Key research findings on human swine influenza – a literature review

Dr. Nelson Lee
Associate Professor
Division of Infectious Diseases
Department of Medicine and Therapeutics
The Chinese University of Hong Kong

1. THE VIRUS
2. CLINICAL PRESENTATIONS
3. HOSPITALIZED AND SEVERE CASES
4. DIAGNOSIS
5. MANAGEMENT ISSUES

THE VIRUS

“Pandemic influenza A/H1N1 2009”

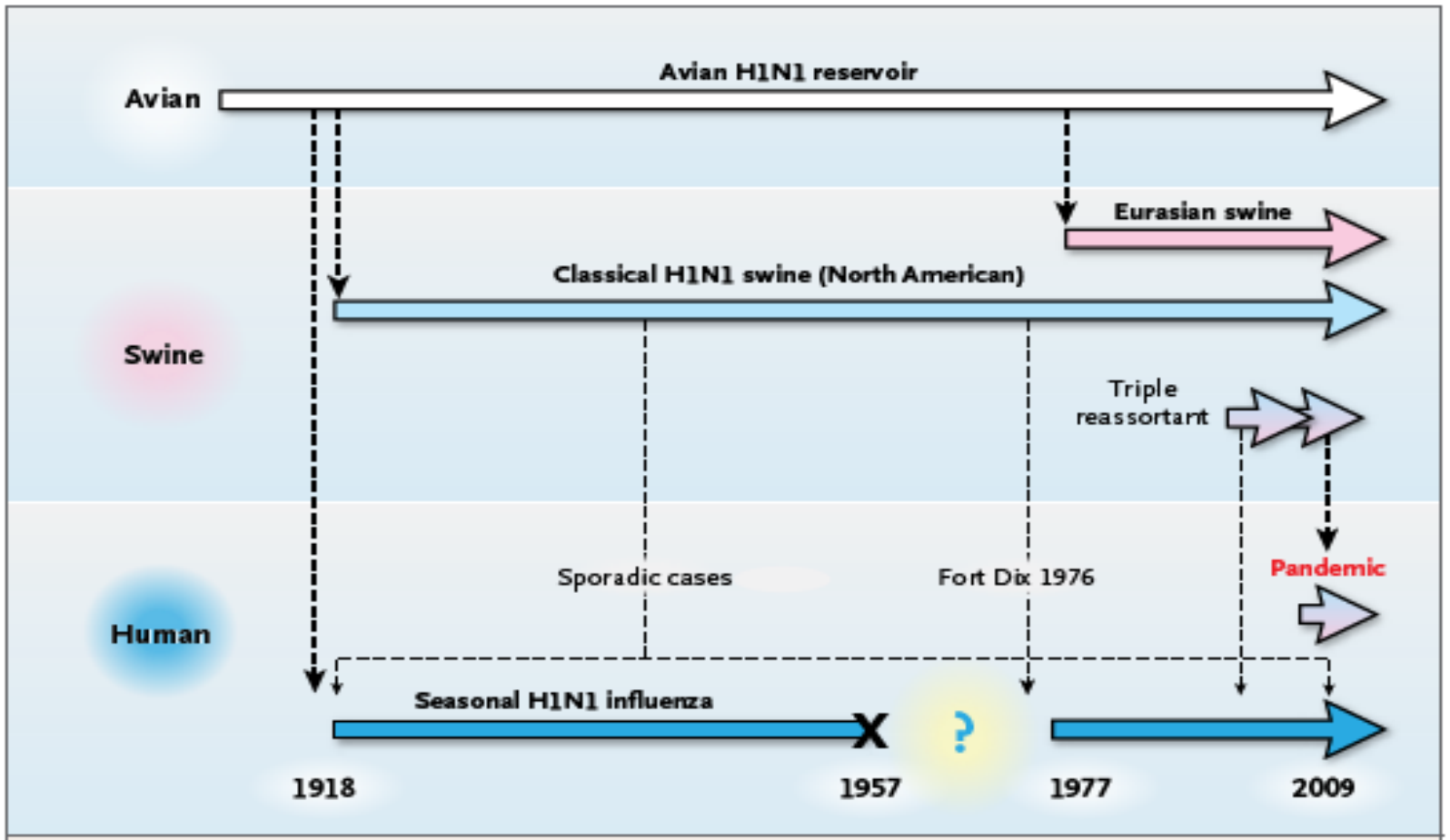


Figure 1. Emergence of Influenza A (H1N1) Viruses from Birds and Swine into Humans.

The diagram shows the important events and processes in the emergence of influenza A (H1N1) viruses during the past 91 years. Avian, swine, and human populations are represented in the top, middle, and bottom of the diagram, respectively. Epidemic or zoonotic viruses are shown as wide horizontal arrows (white for avian viruses, light blue or pink for swine viruses, and dark blue for human viruses). Cross-species transmissions are shown as vertical dashed lines, with thick lines for transfers that gave rise to sustained transmission in the new host and thin lines for those that were transient and resulted in a self-limited number of cases. Principal dates are shown along the bottom of the diagram. The disappearance of H1N1 in 1957 most likely represents competition by the emerging pandemic H2N2 strain in the face of population immunity to H1N1. The reemergence in 1977 is unexplained and probably represents reintroduction to humans from a laboratory source.

Triple-Reassortant Swine Influenza A (H1) in Humans in the United States, 2005–2009

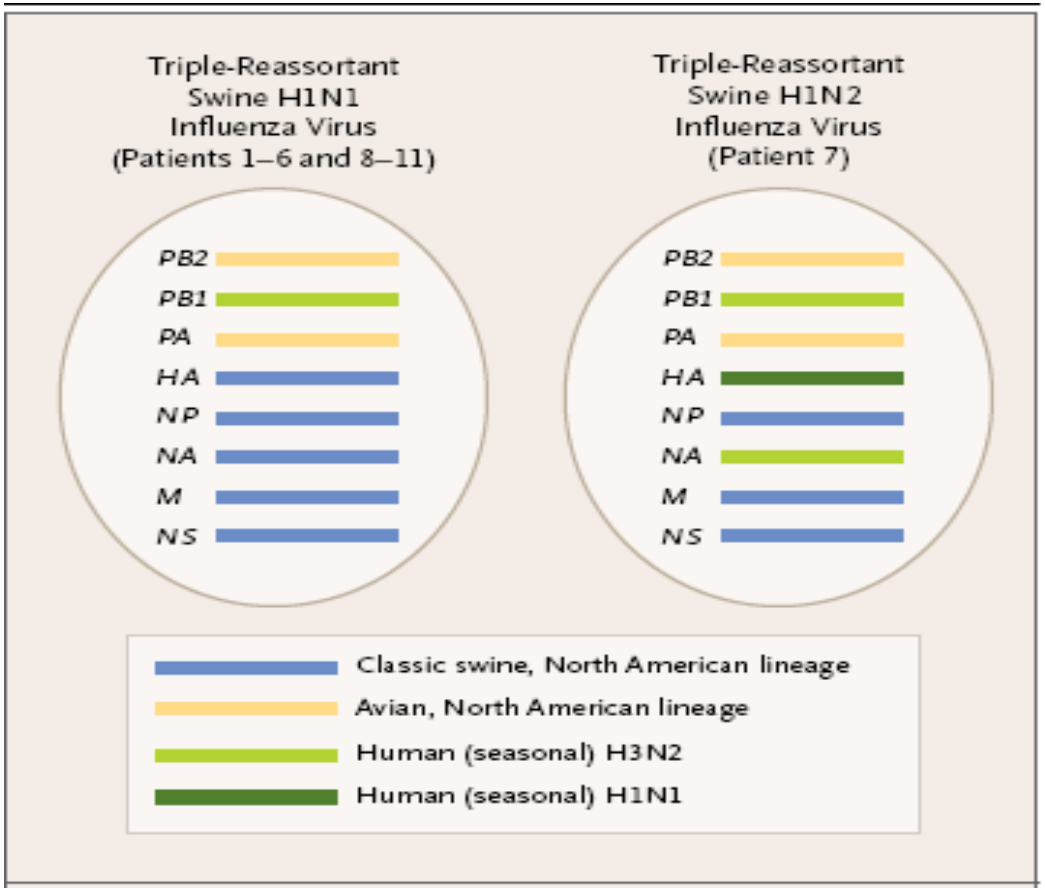
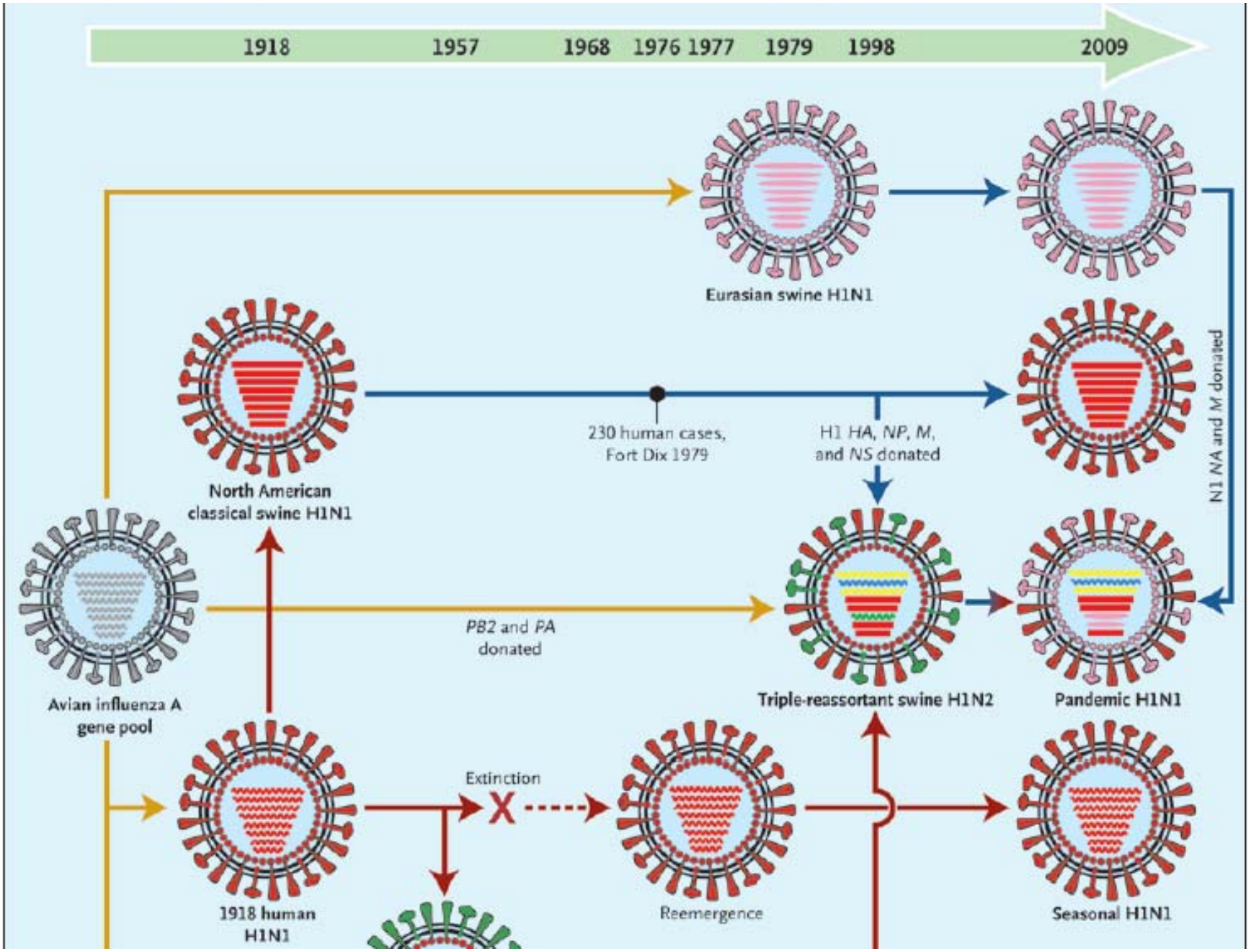


