



Respiratory Threats in the Tropics

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- Thanks:
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 - LTC Anjali Kunz
 - MAJ Leyi Lin



Disclaimer

The views expressed in this presentation are those of the speaker and do not reflect the official policy of the Department of Army, Department of Defense, or U.S. Government



Outline

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



Influenza



Influenza Virus

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

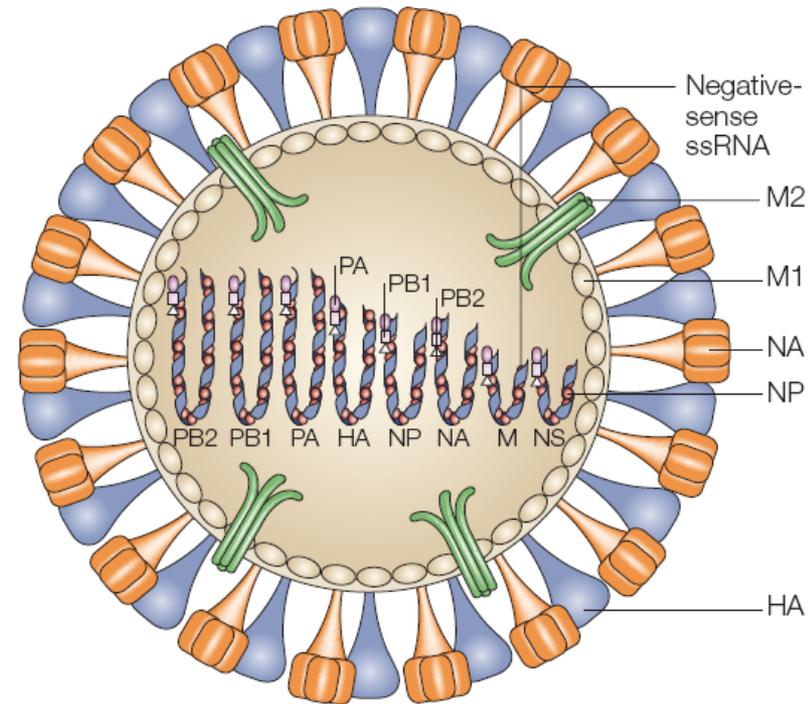


Figure 1 | **Schematic diagram of an influenza A virus virion.** Two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), and the M2 ion-channel protein are embedded in the viral envelope, which is derived from the host plasma membrane. The ribonucleoprotein complex comprises a viral RNA 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.



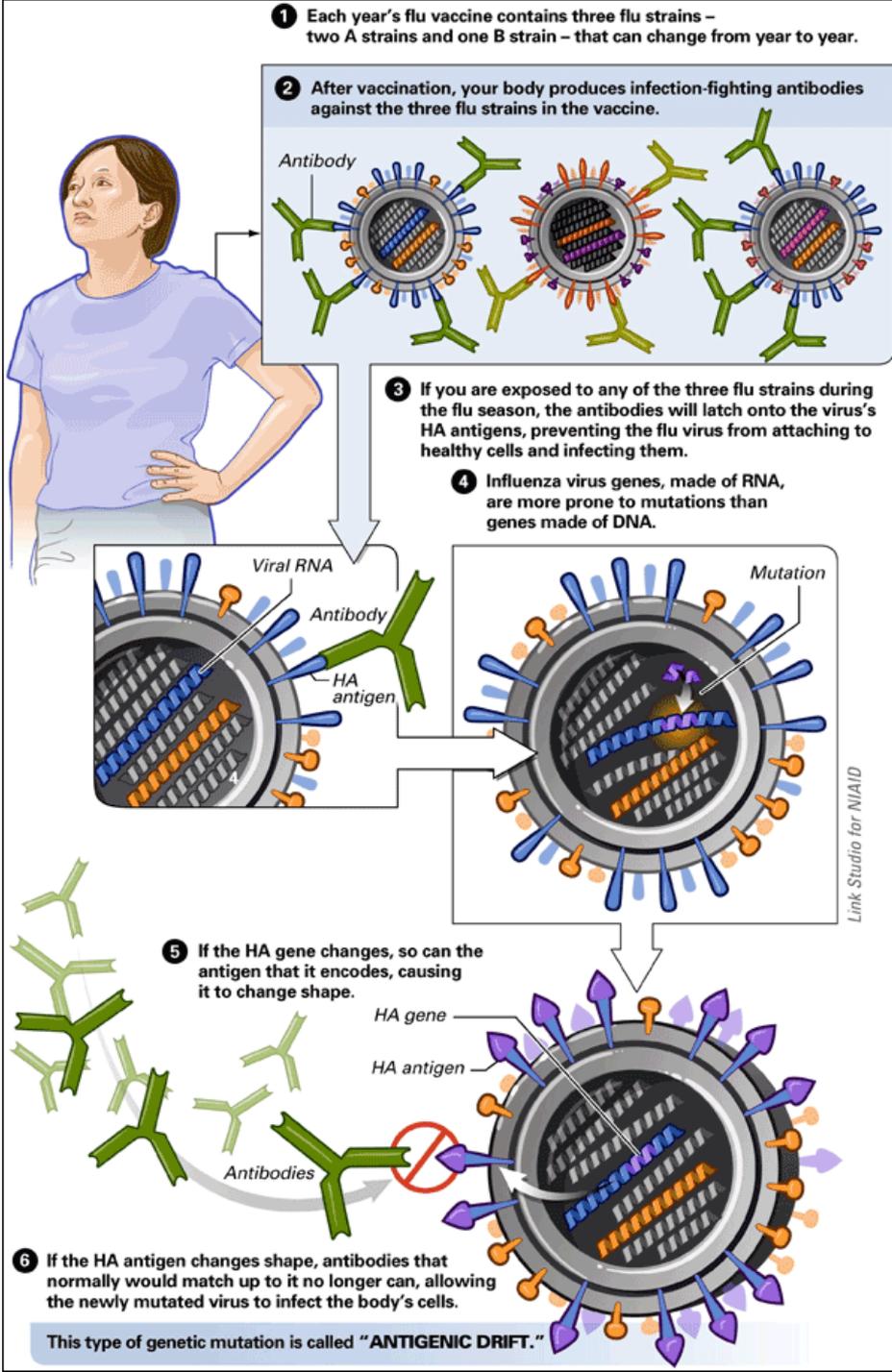
HA and NA

- 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



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>



Case

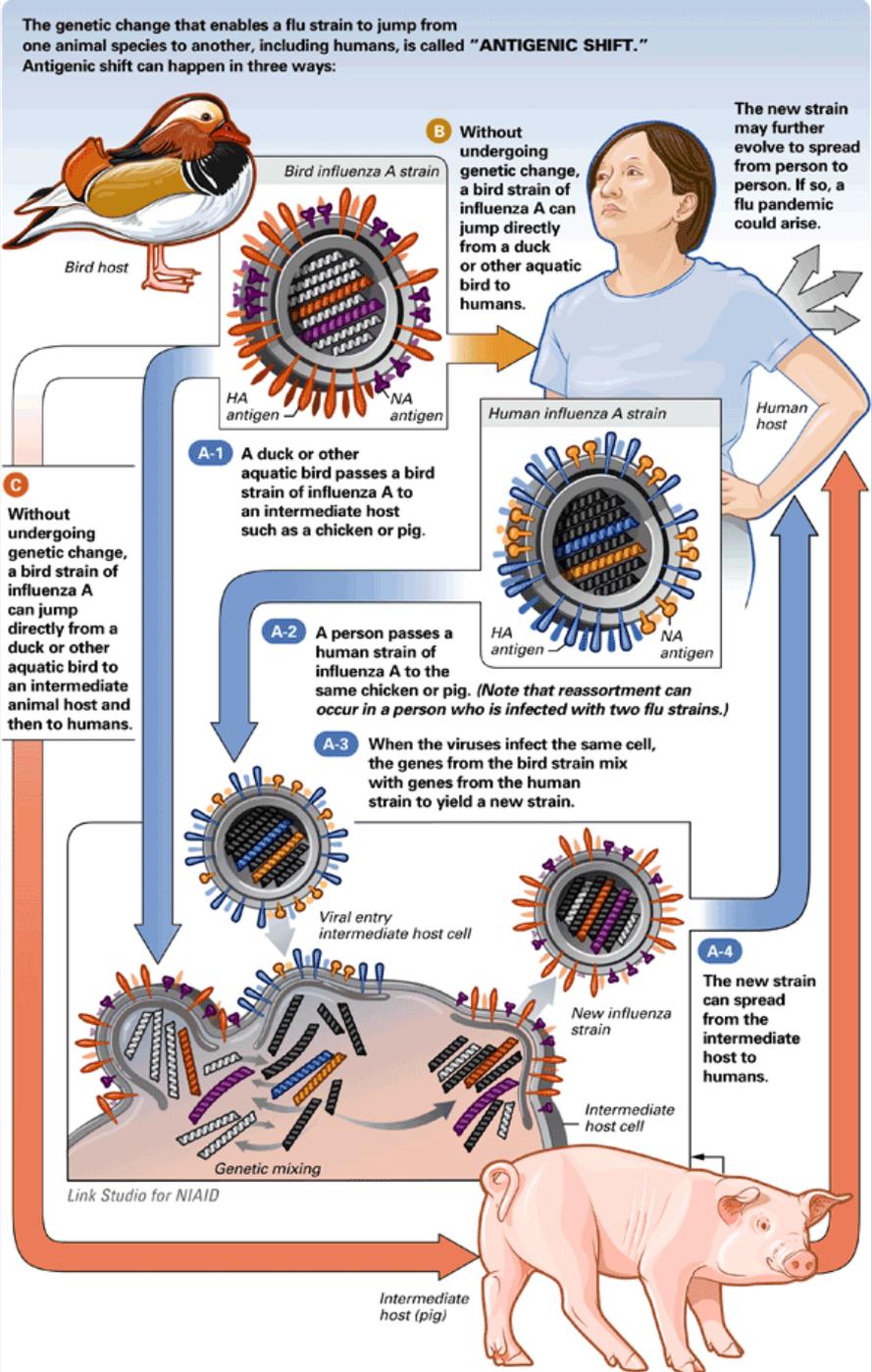
- You are deployed to the Philippines. You see a 24 yo male pig farmer with no medical history, previously in excellent health. The patient appears very ill, complaining of fevers, diffuse myalgias, cough, and shortness of breath. The patient requires intubation, but dies a week later. You hear of several other locals with similar symptoms, some young adults with severe disease.
- Pulmonary aspirates sent on your patient return from the lab in AFRIMS (Bangkok). Samples sent on 3 different days were negative on 2 of the days, and positive for Influenza A on a single sample. Confirmatory testing has not been able to determine the viral subtype.
- WTF?! (i.e. What the Flu?)



Antigenic Shift

- Major changes in HA and NA
- Influenza A viruses only
- Reassortment 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

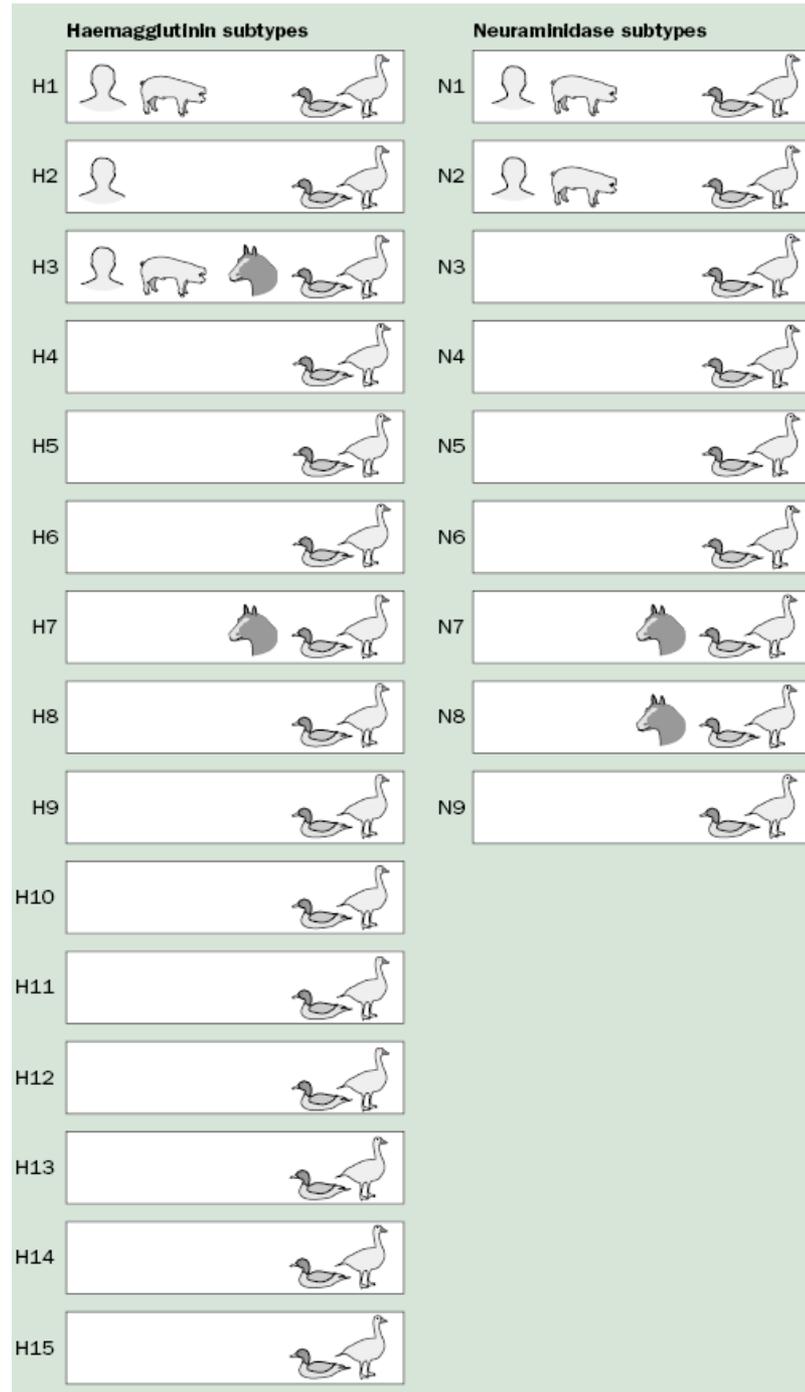
VIDEO OF INTEREST (1918 Spanish Flu): <http://www.youtube.com/watch?v=48Klc3DPdtk>



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



- 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





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)



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

Editor: Steven Riley, Imperial College London, United Kingdom

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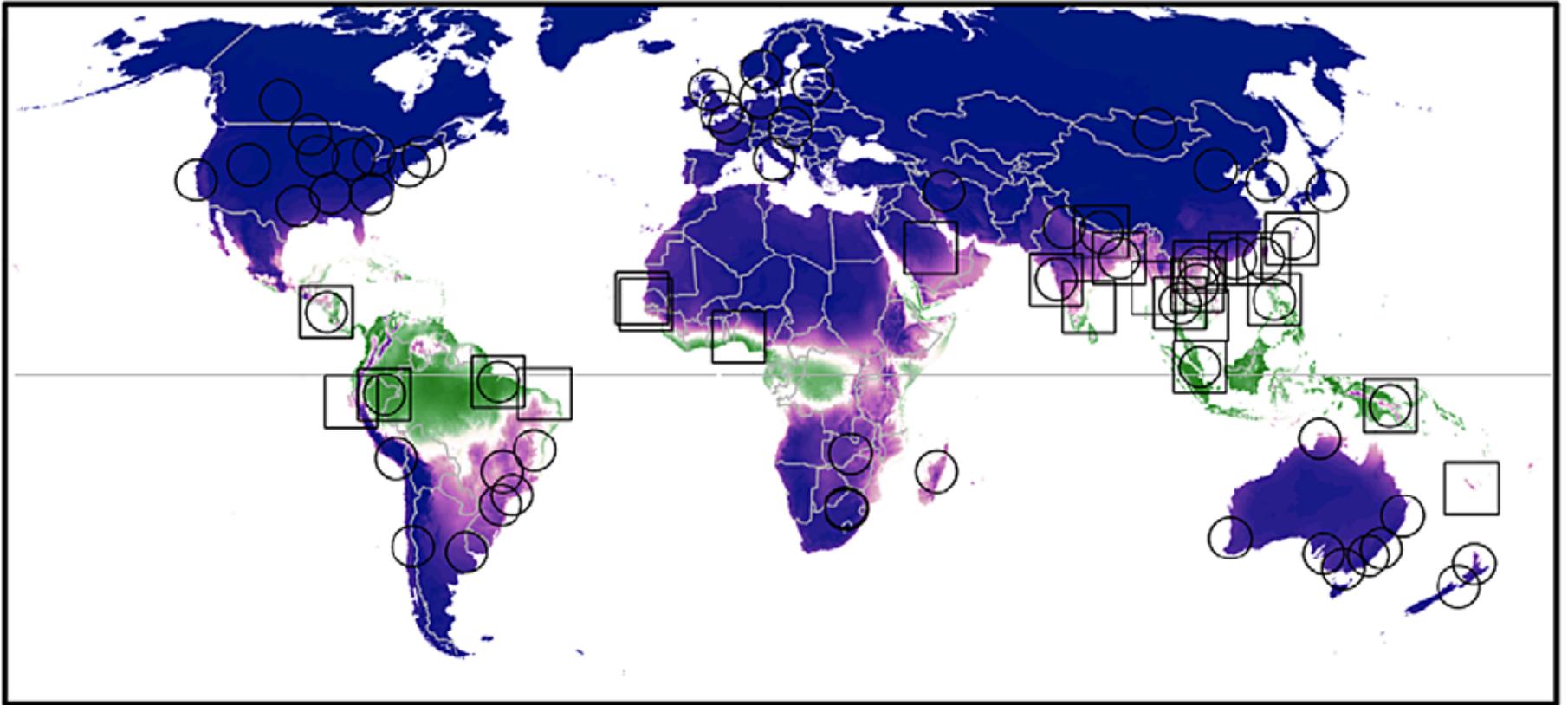


