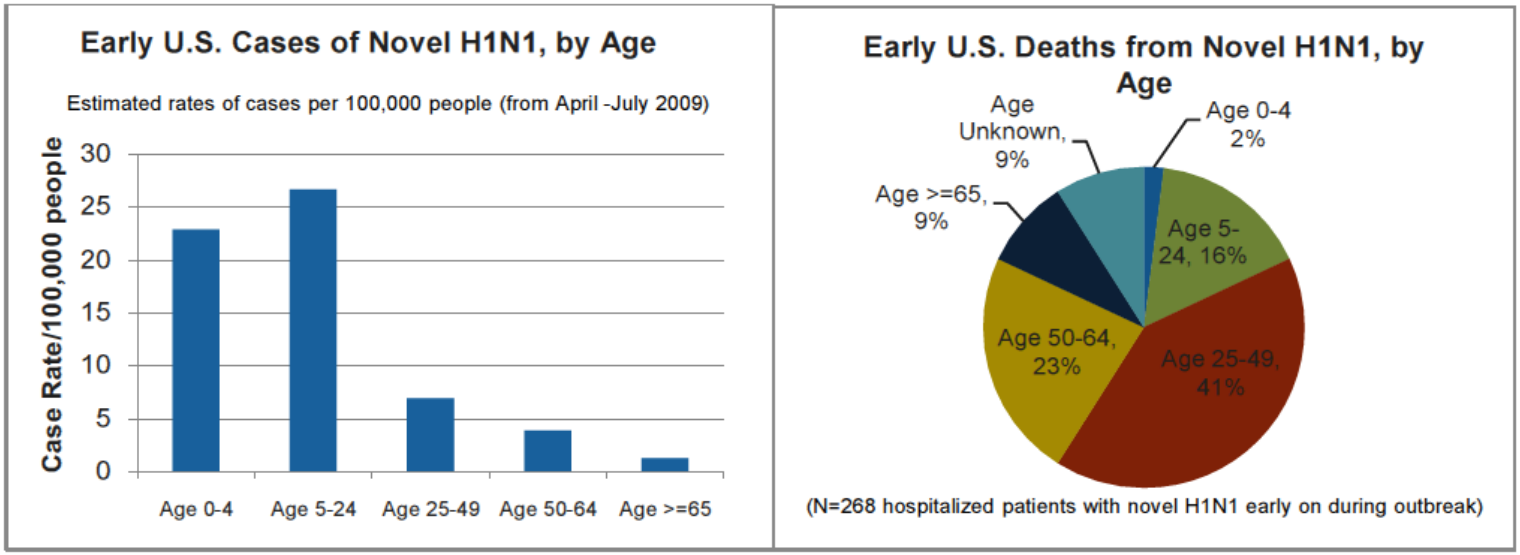


Figure 4: Early outbreak characteristics of the 2009 H1N1 virus in the U.S.: number of cases per 100,000 people from April to July 2009 (left) and early fatalities by age (right) (Date Source: CDC, 2009).

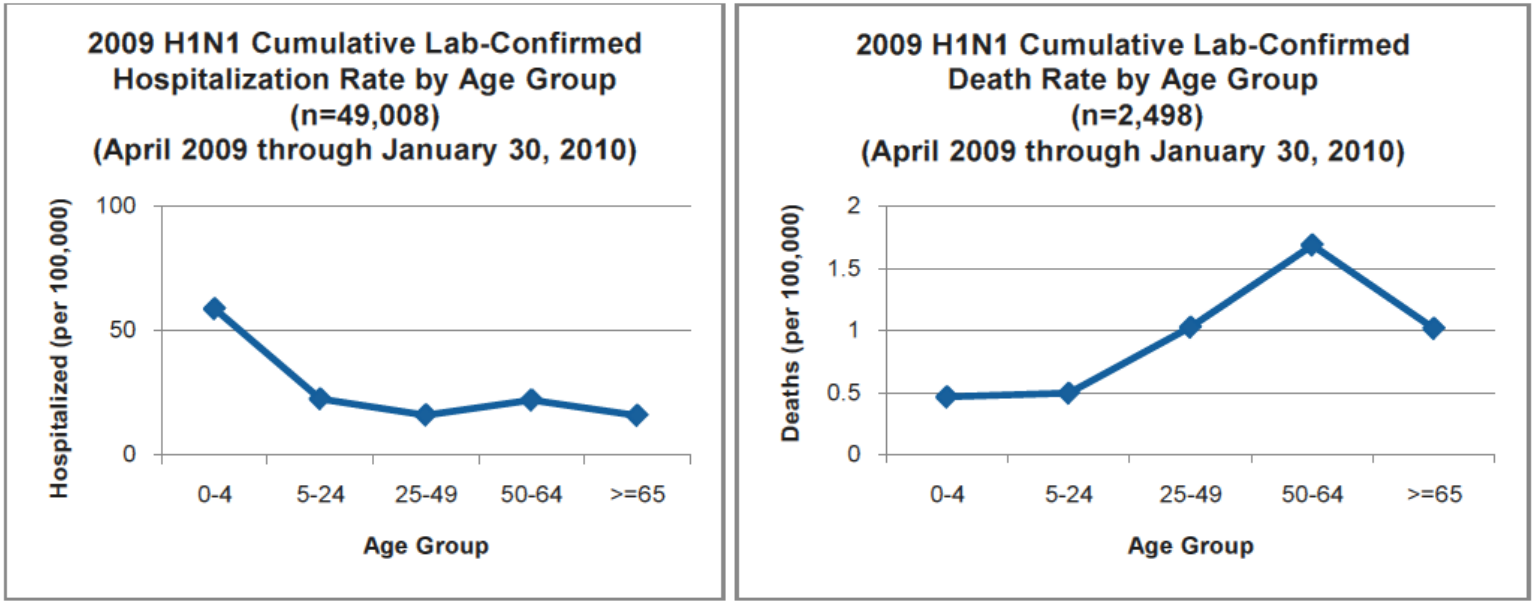


Figure 5: Age distribution of U.S. hospitalized cases (left) and fatalities (right) from the 2009 H1N1 pandemic from April 2009 through January 30, 2010 (Data Source: CDC, 2010c)

2009 H1N1 Pandemic

Table 2: Estimates of fatalities, hospitalizations, and cases for the 2009 H1N1 influenza pandemic, as modeled by RMS and estimated by the CDC as of February 13, 2010 (Data source: CDC, 2010a). Note: The CDC estimates are preliminary and do not represent the entire H1N1 pandemic. These numbers are expected to increase as more data becomes available.

Age	RMS Modeled Expected Value	CDC Lower Bound	CDC Upper Bound
		Fatalities	
0-17 yrs	6,000	890	1,840
18-64 yrs	13,500	6,530	13,500
over 65 yrs	8,500	1,100	2,280
Total	**28,000**	**8,520**	**17,620**
		Hospitalizations	
0-17 yrs	71,660	60,000	125,000
18-64 yrs	155,646	109,000	226,000
over 65 yrs	102,280	19,000	38,000
Total	**329,586**	**188,000**	**389,000**
		Cases	
0-17 yrs	25,000,000	14,000,000	28,000,000
18-64 yrs	37,000,000	24,000,000	50,000,000
over 65 yrs	3,000,000	4,000,000	8,000,000
Total	**65,000,000**	**42,000,000**	**86,000,000**