Figure 1. Genetic Components of Triple-Reassortant Swine Influenza A (H1) Viruses Isolated from 11 Patients between December 2005 and February 2009 in the United States.

HA denotes the hemagglutinin gene, *M* the matrix protein gene, *NA* the neuraminidase gene, *NP* the nucleocapsid protein gene, *NS* the nonstructural protein gene, *PA* the polymerase PA gene, *PB1* the polymerase PB1 gene, and *PB2* the polymerase PB2 gene.

N Engl J Med 2009;361.


1918
1957
1968
1976
1977
1979
1998
2009
Eurasian swine H1N1
North American classical swine H1N1
230 human cases, Fort Dix 1979
H1 HA, NP, M, and NS donated
N1 NA and M donated
Avian influenza A gene pool
PB2 and PA donated
Triple-reassortant swine H1N2
Pandemic H1N1
Extinction
1918 human H1N1
Reemergence
Seasonal H1N1

Spread of a Novel Influenza A (H1N1) Virus via Global Airline Transportation

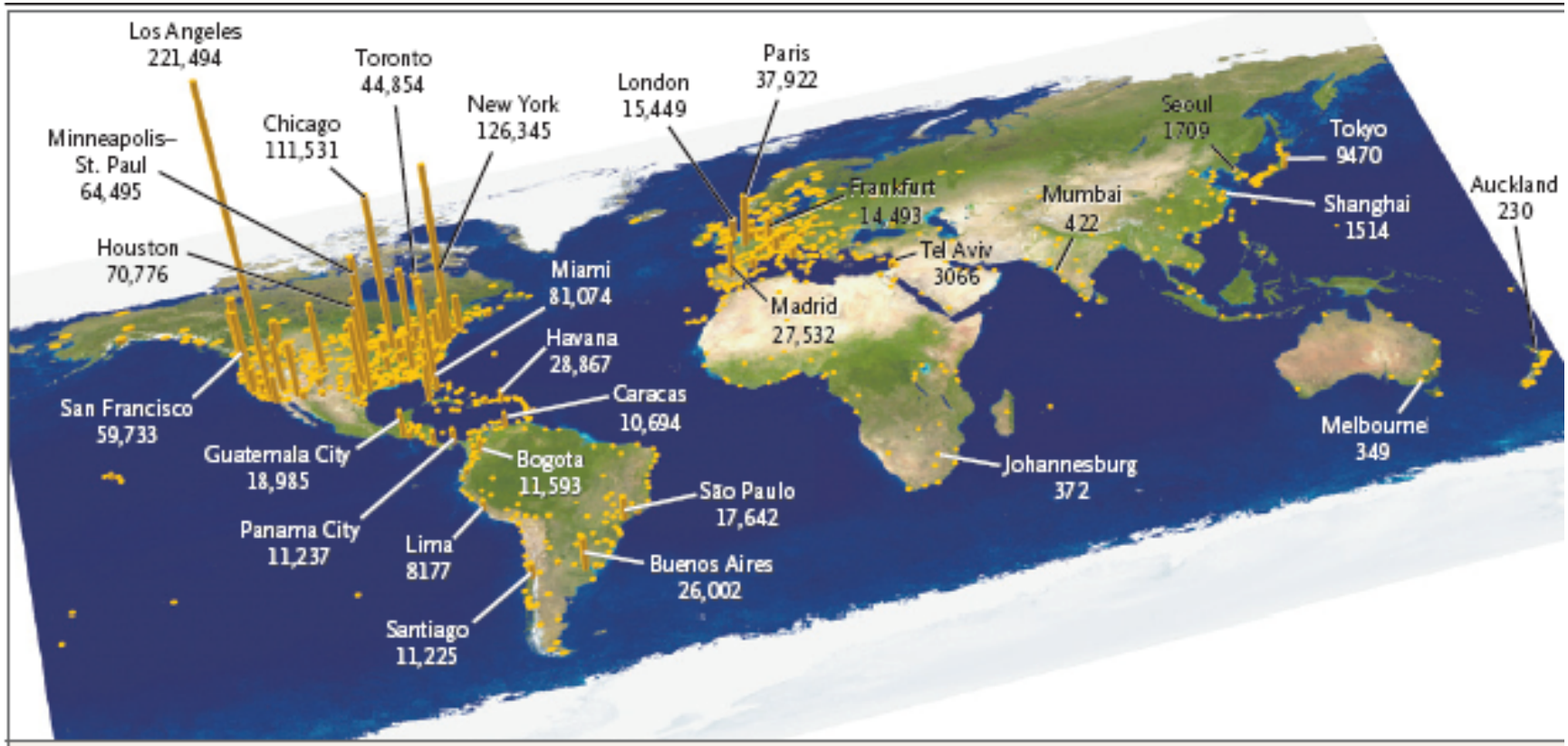


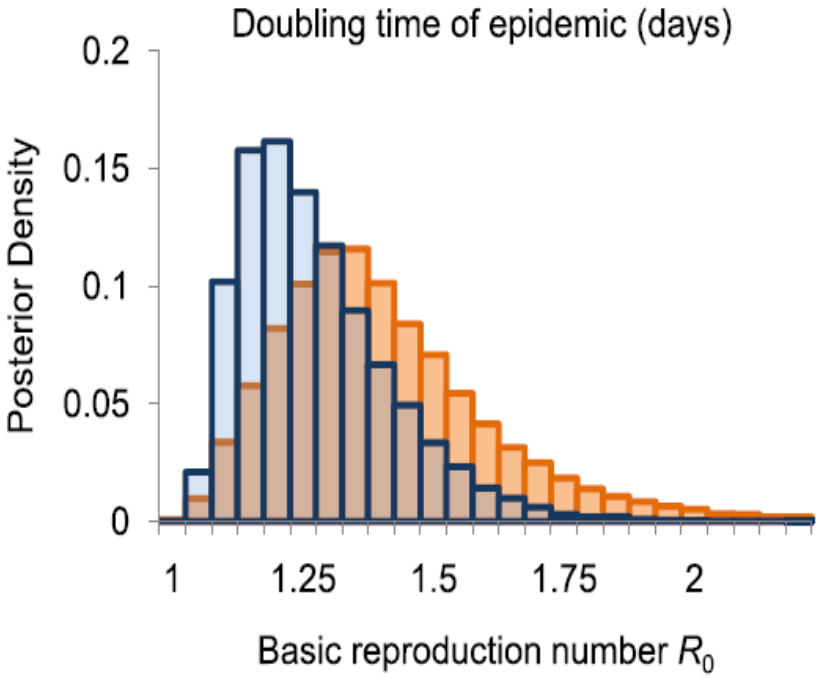
Figure 1. Destination Cities and Corresponding Volumes of International Passengers Arriving from Mexico between March 1 and April 30, 2008.

Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings

Sciencexpress / www.sciencexpress.org / 11 May 2009

that 23,000 (range 6,000-32,000) individuals had been infected in Mexico by late April, giving an estimated case fatality ratio (CFR) of 0.4% (range 0.3% to 1.5%) based on confirmed and suspect deaths reported to that time. In

29%). Three different epidemiological analyses gave R_0 estimates in the range 1.4-1.6, while a genetic analysis gave a central estimate of 1.2.



Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza

Results: The median incubation period was 4 days and the duration of symptoms was 7 days. Recovery was faster among patients less than 18 years old than among older patients (hazard ratio 1.23, 95% confidence interval 1.06–1.44). The risk of hospital admission was 4.5% (95% CI 3.8%–5.2%) and the case-fatality rate was 0.3% (95% CI 0.1%–0.5%). The risk of hospital admission was highest among patients less than 1 year old and those 65 years or older. Adults more than 50 years old comprised 7% of cases but accounted for 7 of 10 initial deaths (odds ratio 28.6, 95% confidence interval 7.3–111.2). From the simulation models, we estimated the following values (and 95% credible intervals): a mean basic reproductive number (R_0, the number of new cases created by a single primary case in a susceptible population) of 1.31 (1.25–1.38), a mean latent period of 2.62 (2.28–3.12) days and a mean duration of infectiousness of 3.38 (2.06–4.69) days. From these values we estimated a serial interval (the average time from onset of infectiousness in a case to the onset of infectiousness in a person infected by that case) of 4–5 days.