Influenza in the tropics





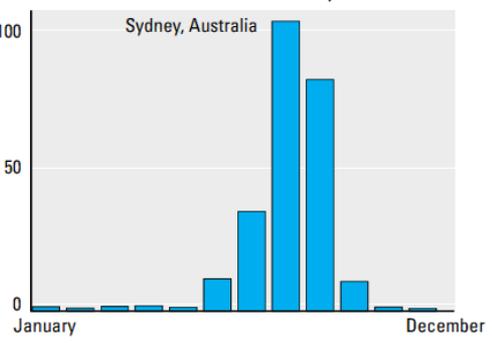
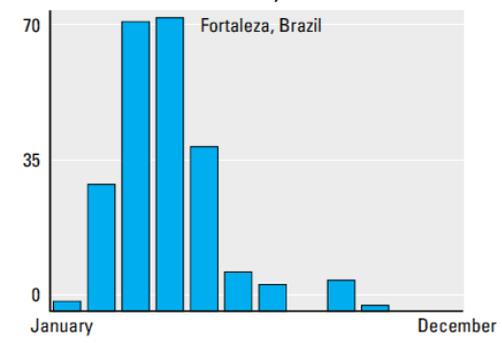
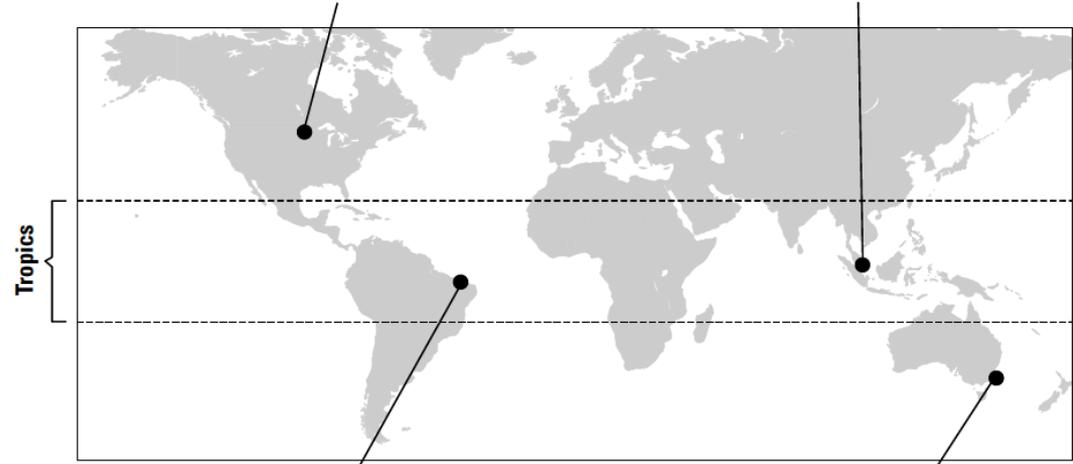
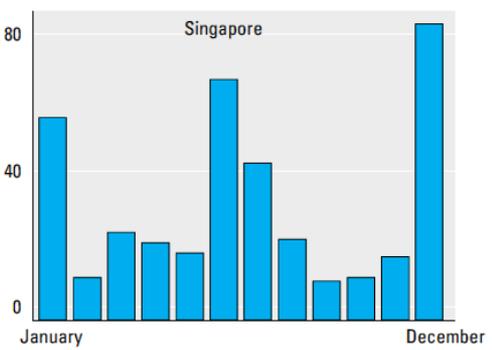
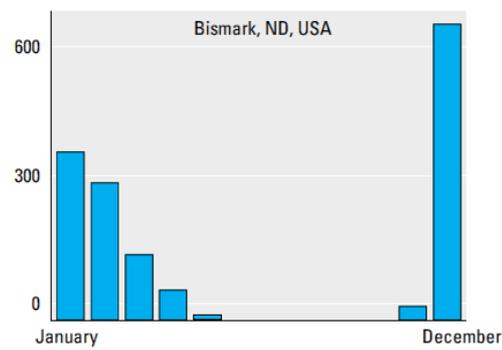
Influenza in the tropics



Cold-Dry Peaks  Humid-Rainy Peaks



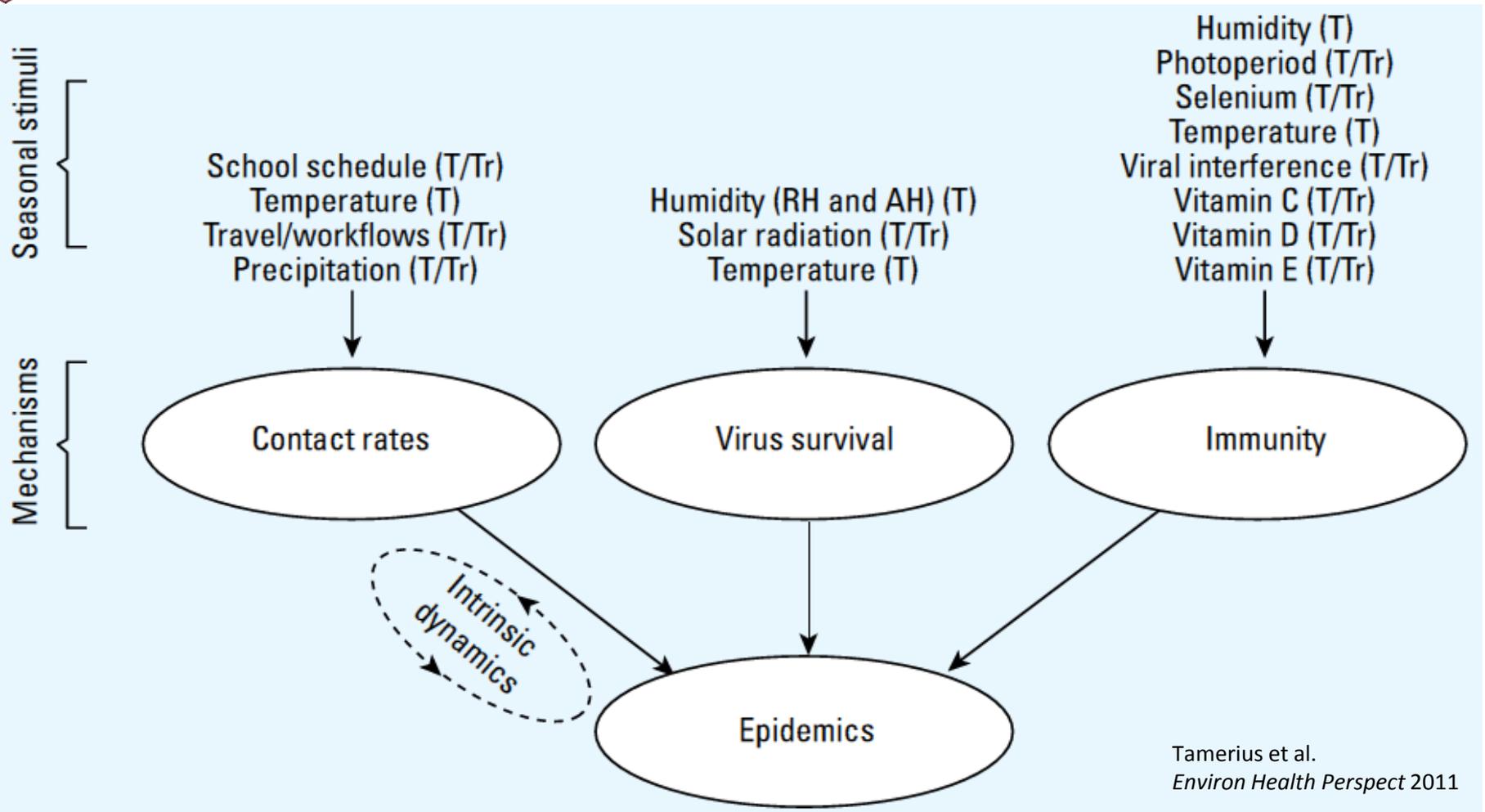
Rainy season = influenza peak



Tamerius et al.
Environ Health Perspect
2011



Multiple Factors Impact Influenza Epidemics



Tamerius et al.
Environ Health Perspect 2011

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 2014-2015 vaccine:
 - A/California/7/2009 (H1N1) pdm09-like virus
 - A/Texas/50/2012 (H3N2)-like virus
 - B/Massachusetts/2/2012-like virus
 - 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 colleagues⁴⁴ 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*

Trivalent Inactivated



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) ³⁵	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

Live Attenuated

Lancet Infect Dis 2012; 12:36-44



Seasonal Influenza Vaccine

- 20 yo soldier is adamant that he does not want to get his flu vaccine because it “gave him the flu” last year the following day.
- Your response is....?



Seasonal Influenza Vaccine

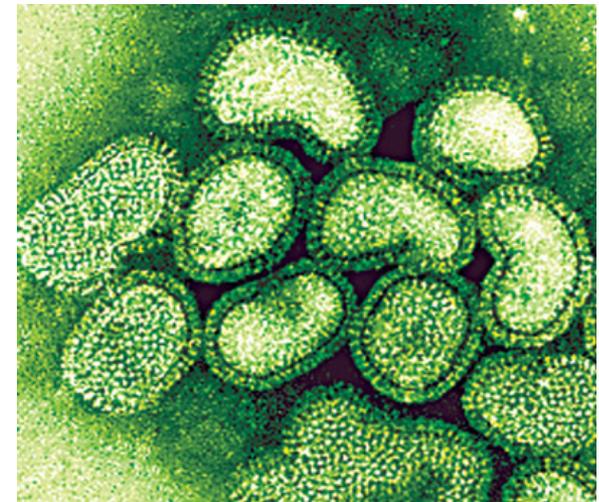
- You can't get the flu from the injection (it's inactivated virus)
- Flumist is a live attenuated virus, but other than causing runny nose and mild congestion for a few days it can't cause the flu in a healthy individual
- There are other viruses that cause the common cold that are circulating the same time of year
- It takes approximately 14 days to develop an immune response to the vaccine
- If there is a mismatch for that year (ahem...like this year), there is the possibility that you can develop influenza despite vaccination



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
- Chest X-ray with bilateral infiltration, lobar collapse, focal consolidation
- Complications
 - Acute respiratory distress, renal failure, **bacterial superinfection**





1918 Influenza Pandemic

- 1/3 of the world's population infected
- Case fatality rates of >2.5%
- 3 waves: spring/summer, summer/fall, winter
- Unclear source of pandemic virus, limited capabilities

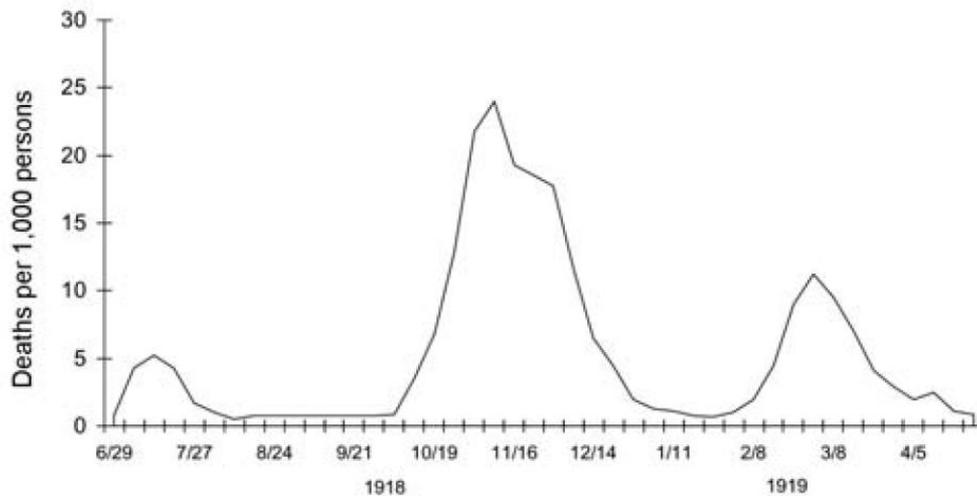


Figure 1. Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919 (21).

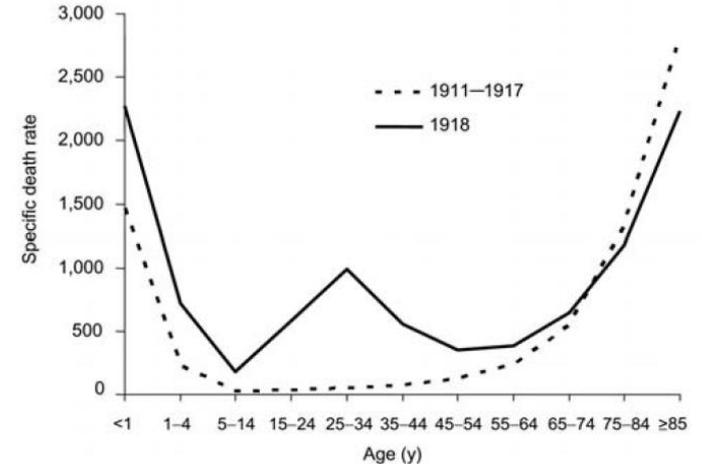


Figure 2. “U-” and “W-” shaped combined influenza and pneumonia mortality, by age at death, per 100,000 persons in each age group, United States, 1911–1918. Influenza- and pneumonia-specific death rates are plotted for the interpandemic years 1911–1917 (dashed line) and for the pandemic year 1918 (solid line) (33,34).



