Disclosure of Relationships to Industry
Richard P. Wenzel, MD, MSc

Company	Research	Consulting
Rib-x		▲
Pfizer	▲	▲
3M		▲
Boerhinger Ingelheim		▲
Biomerieux		▲
Sanofi-Aventis		▲
Vestagen	▲	

No speaking bureau; no stocks, no royalties

H1N1 in Mexico and South America
Onsite Observations and Impressions
(A H1N1/swine/California/004/2009)

Richard P. Wenzel, M.D., M.Sc.
Professor and Chairman
Department of Internal Medicine
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia


COPIADORAS
IMPRESORAS


EL UNIVERSAL

EL GRAN DIARIO DE MÉXICO

La influenza se fortalece pese a los antivirales, advierten en EU

Perú y Ecuador se suman a campaña antimexicana

Demanda la Cancillería el cese de las medidas discriminatorias a connacionales

El brote está activo; habrá más casos: Ssa

DOMINGO

NO SE PUDO...

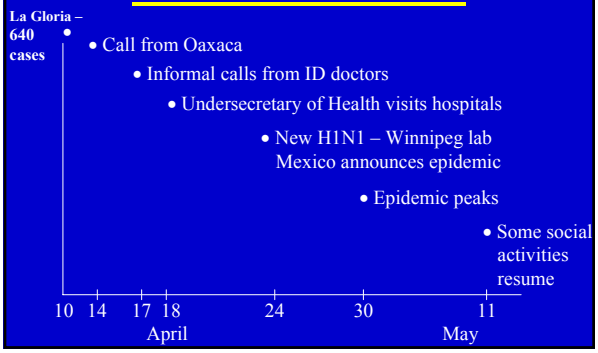
A Case in Oaxaca

- 39 ♀
- 9 April – resp distress CAP
- 10 – ARDS
- 12 – Call to fed health coronavirus – ? SARS
- 13 – death- C-R failure
- 23 – confirmed H1N1 (swine)

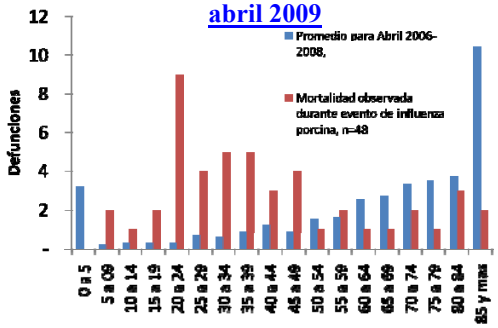
March 5
- La Gloria – 4 cases ILI

March 4
- San Luis – 4 cases

Response to H1N1
The Timeline in Mexico



Distribución de las defunciones por grupo de edad, comparación entre el promedio diario en abril 2006-2008 y lo observado en abril 2009



Respiratory Disease Institute – May 2009

Background flu season pneumonias

20/week 2007-8/2008-9

At peak end of April: 120/week – six times background!

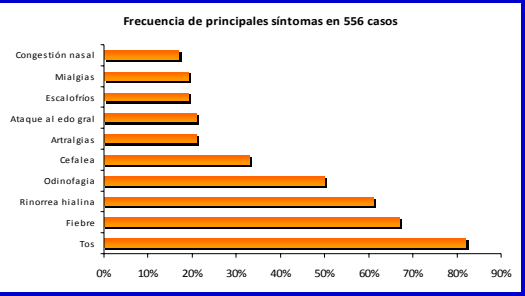
Prevalence at peak 20 patients – most on vent

Mean age 26

≥ 80% dyspnea, cough, malaise

12% diarrhea (6 x/d)

Eventos epidemiológicos relevantes en torno al brote de la Ciudad de México, caso Perote, Veracruz



Fever and H1N1 in Mexico/Chile

Almost all severe cases have fever at triage

One third of milder cases have no fever at triage

~ half of them do not have fever after admission

Chile:

~half of confirmed H1N1 in clinics have no fever

China – one third hospitalized had no fever

NEJM 2009; 361:2507-17

Implications of Absence of Fever and H1N1

- Underestimate impact of epidemic
- Limit value of thermal scans
- Difficulty of control especially in children (shedding)
- Infection control must be assiduous

CASE 1

- **ID:** 22 yo male, Mexico City resident.
- **FH:** HTN and Diabetes
- **Social Hx:** no animal contact, Smoke (+), close contact with 5 persons .
- **PMH:** obese

EVOLUTION

Emergency Room

April 14th

HR 113, RR 34, TA 130/80, T° 38.2 SaO2 86%.