Interpretation: The low estimates for R_0 indicate that effective mitigation strategies may reduce the final epidemic impact of pandemic H1N1 influenza.

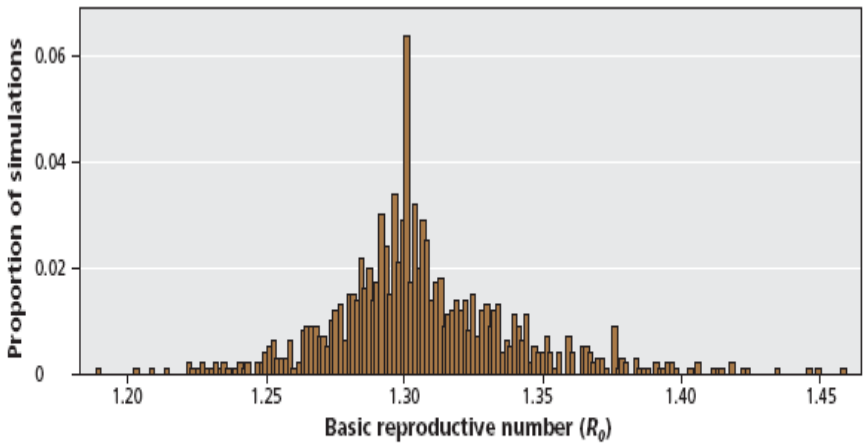
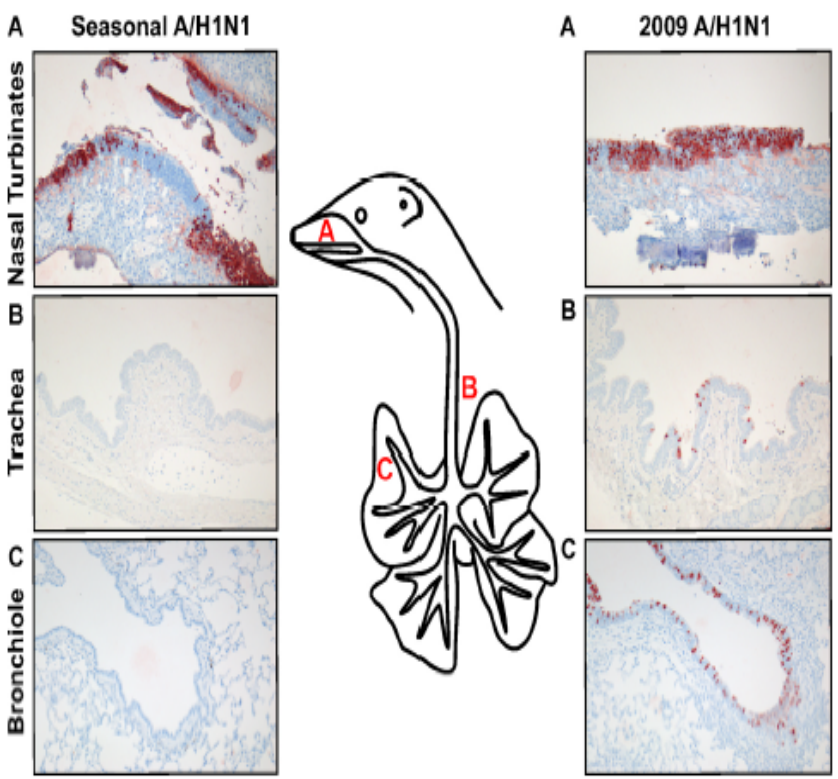


Figure 5: Estimates of the basic reproductive number (R_0, number of new cases created by a single primary case in a susceptible population) in the province of Ontario during the wave of pandemic H1N1 influenza in the spring of 2009. Estimates were generated with the use of Markov Chain Monte Carlo simulation modelling. The mean estimate for R_0 is 1.31 (95% credible interval 1.25–1.38).

Pathogenesis and Transmission of Swine-Origin 2009 A(H1N1) Influenza Virus in Ferrets

occurring in the respiratory tract. Replication of seasonal A(H1N1) virus was confined to the nasal cavity of ferrets, but 2009 A(H1N1) influenza virus also replicated in the trachea, bronchi, and bronchioles. Virus shedding was more abundant from the upper respiratory tract for 2009 A(H1N1) influenza virus by comparison with seasonal virus, and transmission via aerosol or respiratory droplets was equally efficient. These data suggest that the 2009 A(H1N1) influenza virus has the ability to persist in the human population, potentially with more severe clinical consequences.



CLINICAL PRESENTATIONS

Clinical Features of the Initial Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in China

Table 2. Clinical Features of Infection in the 426 Patients.*

Symptom or Sign	Present on Admission *no./total no. (%)*	Median Duration *days (IQR)*
Symptom		
Elevated temperature		3 (2–4)
37.3–38.0°C	134/426 (31.5)	
38.1–39.0°C	114/426 (26.8)	
>39.0°C	39/426 (9.2)	
Cough	296/426 (69.5)	5 (3–6)
Sore throat	156/426 (36.6)	4 (2–5)
Sputum production	104/426 (24.5)	4 (2–6)
White sputum	54/104 (51.9)	NA
Yellow sputum	50/104 (48.1)	NA
Rhinorrhea	101/426 (23.7)	3 (2–5)
Headache	83/426 (19.5)	2.5 (1–4)
Nasal congestion	68/426 (16.0)	3 (2–4)
Fatigue	44/426 (10.3)	3 (1–4)
Myalgia, arthralgia	43/426 (10.1)	3 (2–4)
Chill	32/426 (7.5)	NA
Conjunctival congestion	12/426 (2.8)	2 (1–3)
Diarrhea	12/426 (2.8)	1.5 (1–3.5)
Nausea, vomiting	8/426 (1.9)	NA
Chest pain	2/426 (0.5)	6.5 (6–7)
Sign		
Congestion of throat	319/426 (74.9)	4 (3–6)
Swelling of tonsils	319/426 (74.9)	4 (3–6)
Enlargement of lymph nodes	3/426 (0.7)	5 (4–5)

N Engl J Med 2009;361.

Clinical Features of the Initial Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in China

Table 1. (Continued.)

Characteristic	Value
Incubation period — days‖	
Median	2
Range	1–7
Exposure site — no./total no. (%)	
Airplane	60/148 (40.5)
Home	25/148 (16.9)
Classroom or office	13/148 (8.8)
Car, train, or bus	20/148 (13.5)
Restaurant	4/148 (2.7)
Outcomes — days	
Duration of fever	
Median	3.0
Range	1–11
Viral shedding verified with real-time RT-PCR testing	
Median	6
Range	1–17
Interval between temperature returning to normal and negative real-time RT-PCR test result	
Median	3
Range	<1–13
Adverse events — no. (%)¶	
Abnormal liver function	2 (0.5)
Nausea and vomiting	2 (0.5)
Rash	1 (0.2)

N Engl J Med 2009;361.

- In contrast to seasonal influenza, hospitalized adults are younger (including 20-64 years and ≥65 years, risk increases with age), and many are previously healthy (17-28%);
  - but in up to one-third of the cases (10-34%), ICU admission may be required because of severe pneumonia, which is associated with a high mortality
    - WHO, Echevarría-ZunoS_Lancet09, OliveiraW_EuroS09, Donaldson_BMJ09, Tuite AR_CMAJ09, LouieJK_JAMA09, JainS_NEJM09

- Pregnancy women in their second and third trimesters consist 7-13% of hospital admissions, and they have 10 times higher risk for deterioration
    - WHO, OliveiraW_EuroS09, LouieJK_JAMA09, JainS_NEJM09, LouieJK_NEJM10, JamiesonDJ_Lancet09

- In addition, obese individuals are observed to have higher risks for severe infection
    - WHO, LouieJK_JAMA09, JainS_NEJM09, Domínguez-CheritG_JAMA09

Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis

	Population	ILI (incidence ILI*)	Confirmed H1N1 (incidence confirmed H1N1*)	ILI cases admitted to hospital with severe acute respiratory infection (%)	Admitted with confirmed H1N1 (H1N1 admission rate*)	H1N1 deaths confirmed (population H1N1 mortality rate*)	Proportion H1N1 admissions†	ILI mortality rate‡	Confirmed H1N1 mortality rate§	Confirmed H1N1 admission mortality rate‖
Age (years)										
<1	503 236	1636 (325·10)	248 (49·28)	184 (11%)	33 (6·56)	4 (0·79)	0·10	0·24%	1·6%	12·1%
1–9	5 968 658	11 452 (191·87)	1584 (26·54)	495 (4%)	112 (1·88)	4 (0·07)	0·07	0·03%	0·3%	3·6%
10–19	4 961 194	10 071 (203·00)	1880 (37·89)	306 (3%)	90 (1·81)	3 (0·06)	0·05	0·03%	0·2%	3·3%
20–29	5 261 106	11 502 (218·62)	1381 (26·25)	483 (4%)	105 (2·00)	12 (0·23)	0·08	0·10%	0·9%	11·4%
30–39	5 889 209	8204 (139·31)	661 (11·22)	373 (5%)	76 (1·29)	13 (0·22)	0·11	0·16%	2·0%	17·1%
40–49	4 373 824	5550 (126·89)	410 (9·37)	326 (6%)	47 (1·07)	11 (0·25)	0·11	0·20%	2·7%	23·4%
50–59	3 254 339	3129 (96·15)	200 (6·15)	254 (8%)	37 (1·14)	9 (0·28)	0·19	0·29%	4·5%	24·3%
60–69	2 547 855	1319 (51·77)	70 (2·75)	182 (14%)	19 (0·75)	4 (0·16)	0·27	0·30%	5·7%	21·1%
≥70	2 852 758	1173 (41·12)	29 (1·02)	322 (27%)	7 (0·25)	3 (0·11)	0·24	0·26%	10·3%	42·9%
Missing data	NA	9443	482	64	12	NA	NA	NA	NA	NA
Total	35 612 179	63 479 (178·25)	6945 (19·50)	2989 (5%)	538 (1·51)	63 (0·18)	0·08	0·10%	0·9%	11·7%
Region										
Central Mexico outbreak	9 754 553	12 632 (129·50)	486 (4·98)	924 (7%)	130 (1·33)	45 (0·46)	0·27	0·36%	9·3%	34·6%
Southeast Mexico outbreak	4 022 996	14 196 (352·87)	3511 (87·27)	489 (3%)	160 (3·98)	5 (0·12)	0·05	0·04%	0·1%	3·1%

Data from Mexican Institute for Social Security, July 31, 2009. ILI=influenza-like illness. H1N1= influenza A H1N1. NA=not applicable. *Per 100 000 people affiliated with the Mexican Institute for Social Security. †Admitted to hospital with confirmed H1N1÷total confirmed H1N1. ‡(Deaths÷ILI)×100. §(Deaths÷confirmed H1N1)×100. ‖(Deaths÷H1N1 admissions)×100.