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 strain
- 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



2009 H1N1 Pandemic



- Estimated death and impact varies by method
 - Actual deaths vs. laboratory confirmed
 - Average global H1N1 related fatality estimate: 201,200
- Less severe than 1918 H1N1 pandemic
- Immunity: natural infection, immunization, preexisting immunity from remote infection with related strain



2009 H1N1 Pandemic

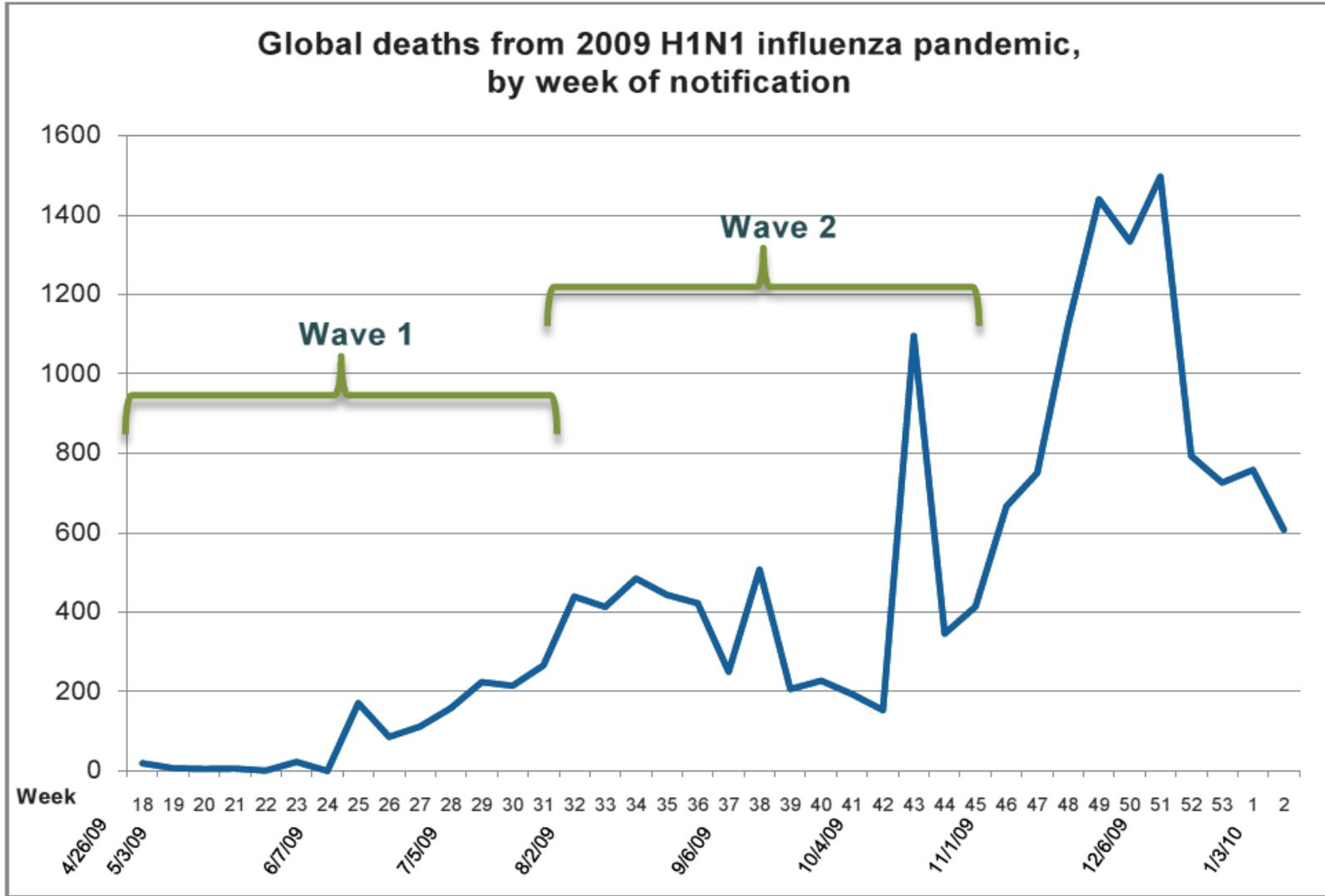


Figure 1: Global deaths from the 2009 H1N1 influenza pandemic, by week (Data Source: ECDC, 2010)

2009 H1N1 Pandemic

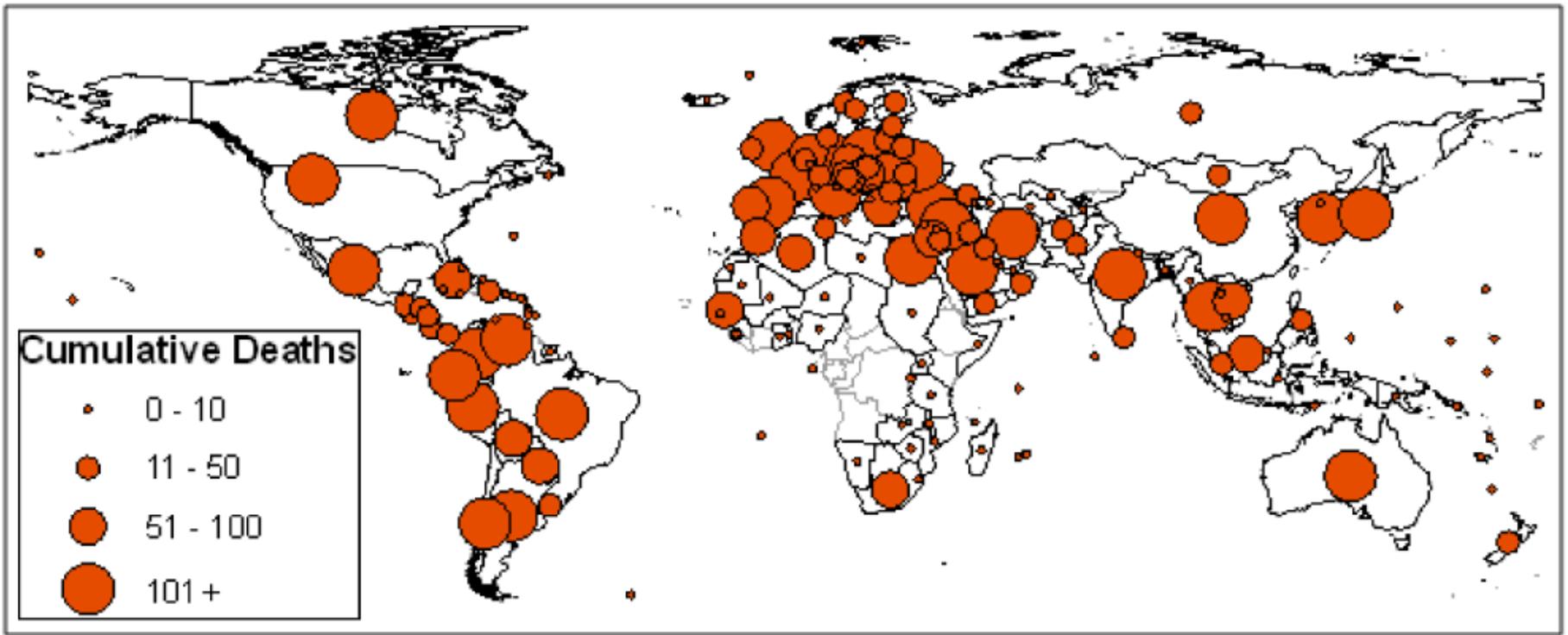


Figure 2: Map of cumulative global deaths from the 2009 H1N1 influenza pandemic, as of February 2010 (Data source: ECDC, 2010)



2009 H1N1 Pandemic

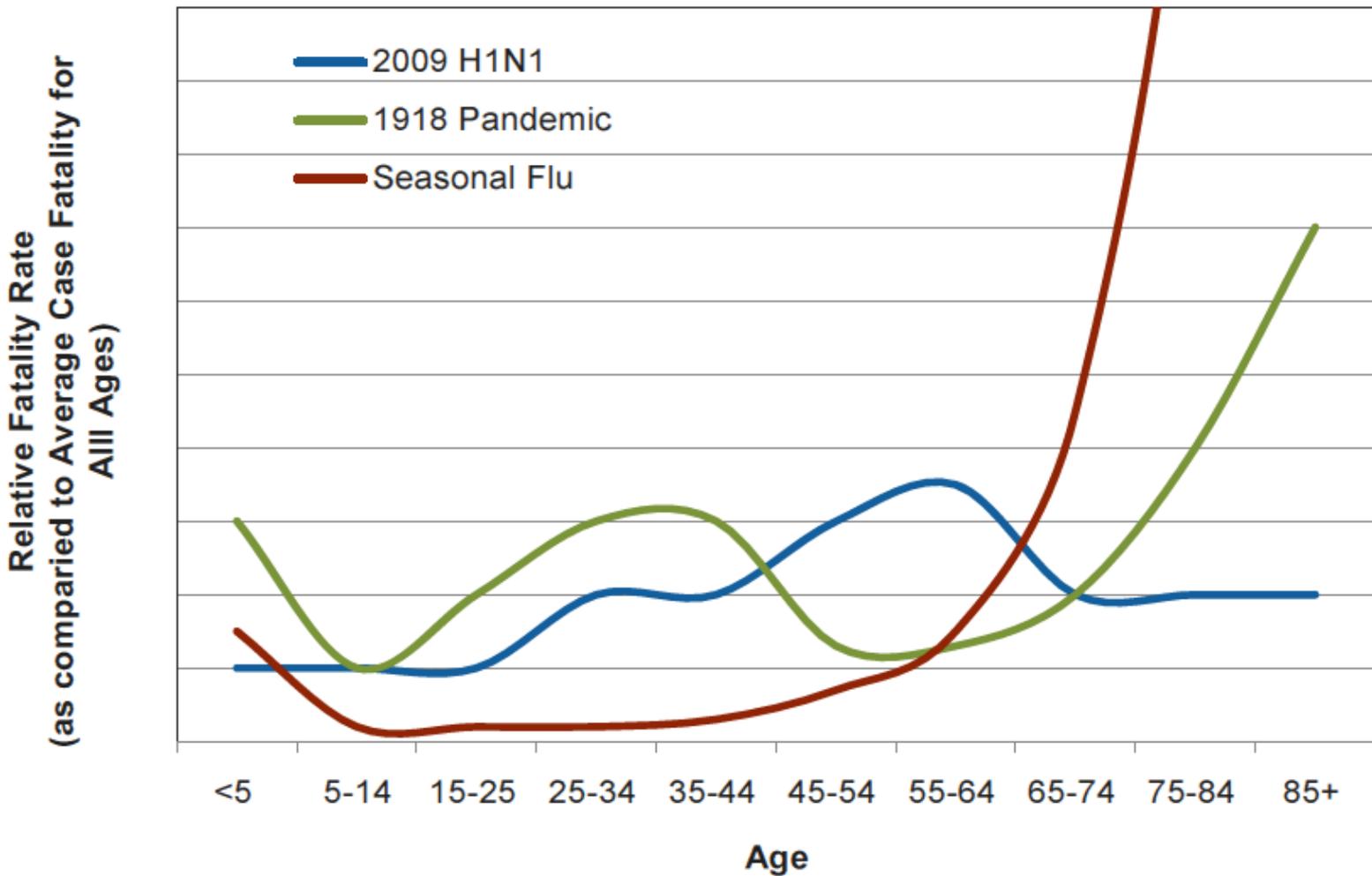
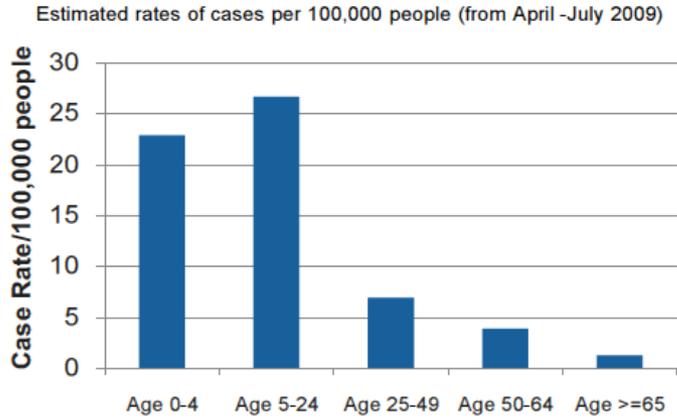


Figure 3: Age distribution of influenza mortality: comparing seasonal flu to the 1918 and 2009 pandemics



Early U.S. Cases of Novel H1N1, by Age



Early U.S. Deaths from Novel H1N1, by Age

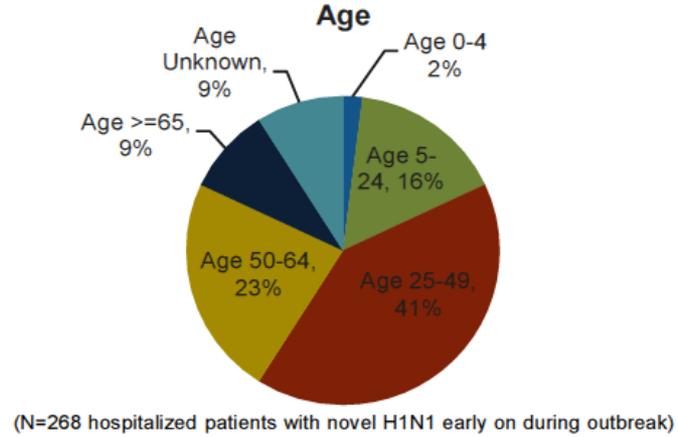
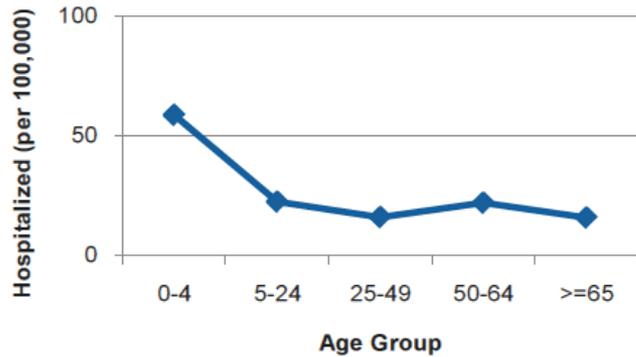


Figure 4: Early outbreak characteristics of the 2009 H1N1 virus in the U.S.: number of cases per 100,000 people from April to July 2009 (left) and early fatalities by age (right) (Date Source: CDC, 2009).

2009 H1N1 Cumulative Lab-Confirmed Hospitalization Rate by Age Group (n=49,008) (April 2009 through January 30, 2010)



2009 H1N1 Cumulative Lab-Confirmed Death Rate by Age Group (n=2,498) (April 2009 through January 30, 2010)

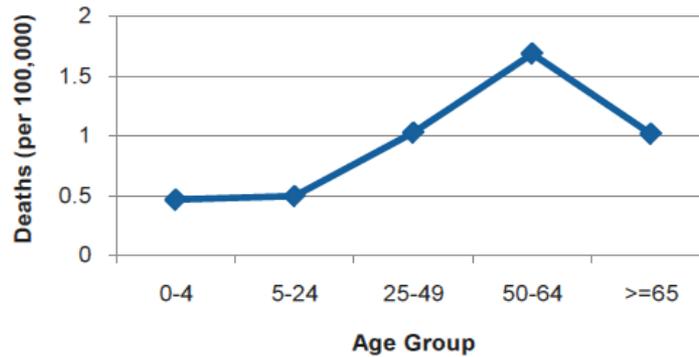


Figure 5: Age distribution of U.S. hospitalized cases (left) and fatalities (right) from the 2009 H1N1 pandemic from April 2009 through January 30, 2010 (Data Source: CDC, 2010c)



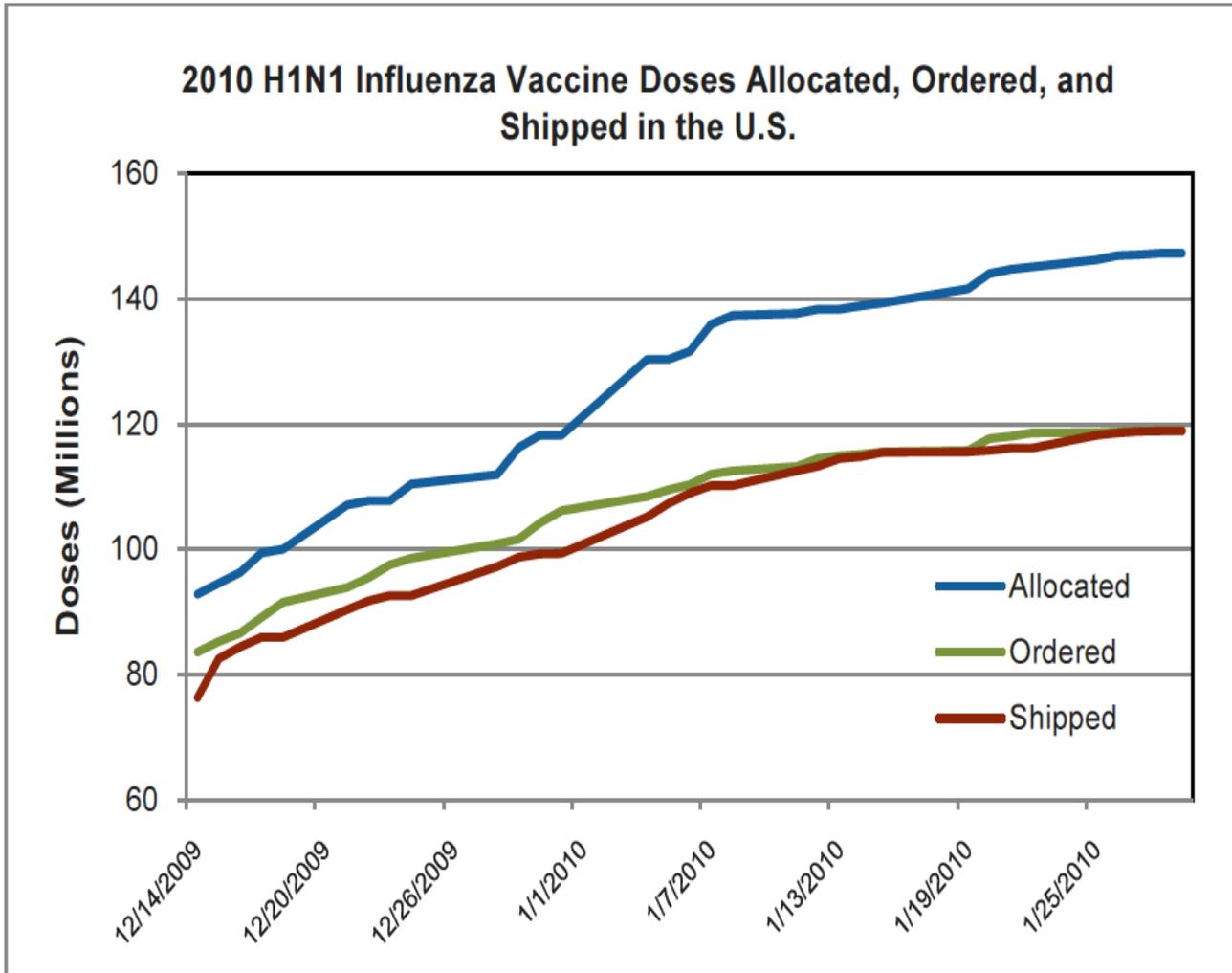
2009 H1N1 Pandemic

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



**March 2009:
Confirmed H1N1
in Veracruz,
Mexico**

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

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



Lessons from 2009 pandemic

- Vigilance and surveillance for novel strains
- Identify at risk populations
- 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 (current treatments and technologies are on our side)