Obese, increased work of breathing, hypoventilated RLB, with bilateral crackles, ΦMRG, rest wnl.

ABG	04/24
pH	7.4
pCO2	41.0
pO2	56
HCO3	22.0
SaO2	86%
Kirby	200

Laboratory Data

April 14th

CBC	04/24
WBC	1.8
PMN	79%
Lymp	12%
Mon	8.0%
Eos	0.3%
Bas	0.0
Bands	0.0
HB	16.6
Hto	48.4
Platelet	80

RADIOLOGIC IMAGES

April 14th

EVOLUTION

ICU

April 15th – 24th

RESPIRATORY: volume control, PEEP 14, FiO2 100%, SaO2 80%. *Pronnated*

CARDIOVASCULAR: required vasopressor support (NE).

ID: febrile for 2 days. April 20th > hypothermia

Blood cultures: (-)
Sputum cultures: (-)
Legionella/Pneum Ag (-)
HIV negative

Bronchoscopy: mucosal edema.

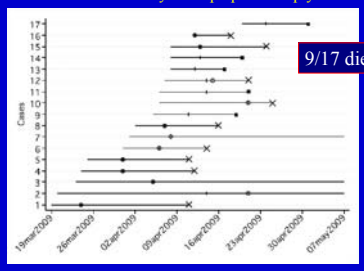
April 18th: Tx: oseltamivir.

PCR + Influenza April 20th

CBC	14/04	15/04	24/05
WBC	1.8	5.7	5.3
PMN	79%	94.8	76.2
Lymp	12%	4.6	11.8
Mon	8.0%	0.6	10.5
Eo	0.3%	0.1	0.2
Bas	0.0	0.0	0.5
Bands	0.0	0.0	0.0
HB	16.6	13.7	12.8
Hto	48.4	40.5	36.7
Platelet	80	90	311

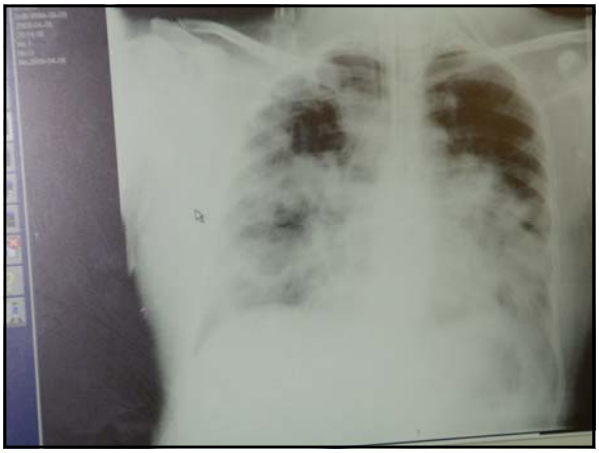
- FIGURE 4. Clinical course of 17 patients.

Dates are depicted in the horizontal axis (from left to right), and described cases in the vertical axis. Deaths are identified with an "X", endotracheal intubation with an empty circle, hospital admission with a vertical line, and discharge from hospital with a full square. Two patients were still hospitalized (2,3 and7). Patients presented to hospital after varied delays (median 6 days). Fatalities were mostly intubated on arrival shown by the superposed empty circle and vertical line.



9/17 died

Perez-Padilla. *NEJM* 2009



Pregnancy, Obesity are Risk Factors for Severity of H1N1

Brazil – Pregnancy: number one cause for ICU admission – more than obesity

Columbia – 1 of 7 deaths in pregnant women

Chile – Equal to obesity as risk for ICU admission

Argentina – one of 4 who died in Buenos Aires (n=85) was pregnant, just above obesity.

U.S. – 13% deaths in pregnant women

H1N1 and Obese Patients in ICU-Michigan

10 patients – median age 46

All on ventilator; 2 ECMO

None had bacterial infection

9/10 – BMI> 30

7/9 BMI>40

5/10 – pulmonary emboli !