Pandemic H1N1 vaccine

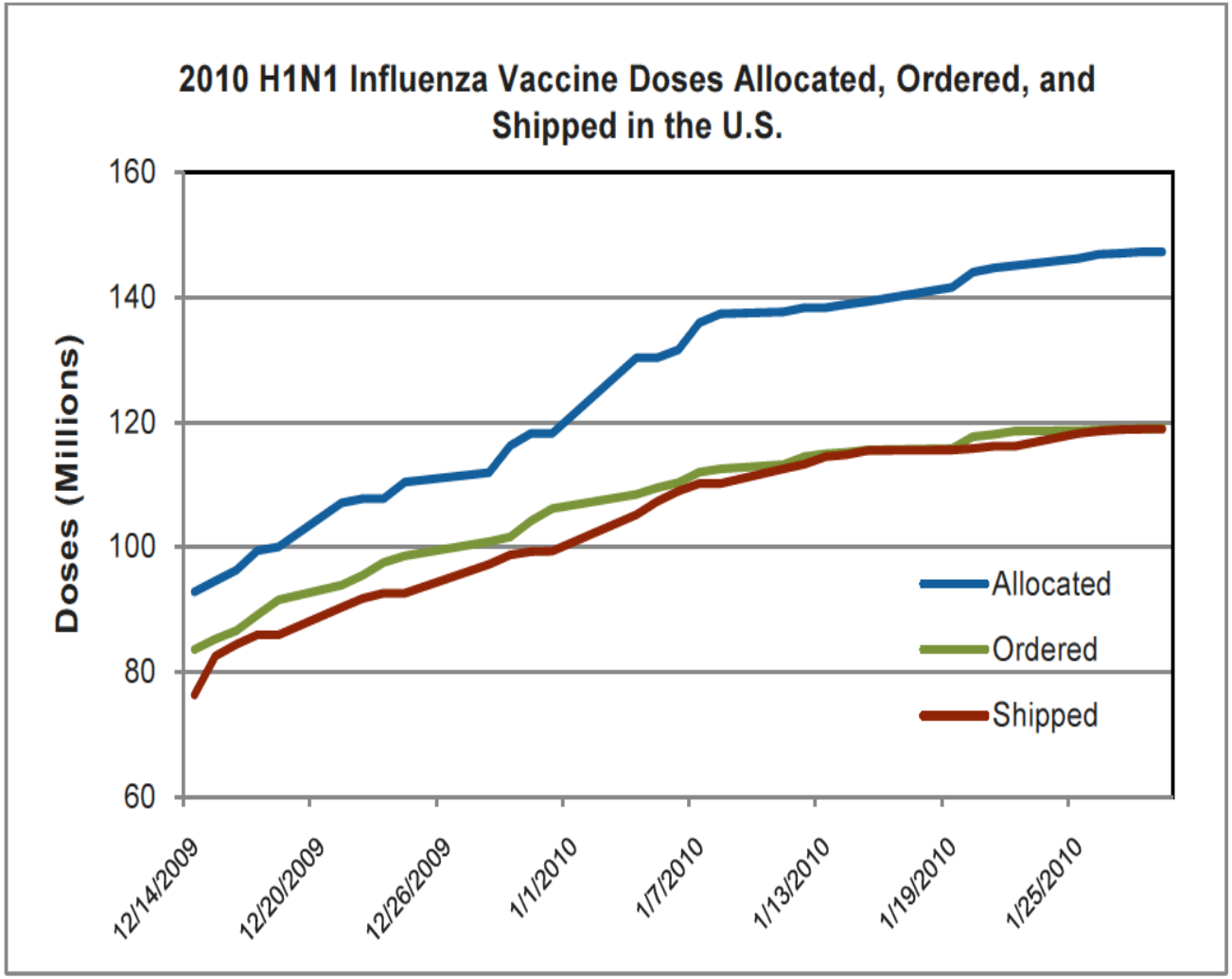


Figure 6: H1N1 vaccine availability in the U.S. from mid-December 2009 to end of January 2010 (Data Source: CDC, 2010)

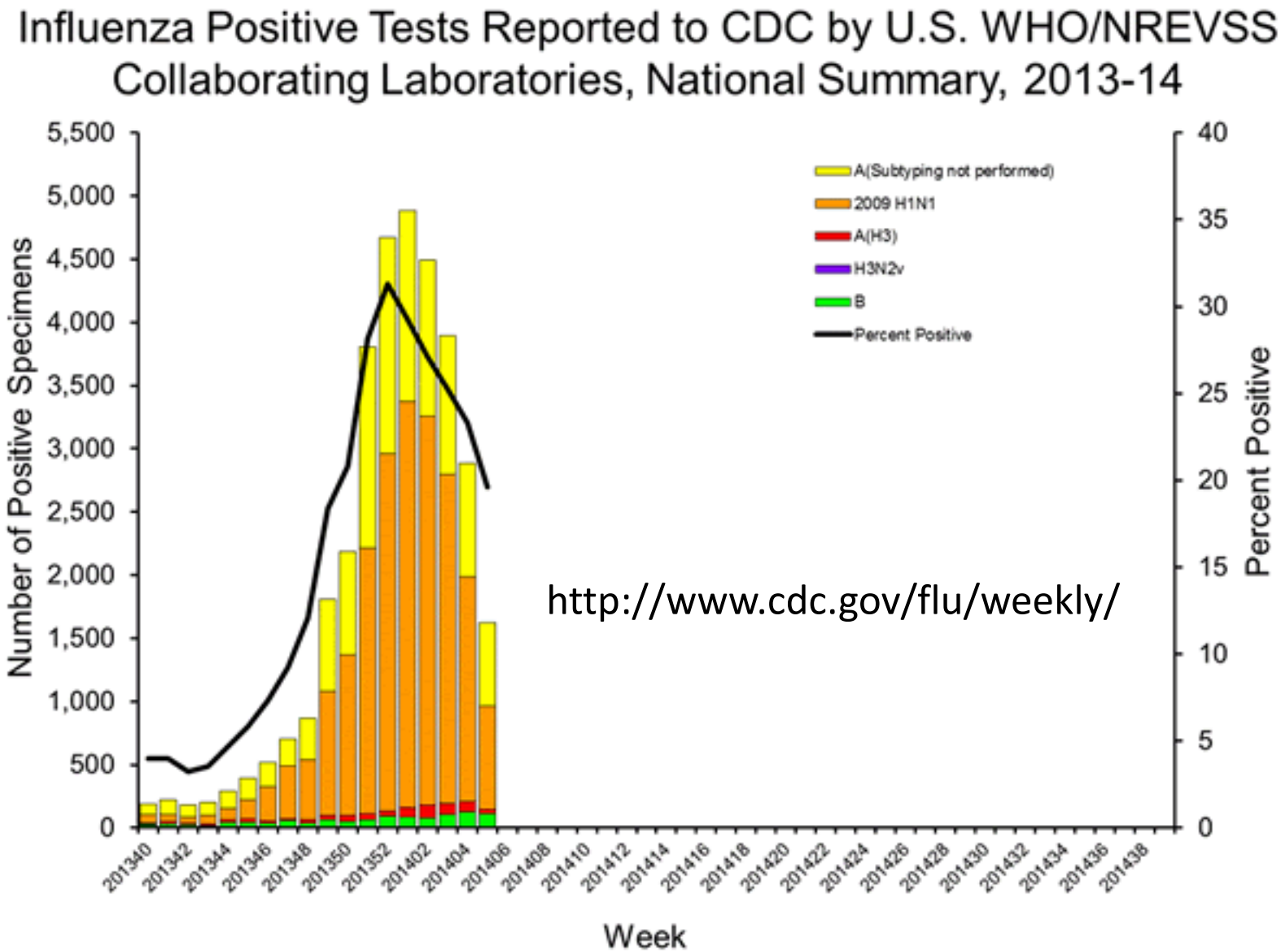
March 2009: Confirmed H1N1 in Veracruz, Mexico

October 2009: First H1N1 vaccine available for administration in the U.S.

Lessons from 2009 pandemic

- Vigilance and surveillance for novel strains
- Identify at risk population
- Limitations of laboratories and hospitals
- Educating the public about preventive measures
- Vaccine manufacturing and quality control
- Availability of antiviral drugs
- Each epidemic, pandemic is different

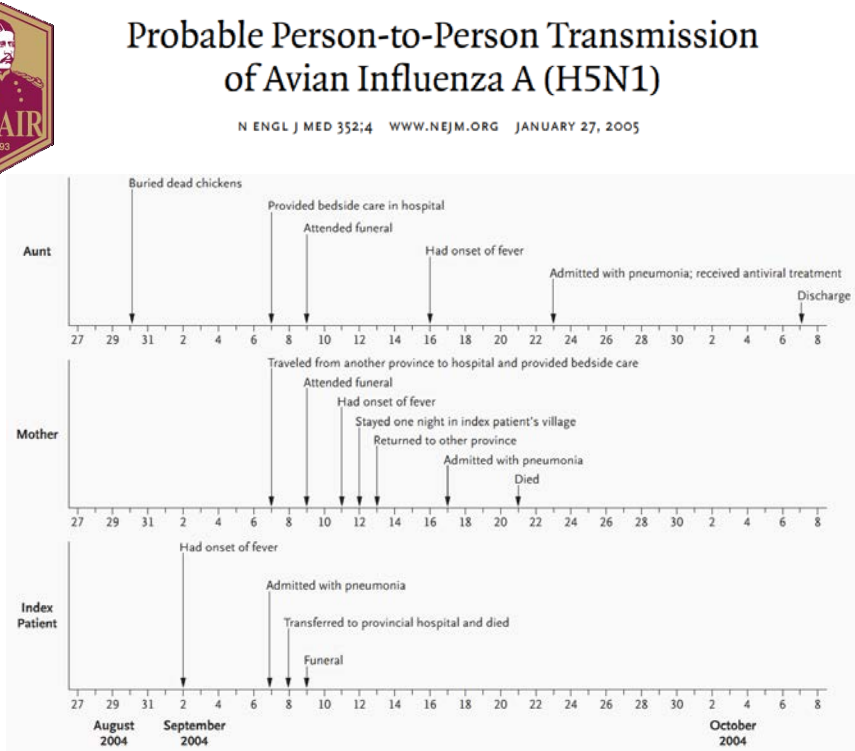
What about 2013-2014 ?