Table 1: Effects of influenza A H1N1 by age-group and region, April–July 2009

Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California

Most pregnant patients (89 of 94 [95%]) were in the second or third trimester, and approximately one third (32 of 93 [34%]) had established risk factors for complications from influenza other than pregnancy. As compared with early antiviral treatment (administered ≤2 days after symptom onset) in pregnant women, later treatment was associated with admission to an intensive care unit (ICU) or death (relative risk, 4.3). In all, 18 pregnant women and 4 postpartum women (total, 22 of 102 [22%]) required intensive care, and 8 (8%) died. Six deliveries occurred in the ICU, including four emergency cesarean deliveries. The 2009 H1N1 influenza–specific maternal mortality ratio (the number of maternal deaths per 100,000 live births) was 4.3.

N Engl J Med 2010;362:27-35.

H1N1 2009 influenza virus infection during pregnancy in the USA

Findings From April 15 to May 18, 2009, 34 confirmed or probable cases of pandemic H1N1 in pregnant women were reported to CDC from 13 states. 11 (32%) women were admitted to hospital. The estimated rate of admission for pandemic H1N1 influenza virus infection in pregnant women during the first month of the outbreak was higher than it was in the general population (0·32 per 100000 pregnant women, 95% CI 0·13–0·52 *vs* 0·076 per 100 000 population at risk, 95% CI 0·07–0·09). Between April 15 and June 16, 2009, six deaths in pregnant women were reported to the CDC; all were in women who had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation.

www.thelancet.com **Published online July 29, 2009**

Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain

Critical Care 2009, **13**:R148 doi:10.1186/cc8044

Results: Illness onset of the 32 patients occurred between June 23 and July 31, 2009. The median age was 36 years (IQR = 31 - 52). Ten (31.2%) were obese, 2 (6.3%) pregnant and 16 (50%) had pre-existing medical complications. Twenty-nine (90.6%) had primary viral pneumonitis, 2 (6.3%) exacerbation of structural respiratory disease and 1 (3.1%) secondary bacterial pneumonia. Twenty-four patients (75.0%) developed multiorgan dysfunction, 7 (21.9%) received renal replacement techniques and 24 (75.0%) required mechanical ventilation. Six patients died within 28 days, with two additional late deaths. Oseltamivir administration delay ranged from 2 to 8 days after illness onset, 31.2% received high-dose (300mg/day), and treatment duration ranged from 5 to 10 days (mean 8.0 $\pm$ 3.3).

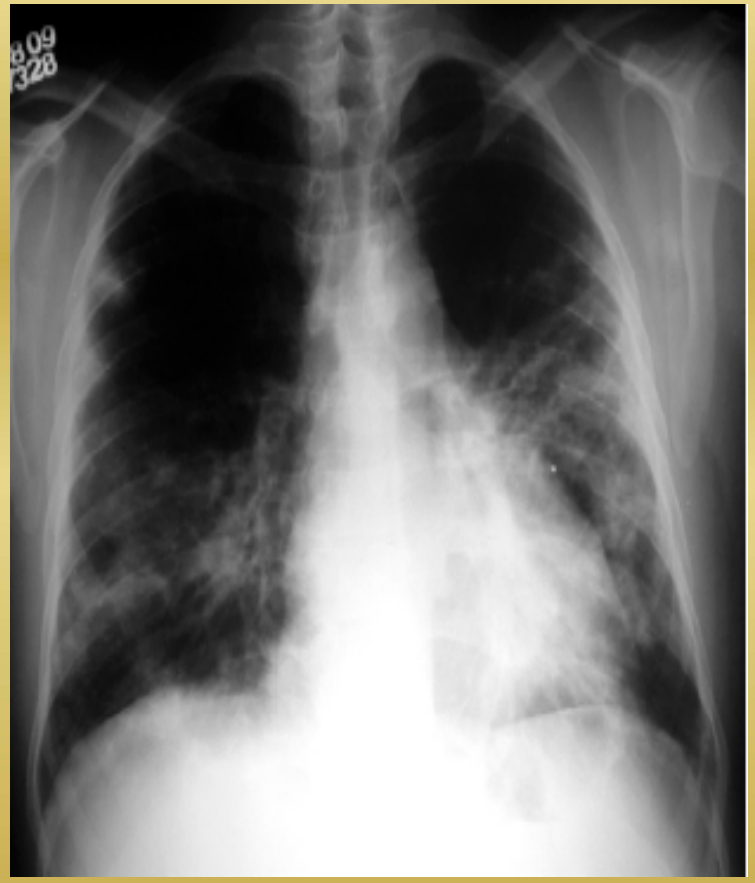
Clinical findings and demographic factors associated with intensive care unit admission in Utah due to 2009 novel influenza A (H1N1) infection

Results: The ICU cohort of 47 influenza patients had a median age of 34, APACHE II score of 21, and body mass index (BMI) of 35. Mortality was 17% (8/47). All 8 deaths occurred among the 64% of patients (n=30) with acute respiratory distress syndrome, twenty-six (87%) of whom also developed multiorgan failure. Compared to the Salt Lake County population, novel H1N1 patients were more likely to be obese (22% versus 74%; $p<0.001$), medically uninsured (14% versus 45%; $p<0.001$), and Hispanic (13% versus 23%; $p<0.01$) or Pacific Islander (1% versus 26%; $p<0.001$). Observed ICU admissions were 15-fold greater than expected for those with BMI ≥40 (SMR 15.8, 95% CI 8.3, 23.4) and 1.5-fold greater among those with BMI 30-39 than expected for age- and sex-adjusted rates for Salt Lake County.

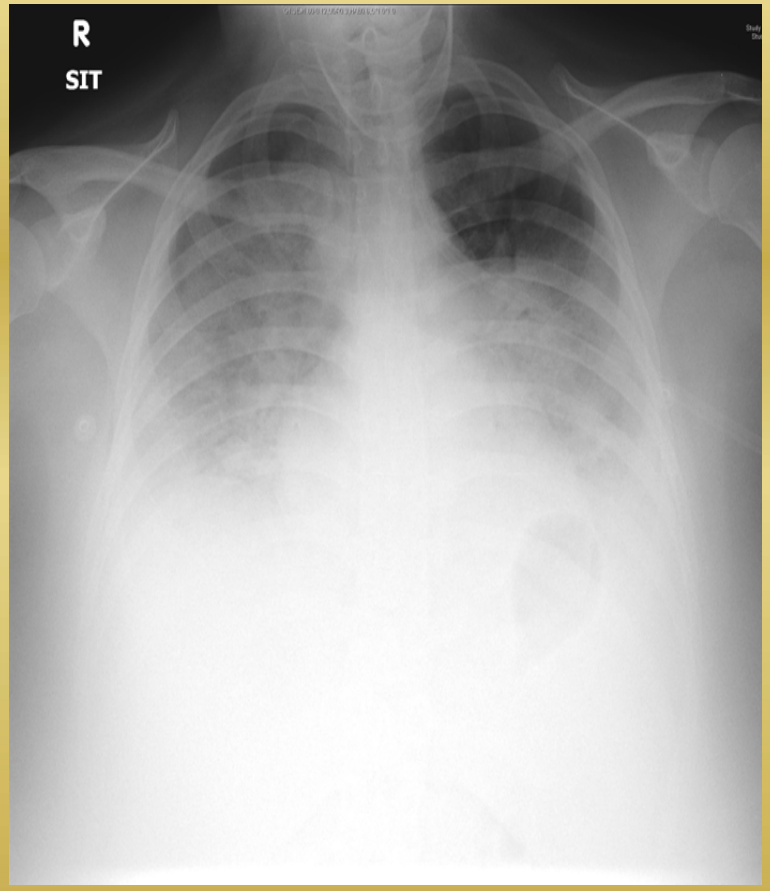
Chest; Prepublished online November 20, 2009;

HOSPITALIZED & SEVERE CASES

- Patients who develop primary viral pneumonia more commonly have pre-existing cardiopulmonary diseases, and usually present with fever, dry cough and dyspnea at >3 days from symptom onset (sorethroat and runny-nose only present in 1/3)
  - Echevarría-ZunoS_Lancet09, JainS_NEJM09, Perez-PadillaR_NEJM09, DenholmJT_MJA10, Domínguez-CheritG_JAMA09, MillerRR_Chest09, RelloJ_CritCare09
- Gastrointestional manifestations, such as vomiting and diarrhea may accompany pneumonia in up to 13-37%
  - Echevarría-ZunoS_Lancet09, JainS_NEJM09, Perez-PadillaR_NEJM09, DenholmJT_MJA10, RiquelmeA_Gut09
- Elevated serum lactate dehydrogenase and creatine kinase levels are also reported
  - Perez-PadillaR_NEJM09, KumarA_JAMA09, Domínguez-CheritG_JAMA09, RelloJ_CritCare09
- Their chest-radiographs may show multifocal patchy, or diffuse ground-glass infiltrates and/or consolidations (lower and central zones), which sometimes mimic pulmonary edema
  - JainS_NEJM09, Perez-PadillaR_NEJM09, DenholmJT_MJA10, RelloJ_CritCare09, WiebeC_Lancet09, AgarwalPP_AJR09, MarchioriE_EJR09



Usual CAP??



Another case of APO??