9/10 MODS

3 deaths

U.S. Study (n=272)
45% obese/morbidly obese
NEJM 2009; 361, in press

MMWR July 10, 2009

Ethnicity and H1N1 Risk

U.S.: hispanics (30%) and blacks (19%) overrepresented in hospitalized cases
NEJM 2009; 361:1935-44

Aust/NZ: Indigenous in Australia (10%) and NZ (25%) overrepresented in ICU cases
NEJM 2009; 361:1925-34

Canada: aboriginals (26%) overrepresented in ICU cases
JAMA 2009 Oct 12 epub

Aboriginals: independently predicted severity
CMAJ 2010. doi:10.1503/cmaj.091884

Organ Transplant Patients Have Severe Outcomes

Argentina - ID Physicians have consistant observations

Chile – 7 year old girl s/p liver transplant acquired H1N1 in hospital

Mexico – H1N1 on hands, hard surfaces, computer mouse

Macias et al JHI in press

Implications for Infection Control

Sequelae of H1N1

- Post infections fatigue/myopathy – 37%
- Need for Oxygen if O_2 in hospital – 30%
- Night sweats – weeks in some
- Late onset, reversible hair loss in some

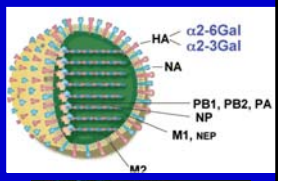
Perez-Padilla Personal communication 07/2009

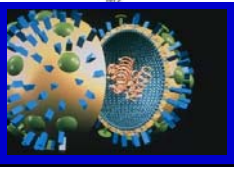
H1N1 ("Swine") Influenza What Was New

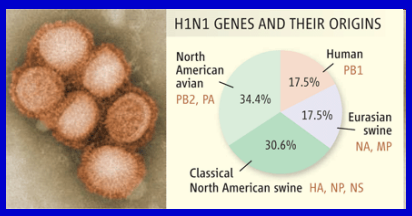
New virus – never seen before
New cohort at risk – young adults
New season – mid-spring
New continent – Northern hemisphere
New virulence – in Mexico ARDS/deaths confirmed in Chile, Argentina
Young adults dying

Two Strategies for Influenza

1. Accumulation of point mutations with no proofreading
2. Reassortment of 8 segments of RNA – "Viral Sex": exchange of genes of 2 viruses coinfecting a host (256 possible offspring)







Science 8 May 2009
324 : 701

Reservoir for influenza is in migratory water fowl

H1
H2
H3
H4
H5
H7
H9
H6,H8, H10-16

H1N1 in turkeys in Chile

Diarrhea and H1N1

- 12% of cases in Mexico City
- 10-20% of cases – Chile
- Virus found in stool in Mexico
- Implications: additional Infection control issue
- Is the GI tract the source of pro-inflammatory response?

Staph aureus Pneumonia - 1918

8100 c̄ flu
1409 pneumonia (17%)
385 died (27%)

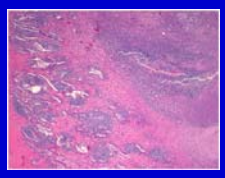
~half of deaths (153) with *S. aureus* cults
92 of 153 (60%) *S aureus* only

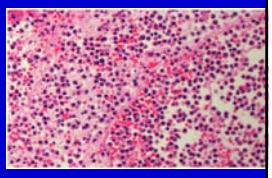
56% deaths by day 10, 72% by 15

Cherry red indigo blue cyanosis
no chills, localized CP
no signs consolidation
fulminating septic course
dirty salmon-pink sputum

Chickering & Park JAMA 1919; 72:617-26

Co-Infection H1N1 and CA-MRSA





Histopathology of pandemic A (H1N1)/cMRSA co-infection

PLoS ONE 5(1): e705.doi:10.1371/journal.pone.0008705

Controlling an Epidemic Mexico City

- Social distancing
- Psychological support for HCWs/families
- Triage patient/with patients
- Reeingeneering of hospital
- Infection control

"Social Distancing"