Avian Influenza

- Reservoir: Aquatic birds, Influenza A virus
- Transmission between birds
  - Direct
  - Indirect (fecal aerosols, water, feed, etc.)
- Clinically
  - Asymptomatic → Mild respiratory illness → Fatal systemic disease
- Most isolates are avirulent
- Epidemic fowl mortality caused by highly pathogenic variants
  - H5 and H7
  - < egg production, respiratory dz, head edema, diarrhea, death

Avian Influenza Human to Human Transmission



Probable person to person transmission of novel avian influenza A (H7N9) virus in Eastern China, 2013: epidemiological investigation

BMJ 2013;347:f4752 doi: 10.1136/bmj.f4752 (Published 6 August 2013)

- A few reports of probable transmission among close family or hospital contacts
- **WHO: limited non-sustained human to human spread**

H5N1 Transmission

Table 2. Serologic and Clinical Characteristics of Avian Influenza A (H5N1) Infection among Contacts of Patients or Infected Animals.*

Group	Location	Year	Assay Method†	No. Tested	No. (%) Positive	Comment	Reference
Household contacts Tour group contacts Workplace contacts	Hong Kong	1997	MN, ELISA, WB	51 26 47	6 (12) 1 (4) 0	Concurrent exposure to poultry in 5 of 6 positive household contacts; 0 of 9 non-household contacts positive	Katz et al.[8]
Poultry cullers	Hong Kong	1997	MN, WB	293	9 (3)	Seroconversion in 1 with mild acute respiratory illness	Bridges et al.[7]
Poultry-market workers	Hong Kong	1997	MN, WB	1525	— (estimated 10%)	Most asymptomatic	Bridges et al.[7]
Health care workers with contact	Hong Kong	1997	MN, WB	217	8 (4)‡	Seroconversion in 2; most asymptomatic	Buxton Bridges et al.[9]
Household contacts§	Vietnam	2004	MN	51	0	0 of 83 controls positive	
Contacts of sick poultry§	Vietnam	2004	MN	25	0	—	
Health care workers with contact	Vietnam	2004	MN	83	0	2 with suspected illness (not confirmed)	Liem et al.[10]
Health care workers with contact	Vietnam	2004	MN, RT-PCR	60	0	No recognized illness	Schultsz et al.[11]
Health care workers with contact§	Thailand	2004	Clinical only	54	0	No recognized illness	
Health care workers with contact	Thailand	2004	Clinical only	35	0	No fever or influenza-like illness	Apisarnthanarak et al.[12]
Poultry cullers§	Indonesia	2005	MN	79	1 (1)	Asymptomatic	

* Some serologic surveys of apparent human-to-human transmission may have been confounded by concurrent exposure to ill poultry.

† MN denotes identification of serum antibody against influenza A (H5N1) by microneutralization, ELISA enzyme-linked immunosorbent assay, WB detection of influenza A (H5)–specific bands by Western blotting, and RT-PCR reverse-transcriptase–polymerase-chain-reaction assay for viral RNA.

‡ P=0.01 for the comparison with 2 of 309 health care workers without contact (0.6 percent).

§ Data are from the WHO Meeting on Case Management and Research on Human Influenza A (H5) held in Hanoi, May 10 through 12, 2005.

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2013

Country	2003-2009*		2010		2011		2012		2013		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	1	1	7	1
Cambodia	9	7	1	1	8	8	3	3	20	11	41	30
China	38	25	2	1	1	1	2	1	2	2	45	30
Djibouti	1	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	4	3	173	63
Indonesia	162	134	9	7	12	10	9	9	2	2	194	162
Iraq	3	2	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	2	1	125	62
Total	**468**	**282**	**48**	**24**	**62**	**34**	**32**	**20**	**31**	**20**	**641**	**380**

* 2003-2009 total figures. Breakdowns by year available on next table

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

Source: WHO/GIP, data in HQ as of 08 October 2013

World Health Organization

Severe Illness from H5N1

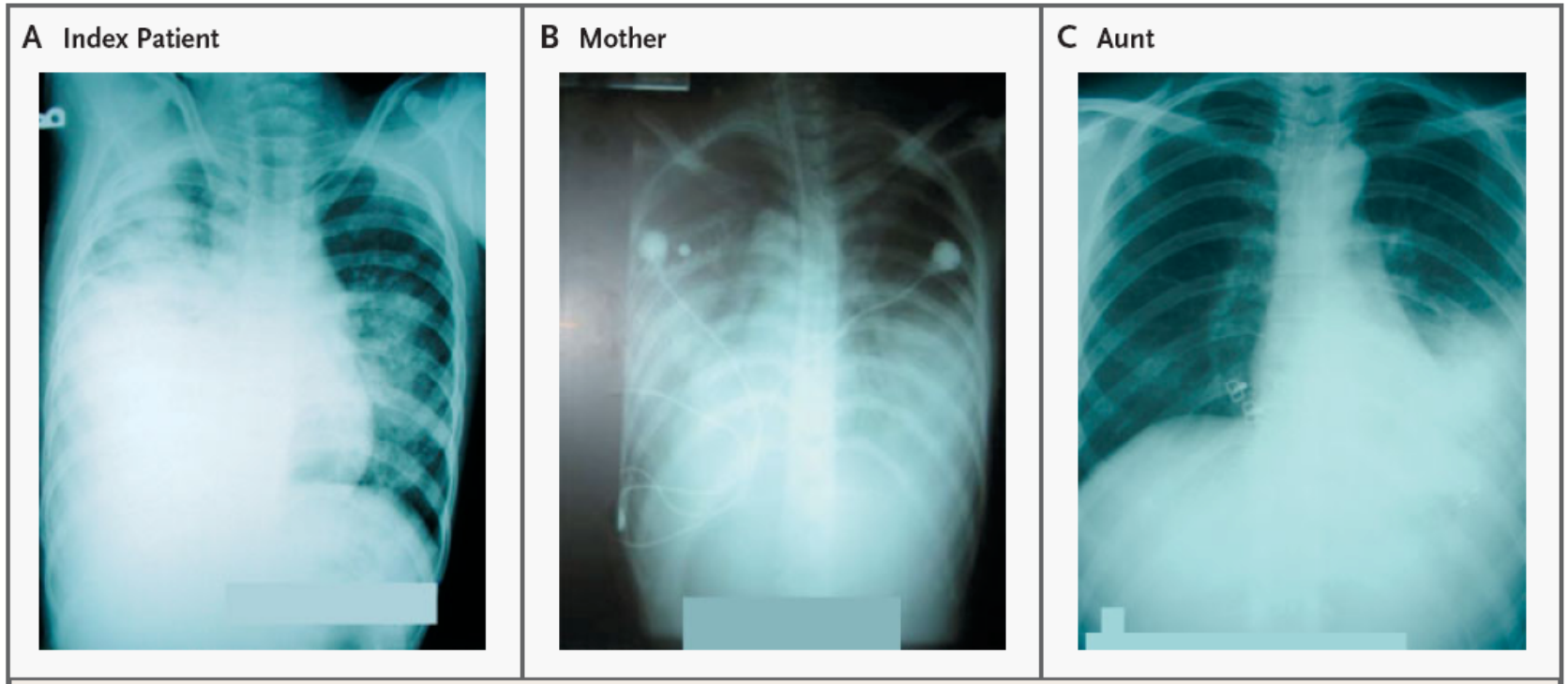


Figure 1. Chest Radiographs from the Three Patients with Avian Influenza A (H5N1).