Table 1. Characteristics of Reported Hospitalized and Fatal Cases of Pandemic 2009 Influenza A(H1N1) Infections in California, April 23 Through August 11, 2009

		Cases Aged 0-17 Years		Cases Aged ≥18 Years	
	All Cases (N = 1088)	Fatal (n = 8)	Nonfatal (n = 336)	Fatal (n = 110)	Nonfatal (n = 634)
Male, No. (%)	532 (49)	3 (38)	203 (60)	56 (51)	270 (43)
Age, median (range), y	27 (<1-92)	6 (<1-14)	6 (<1-17)	46 (18-85)	38 (18-92)
Race/ethnicity, No. (%)[a]	(n = 866)	(n = 8)	(n = 280)	(n = 86)	(n = 492)
Hispanic	374 (43)	6 (75)	144 (51)	32 (37)	192 (39)
White, non-Hispanic	240 (28)	1 (13)	44 (16)	34 (40)	161 (33)
Asian/Pacific Islander	124 (14)	1 (13)	52 (19)	7 (8)	64 (13)
Black, non-Hispanic	96 (11)	0	27 (10)	11 (13)	58 (12)
Other	32 (4)	0	13 (5)	2 (2)	17 (3)
Signs and symptoms, No. (%)					
Fever	972 (89)	8 (100)	319 (95)	91 (83)	554 (87)
Cough	939 (86)	6 (75)	274 (82)	95 (86)	564 (89)
Shortness of breath	605 (56)	3 (38)	112 (33)	89 (81)	401 (63)
Nausea/vomiting	384 (35)	4 (50)	126 (38)	22 (20)	232 (37)
Muscle aches	359 (33)	2 (25)	50 (15)	36 (33)	271 (43)
Sore throat	305 (28)	2 (25)	70 (21)	21 (19)	212 (33)
Chills	221 (20)	0	25 (7)	27 (25)	169 (27)
Diarrhea	215 (20)	2 (25)	63 (19)	20 (18)	130 (20)
Rhinorrhea	213 (20)	2 (25)	102 (30)	10 (9)	99 (16)
Headache	211 (19)	0	46 (14)	17 (15)	148 (23)
Altered mental status	60 (6)	0	13 (4)	13 (12)	34 (5)
Conjunctivitis	21 (2)	0	13 (4)	1 (<1)	7 (1)
Clinical findings and course, No. (%)					
Positive rapid test result[a]	410/618 (66)	5/6 (83)	176/207 (85)	24/55 (44)	205/350 (59)
Infiltrates on chest radiograph[a]	547/833 (66)	4/5 (80)	134/224 (60)	91/94 (97)	318/510 (62)
Admitted to intensive care unit	340 (31)	6 (75)	84 (25)	88 (80)	162 (26)
Mechanical ventilation[a]	227/915 (25)	7/8 (88)	27/282 (10)	95/102 (93)	98/523 (19)
Secondary bacterial infections[b]	46 (4)	1 (13)	7 (2)	15 (14)	23 (4)
Antiviral treatment[a]	701/884 (79)	5/8 (63)	205/267 (77)	65/89 (73)	426/520 (82)
Received ≤48 h after symptom onset	357 (51)	1 (20)	117 (57)	17 (26)	222 (52)

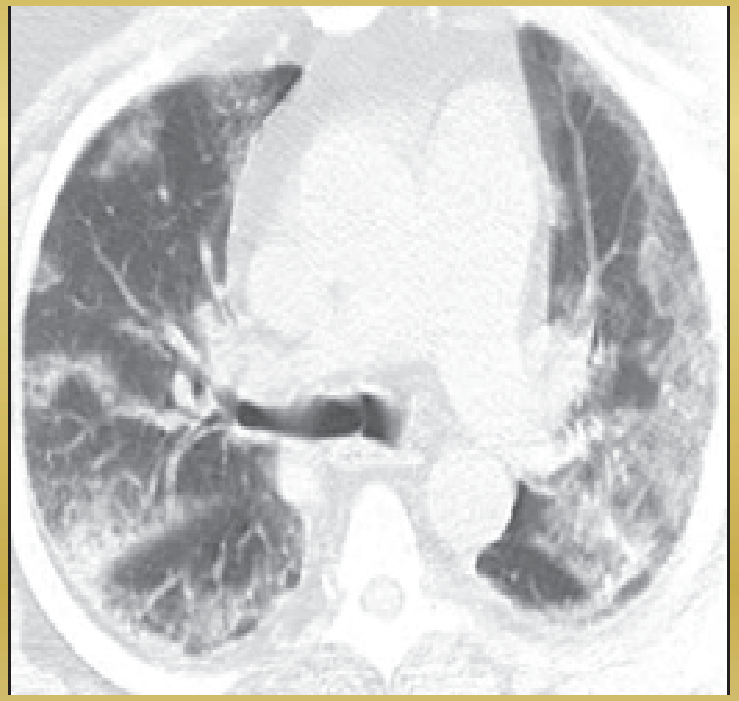
[a] Includes cases with known information only.
[b] Includes *Staphylococcus aureus* of all susceptibility patterns, group A *Streptococcus*, *Streptococcus pneumoniae*, and gram-negative rods.

- The clinical course can become rapidly progressive within 1-2 days, resulting in refractory hypoxemia and the requirement of intubation and mechanical-ventilation
  - KumarA_JAMA09, Domínguez-CheritG_JAMA09, RelloJ_CritCare09, Writing_NEJM08, SchünemannHJ_LID07

- In many cases of H5N1 infection, in some cases of pandemic H1N1 influenza, and less frequently with seasonal influenza strains, acute respiratory distress syndrome (ARDS) and multi-organ failure develop, resulting in high fatality
  - LouieJK_JAMA09, JainS_NEJM09, Perez-PadillaR_NEJM09, KumarA_JAMA09, Domínguez-CheritG_JAMA09, MillerRR_Chest09, RelloJ_CritCare09, Writing_NEJM08, SchünemannHJ_LID07

  - 'Extrapulmonary' detection in 13-28%
    - Lee N et al. Abstract, XII ISRVI, March 2010
  - Barotrauma (pneumothorax, pneumomediastinum) may further complicate ARDS → a low tidal-volume ventilation strategy is generally advisable

- Development of bronchiolitis obliterans organizing pneumonia –like illness, as supported by computed-tomography findings, has also been reported to complicate influenza
  - RothbergMB_AJM08, AgarwalPP_AJR09, AjlanAM_AJR09



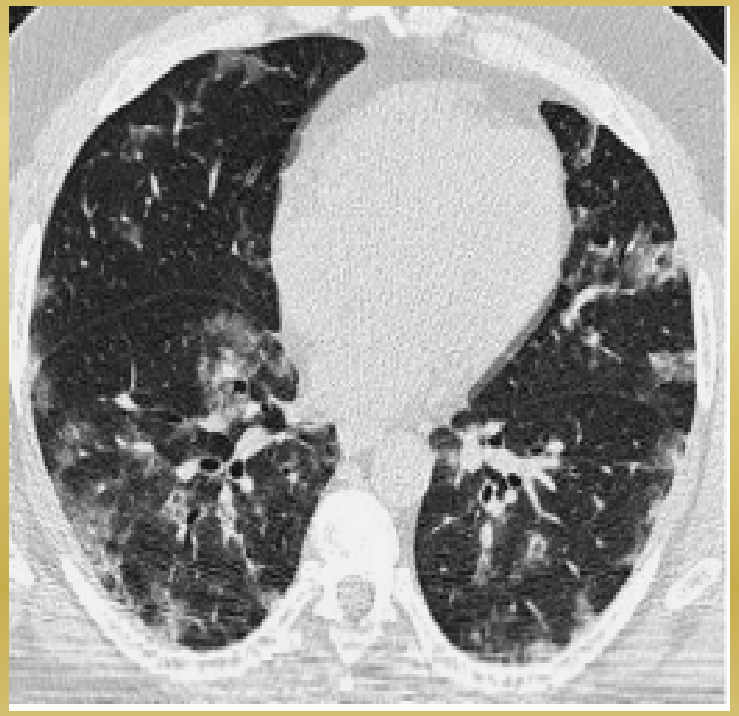
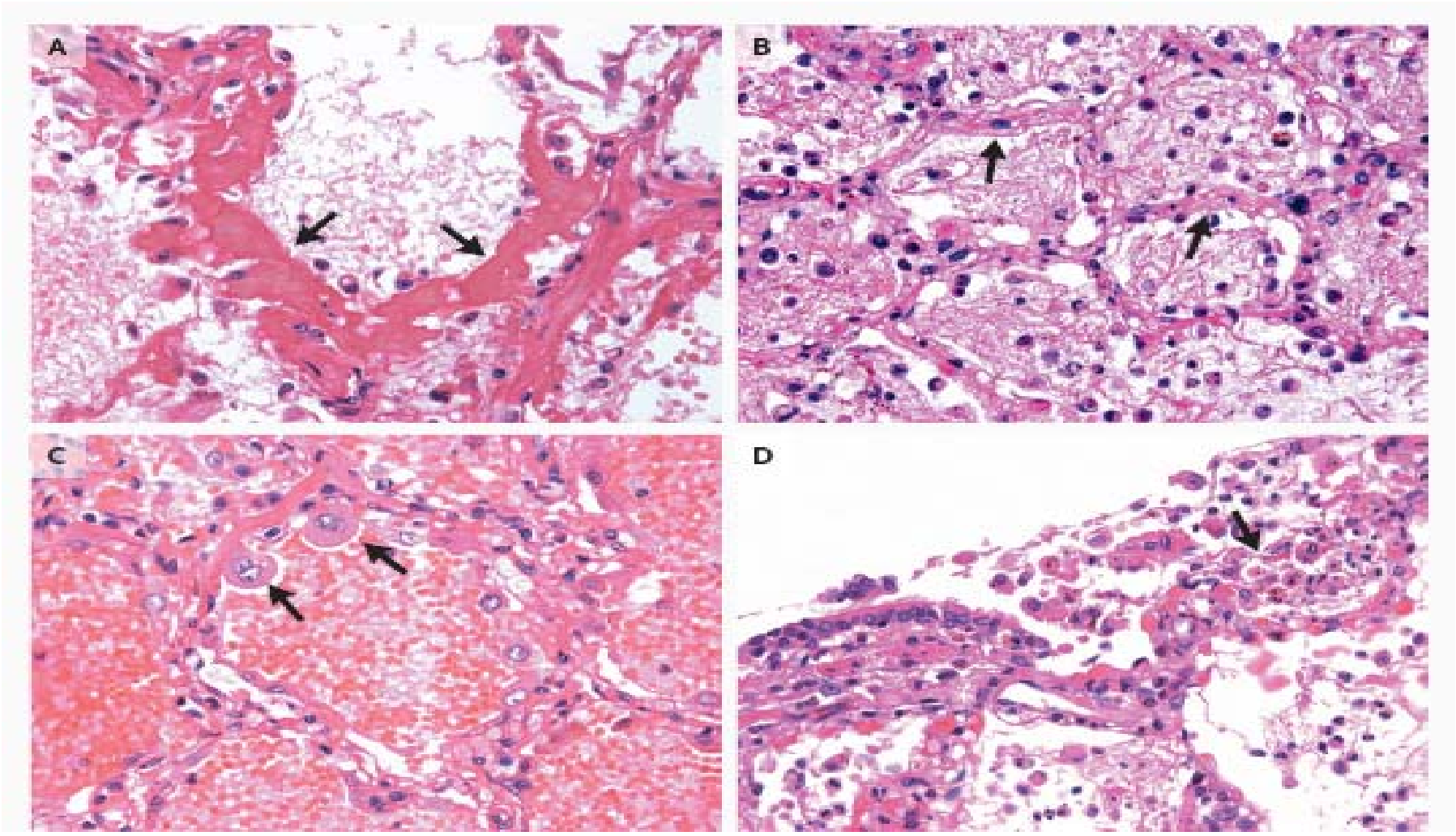