Avian Influenza

- Reservoir: Aquatic birds
- 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
 - Decreased egg production, respiratory disease, head edema, diarrhea, death

Asian Bird Migratory Patterns

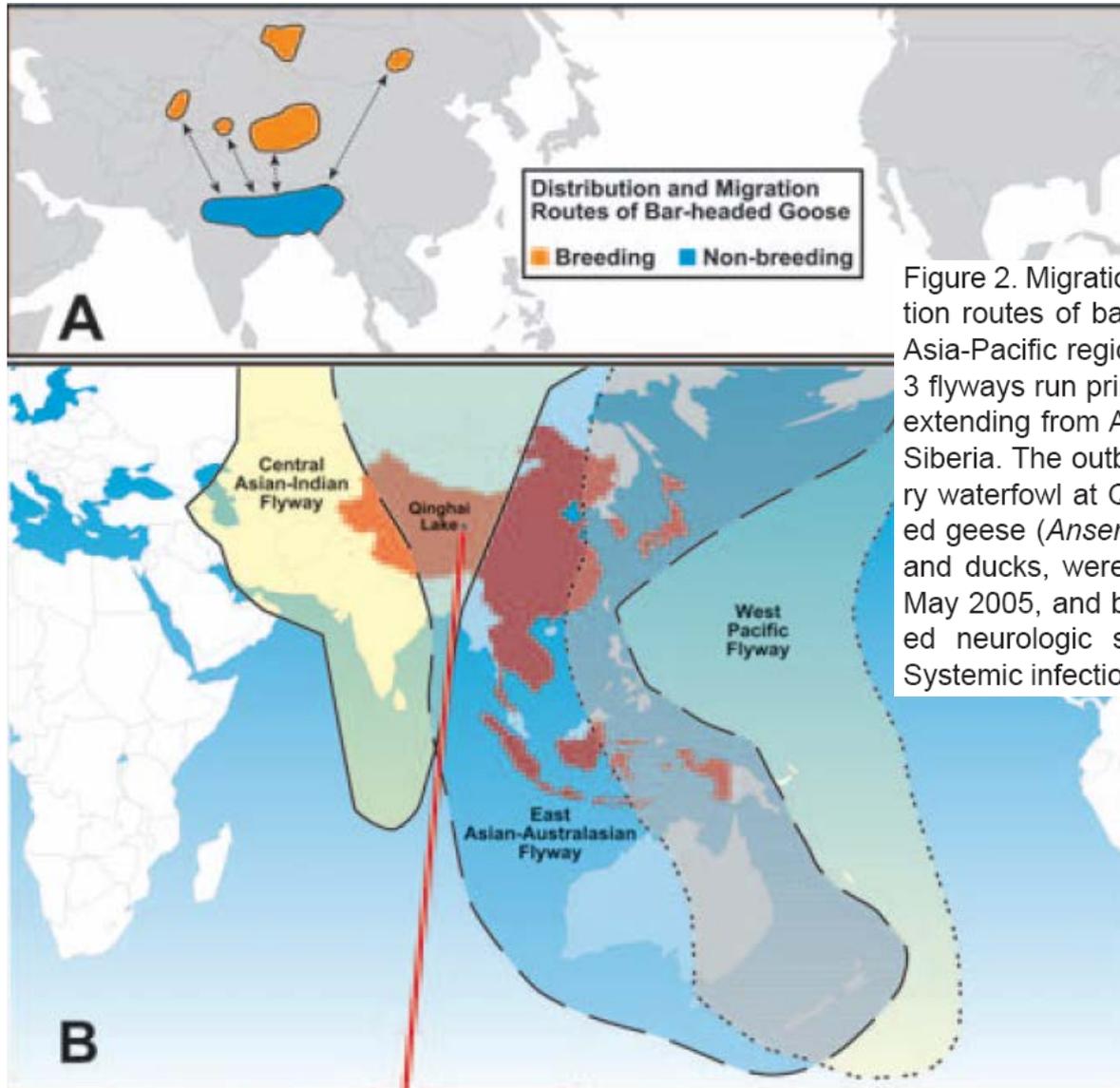


Figure 2. Migration routes of Asian birds. A) Distribution and migration routes of bar-headed geese (courtesy of P. Leader). B) The Asia-Pacific region contains >240 species of migratory birds. The 3 flyways run primarily in a north-south direction, overlapping and extending from Australia/New Zealand to India, Central Asia, and Siberia. The outbreak of highly pathogenic (HP) H5N1 in migratory waterfowl at Qinghai Lake, China, affected primarily bar-headed geese (*Anser indicus*); however, other species, including gulls and ducks, were affected (16,17). The outbreak started in early May 2005, and by June >5,000 birds had died. The birds exhibited neurologic signs, inability to stand, diarrhea, and death. Systemic infection was detected in all organs tested. C) Bar-head-



H5N1 Transmission

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

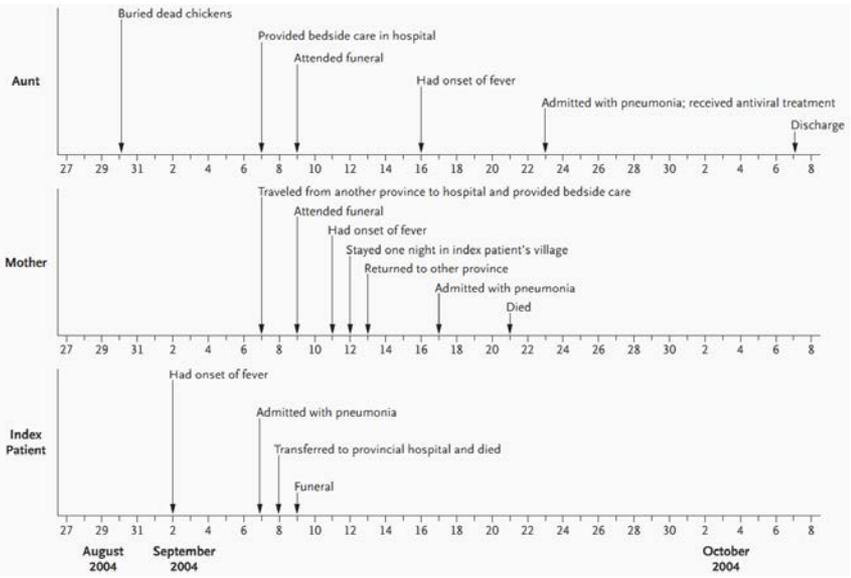
Group	Location	Year	Assay Method†	No. Tested	No. (%) Positive	Comment	Reference
Household contacts	Hong Kong	1997	MN, ELISA, WB	51	6 (12)	Concurrent exposure to poultry in 5 of 6 positive household contacts; 0 of 9 non-household contacts positive	Katz et al. ⁸
Tour group contacts				26	1 (4)		
Workplace contacts				47	0		
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.



Probable Person-to-Person Transmission of Avian Influenza A (H5N1)

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



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)

Avian Influenza Human to Human Transmission

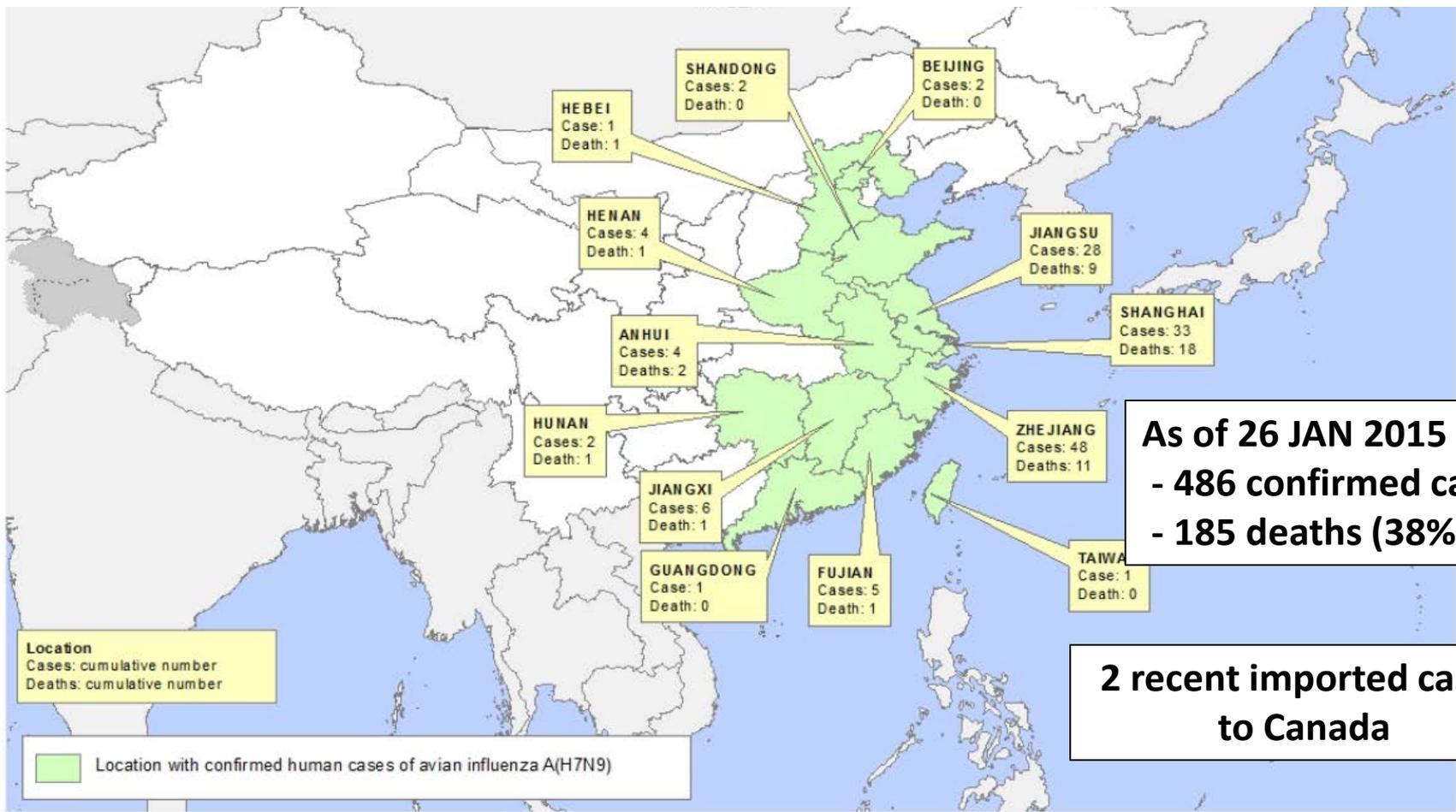
- A few reports of probable transmission among close family or hospital contacts
- WHO: limited non-sustained human to human spread





Avian Influenza A (H7N9)

Total	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
	4	3	33	18	94	23	2	0	0	0	2	1	0	0	0	0	2	0	137	45



As of 26 JAN 2015
 - 486 confirmed cases
 - 185 deaths (38% CFR)

2 recent imported cases to Canada

Location
 Cases: cumulative number
 Deaths: cumulative number

Location with confirmed human cases of avian influenza A(H7N9)



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

As of 26 JAN 2015
- 718 confirmed cases
- 413 deaths (CFR 58%)





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

Table 3. Presentation and Outcomes among Patients with Confirmed Avian Influenza A (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)
Age — yr					
Median	9.5	14	13.7†	19.4†	22
Range	1–60	2–58	5–24	6–35	8–28
Male sex — no. (%)	8 (44)	9 (53)	6 (60)	3 (30)	1 (25)
Time from last presumed exposure to onset of illness — days					
Median	NS	4	3	NS	NS
Range		2–8	2–4		
No. of family clusters		1	2	1	1
Patients with exposure to ill poultry — no./total no. (%)	11/16 (70) visited poultry markets	14/17 (82)	8/9 (89)	6/6 (100) Status of 4 unknown	3/4 (75)
Time from onset of illness to presentation or hospitalization — days					
Median	3	NS	6	6	8‡
Range	1–7		3–8	4–7	5–8
Clinical presentation — no./total no. (%)					
Fever (temperature >38°C)	17/18 (94)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Headache	4/18 (22)	NS	NS	1/10 (10)	4/4 (100)
Myalgia	2/18 (11)	9/17 (53)	0	2/10 (20)	NS
Diarrhea	3/18 (17)	7/17 (41)	7/10 (70)	NS	2/4 (50)
Abdominal pain	3/18 (17)	4/17 (24)	NS	NS	2/4 (50)
Vomiting	6/18 (33)	4/17 (24)	NS	1/10 (10)	0
Cough§	12/18 (67)	16/17 (94)	10/10 (100)	10/10 (100)	4/4 (100)
Sputum	NS	13/17 (76)	5/10 (50)	3/10 (30)	NS
Sore throat	4/12 (33)	12/17 (71)	0	0	1/4 (25)
Rhinorrhea	7/12 (58)	9/17 (53)	0	0	NS
Shortness of breath§	1/18 (6)	13/17 (76)	10/10 (100)	10/10 (100)	NS
Pulmonary infiltrates	11/18 (61)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Lymphopenia¶	11/18 (61)	7/12 (58)	NS	8/10 (80)	1/2 (50)
Thrombocytopenia	NS	4/12 (33)	NS	8/10 (80)	1/2 (50)
Increased aminotransferase levels	11/18 (61)	8/12 (67)	5/6 (83)	7/10 (70)	NS

- Typically younger
- Short incubation period
- High level of poultry exposure
- **Common Symptoms:**
 - Fever
 - Cough
 - Runny nose
 - Shortness of breath
 - Abnormal CXR
 - Low lymphocytes
 - Low platelets
 - Increased AST/ALT

Severe Illness from H5N1

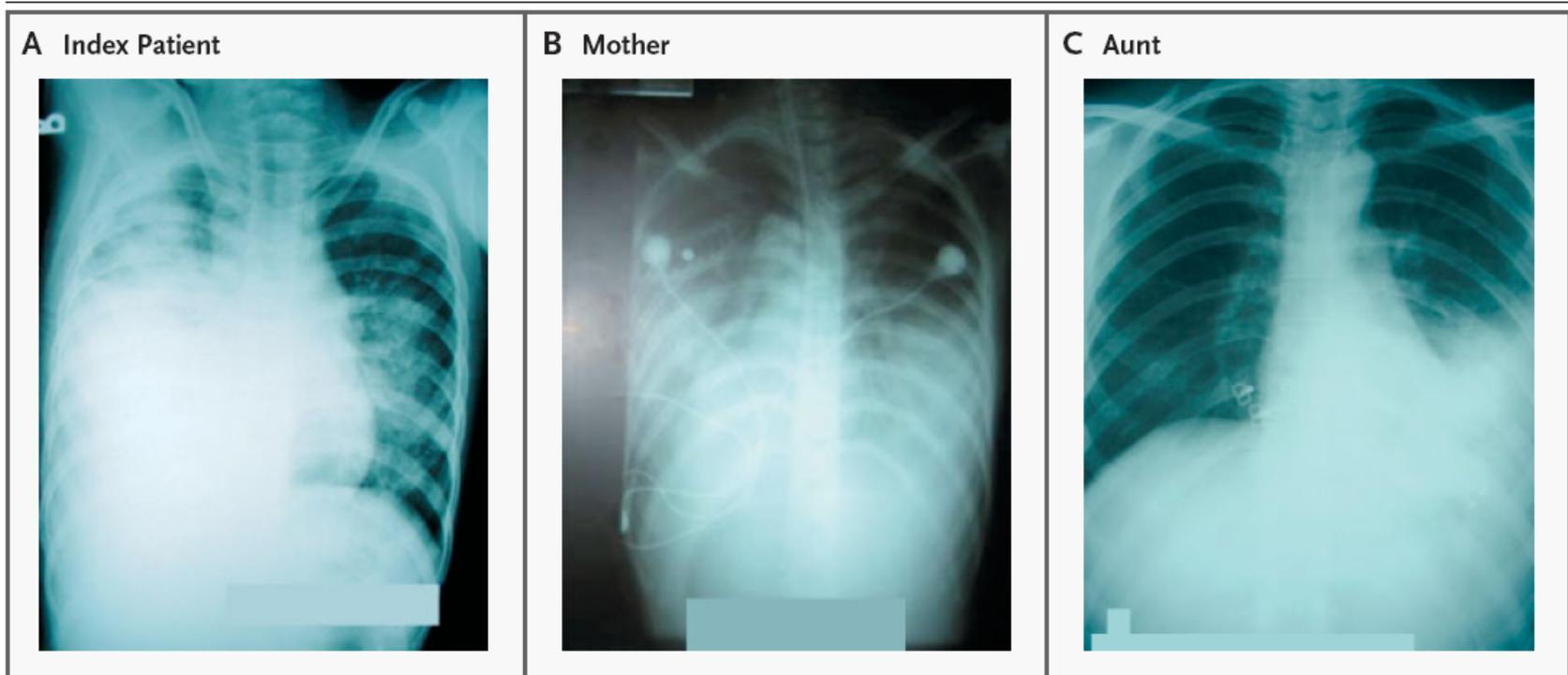


Figure 1. Chest Radiographs from the Three Patients with Avian Influenza A (H5N1).