Panel A shows a chest radiograph from the index patient, an 11-year-old girl, on day 6 of her illness. The image shows right-lower-lobe consolidation and patchy left-lower-lobe infiltrates. Panel B shows a radiograph from the girl's 26-year-old mother on day 9 of her illness. There is bilateral lower-lobe consolidation. Panel C shows a radiograph from the girl's 32-year-old aunt on day 7 of her illness; left-lower-lobe consolidation is visible.

N ENGL J MED 352;4 WWW.NEJM.ORG JANUARY 27, 2005

Severe Illness from H5N1

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Hospital course — no. (%)					
Respiratory failure	8 (44)	13 (76)	9 (90)	7 (70)	4 (100)
Cardiac failure	NS	7 (41)	NS	0	NS
Renal dysfunction	4 (22)	5 (29)	1 (10)	2 (20)	NS
Antiviral therapy‖					
Amantadine	10 (56)	0	0	0	NS
Ribavirin	1 (6)	0	2 (20)	0	
Oseltamivir	0	10 (59)	5 (50)	10 (100)	
Corticosteroids**	5 (28)	8 (47)	7 (70)	5 (50)	NS
Inotropic agents	NS	8 (47)	2 (20)	NS	
Time from onset of illness to death — days					
Median	23	12	9	12.8†	8
Range	8–29	9–30	4–17	4–21	6–10
Deaths — no. (%)	6 (33)	12 (71)	8 (80)	8 (80)	4 (100)

N ENGL J MED 353;13 WWW.NEJM.ORG SEPTEMBER 29, 2005

Other Avian Influenza

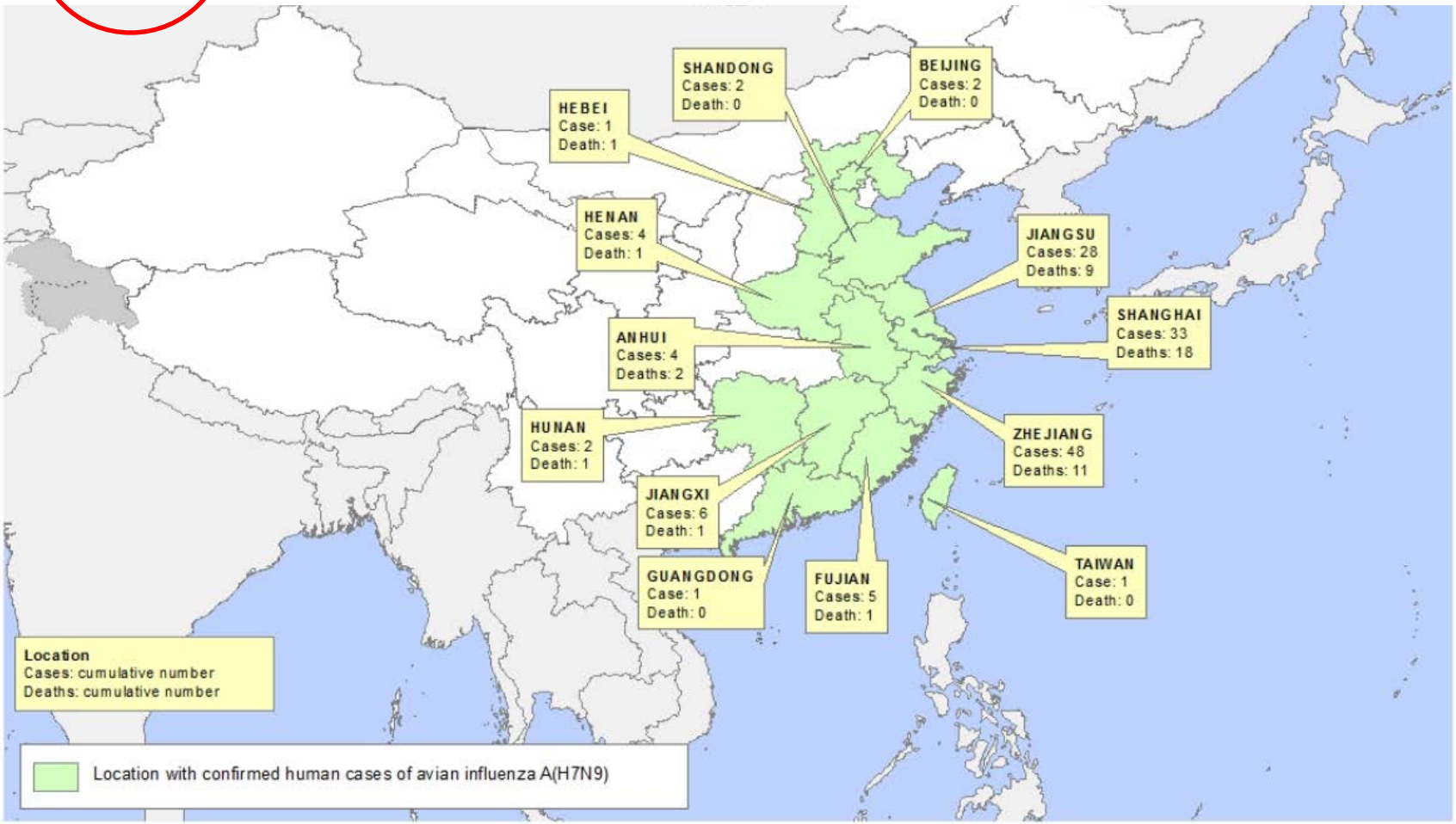
Table 1. Direct transmission of avian influenza viruses to humans

Virus subtype	Year	Location	No. cases (no. deaths)	Clinical features	Notes	Reference(s)
H5N1	1997	Hong Kong	18 (6)		Associated with outbreak of highly pathogenic AI in poultry in the region	(*5,6*)
H9N2	1999	Hong Kong	2 (0)	Mild influenzalike illness		(*7*)
H9N2	1999	Guangdong Province, China	5 (0)	Mild influenzalike illness		(*8*)
H9N2	2003	Hong Kong	1 (0)	Mild influenzalike illness		(*9*)
H5N1	2003	Hong Kong	2 (1)	Primary viral pneumonia, lymphopenia, respiratory distress	7-year-old girl died in Fujian Province, China, and H5N1 infection was not confirmed. Her 33-year-old father died from confirmed H5N1 influenza infection in Hong Kong, and her 8-year-old brother recovered from H5N1 infection.	(*10*)
H7N7	2003	Netherlands	89 (1)	Conjunctivitis (78 cases), mild influenzalike symptoms (2 cases) or both (5 cases). In fatal case, pneumonia followed by respiratory distress syndrome	Most cases were in persons involved in handling poultry (86), with 3 family members also affected.	(*11*)
H10N7	2004	Egypt	2 (0)	Fever and cough	Both cases were in infants, who recovered without complications	(*12*)
H5N1	2003–present	Asia (Vietnam, Thailand, Cambodia, Indonesia)	116 (60)*	Fever, respiratory symptoms, lymphopenia, elevated liver enzymes. Severe cases progress to respiratory failure, multiple organ dysfunction, and death.	Human cases concomitant with unprecedented outbreaks of highly pathogenic H5N1 AI in poultry	WHO* (*13–15*)

*WHO, World Health Organization. As of September 29, 2005. Source: http://www.who.int/csr/disease/avian_influenza/country/en

Avian Influenza A (H7N9)

	February		March		April		May		June		July		August		September		October		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Total	4	3	33	18	94	23	2	0	0	0	2	1	0	0	0	0	2	0	137	45