Close all:
- schools
- restaurants
- bars
- football (soccer) games
- malls
- theaters
- swimming pools

No embraces, kissing, handshaking
Open – grocery stores
Suggest – "stay home"
- No ties in Mexico city
- wear masks in public

No data for any aspect of social distancing

Managing Fear Among HCWs/families

Anecdotes – ID personnel
Consultations and fear more if not ID
Converse with HCWs
24/7 access to special care clinic
24/7 hotline
"We will take care of you"

Infection Control

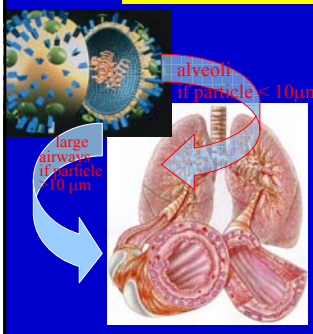
- Handwashing, gloves, mask
- "Don't touch your face"
- Cohort nurses with specific patients during day
- Triage HCWs/patients
- Cohort patients with respiratory symptoms

Interrupting the Spread of Influenza: Meta-Analysis of 6 Case-Control Studies

Intervention	No studies	OR (CI_{95})	NNT
Handwashing ≥10 x/day	6	0.45 (.36-.57)	4
Wearing masks	5	0.32 (.25-.40)	6
Wearing N-95 masks	2	0.09 (.03-.30)	3
Wearing gloves	4	0.43 (.29-.65)	5
Wearing gowns	4	0.23 (.14-.37)	5
HW/masks/gloves/gown	2	0.09 (.02-.35)	3

BMJ 2009; 339:63675 doi:10.1136/bmj b3675

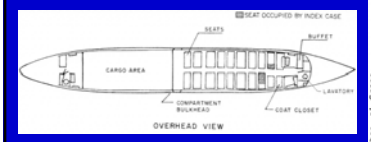
Influenza Pathogenesis



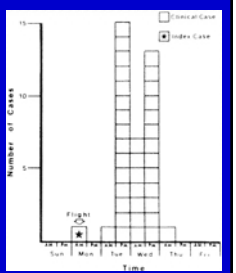
- Incubation 1-4 d
- 50% cases asymptomatic (still shedding)
- Adults – shed virus 3-5 d
- Young children shed virus to 3 weeks
- Immune compromised shed virus > 3 weeks

NEJM 1966; 274:527-35
JID 1979; 140:610-3
Ped Inf Dis 1999; 18:811-5

Evidence for Airborne Transmission of Influenza H3N2

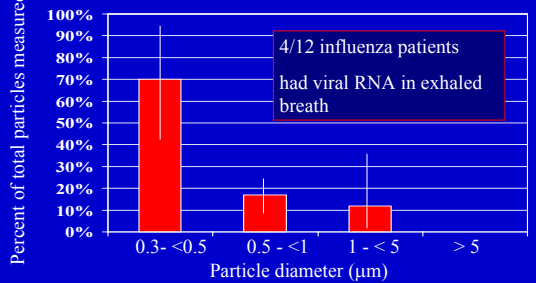


Boeing 737



Am J Epidemiol 1979; 110:1-6

Particle Size During Tidal Breathing in Patients with Influenza



Fabian et al *PLoS One*. 2008; 3:e2691

Is It Possible to Control Influenza?

- **Large droplets**
- **Droplet nuclei**
- **Environmental contamination**
- **Shedding in adults/children**
  Mild cases without fever
- **Virus in stool**

N-95 vs Surgical Masks for Influenza Control

For HCWs

- Influenza virus .08-.12 microns
- N-95 testing - .3 micron particles
- Experimental model (N-95) using bacteriophage .02 microns -95 to 96% effective
- Surgical masks – 15%-80%