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.



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)



Avoid These



Table 4. Exposures That May Put a Person at Risk for Infection with Influenza A (H5N1).*

Countries and territories where influenza A (H5) viruses have been identified as a cause of illness in human or animal populations since October 1, 2003

During the 7 to 14 days before the onset of symptoms, one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds or domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Unprotected contact (within touching or speaking distance) with a person for whom the diagnosis of influenza A (H5N1) is confirmed or being considered
- Unprotected contact (within touching or speaking distance, 1 m) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†

Countries and territories where influenza A (H5) viruses have not been identified as a cause of illness in human or animal populations since October 1, 2003

During the 7 to 14 days before the onset of symptoms, close contact with an ill traveler from one of the areas with known influenza A (H5) activity, history of travel to a country or territory with reported avian influenza activity due to influenza A (H5N1) in the animal populations, or living in an area in which there are rumors of the death of domestic fowl, and one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds in any setting or with domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Contact (within touching or speaking distance) with a patient with a confirmed case of influenza A (H5)
- Contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†



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

* These summaries do not present formal WHO guidelines, although they contain content from WHO documents.¹

† At-risk occupations include domestic-fowl worker, worker in a domestic-fowl processing plant, domestic-fowl culler (catching, bagging, or transporting birds or disposing of dead birds), worker in a live-animal market, chef working with live or recently killed domestic fowl, dealer or trader in pet birds, health care worker, and a worker in a laboratory processing samples possibly containing influenza A (H5N1) virus.



Pandemic and Avian Influenza: Management

- Early suspicion and recognition
- Isolation and testing
- Symptom management
- Neuraminidase inhibitors
 - Oseltamivir (oral), zanamivir (inhaled), and peramivir (IV)
 - Effective for both influenza A and B (unlike amantadine)
 - Give within 48 hr of symptom onset
 - Prevention of H5N1 but resistance develops rapidly
- Vaccine if available
 - Pandemic H1N1 influenza vaccine in 2009-2010
 - H5N1 avian influenza vaccine manufactured by Sanofi Pasteur approved by FDA in 2007
 - Testing H7N9 avian influenza vaccine (NIH sponsored)

Good Rule of Thumb:

Severe Respiratory Disease → isolate patient until you know you're dealing with



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
- **Standard 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

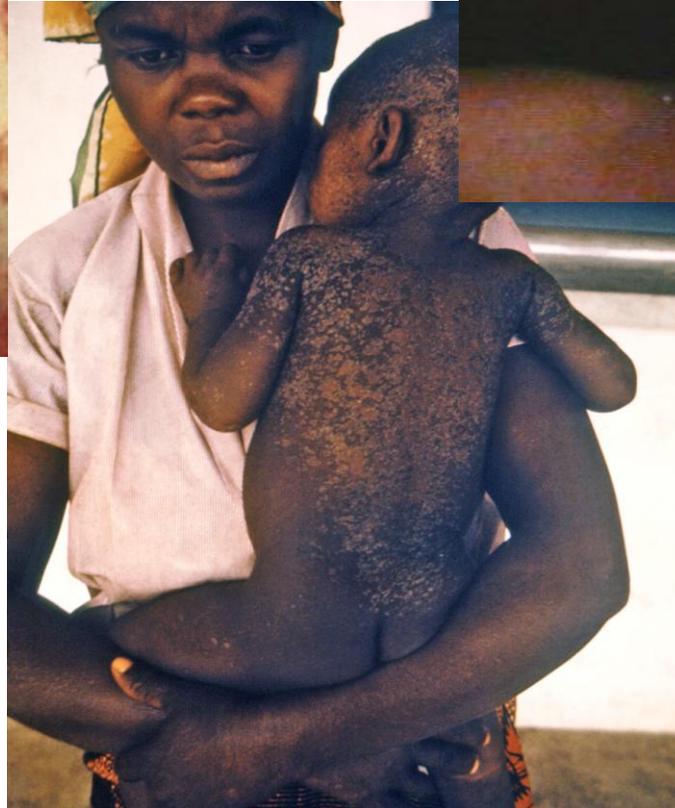
- CDC dose NOT recommend widespread prophylaxis use.
- Vaccination and close monitoring as alternative
- 70-90% effective
- **75 mg once daily, exposure time + 7 days**
 - Likely not helpful to start > 48 hrs since exposure.
 - 2 weeks after last case in long-term care facilities



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 virus
 - Severe respiratory infections: SARS CoV (2003), MERS CoV (2013)





All photos from CDC website



Measles

- Incubation period typically 7-14 days
- **Highly contagious (AIRBORNE transmission)----- 154 cases in 2015**
 - Can spread to others up to 4 days prior to rash
 - Adults can be affected
- Typical presentation (high fever, cough, runny nose, conjunctivitis, and rash erupting a few days later)
 - Rash spreads from face and head downward (fever spikes)
- Complications (This kills kids – 1 to 2 kids/1000 die)
 - ~25% require hospitalization
 - Ear infections in 10% (can result in hearing loss)
 - Diarrhea (10%)
 - Pneumonia (5%) – **most common cause of death**
 - Encephalitis (0.1%) – can result in major neurologic sequelae
 - Subacute Sclerosing Panencephalitis (SSPE)
 - Rare, but fatal occurring ~10 years after full recovery from infection



Measles Cases and Outbreaks

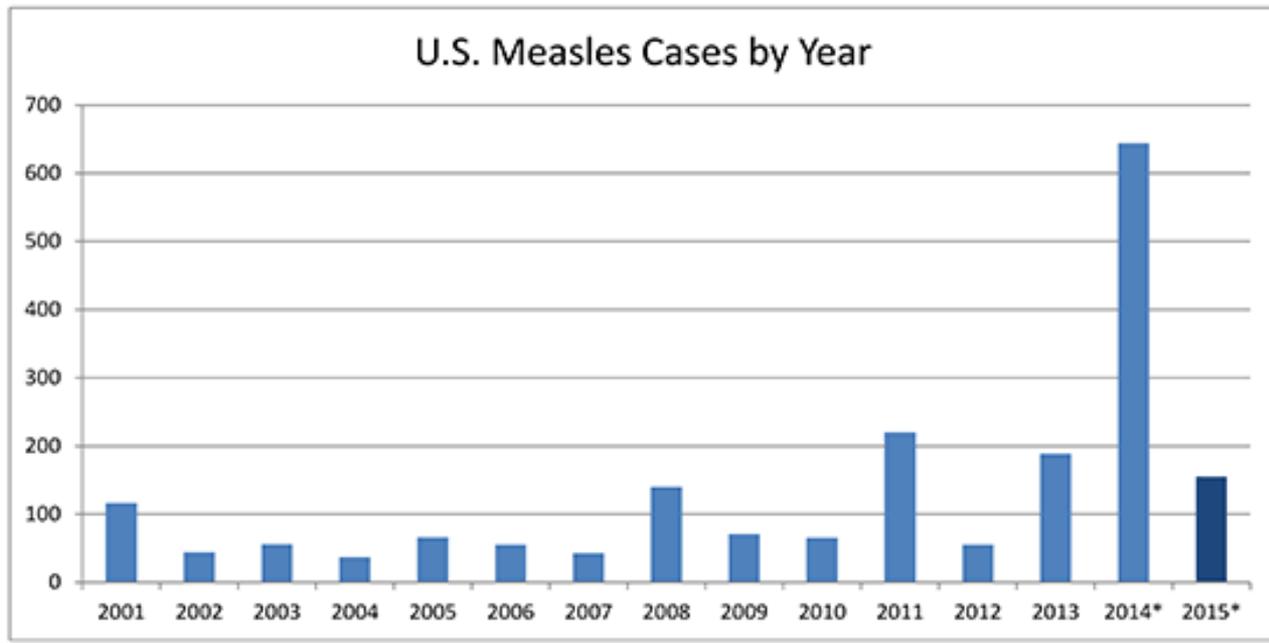
January 1 to February 20, 2015*

154
Cases

reported in 17 states and Washington DC: Arizona, California, Colorado, Delaware, Georgia, Illinois, Michigan, Minnesota, Nebraska, New Jersey, New York, Nevada, Pennsylvania, South Dakota, Texas, Utah, Washington

3
Outbreaks

representing 90% of reported cases this year

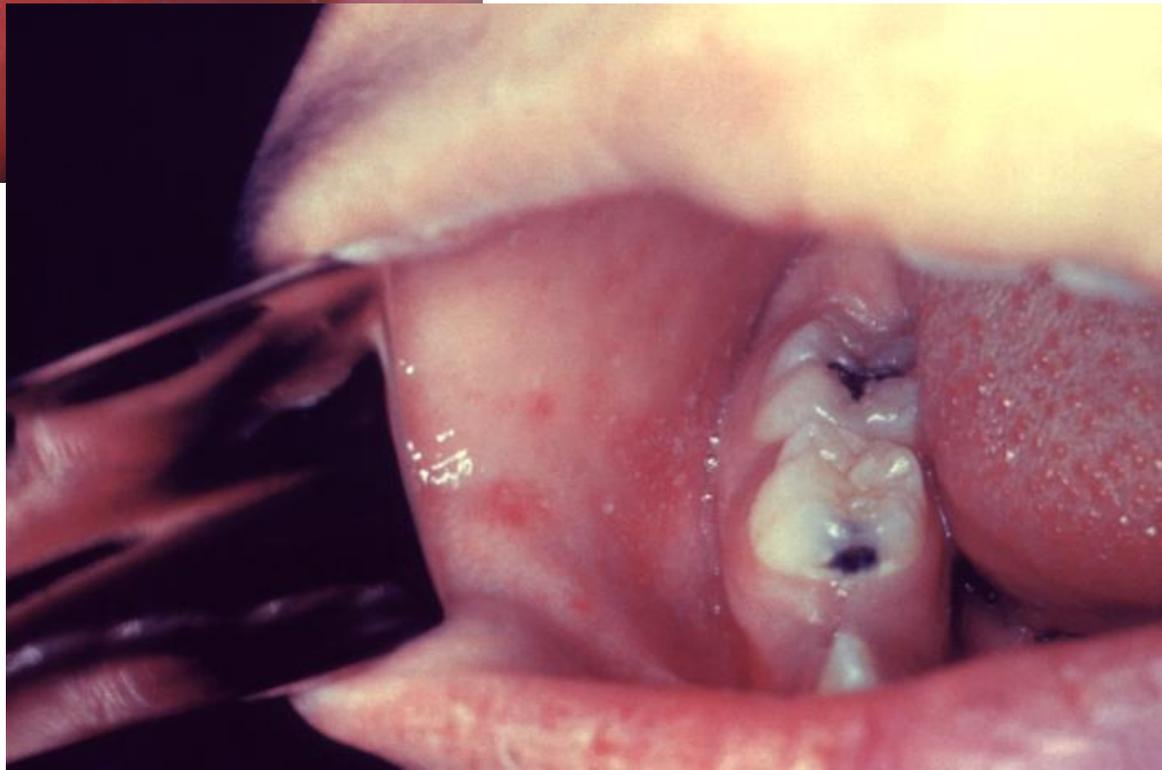


*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases





Koplik Spots





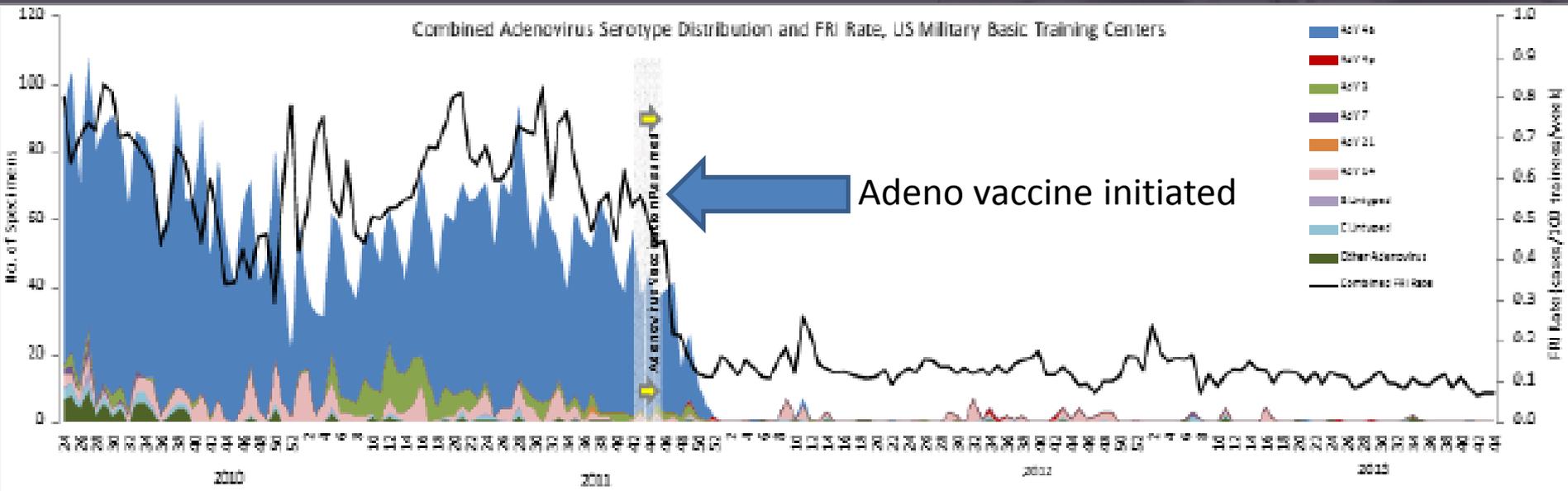
Measles

- Vaccination with MMR
 - Single dose is 93% protective (97% with 2 doses)
 - First dose just after first birthday (can get it as early as 6 mo*)
 - Second dose generally ages 4 to 6 years**
 - Not available in many developed nations
 - 20 million cases worldwide with 146,000 deaths
- Treatment
 - Supportive care
 - Monitor for bacterial superinfections
 - Vitamin A once daily x 2 days (50k to 200k IU/dose)
 - Ribavirin?

*If traveling overseas, but would need 2 additional doses after first birthday

**Can get second dose as early as 28 days after first dose

Impact of Adenovirus type 4 & 7 Vaccination Among Recruits at Eight Training Centers





Case

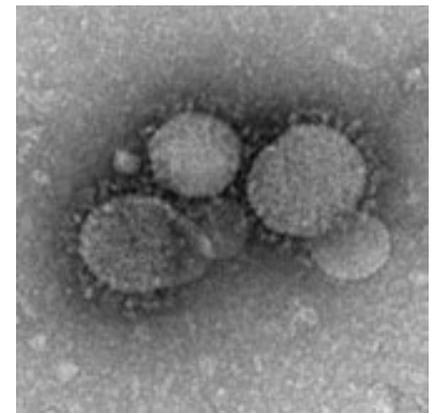
- You are deployed to Kuwait and you admit a young male SM, smoker with flulike illness, with fevers, shortness of breath and intermittent diarrhea. The SM develops ARDS and is intubated in critical condition. Within 4 days of admission, 2 of your staff are developing similar symptoms.
- What might this be?