Data as of 25 October 2013, 8:00 GMT+1
Source: WHO/GIP

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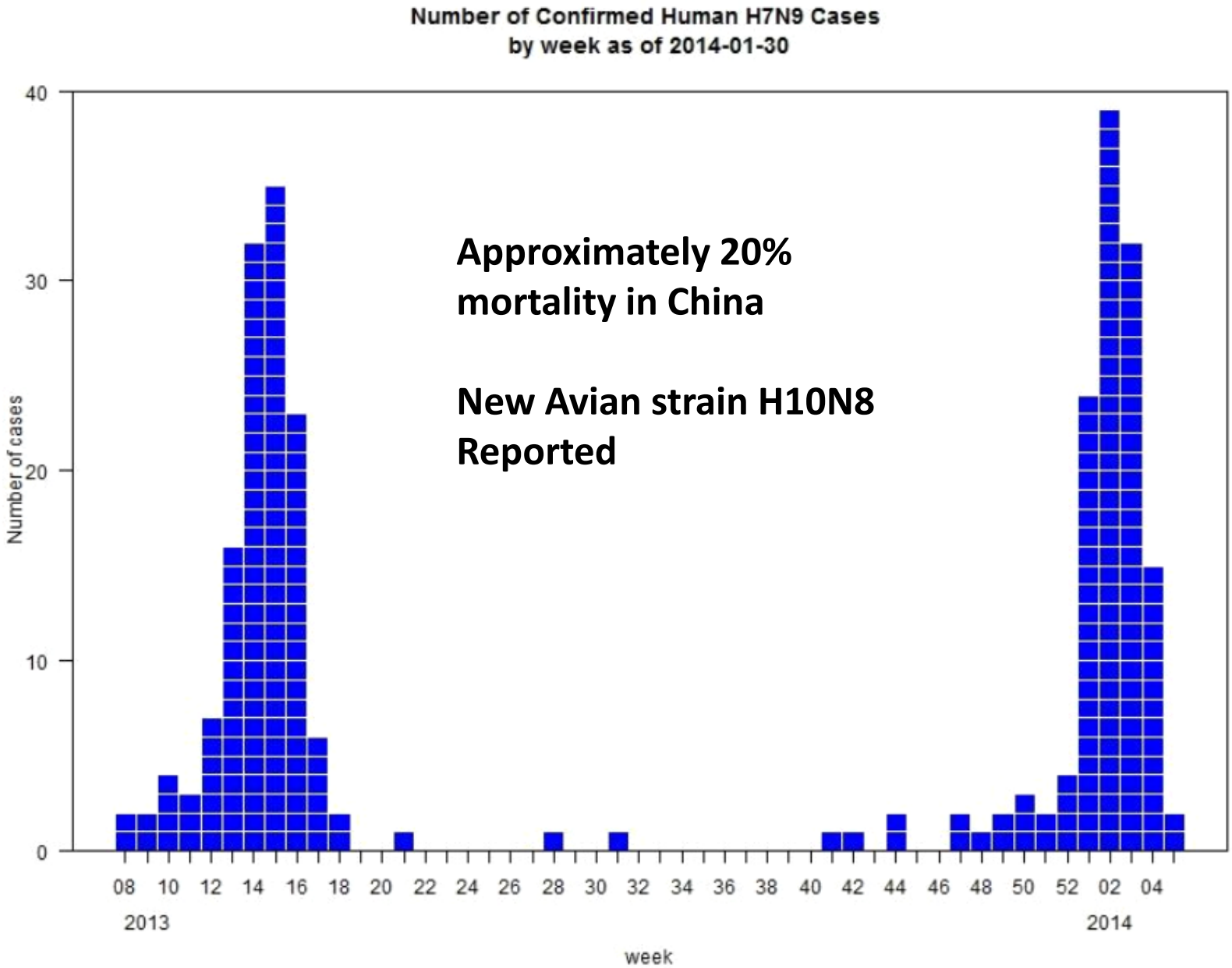

Number of Confirmed Human H7N9 Cases
by week as of 2014-01-30
Number of cases
0
10
20
30
40
08 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48 50 52 02 04
2013
2014
week
Approximately 20% mortality in China
New Avian strain H10N8 Reported

Avoid These

- **Do not touch birds, pigs, or other animals.**
  - Do not touch animals whether they are alive or dead.
  - Avoid live bird or poultry markets.
  - Avoid other markets or farms with animals (wet markets).

Figure 2. The effect of highly pathogenic H5N1 virus on ducklings in Vietnam (photo T Tumpey).

- **Eat food that is fully cooked.**
  - Eat meat and poultry that is fully cooked (not pink) and served hot.
  - Eat hard-cooked eggs (not runny).
  - **Don't** eat or drink dishes that include blood from any animal.
  - **Don't** eat food from street vendors.
- **Practice hygiene and cleanliness**:
  - Wash your hands often.
  - If soap and water aren't available, clean your hands with hand sanitizer containing at least 60% alcohol.
  - Don't touch your eyes, nose, or mouth. If you need to touch your face, make sure your hands are clean.
  - Cover your mouth and nose with a tissue or your sleeve (not your hands) when coughing or sneezing.
  - Try to avoid close contact, such as kissing, hugging, or sharing eating utensils or cups, with people who are sick.

Influenza management

- Early suspicion and recognition
- Isolation and testing
- Symptom management
- Neuraminidase inhibitors
  - Oseltamivir (oral) and zanamivir (inhaled)
  - Effective for both influenza A and B (unlike amantadine)
- Vaccine if available
  - Pandemic influenza vaccine in 2009-2010
  - H5N1 avian influenza vaccine manufactured by Sanofi Pasteur approved by FDA in 2007
  - Testing at NIH for H7N9 avian influenza vaccine

Neuraminidase Inhibitor Resistance Testing Results on Samples Collected Since October 1, 2013 in the US (from CDC)

	Oseltamivir		Zanamivir	
	Virus Samples tested (n)	Resistant Viruses, Number (%)	Virus Samples tested (n)	Resistant Viruses, Number (%)
Influenza A (H3N2)	138	0 (0.0)	138	0 (0.0)
Influenza B	43	0 (0.0)	43	0 (0.0)
2009 H1N1	2,778*	23 (0.8)	969	0 (0.0)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection

Menno D. de Jong, M.D., Ph.D., Tran Tan Thanh, M.Sc.,
Truong Huu Khanh, M.D., Vo Minh Hien, M.D., Gavin J.D. Smith, Ph.D.,
Nguyen Vinh Chau, M.D., Bach Van Cam, M.D., Phan Tu Qui, M.D.,
Do Quang Ha, M.D., Ph.D., Yi Guan, M.D., Ph.D., J.S. Malik Peiris, D.Phil., M.D.,
Tran Tinh Hien, M.D., Ph.D., and Jeremy Farrar, D.Phil., F.R.C.P.

Oseltamivir Treatment

- Shortens symptoms and may reduce risk of complications, especially started within 48 hrs.
- Highest benefit:
  - Hospitalized, children < 2, adults > 65, chronic illness, immunocompromised, pregnant, those < 19 and receiving aspirin therapy, American Indians/Alaska Natives, morbidly obese, nursing home residents
- Do not wait for laboratory confirmation
- **Dose is 75 mg twice daily for 5 days**
  - Dose adjust but approved for 2 weeks and older
- Side effects: mostly nausea, vomiting, neuropsychiatric in Japan.

Oseltamivir Prophylaxis

- CDC dose NOT recommend widespread prophylaxis use. WHY ?
- Vaccination and close monitoring as alternative
- 70-90% effective
- **75 mg once daily, exposure time + 7 days**
  - Likely not helpful to start > 48 hrs since exposure.
  - 2 weeks after last case in long-term care facilities

Other Common Respiratory Viruses

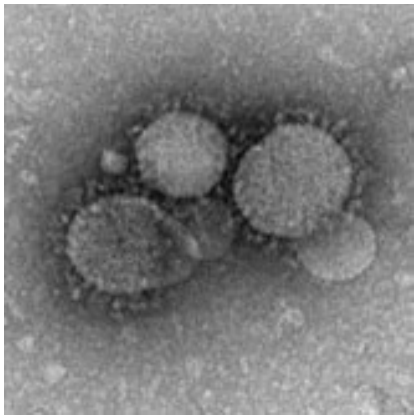
- **Respiratory syncytial virus (RSV)**
  - Annual epidemics, bronchiolitis in infants
- **Human metapneumovirus (HMPV)**
  - Similar to RSV
- **Parainfluenza virus**
  - Four types, type 3 in spring and early summer
- **Adenovirus**
  - 51 serotypes, types 1-7 responsible for most infections.
  - Oral adenovirus type 4 & 7 vaccine for military recruits
- **Rhinoviruses**
  - Common cold virus, 100 + serotypes, year-round in tropics
- **Coronaviruses**
  - Common Cold
  - Severe respiratory infections: SARS CoV (2003), MERS CoV (2013)

What does a negative influenza rapid test mean ?