Figure 1. Micrographs of Lung Tissue from Five Patients with Fatal 2009 H1N1 Influenza.

Panel A shows hyaline membranes (arrows). Panel B shows a thickened alveolar septum associated with predominant edema (arrows). Panel C shows hyperplasia of type II pneumocytes (arrows). Panel D shows an inflamed, necrotized bronchiole wall with partial loss of the coating epithelium (arrow). Panel E shows inflammatory infiltrate in



- For pandemic H1N1 infection, although the overall case fatality rate is <1% among all infected persons
  - LouieJK_JAMA09, WHO, Echevarría-ZunoS_Lancet09, Donaldson LJ_BMJ, Tuite AR_CMAJ09
- the mortality rate among hospitalized patients in general is 9-15%, despite their younger age
  - LouieJK_JAMA09, JainS_NEJM09, DenholmJT_MJA10
- About 10-34% of patients require ICU admission because of severe pneumonia
  - WHO, LouieJK_JAMA09, JainS_NEJM09, DenholmJT_MJA10
- among these patients, the mortality rate may be up to 17-41%
  - Perez-PadillaR_NEJM09, KumarA_JAMA09, Domínguez-CheritG_JAMA09, RelloJ_CritCare09, MillerRR_Chest09

DIAGNOSIS

- For pandemic H1N1 infection, the sensitivity of RIDT is lower (10-67%); mismatch of viral nucleoprotein is likely a contributory factor
  - CDC, DrexlerJF_EID09, ChengPK_JCV09, KokJ_JCM09, FaixDJ_NEJM09, VasooS_CID09, UyekiTM_NEJM09
  - Therefore a negative test result must be interpreted with caution, as it does not exclude the diagnosis of influenza

- Early data suggest that for pandemic H1N1 virus, IF has a sensitivity of 48-93% and specificity of >95% when compared with PCR, but further study is required
  - UyekiTM_NEJM09, GinocchioCC_JCV09, PollockNR_CID09, Landry ML_JCM09
  - An advantage of IF is the possible simultaneous detection of other respiratory viruses
    - LeeN_AVT07, LeeN_JID09, HarperSA_CID09, PetricM_JID06

- PCR is now considered the test of choice and ‘gold standard’ for the diagnosis of seasonal and pandemic influenza because of its high sensitivity and specificity
  - it may allow virus detection in later-presenting patients and use of wider range of specimen types (e.g. swabs)
    - UyekiTM_NEJM09, FaixDJ_NEJM09, CDCdiagnosis_09

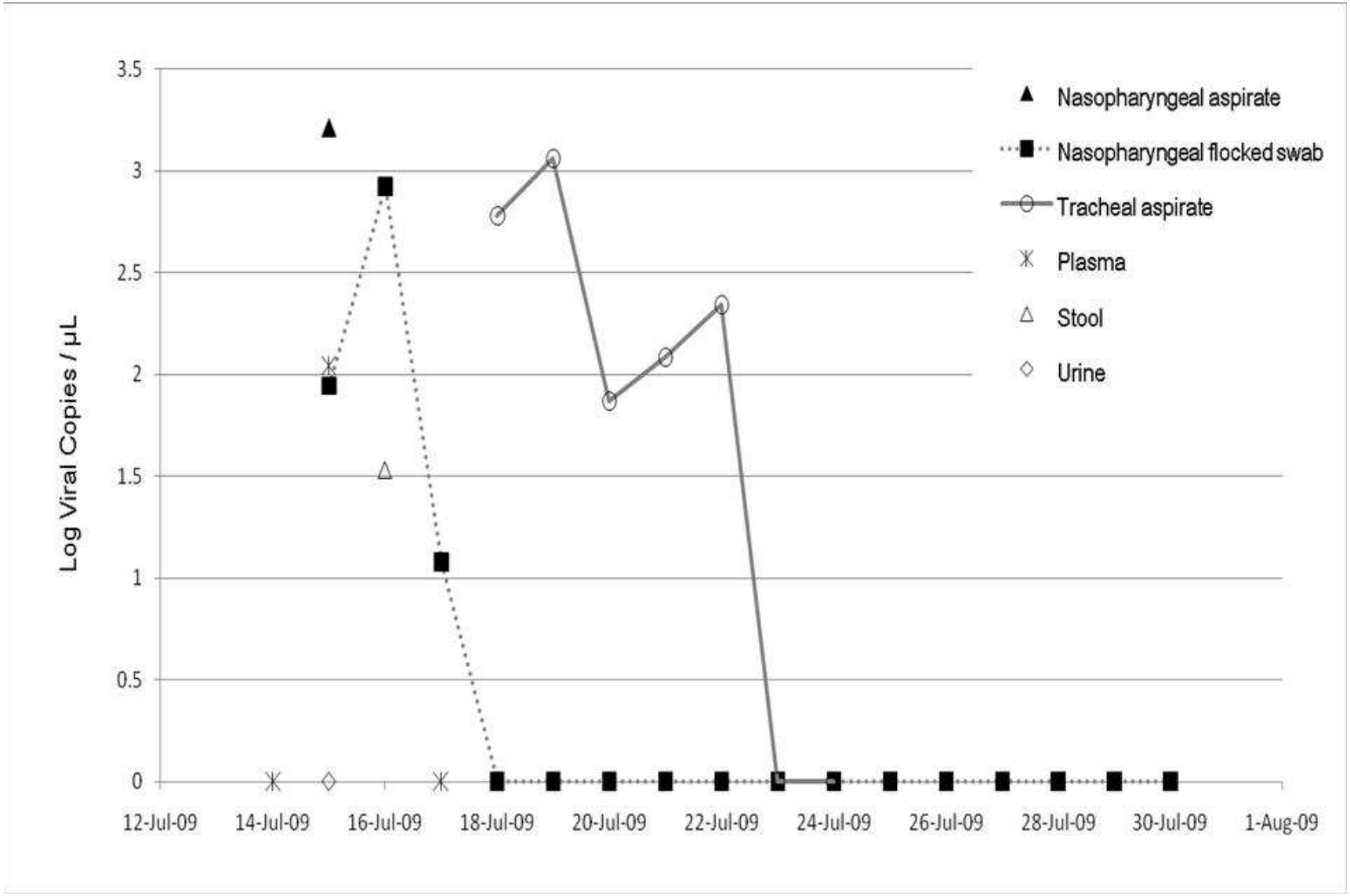
- pandemic H1N1 influenza pneumonia, false-negative results have been encountered with the use of upper respiratory tract specimens
    - UyekiTM_NEJM09, YehE_CID10

- In such cases, lower respiratory tract (site of active viral replication) specimens such as endotracheal aspirates and bronchoaveolar lavage should be considered for testing if available
    - MainesTR_Sci09, MunsterVJ_Sci09, BlythCC_NEJM09, RelloJ_CC09, HarperSA_CID09, WHOmanagement_09

Performance of laboratory diagnostics for the detection of influenza A(H1N1)v virus as correlated with the time after symptom onset and viral load

Table 1
Comparison of viral culture and RT-PCR for the detection of influenza A(H1N1)v infection.