Coronavirus



- Meaning 'crown or halo'
- Large, positive sense RNA virus
- Family *Coronaviridae*
- Infects humans, mammals, birds
- **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 and other 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**



CDC Image





Middle East Respiratory Syndrome Coronavirus (MERS-CoV)



- Severe, contagious, respiratory illness
 - 376 deaths in 1026 lab confirmed cases (37% case fatality rate)
 - as of 23 FEB 2015
- 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)
- Reservoir (bats ? **camels** ← EID 2014 Dec; 20: 1999)
- Geographically diverse animal reservoir, initial emergence in July 2011, sporadic introduction into humans and human-to-human transmission



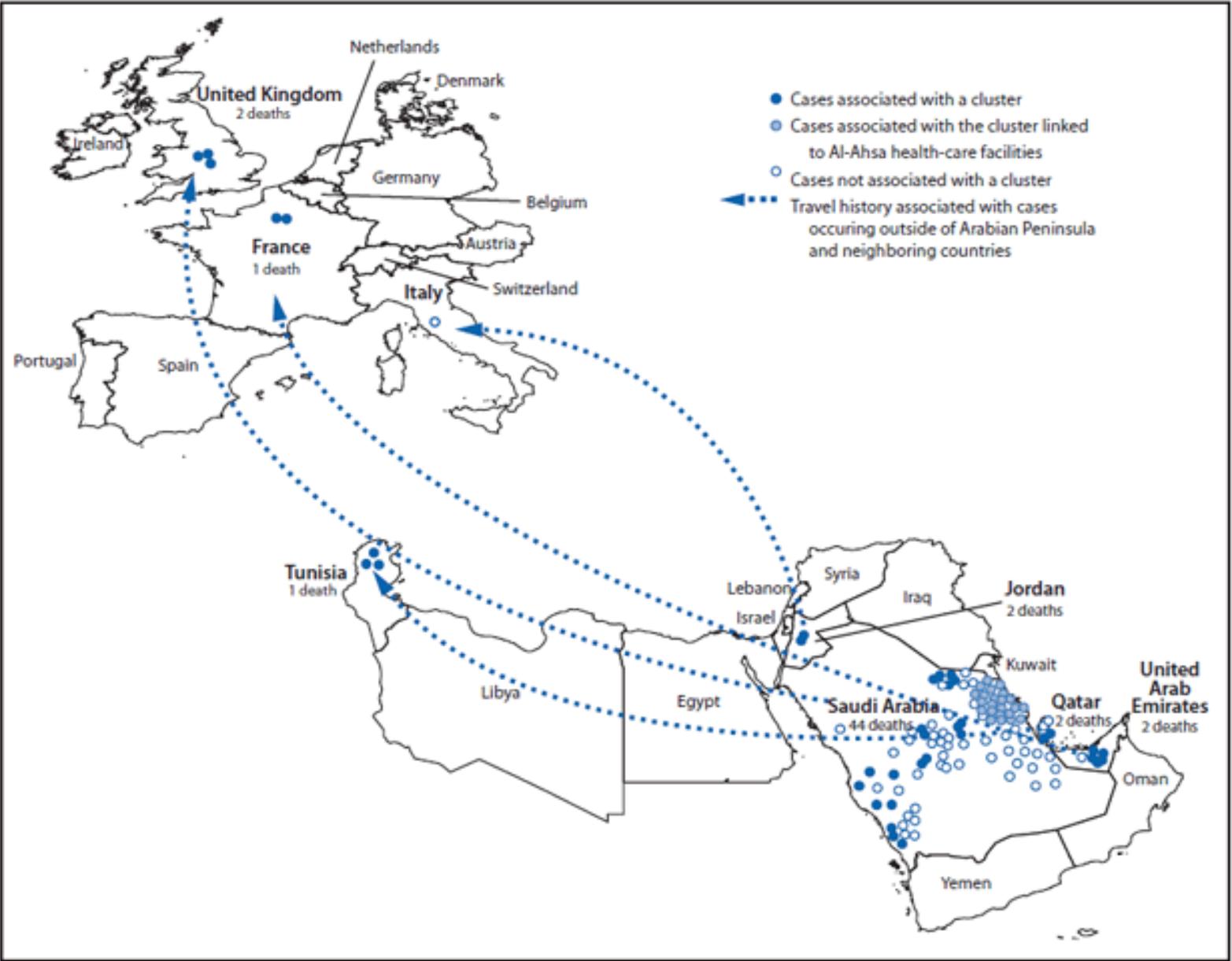
MERS-CoV

- **Countries in or near the Arabian Peninsula with Cases**

- Saudi Arabia
- United Arab Emirates (UAE)
- Qatar
- Oman
- Jordan
- Kuwait
- Yemen
- Lebanon
- Iran

- **Countries with Travel-associated Cases**

- United Kingdom (UK)
- France
- Tunisia
- Italy
- Malaysia
- Philippines
- Greece
- Egypt
- United States of America (USA)
- Netherlands
- Algeria
- Austria
- Turkey





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-Rabeeh, Fahad A Al-Rabiah, Sami Al-Hajjar, Ali Al-Barrak, Hesham Flenb 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

Overall CFR = 36%
Any comorbidity = 60%

MERS Co-V

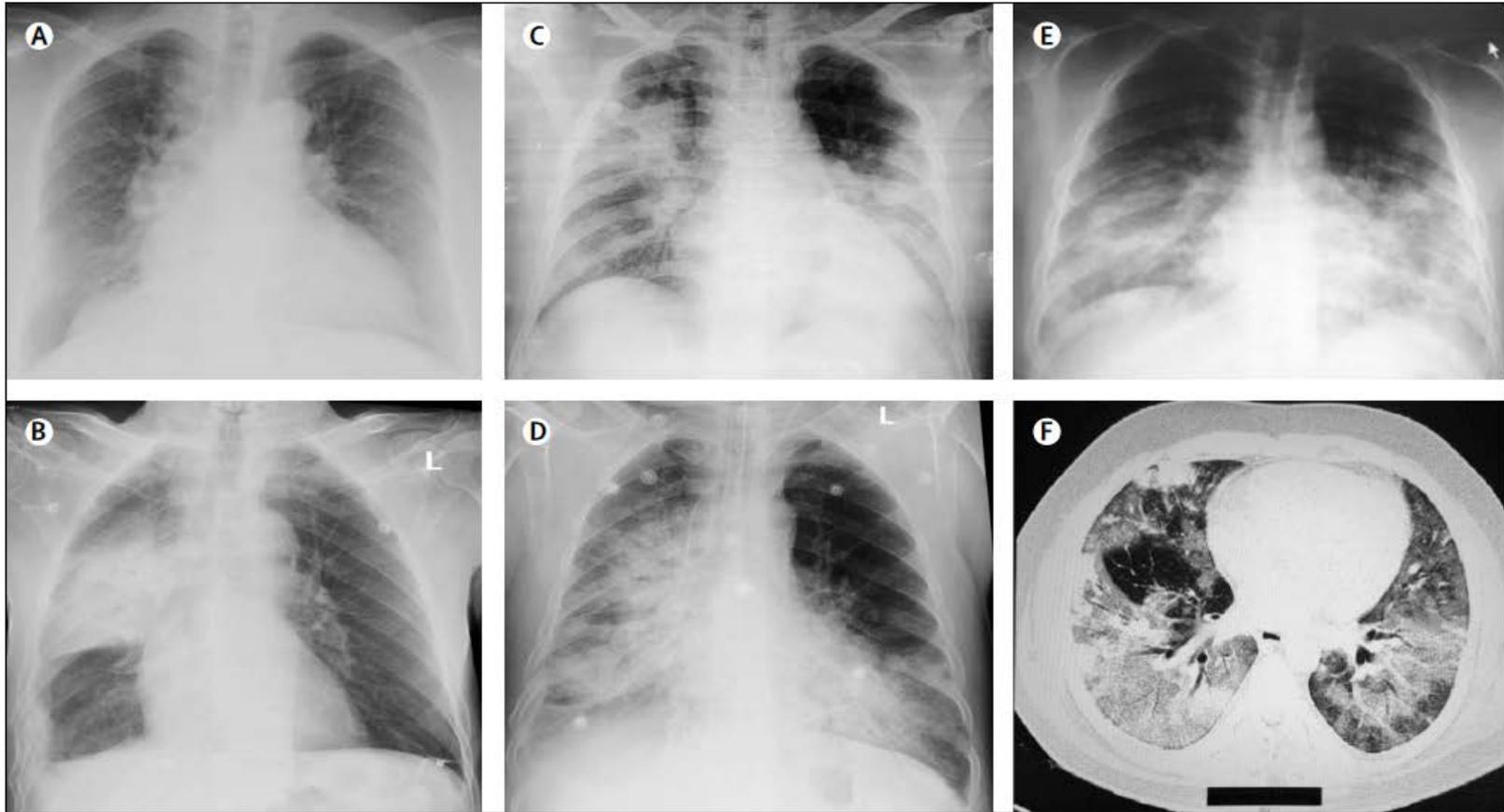


Figure 1: Imaging findings at presentation in Saudi patients with Middle East respiratory syndrome

(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 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.



MERS Co-V 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



Current Guidance – MERS-CoV

- All cases linked to travel or residence in affected areas
- Assess risk, suspect disease
- Lower respiratory tract specimen for rRT-PCR preferred
 - Nasopharyngeal wash or swabs
 - Serum for PCR and serologic testing
 - Stool for PCR
- Follow up serology testing
- Isolation Precautions
 - Airborne for suspected cases
 - For SARS, CDC: ‘airborne precaution preferred’
 - Other standard AND contact precautions



N95 Mask



Current Guidance – MERS-CoV: Case Definition

- **PATIENT UNDER INVESTIGATION (PUI) PER CDC WEBSITE:**
 - FEVER AND PNEUMONIA OR ARDS **AND**:
 - A HISTORY OF TRAVEL FROM COUNTRIES IN OR NEAR THE ARABIAN PENINSULA WITHIN 14 DAYS BEFORE SYMPTOM ONSET, **OR**
 - CLOSE CONTACT WITH A SYMPTOMATIC TRAVELER WHO DEVELOPED FEVER AND ACUTE RESPIRATORY ILLNESS (NOT NECESSARILY PNEUMONIA) WITHIN 14 DAYS AFTER TRAVELING FROM COUNTRIES IN OR NEAR THE ARABIAN PENINSULA¹ **OR**
 - A MEMBER OF A CLUSTER OF PATIENTS WITH SEVERE ACUTE RESPIRATORY ILLNESS (E.G., FEVER AND PNEUMONIA REQUIRING HOSPITALIZATION) OF UNKNOWN ETIOLOGY IN WHICH MERS-COV IS BEING EVALUATED, IN CONSULTATION WITH STATE AND LOCAL HEALTH DEPARTMENTS.

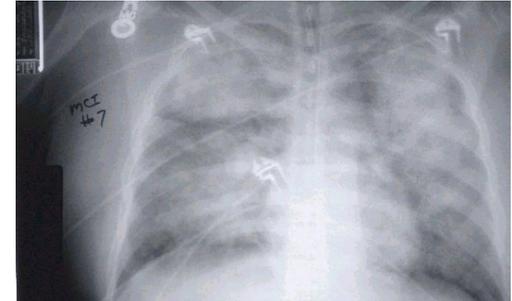
OR

- FEVER AND SYMPTOMS OF RESPIRATORY ILLNESS AND BEING IN A HEALTHCARE FACILITY WITHIN 14 DAYS BEFORE SYMPTOM ONSET IN A COUNTRY OR TERRITORY IN OR NEAR THE ARABIAN PENINSULA IN WHICH RECENT HEALTHCARE-ASSOCIATED CASES OF MERS HAVE BEEN IDENTIFIED.

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





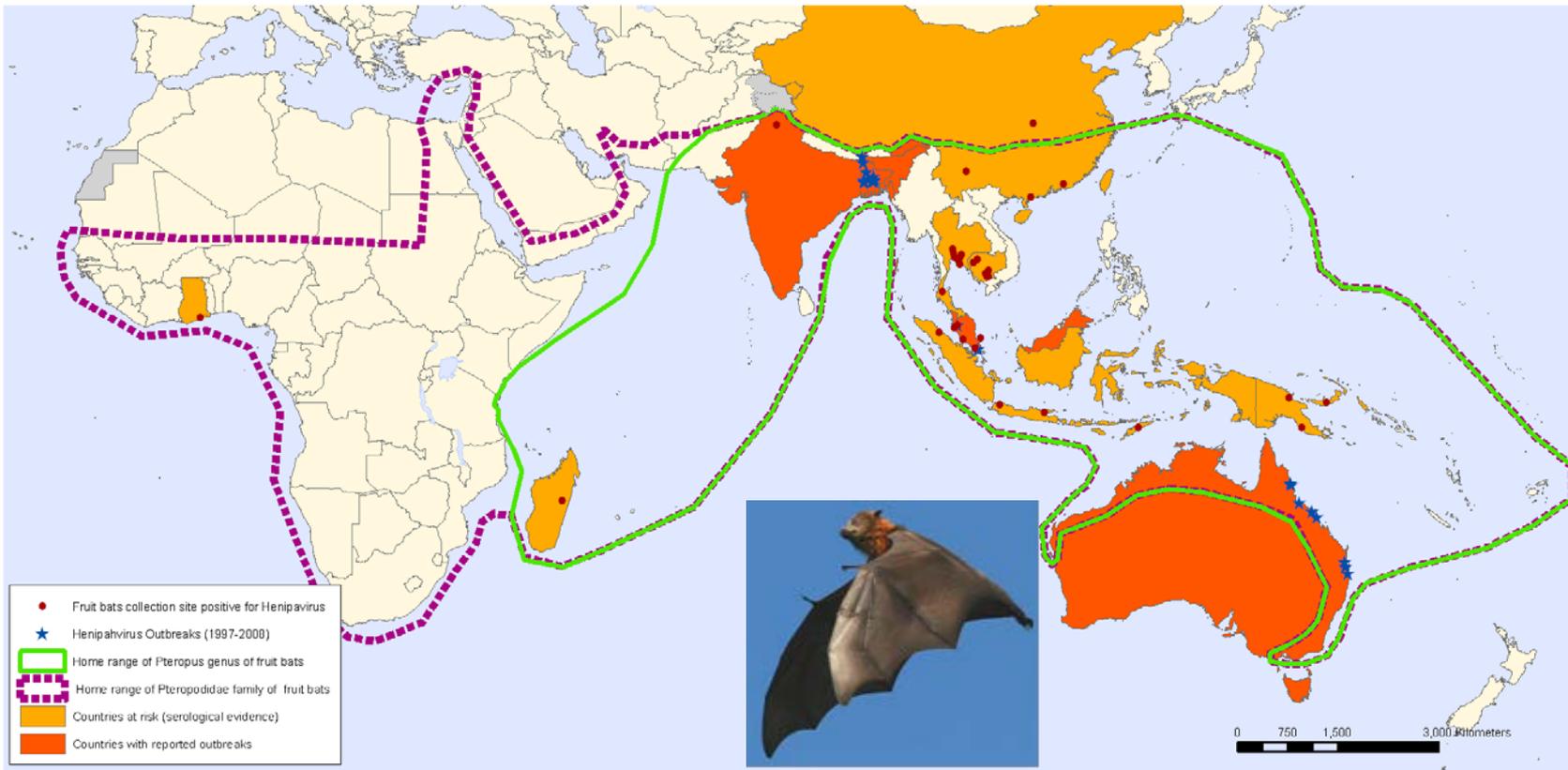
Nipah Virus



- 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 develop 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

Geographic distribution of Henipavirus outbreaks and fruit bats of Pteropodidae Family



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

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



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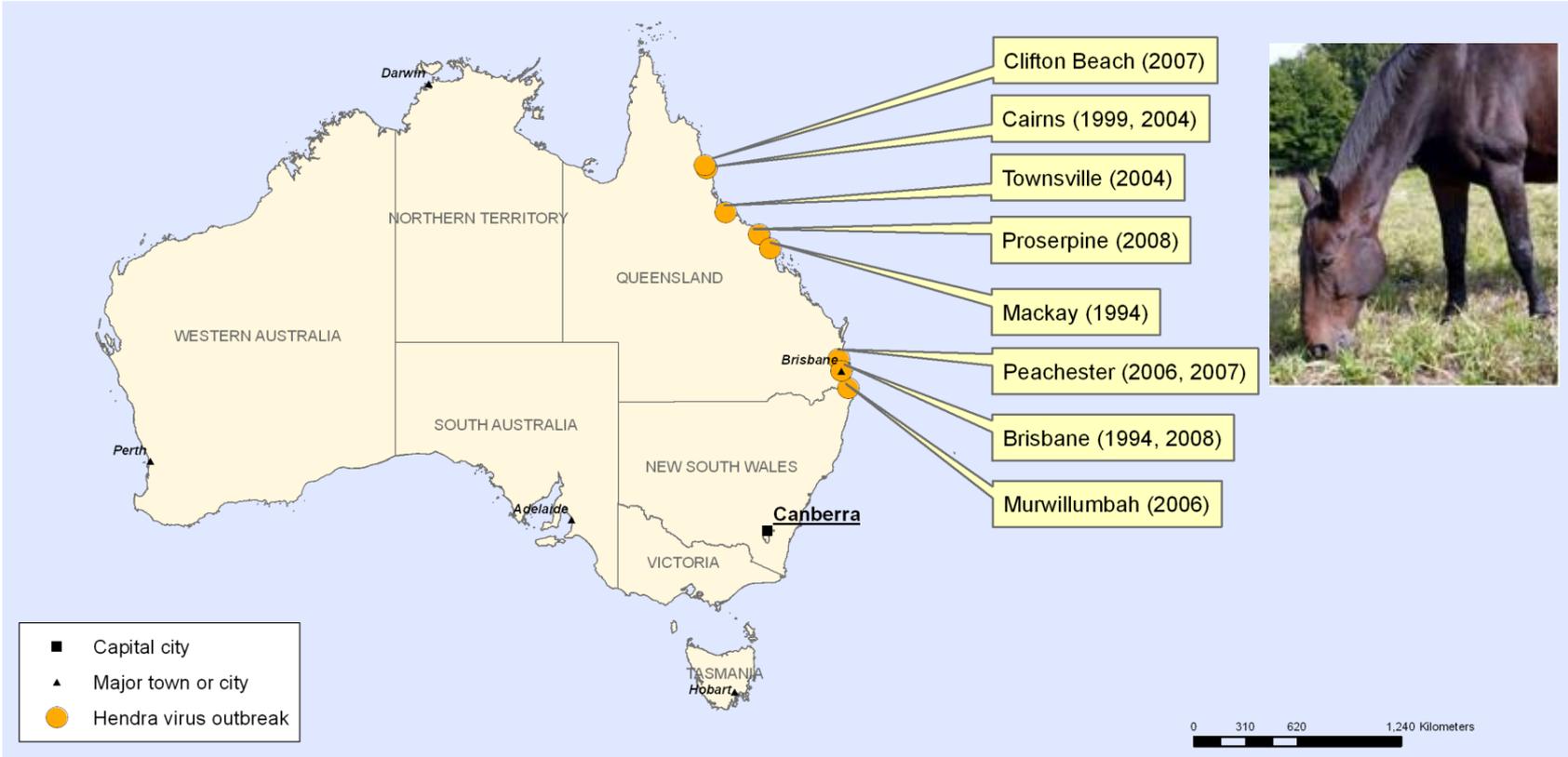
Hendra Virus