- More than 15 approved rapid influenza tests
  - Collected on wash, aspirate, swab
  - Results 10 – 15 minutes
- "Gold Standard" is cell culture or RT-PCR
- Sensitivity of rapid tests: 50-70%
- Specificity of rapid tests: 90-95%
- High disease prevalence increases positive predicative value

Coronavirus

- Meaning ‘crown or halo’
- Large, positive sense RNA virus
- Family *Coronaviridae*
- Infects humans, mammals, birds



CDC Image

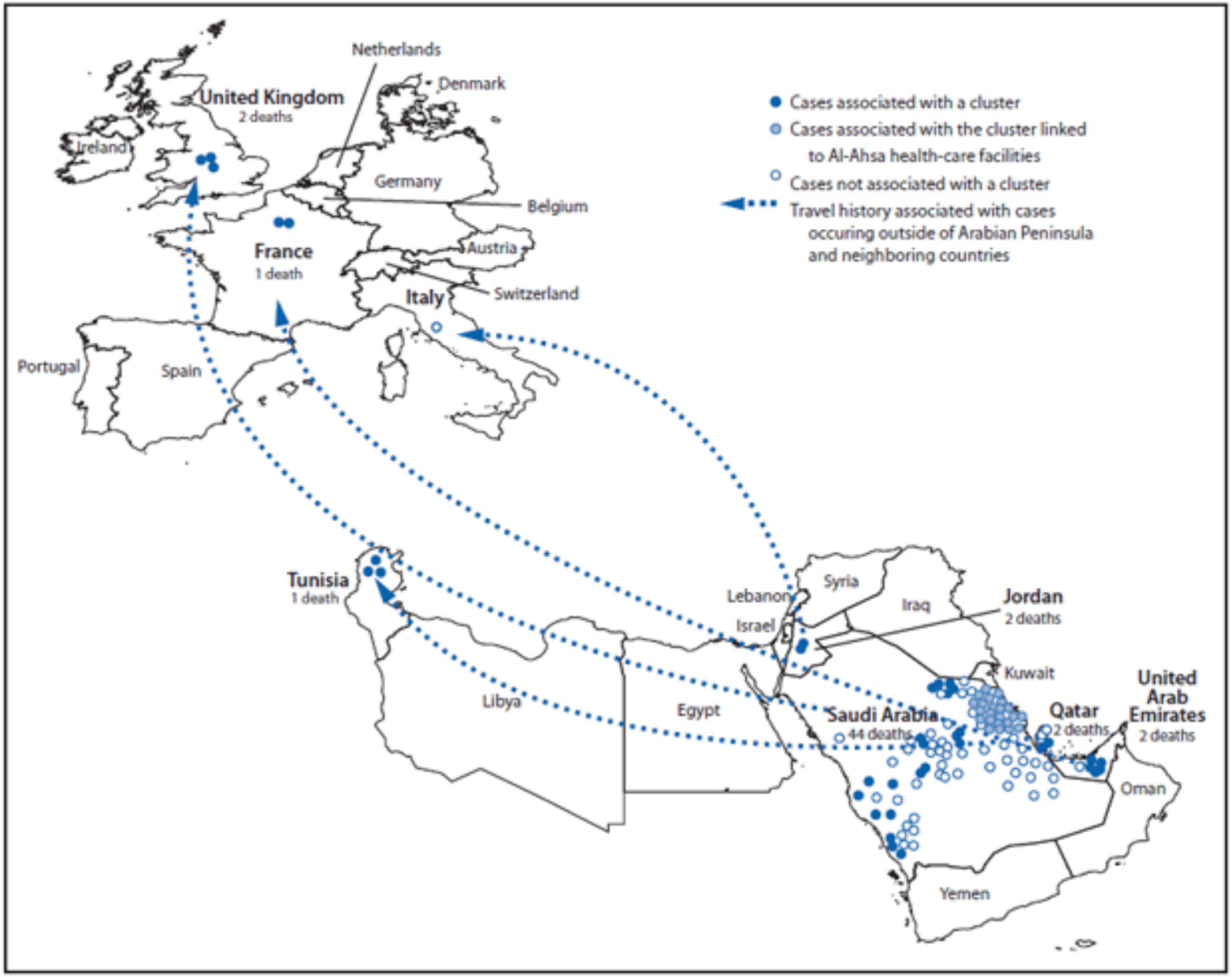
- Severe acute respiratory syndrome coronavirus (SARS-CoV)
  - Rapid human to human spread worldwide
  - 774 probable deaths, 10% fatality rate
  - Started in Hong Kong Feb. 2003
    - Civet cats, small mammals to humans ?
  - Delayed peak transmission period
    - Rare within first 5 days of symptom onset
    - Easier recognition, isolation, and interruption
  - No cases since 2004

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

- Severe, contagious, respiratory illness
- First cluster in Jordan, April 2012
- First Saudi Arabia case, June 2012
- Cluster among family contacts, returning travelers in Europe
- Nosocomial transmission (24% of cases)
- Unidentified reservoir
  - Identified in camels
  - ? Bats
- Geographically diverse animal reservoir, initial emergence in July 2011, sporadic introduction into humans and human-to-human transmission

MERS-CoV
April 2012 - Present

- 182 lab confirmed cases, 79 deaths (Feb 3, 2014)
- People with existing illness at highest risk
- Outbreaks in hospitals
- Most in Saudi Arabia
  - United Arab Emirates (UAE), Oman, Qatar, Jordan, Tunisia, United Kingdom, France, Italy



CDC MMWR Sept 27, 2013, 62(38); 793-6

Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study

Lancet Infect Dis 2013; 13: 752–61

Abdullah Assiri, Jaffar A Al-Tawfiq*, Abdullah A Al-Rabeeah, Fahad A Al-Rabiah, Sami Al-Hajjar, Ali Al-Barrak, Hesham Flemb Wafa N Al-Nassir, Hanan H Balkhy, Rafat F Al-Hakeem, Hatem Q Makhdoom, Alimuddin I Zumla*, Ziad A Memish**

	Patients (n=47)
Fever	46 (98%)
Fever with chills or rigors	41 (87%)
Cough	39 (83%)
Dry	22 (47%)
Productive (sputum)	17 (36%)
Haemoptysis	8 (17%)
Shortness of breath	34 (72%)
Chest pain	7 (15%)
Sore throat	10 (21%)
Runny nose	2 (4%)
Abdominal pain	8 (17%)
Nausea	10 (21%)
Vomiting	10 (21%)
Diarrhoea	12 (26%)
Myalgia	15 (32%)
Headache	6 (13%)

Table 3: **Symptoms of Middle East respiratory syndrome in 47 Saudi cases at presentation**

	Patients (n=47)	Deaths (%)*
Any comorbidity	45 (96%)	28 (60%)
Diabetes	32 (68%)	21 (66%)
Chronic kidney disease	23 (49%)	17 (74%)
Chronic heart disease	13 (28%)	10 (77%)
Hypertension	16 (34%)	13 (81%)
Chronic lung disease	12 (26%)	10 (83%)
Obesity	8 (17%)	5 (63%)
Smoking	11 (23%)	7 (64%)
Malignant disease	1 (2%)	1 (100%)
Steroid use	3 (6%)	3 (100%)

*Proportion of patients who died according to comorbidity.