Days after symptom onset	All respiratory specimen types				Nasopharyngeal aspirate				Throat and nasal swabs				Other respiratory specimens			
	No, tested	Positive rate by the following methods			No, tested	Positive rate by the following methods			No, tested	Positive rate by the following methods			No, tested	Positive rate by the following methods		
		Viral culture and RT-PCR	Viral culture	RT-PCR		Viral culture and RT-PCR	Viral culture	RT-PCR		Viral culture and RT-PCR	Viral culture	RT-PCR		Viral culture and RT-PCR	Viral culture	RT-PCR
0	85	90,6	95,3	95,3	29	100,0	100,0	100,0	31	83,9	93,5	90,3	25	88,0	92,0	96,0
1	216	96,3	97,7	98,6	79	98,7	98,7	100,0	78	92,3	94,9	97,4	59	98,3	100,0	98,3
2	123	94,3	96,7	97,6	44	95,5	95,5	100,0	49	91,8	95,9	95,9	30	96,7	100,0	96,7
3	89	93,3	94,4	98,9	40	92,5	92,5	100,0	31	90,3	93,5	96,8	18	100,0	100,0	100,0
4	38	84,2	84,2	100,0	18	83,3	83,3	100,0	15	80,0	80,0	100,0	5	100,0	100,0	100,0
>4	36	66,7	66,7	100,0	19	63,2	63,2	100,0	11	72,7	72,7	100,0	6	66,7	66,7	100,0
Total	587	92,0	93,9	98,1	229	93,0	93,0	100,0	215	88,8	92,6	96,3	143	95,1	97,2	97,9



Hui DS, Lee N, Chan PK. Chest 2009

- Newer multiplex PCR techniques allow simultaneous detection of multiple respiratory viruses and differentiation of influenza A subtypes, which may have important treatment (e.g. viruses with different drug-resistance profiles) and infection control implications (e.g. patient cohorting)
  - GinocchioCC_JCV09, LamWY_JMV09, LeBlanc_JCM09, GunsonR_JVM09, LamWY_JCM07, PetricM_JID06

Co-infection of pH1N1 and H3N2

Lee N, Chan PK, et al. *Ann Intern Med* (in press)

Diagnostic assays	Advantages	Disadvantages
Rapid influenza diagnostic tests (RIDT)	✓ Results available within a few minutes; simple specimen collection of nasal and throat swabs; may differentiate between influenza A vs B; used for 'point-of-care' testing	× Cannot distinguish influenza A subtypes; generally have low sensitivities (<40-60%), thus a negative test result cannot exclude influenza. Sensitivity for pandemic H1N1 virus is lower.
Immunofluorescence microscopy (IF) – direct or indirect immunofluorescent antibody staining	✓ Higher sensitivity than RIDT; provide results in a few hours; possible simultaneous detection of other respiratory viruses (e.g. RSV, parainfluenza, adenovirus) that commonly cause ILI	× Lower sensitivity than culture or PCR; cannot distinguish influenza A subtypes; require laboratory expertise for interpretation; a quality specimen that contains enough epithelial cells for IF staining is required (e.g. nasopharyngeal aspirates or flocked swabs);
Virus isolation	✓ High sensitivity and specificity; allows virus subtyping, strain identification, and detection of antiviral resistance	× Lower sensitivity than PCR; slow result limits its role in acute patient care (conventional culture 3-10 days; shell-vial culture 2-3 days); currently requires biosafety-level-3 facilities for pandemic H1N1
Reverse-transcription polymerase chain reaction (PCR)	✓ Highest sensitivity and specificity; rapid results; wide range of specimen types acceptable; possible influenza subtype-specific virus detection; multiplex PCR allows simultaneous detection of other respiratory viruses.	× Availability, cost and technical demands; false-negative results have been reported for upper-respiratory tract specimens in cases of pandemic H1N1 pneumonia; cannot distinguish viable and non-viable viruses.

MANAGEMENT ISSUES

- In both seasonal and pandemic H1N1 influenza, secondary bacterial infection is evident in about 9-13% and 5-15% of all hospitalized cases respectively (but up to 25-30% in ICU or fatal cases), either at presentation or after hospitalization
  - McGeerA_CID07, LeeN_AVT07, BabcockHM_ICHE06, MurataY_JID07, OliveiraEC_Chest01, LouieJK_JAMA09, Perez-PadillaR_NEJM09, KumarA_JAMA09, MillerRR_Chest09, RelloJ_CritCare09, CDCbact_MMWR09, WrightPF_NEJM09, ChienYW_NEJM09.
- The commonest pathogens identified at presentation include *S. pneumoniae*, *S. aureus* (MSSA or MRSA, if endemic), *H. influenzae*, and *S. pyogenes*
  - gram-negative bacilli, such as *P. aeruginosa, E. coli* and *Acinetobacter* species may infect compromised patients or complicate patient's hospital course

- Virus-bacteria synergy:
  - viral neuraminidase cleaves sialic acid to release new virons from epithelial cells→ cell damage and exposes binding sites for bacterial adhesion;
  - bacterial toll-like receptor ligands desensitized;
  - the viral accessory protein PB1-F2→enhance inflammation and severity of bacterial infection; bacterial neuraminidase can upregulate influenza infection
    - McAuleyJL_Cellhost07, McCullersJA_JID04, MorensDM_JID08, PeltolaVT_JID05
- Definitive diagnosis of bacterial super-infection can be difficult; but typically there is initial clinical improvement followed by recrudescence of fever and productive cough, leukocytosis, and new consolidation on chest-radiographs
    - WrightPF_NEJM09, MandellLA_CID07
- Failure to recognize and treat bacterial infection can result in devastating outcomes
    - MMWR09, WrightPF_NEJM09, ChienYW_NEJM09

Susceptibility of currently available antivirals among different seasonal and emerging influenza viruses

Influenza Virus Subtype	Seasonal influenza strains			Emerging / novel influenza strains		
	A/H3N2	A/H1N1	B	H1N1[a] (2007-2008)	H1N1 (S-OIV)[b] (2009)	H5N1[c]
Oseltamvir	S	S	S	R	S	S
Zanamivir	S	S	S	S	S	S
Rimantadine or Amantadine	R	S	R	S	R	variable

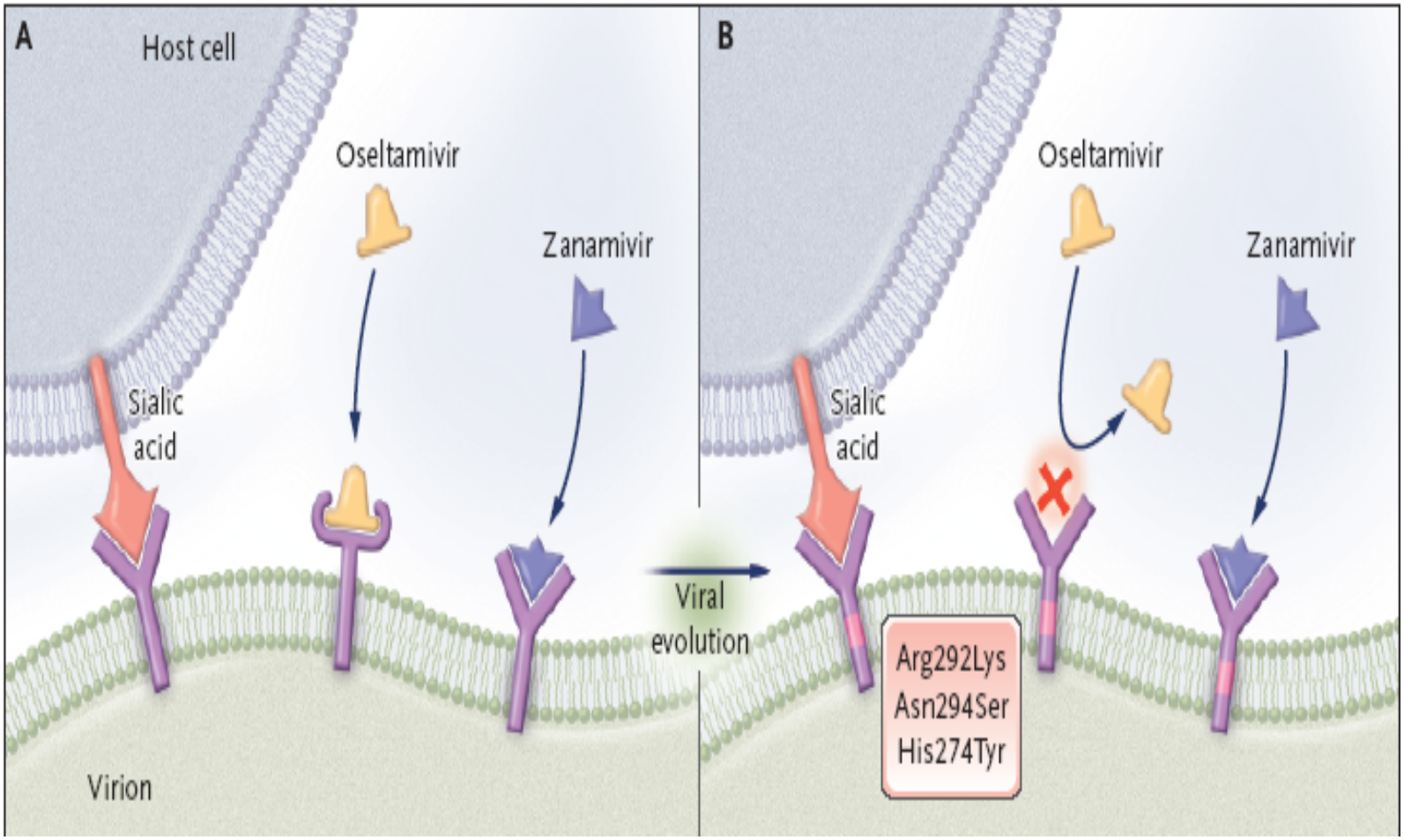
a. emerging H1N1 virus with H274Y mutation, leading to oseltamivir resistance
b. S-OIV — Swine-Origin Influenza A (H1N1), novel virus that emerged in 2009, preliminary susceptibility testing suggest resistance to adamantanes
c. H5N1 (avian influenza) — oseltamivir 150 mg b.i.d. for 10 days has been suggested, reduced susceptibility or secondary resistance had been reported; few data exists on clinical use of inhalational zanamivir; susceptibility of adamantanes varies with the circulating clade/subclade of virus

- H275Y is the most frequently recognized resistance-associated mutation in the H5N1 and pandemic H1N1 viruses post-oseltamivir exposure
  - HaydenF_CID09, OngAK_JID07, deJongMD_NEJM05, CDCimsp_MMWR09, CDCprophy_MMWR09, BazM_NEJM09
- As of December 2009, 109 cases of oseltamivir-resistant pandemic H1N1 infections have been reported worldwide (WHO), and continuous monitoring of the situation is necessary
- High viral load and prolonged shedding (e.g. in children and immunocompromised patients) and exposure to low drug concentrations (e.g. with post-exposure prophylaxis) are the risk factors for secondary resistance's emergence
  - OngAK_JID07, CDCimsp_MMWR09, CDCprophy_MMWR09, BazM_NEJM09, GooskensJ_JID09, IsonMG_JID06
- Surveillance data suggest that zanamivir-resistance is rare, and most oseltamivir-resistant virus (seasonal or pandemic H1N1) remain susceptible to zanamivir
  - HaydenF_CID09, OngAK_JID07, SheuTG_AAC08, GaurAH_NEJM09

Global Transmission of Oseltamivir-Resistant Influenza

Anne Moscona, M.D.