AJIC 2006; 34:51-7

For patients

9 patients with influenza
Neg PCR – 20 cm from coughing X 5

CID 2009; 49:215-7

Antiviral Treatment of Influenza – H1N1

Dosage in adults
Approved: 75 mg bid x 5
Consider 150 mg bid x 10

9 cases of Resistance – U.S. *MMWR* 9/11/09

2 inhalations of 5 mg each bid x 5
Diskhalar inhalation device

Most strains are highly resistant to M2 inhibitors – amantadine and rimantadine

Under study: peramivir, ribavirin, interferon alpha

NEJM 2005; 353:1374-85 *AAC* 2001; 45:2723-32
JID 2005; 192:665-72

Neuraminidase Inhibitors: Updated Cochrane Systematic Review – Meta-analysis

Prophylaxis against influenza
Zanamivir reduced symptomatic, lab confirmed flu (0.38; 0.17-.85)
Oseltamivir similar (0.39; .18-.85)
*Neither drug protected against asymptomatic illness
Post-exposure prophylaxis (households)
2 trials – Zanamivir: 0.19 and 0.2
2 trials – Oseltamivir: 0.16 and 0.42
Treatment – 8 trials Zanamivir and 5 Oseltamivir reduce symptoms (mild illness) 1 day

BMJ 2009; 339:65106 doj:10.1136/bmj.65106

Key Points: NIs

1. NIs reduce symptoms modestly by ~ 1 day
2. No data that the benefits are same for ill, hospitalized
3. NIs do not prevent infection or stop nasal viral excertion:
   suboptimal for interrupting a pandemic.
4. Authors Jefferson et al do not recommend for routine control of seasonal influenza.

BMJ 2009; 339:65106 doj:10.1136/bmj.65106

Models of 2009 H1N1 Suggest Value of Early Treatment with NIs

ARDS and H1N1:

older age, high APACHE II and SOFA scores, and delay of initiation of oseltamivir linked to mortality

Ann Fr Anesth Reanim 2010, Jan 28, epub

Hospitalized patients with pneumonia (Taiwan)

Development of respiratory failure linked to SOFA ≥ 4 on admission, lymphocyte count ≤ 800 c/mnL and duration of symptoms to initiation of oseltamivir ≥ 48 h

J Infect 2009 (Dec 29) epub

Predicting admission to ICU among pregnant patients

> 2 days after symptoms to initiate of antivirals (RR4.3)

NEJM 2010; 362:27-35

Unanswered Questions

- Any role for anti-inflammatory agents eg human activated protein C?
- If huge pro-inflammatory response, role for exchange transfusion? IVIG? Mesalazine?
- Will virulence change?
- Added value with intravenous Zanamivir or Peramivir?
- Will H1N1 recur as a 'seasonal' virus?

Unanswered Questions

Steroids – when/dose/may ↑ shedding of virus

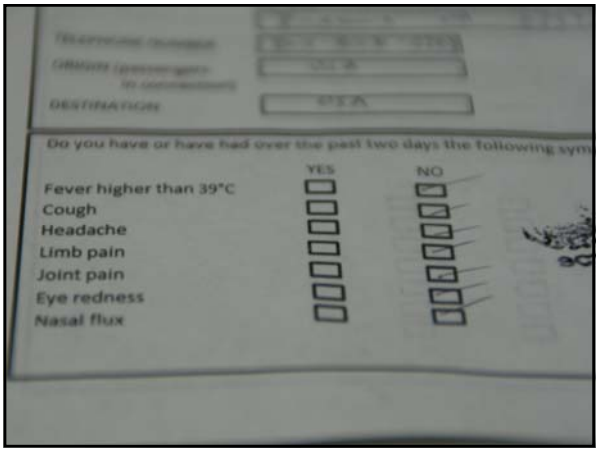
Value of aerosolized NIs – may plug tubing!

no data. Can obstruct filter!

have tried in severe cases

plus oral oseltamavir

Value of ECMO?



Future Issues

- Failure to admit patients to ICU initially
- Complacency!
- Communication
  - Credible, factual, clear
  - Do not overpromise
- Rapid availability of cell-based vaccines
- Response implications for bioterror

Pandemics in Perspective

	Case Mortality-Estimates	Deaths in terms of current population in the US
1918-19 "Spanish"	2.5%	900,000
1957 "Asian"	0.2 -0.5%	180,000
1968 "Hong Kong"	0.2-0.5%	
Annual influenza epidemics	0.1%	36,000

WHO Declares H1N1 a "Pandemic 6"