Table 4: **Comorbidities in 47 Saudi cases of Middle East respiratory syndrome**

MERS Co-V

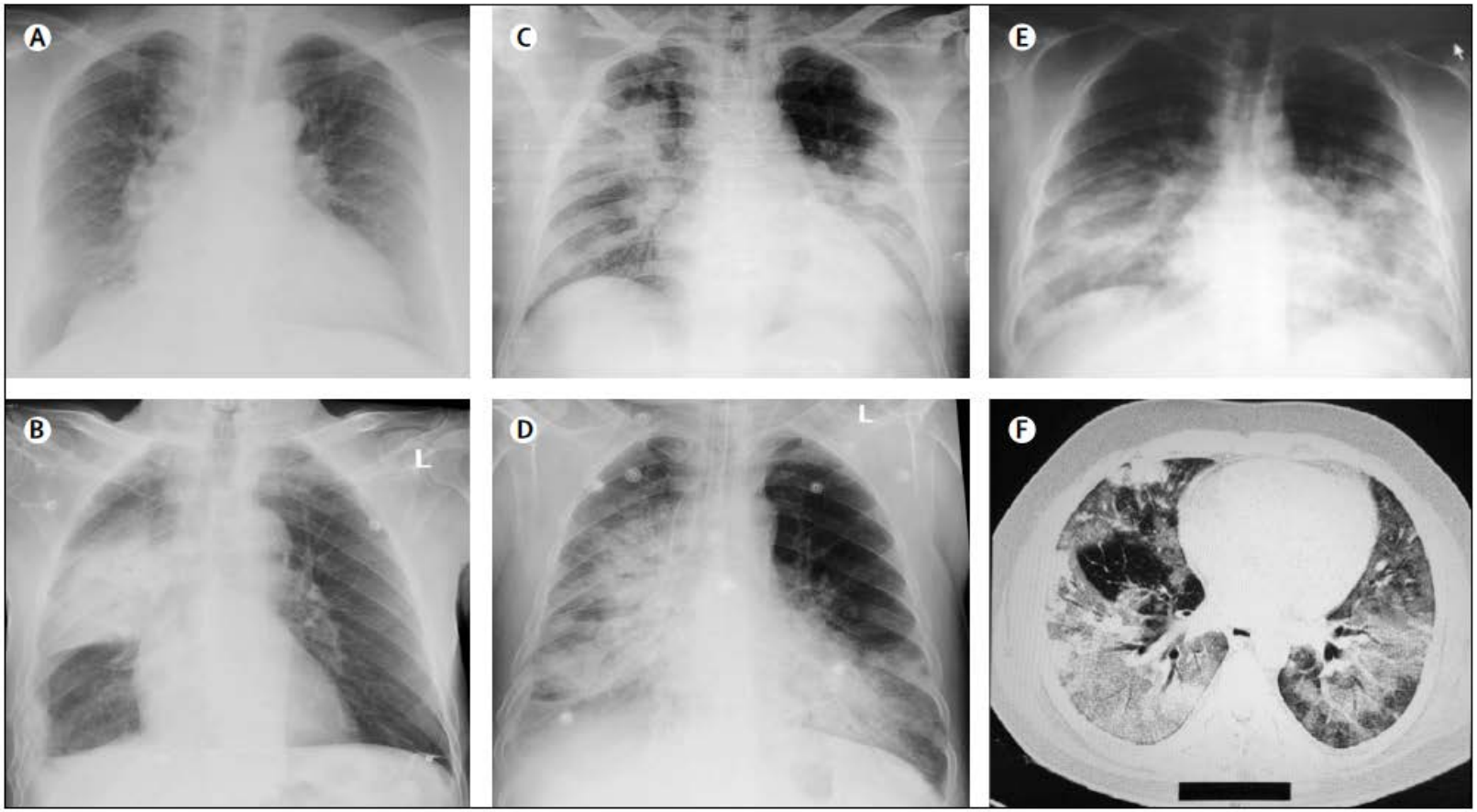


Figure 1: **Imaging findings at presentation in Saudi patients with Middle East respiratory syndrome**
(A) Chest radiograph of a 61-year-old man, showing bilateral fine reticulonodular air-space opacities, increased vascular markings, and cardiomegaly. (B) Chest radiograph of an 83-year-old man, showing right lung consolidation, right basal pleural thickening, and reticulonodular air-space opacities; rib fractures on the right are old. (C) Chest radiograph of a 56-year-old man, showing extensive bilateral extensive diffuse and focal alveolar space opacities, with opacification of the left lower lobe. (D) Chest radiograph of a 67-year-old man, showing extensive bilateral disease, with diffuse alveolar space densities, opacification, reticulonodular opacities, and bronchial wall thickening. (E) Chest radiograph of a 49-year-old man, showing extensive bilateral mid and lower zone disease, with diffuse reticulonodular alveolar space opacities. A thoracic CT scan in the same patient (F) shows extensive bilateral opacities and ground-glass reticulonodular shadowing and bronchiolar wall thickening.

Lancet Infect Dis 2013; 13: 752–61

MERS-CoV vs. SARS

	MERS-CoV	SARS, global[27 34]
Demographic factors		
Date of first case report (place)	April, 2012 (Jordan); June, 2012 (first Saudi case)	November, 2002 (China)
Mean (95% CI) incubation period (days)	5·2 (1·9–14·7); range 2–13	4·6 (3·8–5·8); range 2–14
Serial interval (days)	7·6	8·4
Age distribution	98% adults, 2% children	93% adults, 5–7% children
Mean (range) age (years)	56 (14–94)	39·9 (1–91)
Sex distribution	77% male, 23% female	43% male, 57% female
Sex ratio (male:female)	3·3:1	1:1·3
Clinical features		
Mortality	55%	0–40%
Case-fatality rate (overall)	Undefined	9·6%
In patients with comorbidities	60%	1–2%
Mean time from onset to death (days)	16·5	23·7

Lancet Infect Dis 2013; 13: 752–61

Current Guidance – MERS-CoV

- All cases linked to travel or residence:
  - Saudi Arabia, Qatar, Jordan, United Arab Emirates
- CDC not yet recommending against travel to Arabian Peninsula. Travelers should pay attending to their health and seek care for respiratory symptoms
- Saudi government: recommend person with medical problems not attend Hajj
- Assess risk, suspect disease
- Lower respiratory tract specimen for rRT-PCR
- Follow up serology testing
- Isolation Precautions
  - Airborne for suspected cases
    - For SARS, CDC: ‘airborne precaution preferred’
  - Other standard precautions

Hantavirus Pulmonary Syndrome

- Bunyavirus, enveloped, neg. SS RNA
- New World Hantavirus
    - Approx. 300 cases per year, mortality up to 50%
    - Sporadic cases in the North America: US, Canada
    - Sporadic cases and outbreaks in South America: Argentina, Bolivia, Brazil, Chile, Panama, Paraguay, Uruguay
- **Mice and rats are reservoirs**
  - Urine, dropping, nesting materials are aerosolized and inhaled by humans
  - Bites and ingestion of contaminated food
  - Barns, outbuildings, and shed are exposure sites
- Incubation 1-4 weeks, initially non-specific myalgia, HA, chills, nausea, vomiting, GI symptoms
- Shortness of breath and cough develops later
  - Rapidly progressive cardiopulmonary phase
  - Bilateral infiltrates, pulmonary edema)
- Conjunctival injection, renal involvement, and hemorrhage reported