N ENGL J MED 360;10 NEJM.ORG MARCH 5, 2009



- In hospitalized patients who cannot take medications by mouth (e.g. intubation, swallowing difficulties), oseltamivir suspension/solution may be given via a nasogastric tube.
  - High serum concentration of the active metabolite oseltamivir carboxylate had been detected using this delivery method in intubated patients without GI malfunction [TaylorWR_PLOSone08]

- Inhalational zanamivir results in high concentration in the respiratory tract (oropharynx ≈80%, lung 10-20%) without significant systemic bioavailablity [MosconaA_NEJM05]

- Delivery challenges such as difficulty in handling the device, and the poor inspiratory capacity and the risk of bronchospasm in patients with current or underlying lung diseases (e.g. COPD, asthma) can limit its use.
  - The adequacy of drug delivery to the lungs in cases of severe viral pneumonia, pulmonary edema or ARDS is also uncertain
    - WHOmanagment_09, SchünemannHJ_LID07, HaydenF_CID09, OngAK_JID07, MosconaA_NEJM05, MedeirosR_AVT07

- Of note, zanamivir dry powder should not be administered by nebulization, as the lactose sugar in the formulation can obstruct proper functioning of mechanical ventilator equipments [GSK_09]

- Both oseltamivir and zanamivir are pregnancy category C medications, though limited clinical experiences have suggested their tolerability without major teratogenicity;
    - given the mortality risk of complicated influenza in pregnancy, these drugs are currently not considered as contraindicated for treating such patients
        - LouieJK_NEJM10, JamiesonDJ_Lancet09, TanakaT_CMAJ09, CDCtreatment_09, WHOmanagement_09

- Preliminary data on pandemic H1N1 influenza suggest that timely antiviral treatment is associated with enhanced viral clearance, as well as improved survival in the hospitalized patients
  - JainS_NEJM09, CaoB_NEJM09, Domínguez-CheritG_JAMA09, LiIW_Chest10

- In one study, it was found that 45% of survivors had received antivirals within 48 hours from onset, in contrast to only 23% among the cases with poorer outcomes ($p<0.05$) -- JainS_NEJM09

Clinical Features of the Initial Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in China

Table 4. Risk of Viral Shedding for More Than 5 Days.*

Variable	Viral Shedding for More Than 5 Days (N=350)	
	Odds Ratio (95% CI)	P Value
Age		0.02
<14 yr	1.94 (1.13–3.31)	
≥14 yr	1.00	
Sex		0.02
Male	1.69 (1.07–2.66)	
Female	1.00	
Fever		0.82
Yes	1.10 (0.50–2.41)	
No	1.00	
Cough, sore throat, or sputum production		0.09
Yes	1.58 (0.93–2.70)	
No	1.00	
Interval from symptom onset to oseltamivir therapy		<0.001
>48 hr	4.46 (2.58–7.72)	
≤48 hr	1.00	

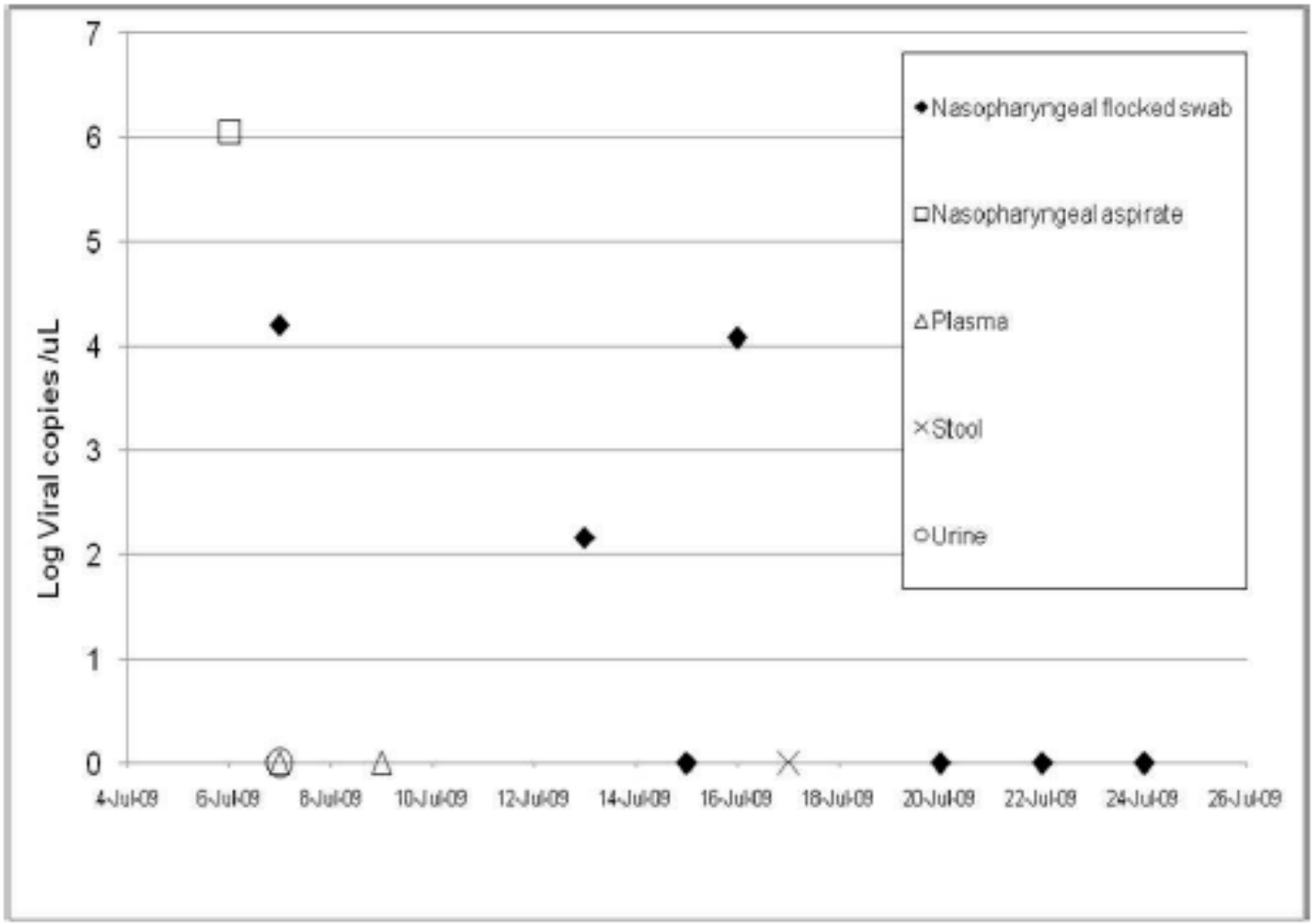
N Engl J Med 2009;361.

Critically Ill Patients With 2009 Influenza A(H1N1) in Mexico

Results Critical illness occurred in 58 of 899 patients (6.5%) admitted to the hospital with confirmed, probable, or suspected 2009 influenza (A)H1N1. Patients were young (median, 44.0 [range, 10-83] years); all presented with fever and all but 1 with respiratory symptoms. Few patients had comorbid respiratory disorders, but 21 (36%) were obese. Time from hospital to ICU admission was short (median, 1 day [interquartile range {IQR}, 0-3 days]), and all patients but 2 received mechanical ventilation for severe acute respiratory distress syndrome and refractory hypoxemia (median day 1 ratio of PaO_2 to fraction of inspired oxygen, 83 [IQR, 59-145] mm Hg). By 60 days, 24 patients had died (41.4%; 95% confidence interval, 28.9%-55.0%). Patients who died had greater initial severity of illness, worse hypoxemia, higher creatine kinase levels, higher creatinine levels, and ongoing organ dysfunction. After adjusting for a reduced opportunity of patients dying early to receive neuraminidase inhibitors, neuraminidase inhibitor treatment (vs no treatment) was associated with improved survival (odds ratio, 7.4; 95% confidence interval, 1.8-31.0).

JAMA. 2009;302(17):(doi:10.1001/jama.2009.1536)

- For seasonal influenza, antiviral started within 96 hours has been associated with better clinical/virological outcomes than nil treatment
  - McGeerA_CID07, LeeN_CID08, LeeN_ICAAC09
- As viral replication in pandemic H1N1 influenza also appears to be more prolonged, withhold antiviral treatment in those late-presenters with severe pneumonia is unadvisable
  - CDC_09, WHO_09, ChengPK_JCV09, CaoB_NEJM09, WitkopCT_AJPM09, LiIW_Chest10



Virus shedding profile of a 68 yr-old male who was hospitalized with acute exacerbation of COPD on 6 July 2009 with 2 days history of cough, fever and increased dyspnea. His chest radiograph showed no consolidation. He was given prednisolone 30mg daily for 10 days and amoyxcillin-clavulanate 1g bd for acute exacerbation of COPD. RT-PCR from his nasopharyngeal aspirate taken

Hui DS, Lee N, Chan PK. Chest 2009

- At present, parental NAI is not routinely available. In October 2009, the Food and Drug Administration in US has approved emergency, conditioned use of intravenous peramivir for treating severe pandemic H1N1 infection
  - BirnkrantD_NEJM09, KohnoS_ICAAC09
- Intravenous zanamivir may only be accessible through compassionate-use programs
  - GaurAH_NEJM09, KiddIM_Lancet09
    - Clinical experience with these agents is limited
- Combination regimes involving 2-3 drugs of from the classes of NAI, adamantanes and ribavirin are of interest because of potential synergism and lower risk of resistance during treatment of severe influenza
  - IsoMG_AVT03, HaydenF_CID09, Govorkova EA_AAC04, ChanTack_NEJM09
  - In an animal model, such triple-combination has been shown to effectively suppress replication of the pandemic H1N1 virus [NguyenJT_AAC09]

Summary

- pH1N1 is an emerging infection that can cause severe disease
- Diagnosis can be difficult sometimes
- Many management issues are still unresolved, and require further study