- 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



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

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



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Tuberculosis



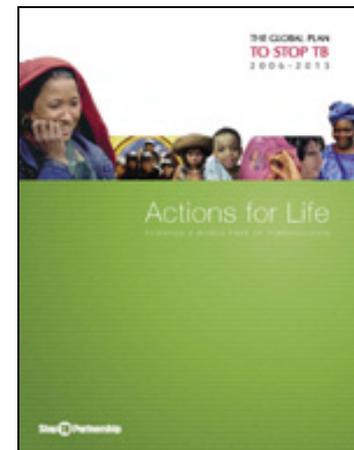
Outline

- Global Burden of Tuberculosis
- Active vs. Latent TB Infection
- Diagnosis and Treatment of Active TB
- Diagnosis and Treatment of Latent TB
- Military screening policies
- Managing Exposure in a Deployed Environment
- Other issues

Global Burden of Tuberculosis



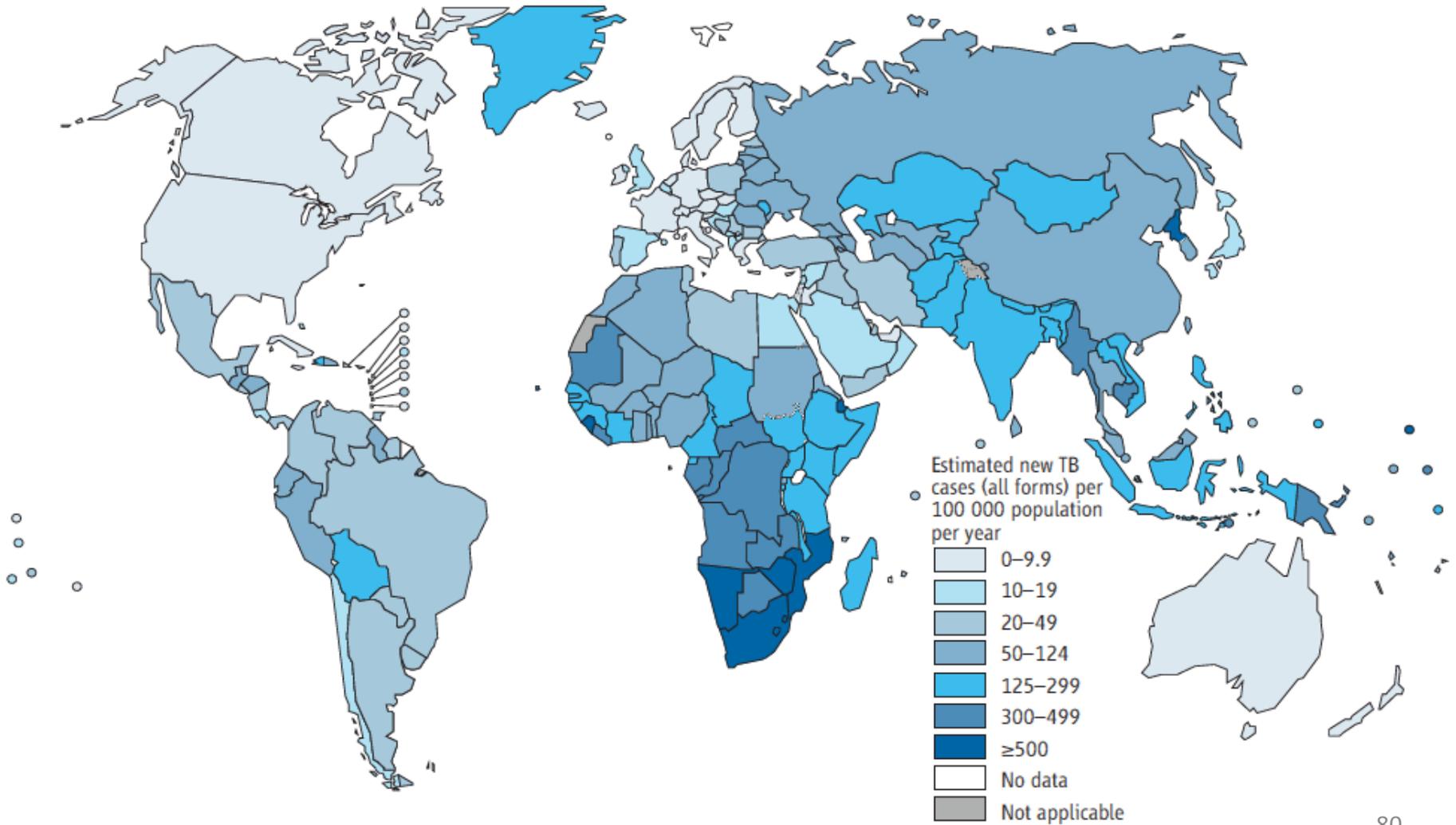
- 9.2 million cases and 1.7 million deaths yearly
- Associated with co-pandemic of HIV
- Drug-resistance increasingly common
- One third of the world's population is infected with LTBI
 - Focus is on identification and treatment of active TB (DOTS)
 - Screening for LTBI is not routinely done in most countries
 - Increasing efforts to extend LTBI treatment to HIV populations





Global Burden of Tuberculosis

Estimated TB incidence rates, 2012





TB Pathophysiology

- Spread person-to-person through the air
- Droplet nuclei may remain in the air
- Primary infection
 - Inhale tubercle bacilli
 - Reach alveoli, engulfed by macrophages
 - Some multiply intracellularly and released
 - Immune system (cell-mediated) prevents progression
- Activation
 - Tubercle bacilli overcome immune system
 - “5% risk in 2 years, 10% lifetime” (may be lower – **Am J Respir Crit Care Med 2014 NOV 1; 190: 1044**)





Active TB

- Chronic infection with *Mycobacterium tuberculosis*.
- Pulmonary most common (80%)
 - Pulmonary and laryngeal TB are contagious
- Extrapulmonary (20%)
 - Lymphadenitis (scrofula)
 - Skeletal
 - Renal
 - Meningeal



Diagnosis of TB

- Clinical symptoms and signs
- CXR (not confirmatory)
- Detection of tubercle bacilli
 - AFB Smear (sensitivity 50%)
 - Culture and sensitivity testing
 - Nucleic Acid Amplification Tests



Symptoms of Active TB

- Fever
- Chronic cough
- Night sweats
- Hemoptysis
- Weight loss
- Fatigue

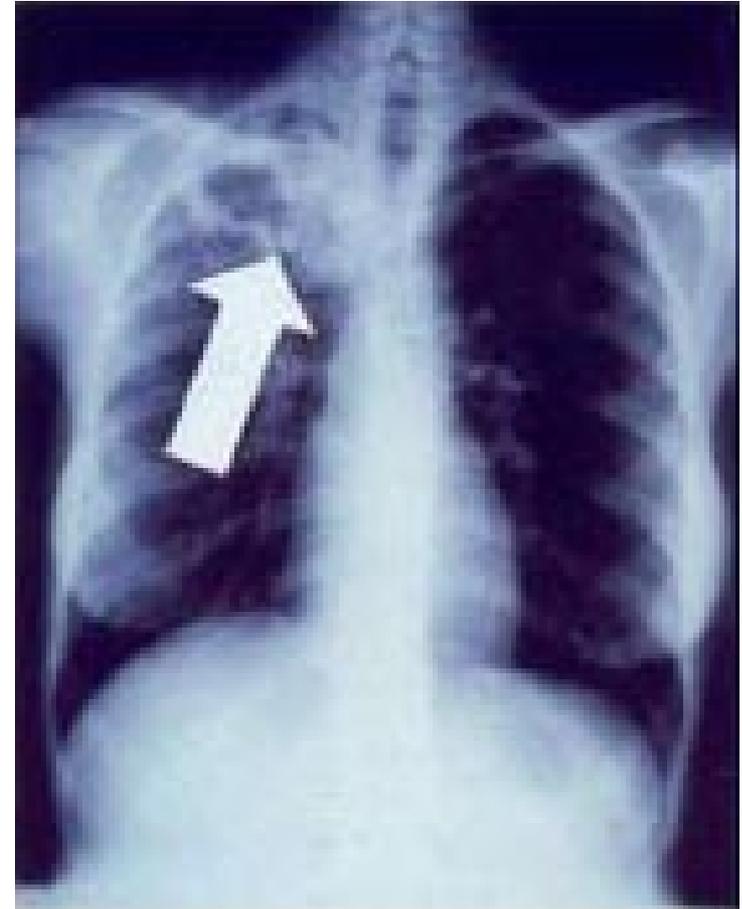




CXR



- Patchy or nodular infiltrate
- Apical- or subapical- posterior areas of the upper lobes or the superior segment of a lower lobe
- Especially if bilateral or associated with cavity formation





AFB Smear

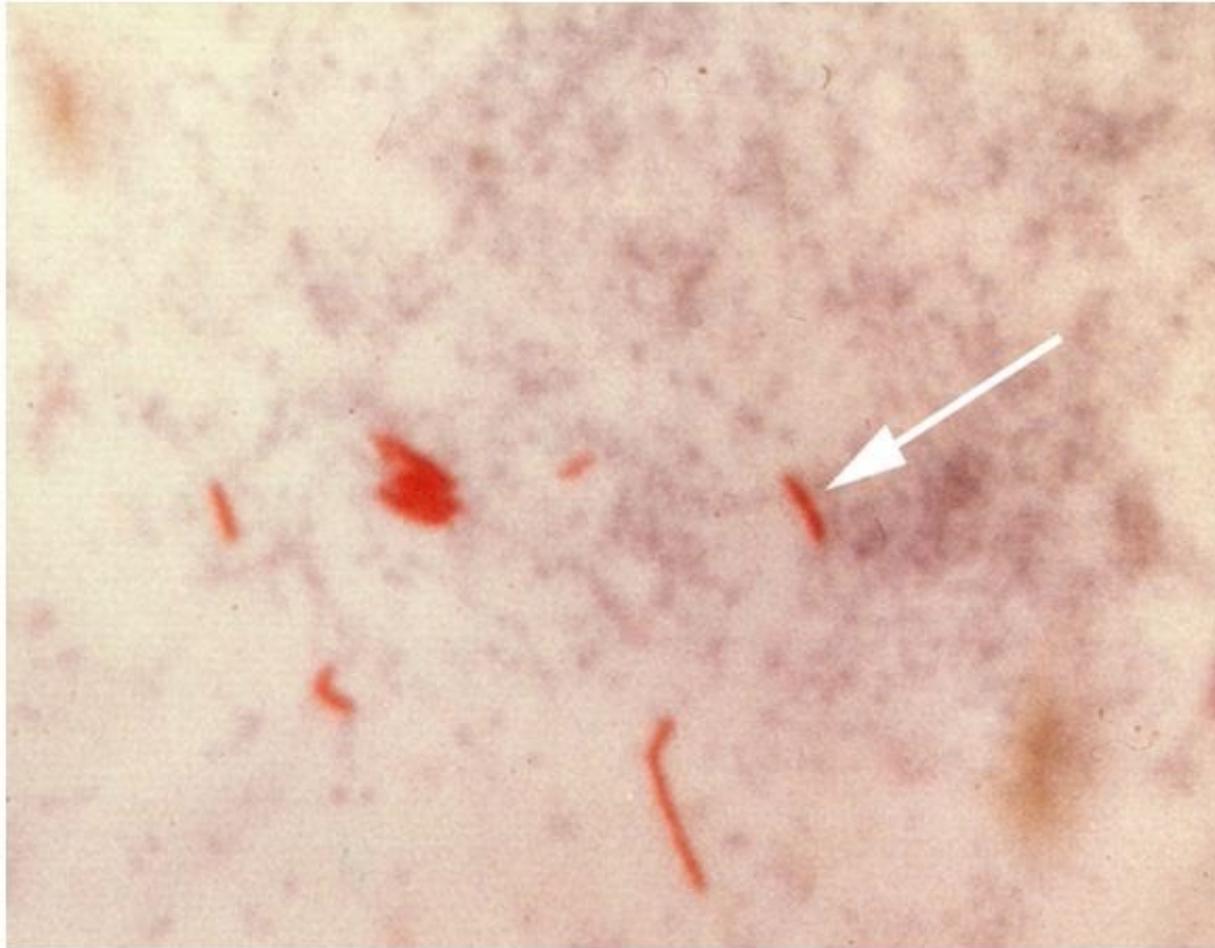


Figure 9. Sputum specimen demonstrating acid fast bacilli (AFB) (arrow). Source CDC.



Treatment of ACTIVE TB

- “4 for 2 and 2 for 4”
 - INH, RIF, PYR, ETH X 2 months, then
 - INH, RIF X 4 months
- Modify regimen if necessary after antibiotic susceptibility results are available
- Check bacteriologic response monthly
- HIV test
- “Never add a single drug to a failing regimen”

INH = isoniazid
PYR = pyrimethamine

RIF = rifampin
ETH = ethambutol



When are they non-infectious?

- On adequate therapy
- Clinical response
- **Three consecutive negative sputum smears from sputum collected on different days**



Infection Control

- Administrative controls
 - Primary strategy for infection control! *****
 - “Develop policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB”
- Engineering controls (ventilation)
 - Isolation
 - Negative pressure rooms
- Personal respiratory protection (N95)



HIV and TB

- 10% risk of progression per year
- Atypical presentations, anergy
- Leading cause of death in HIV patients
- MDR and XDR TB
- Drug interactions
- Reconstitution syndrome

MDR = multi-drug resistant

XDR = extremely drug resistant



MDR and XDR

- MDR=INH and RIF resistance
- XDR=MDR+
 - Any fluoroquinolone; **AND**
 - 1 of 3 injectable second line drugs
 - Capreomycin
 - Kanamycin
 - Amikacin

MDR = multi-drug resistant
XDR = extremely drug resistant

INH = isoniazid
RIF = rifampin



LTBI vs. Pulmonary TB Disease

LTBI

- TST* or IGRA[†] positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease

Active Pulmonary TB

- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens *may* be smear or culture positive

* Tuberculin Skin Test (TST)

† Interferon Gamma Release Assay (IGRA)



What defines a positive TB test?

- a) 5 mm
- b) 10 mm
- c) 15 mm
- d) It depends on the epidemiological characteristics and degree of TB exposure of the patient



Table 7. Criteria for tuberculin positivity, by risk group

Reaction ≥5 mm of induration	Reaction ≥10 mm of induration	Reaction ≥15 mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees [†] of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunioileal bypass Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

Includes patients taking TNF-α antagonists

* Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19-34.



CDC Guidelines Call for Targeted Testing Only

- Targeted testing:
 - “...targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk.” (MMWR 2000)
 - All military services conduct testing at accession
- CDC clearly considers high-risk:
 - Hospitals and health care settings
 - Prisons
 - HIV-infected
 - Homeless
 - Contacts of active case
 - **NOT Military**



Testing for *M. tuberculosis* Infection



Mantoux tuberculin skin test (TST)

Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

Interferon Gamma Release Assays (IGRAs)

Blood tests that measure and compare amount of interferon-gamma (IFN- γ) released by blood cells in response to *M. tuberculosis* antigens.

These include:

1. *Quantiferon*[®] *Gold-in-tube* (QFT-GIT)
2. *T-SPOT*[®].TB



Harnessing the power of T cell measurement





The Tuberculin Skin Test

- Cell-free purified protein fraction extracts obtained from a human strain of *M. tuberculosis*
- In use for over a century
- Problems with TST
 - ***Positive predictive value is low if prevalence of infection is low***
 - Errors and variability in administration
 - False negatives and false positives
- Pseudoepidemics of TST reactions reported in hospitals, prisons, reservations, military populations



Administering the TST



- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produces a wheal 6 to 10 mm in diameter





Reading the TST



- Measure reaction in 48 to 72 hours
- Measure induration, **not erythema**
- Record reaction in millimeters, not “negative” or “positive”
- Ensure trained health care professional measures and interprets the TST





Boosting and Two-Step Testing

- Boosting
 - May have an initially negative test due to waning responsiveness
 - First test may stimulate immune response for second test
 - Second test positive=boosted reaction
- Two-step testing
 - Done on initial test if annual testing is planned
 - Prevents interpreting a subsequent annual TST as a new seroconversion
 - A negative first test with a positive second test should be evaluated for LTBI.