- Pandemic: sustained spread in different continents?
- Q: What is different?
  - Seasonal flu kills 500,000 and no pandemic 6 level
- Suggest: stratify levels by surge capacity needed for resources, communication and cooperation
- Thus, key elements are transmissibility and severity

RP Wenzel – Huffington blog 16 June 2009

Droplets and Droplet Nuclei in Influenza: Volunteer Studies

> 10 µm

< 10 µm
Droplet nuclei

- droplet administration

⇒Milder disease in volunteers, required larger inoculum

- more likely to cause infection of lower respiratory tract

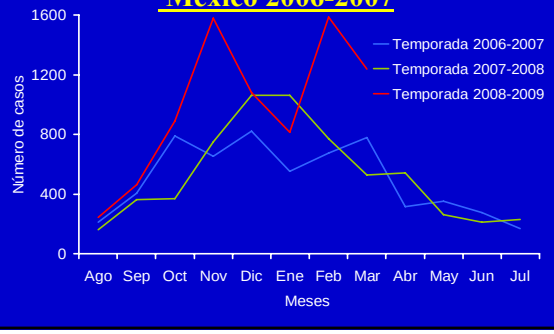
J Immunol 1945; 52:145-65
Proc Soc Exp Biol Med 1966; 122:800-4
Soc App Bact Symp Ser 1974; 3:135-54

CASE 1

- **ID:** 22 yo male, Mexico City resident.
- **FH:** HTN and Diabetes
- **Social Hx:** no animal contact, Smoke (+), close contact with 5 persons
- **PMH:** Obese

CC: *"Fever and cough".*
History of present illness: onset of fever (39.0°C), CHILLS, malaise & fatigue and productive COUGH on April 9th. The patient was seen on an OSH and was treated with penicillin and pain medication. During his follow-up he presented with DYSPNEA and PLEURITIC CHEST PAIN; he was further treated with IM ceftriaxone.

Casos de influenza estacional por temporada México 2006-2007



Avian Influenza A (H5N1): 10 Confirmed Cases in Vietnam

- Mean age: 13.7 years (5-24 years)
- 9 of 10 had direct contact with poultry (mean 3 days before)
- All had fever (38.5-40°C), shortness of breath, cough
- 7 of 10 had diarrhea - + virus
- Respiration: 55 breaths/min (20-70)
- All had rales

Mean laboratory values:

Hemoglobin 12.5 g/dL

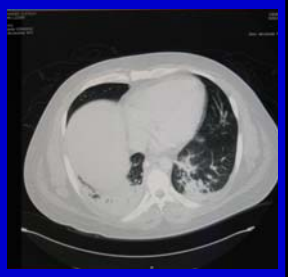
Total leukocyte count 2100 mm³

Platelet count 75,500 mm³

8 of 10 (80%) died

Tran TH, et al. *N Engl J Med*. 2004;350:1179-1188.

RADIOLOGIC IMAGES



April 23rd

As of May 12, WHO reported 4694 cases worldwide, including Finland, Cuba and Thailand

Creation of Pandemic Influenza: Two Tales

1957 (Asian) H2N2 **and** **1968 (Hong Kong) H3N2**

coinfection with avian and human flu and reassortment of 2-3 avian gene segments (H,N, PB1)

***J Virol* 1989; 63:6403-8**
***Virol* 1978; 87:13-20**

Swine H1N1

1918 ("Spanish") H5N1 in Vietnam

direct bird to man and adaptation by avian strain

Nature 2005; 437-889-93

Coinfection with RSV May Be Risk for Severity in Children

Not unusual to see coinfections with seasonal flu

ID Physicians in Argentina think coinfections overrepresented in severe cases (July 09 – "Winter")

Implications for Infection Control

Triage at Entrance - Outside

At peak – 1500 patients/day
20% arrive by bus
Elicit symptoms
Lung exam
If no flu-like illness and non-essential – go home
If flu-like – cohort after alcohol hw/mask
If no flu-like illness – separate room

Children (< 18 years) with H1N1-U.S.

- 36 (7.5%) 977 deaths in U.S.
- 7/36 (19%) < age 5
  - 24/36 (67%) – hi risk
  - 22/24 (92%) – neuro developmental disease
  - 10/23 (43%) – bacterial coinfection

MMWR, Sept 4, 2009