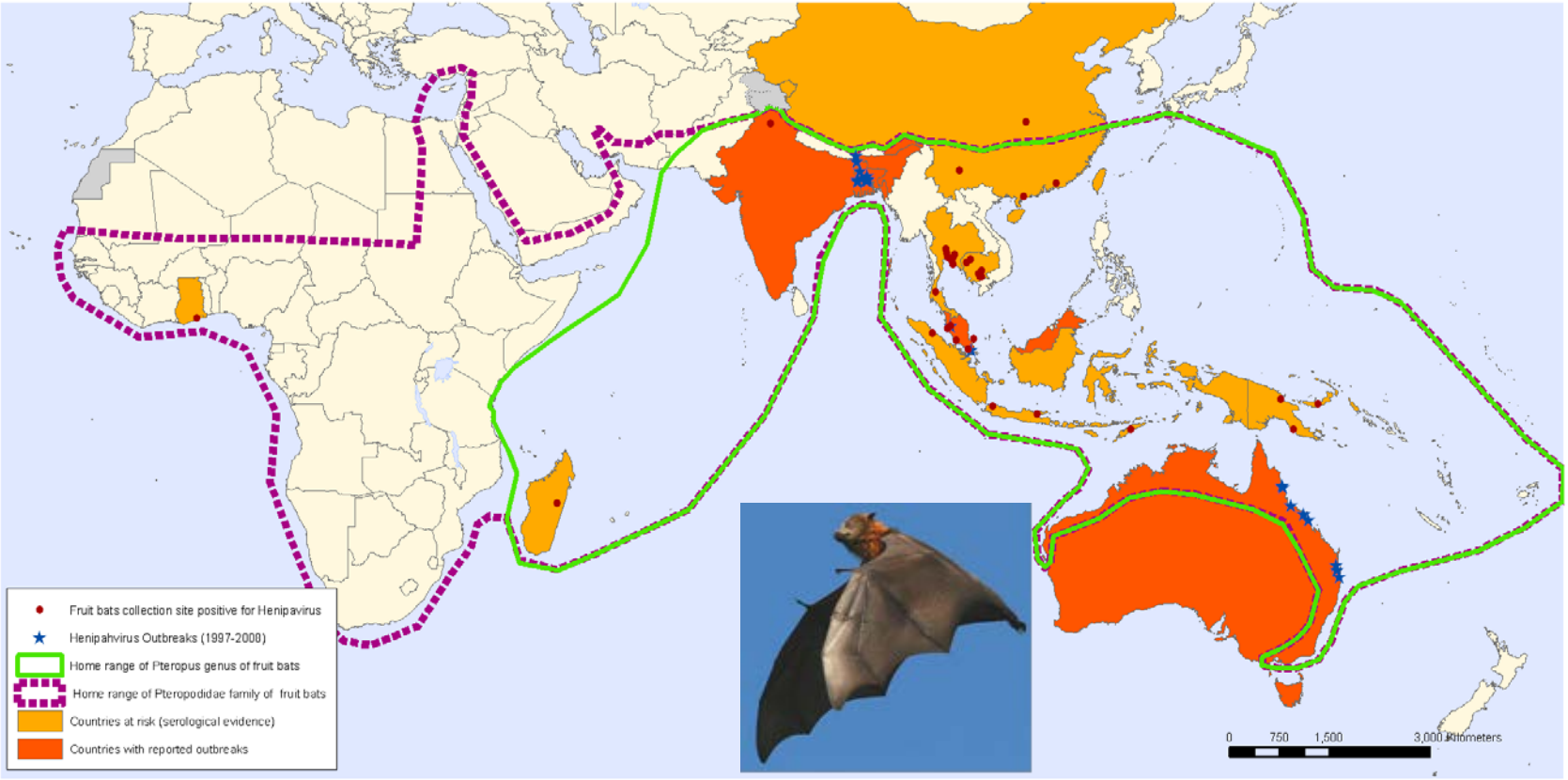
New World Hantaviruses

Virus Research December 2011 (162)

Nipah Virus

- RNA virus, paramyxoviruses, henipavirus
- Recent outbreaks in **Malaysia and Bangladesh**
- Reservoir are **bats** in China, SE Asia, India, Madagascar, and Ghana.
- **Pigs are hosts**
- Humans, cats, dogs infection through direct contact with pig respiratory secretions and urine
- Malaysia outbreak: ? Person to person transmission
- Viral encephalitis with progression to coma, + respiratory symptoms, high mortality

Nipah Virus



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Data Source: Global Alert and Response Department
World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

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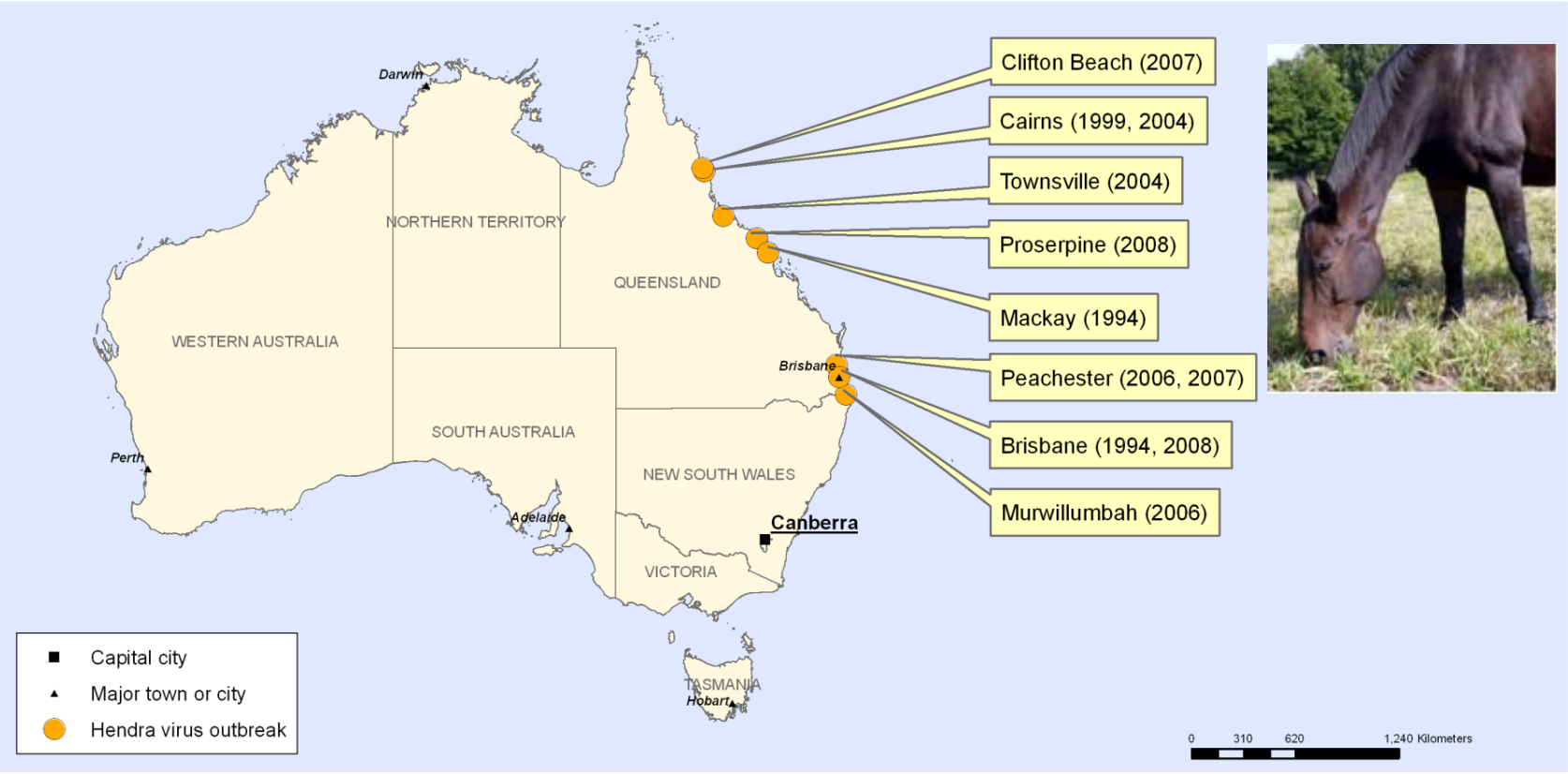
Hendra Virus

- RNA virus, paramyxoviruses, henipavirus
- **Bats are the natural reservoir**
- **Outbreak in horses in Australia**
- Four identified human cases in after close contact with horses
  - Two died
- Acute influenza-like illness, meningoencephalitis, seizures, coma

Hendra Virus

Geographic distribution of Hendra virus outbreaks in Australia from 1994 to July 2008



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

World Health Organization

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Summary

- **Respiratory virus are constantly evolving and novel highly virulent respiratory viruses WILL circulate in the future**
- **An influenza strain that is highly transmissible (H1N1) and highly virluent (H5N1) will likely result in high mortality**
- **Get vaccinated, protection even when mismatches occur and you may be partially protected against new strains**
- **Maximize good hand hygiene, distance from others, and personal protective measures**
- **Consider isolation of patients and assume worst case initially**
- **Use common sense and avoid contact with animals, local markets, and areas with known outbreaks of respiratory infections**

Thank You

Questions ?

Tropical Medicine Course: 'Respiratory Viruses in the Tropics' Lecture Questions:

1). A main difference between the recent H1N1 influenza pandemic and epidemics of avian influenza (H5N1 and H7N9) is:

a). A vaccine is available for H1N1 whereas avian influenza vaccines are impossible to make
b). Oseltamivir is only effective for avian influenza but not H1N1
c). H1N1 is an influenza A virus whereas the avian influenza viruses are influenza B viruses
d). H1N1 has sustained human to human transmission but this is not true for avian influenza

2). A 24 y.o. SM began experiencing fever, chill, gastrointestinal symptoms, and a cough shortly after returning from a trip in Argentina. After reading about a recent outbreak in Yosemite National Park, you suspect hantavirus as a possible pathogen. Which of the following answers would support you suspicion ?

a). He visited several rural villages and saw mice
b). He fed some pigs and explored caves inhabited with bats
c). He was bitten by several mosquitoes
d). He rode horses

3). Which of the following is NOT likely to improve overall outcome at your facility when managing a patient with flu-like illness and respiratory symptoms for 4 days who recently visited Saudi Arabia ?

a). Closely monitor those who came in contact or traveled with the sick individual
b). Start oseltamivir immediately on the patient
c). Airborne precautions for the patient and N-95 mask for visitors if available or at minimum droplet precautions
d). Obtain lower respiratory tract specimens for testing for MERS-CoV

Answers: D, A, B