- Measures interferon- γ released from lymphocytes incubated with antigens to MTB
 - *Unknown rate of progression to active TB*
 - *Lack of “gold standard” for LTBI prevents defining the sensitivity and specificity of the test*

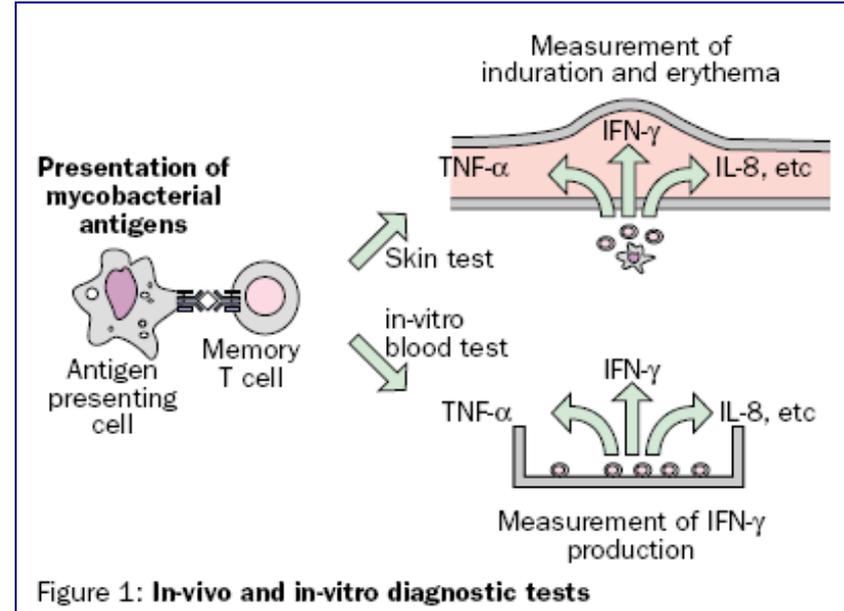


Figure 1: In-vivo and in-vitro diagnostic tests

Andersen P et al. *Lancet* 2000;356:1099.



When should I use the IGRA?

- Depends who you talk to
 - CDC guidelines: may be used to replace TST, but don't do both
 - UK, many other European countries: use IGRA as confirmatory test
 - Military policies conform with CDC, but Navy Great Lakes was using it as a confirmatory test
- Evolving issue, not resolved yet
 - More data
 - Evolving technology
- IGRA preferred among BCG vaccinated



Other LTBI Testing Issues

- Must maintain good quality testing program, whether TST or IGRA
 - Both are difficult in the field
 - **Should only be performed for contact investigations**
 - Useful QA/QC guidelines for TST quality control in Appendix F of: CDC.*MMWR* 2005;54(RR-17):138-9
- **Tubersol[®] is the only TST that should be used**
 - False positives with Aplisol[®]
 - HA Policy 08-012 (29 Sept 08)



Decision to treat



- “A decision to test is a decision to treat”
 - Don’t ignore a positive test
 - But be skeptical in low-risk populations (don’t test)
- **Must rule out active TB first**
 - Symptoms of active TB
 - Compatible chest x-ray findings
 - **If symptoms → 3 sputum smear, culture, at least 1 NAAT test**
- Look at criteria to determine cutoff
- **Assess risks & benefits for each individual patient**
 - Medical history (esp. liver disease, alcohol abuse)
 - How recent was TB exposure?
 - Pregnancy
 - Allergies



Decision to treat

- LTBI Treatment options:
 - Isoniazid x 9 months 5 mg/kg daily (max 300 mg daily)
 - Isoniazid x 9 months 15 mg/kg twice weekly (max 900 mg daily)
 - Don't use the 6 month option if your patient can tolerate the longer option
 - Isoniazid 15 mg/kg (max 900 mg) + Rifapentine once weekly for x 3 months given once weekly
 - 10.0–14.0 kg 300 mg
 - 14.1–25.0 kg 450 mg
 - 25.1–32.0 kg 600 mg
 - 32.1–49.9 kg 750 mg
 - ≥ 50.0 kg 900 mg maximum
 - Rifampin 10 mg/kg (max 600 mg) x 4 months

When dosing, round up to the nearest 50-100 mg

TREATMENT DOSE NOT ELIMINATE THE RISK OF ACTIVE DISEASE*



Screening for LTBI in the US Military

- Over 250,000 tests per year among recruits
- Accessions: all services do universal screening
 - Army (DA PAM 40-11; 20 Oct 2008)
 - Navy (BUMED Instruction 6224.8A; 12 Feb 2009)
 - Air Force (AFI 48-105; 1 Mar 2005)
- Prevalence of TST reactors
 - Navy: 5%
 - Army: 3%
 - Air Force: 1.5%
 - *Depends on proportion of foreign-born*
- **Deployment-related screening**



What about guidelines for travelers?

- US Guidelines (CDC Yellow Book): both pre- and post-travel testing for those with “prolonged exposure to tuberculosis...e.g. [routine contact with] hospital, prison, and homeless shelter populations”
- IDSA Guidelines: TST “should be performed for those with anticipated exposure to TB or long-term stays in developing areas or when requested by the traveler because of concern about exposure”
- TRAVAX: “travelers to countries with high risk (i.e., > 100 cases per 100,000) should have pre-departure testing if staying for > 1 month; travelers to countries with moderate risk (approximately 25-100 cases per 100,000) should have pre-departure testing if they plan on staying for > 3 months”
- Canadian Guidelines: a single, post-travel test based on duration of travel as well as TB incidence in the country visited.

1. MF Iademarco. Tuberculosis. In: Health Information for International Travel 2008. Atlanta, GA: CDC, 2008.
2. Hill et al. *CID* 2006;43:1514.
3. Shoreland. Tuberculosis. Available at www.travax.com ; Accessed 6 June 2009.
4. W Wobeser et al. Surveillance and screening in tuberculosis control. In: Canadian tuberculosis standards: Public Health Agency of Canada, 2007.



What does the US military do for deployers?



- Air Force
 - Targeted testing after deployment since '05 (AFI 48-105)
- Navy
 - Used to test operational units yearly with TST
 - Now targets testing during PHA with questionnaire (BUMEDINST 6224.8A, 12 Feb 2009)
- Army
 - Used to test before deployment, after deployment, and then again 3-6 months after deployment (3 tests per deployment)
 - In 2008, moved to targeted testing after deployment using DD 2796 (OTSG Memo, 25 Sept 2008)
 - Testing **SHOULD NOT** be routinely performed during deployment
- See <http://www.pdhealth.mil/tuberculosis.asp>



Recent Deployment TB Epidemiology

- Outbreaks on Navy ships—common in the 1960s
 - USS Wasp (1998): 21 infected from failure to diagnose index case
 - USS Ronald Reagan (2003): 1 reactivation despite prior INH Rx
- Active TB: **lower rate of disease than in the US population**
- TST reactors during deployment
 - Prevalence of TST conversion: 1-2% without specific exposure history (similar to prevalence in recruits)
 - Numerous false positives and pseudo-outbreaks reported

Lamar. *Mil Med* 2003; 168(7):523-7.

CDC. *MMWR*. 2007;55:1381-2.

Camarca MM and Krauss MR. *Mil Med* 2001;166(5):452-6

Mancuso J. *AJRCCM* 2008;177:1285-9.



Managing TB Exposure in a Deployed Setting



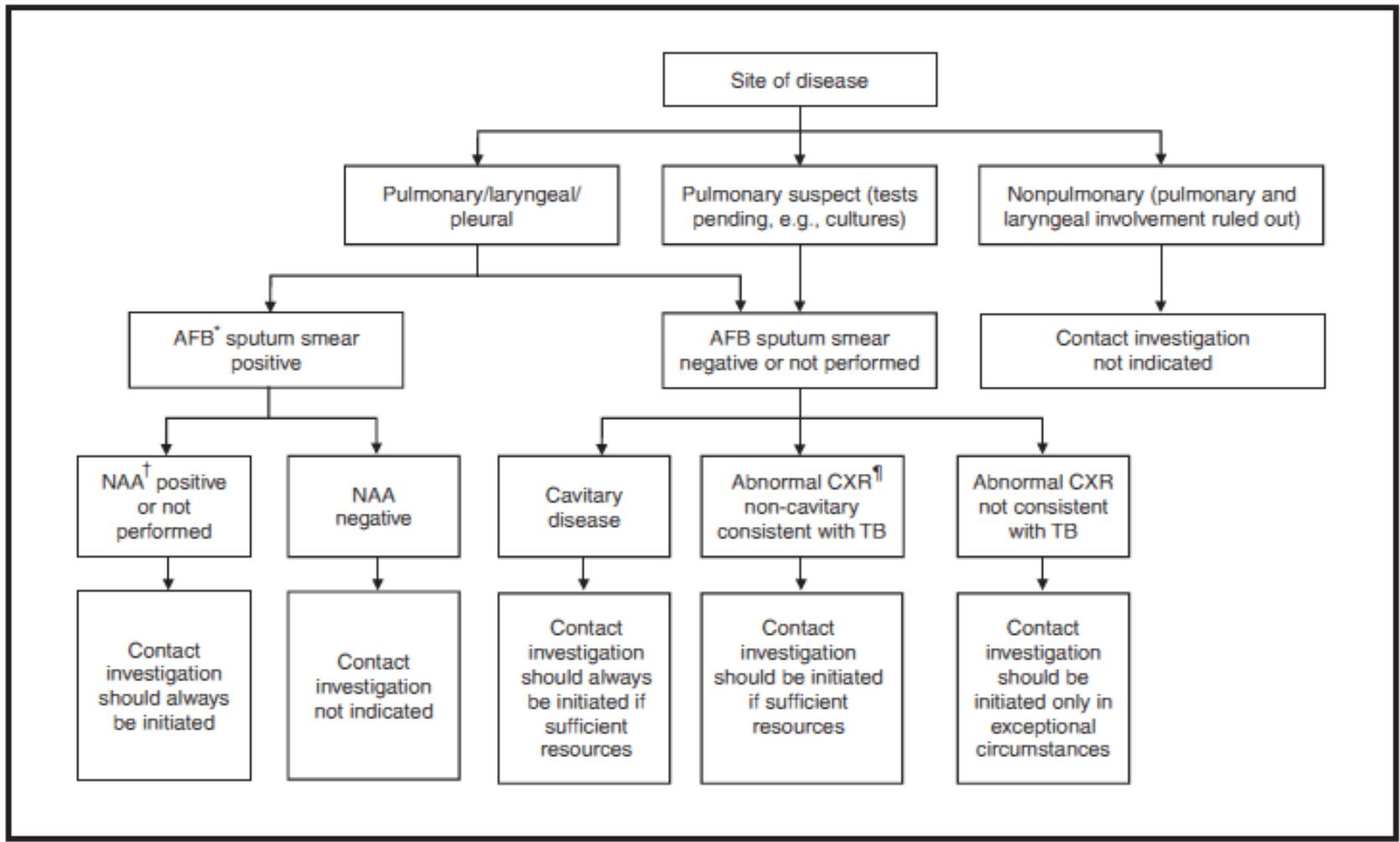
- Refer to Preventive Medicine



Managing TB Exposure in a Deployed Setting



FIGURE 1. Decision to initiate a tuberculosis (TB) contact investigation



* Acid-fast bacilli.
 † Nucleic acid assay.
 § According to CDC guidelines.
 ‡ Chest radiograph.



Managing TB Exposure in a Deployed Setting

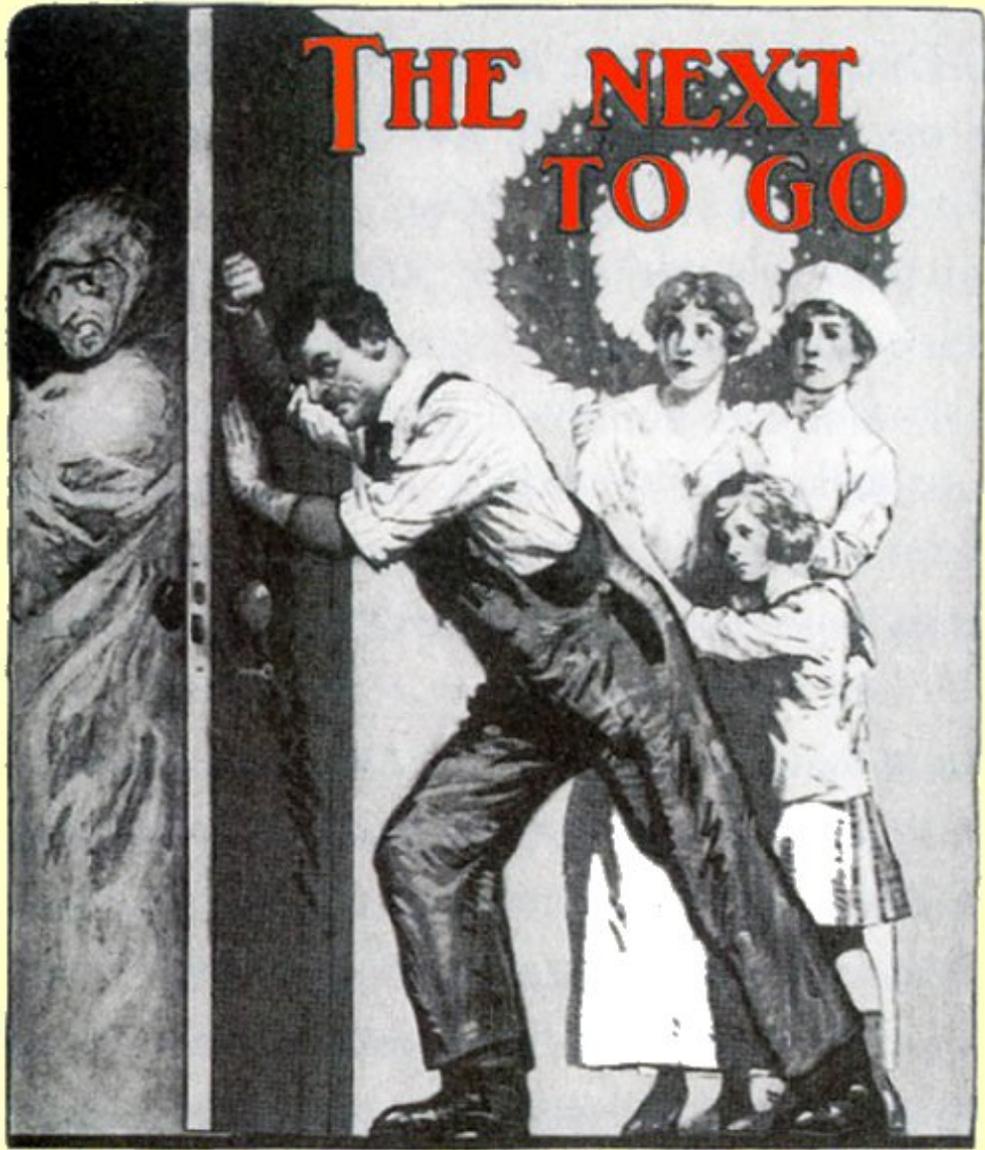


- Document TB symptoms (or the lack thereof)
- High or medium priority contacts should receive TST at initial encounter
- All contacts should have a TST at 8-10 weeks post-exposure
- A diameter >5 mm is positive for any contact
- Any contact with TB symptoms should be managed immediately regardless of skin test results



Other important management issues

- Directly observed therapy (DOT)
 - Standard of care for **Active** TB
 - May be used for LTBI, but uncommon
 - **Refer to Preventive Medicine**
- Disease reporting
 - **Active TB is a reportable disease**, LTBI is not
 - Positive TST or IGRA must be documented in an electronic registry (ALTHA, MEDPROS, etc)
 - Reportable diseases are reported to Preventive Medicine both in garrison and on deployment



FIGHT TUBERCULOSIS!
Red Cross Christmas Seal Campaign †



Summary

- Virus are constantly evolving and novel highly virulent respiratory viruses WILL circulate in the future
- An influenza strain that is highly transmissible (e.g. H1N1) AND highly virulent (e.g. H5N1) will likely result in high mortality
- Get vaccinated, some protection even when mismatches occur
- 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



Summary

- Remember for TB testing, a decision to test is a decision to treat
- LTBI is not symptomatic and has normal Chest X-ray
- Targeted testing for TB with skin test or IGRA (“TB blood test”)
- Measure the swelling, not the redness on a TB skin test
- Consider IGRA for foreign born individual who may have receive BCG as child
- Always rule out active TB before treating for LTBI
- Active TB requires airborne isolation when possible
- Report active TB cases to preventive medicine
- Directly observed minimum 4 drug therapy for active TB



Thank You

Questions ?