

Seasonal Influenza

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JOHNS HOPKINS
MEDICINE
CONTINUING MEDICAL EDUCATION

Overview

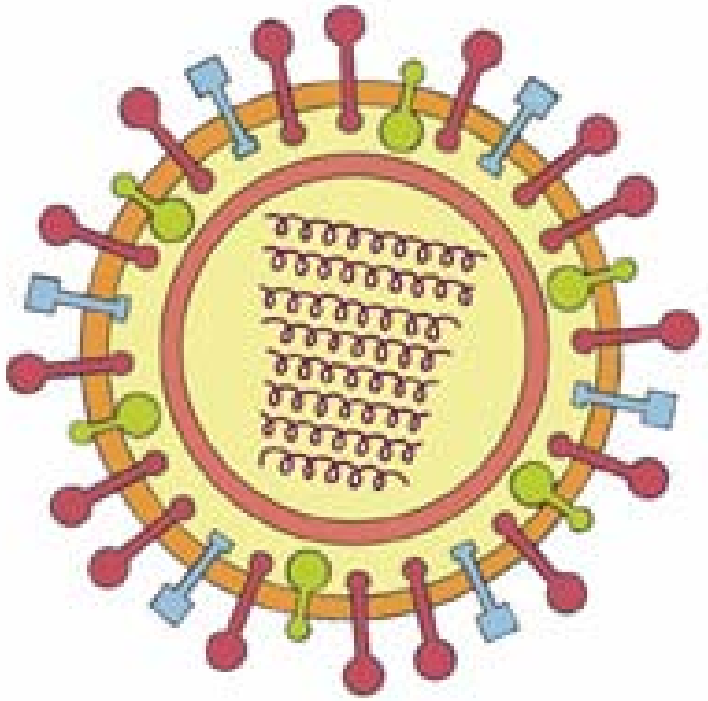
- Epidemiology and Disease Burden
- Impact on specific settings
  - Workforce
  - Healthcare setting
- Options for prevention and control
  - Vaccination
  - Antivirals

Learning Objectives

- Describe the epidemiology of seasonal influenza
- Describe the burden of influenza and its complications for individuals
- Describe the impact of influenza on the workplace and healthcare settings
- Identify high-priority groups targeted for annual vaccination
- Compare the 2 types of influenza vaccines approved for use in the US
- Identify indications for antiviral prophylaxis and benefits of antiviral treatment

Influenza Virus

- Orthomyxovirus
  - Single-stranded RNA virus (segmented genome)
    - Type A:
      - humans, animals, birds, more severe in the elderly
    - Type B:
      - humans only, more common in children
    - Type C:
      - uncommon in humans
  - 2 surface glycoproteins
    - Hemagglutinin (HA)
      - attachment and entry
    - Neuraminidase (NA)
      - release



Influenza A Virus

Epidemics, Pandemics and Antigenic Changes

- Influenza viruses cause epidemics and pandemics
  - Size and relative impact result of
    - Antigenic variation, amount of immunity in populations, and relative virulence
- Antigenic variation result of changes in genes encoding for HA and NA
  - Drift – point mutations (both A and B)
    - Minor changes, same subtype
      - Associated with epidemics
  - Shift – genetic reassortment (A)
    - Major change, new subtype
      - Associated with pandemics

Epidemic Influenza Is a Common, Miserable, and Often Serious Illness

- Acute respiratory illness
  - Abrupt onset of symptoms
- Incidence: 5% to 20% of population
  - Higher in children
- Serious complications not uncommon
- Case fatality: 0.5 to 1 per 1000
  - Higher in elderly
- Spread by coughing and sneezing

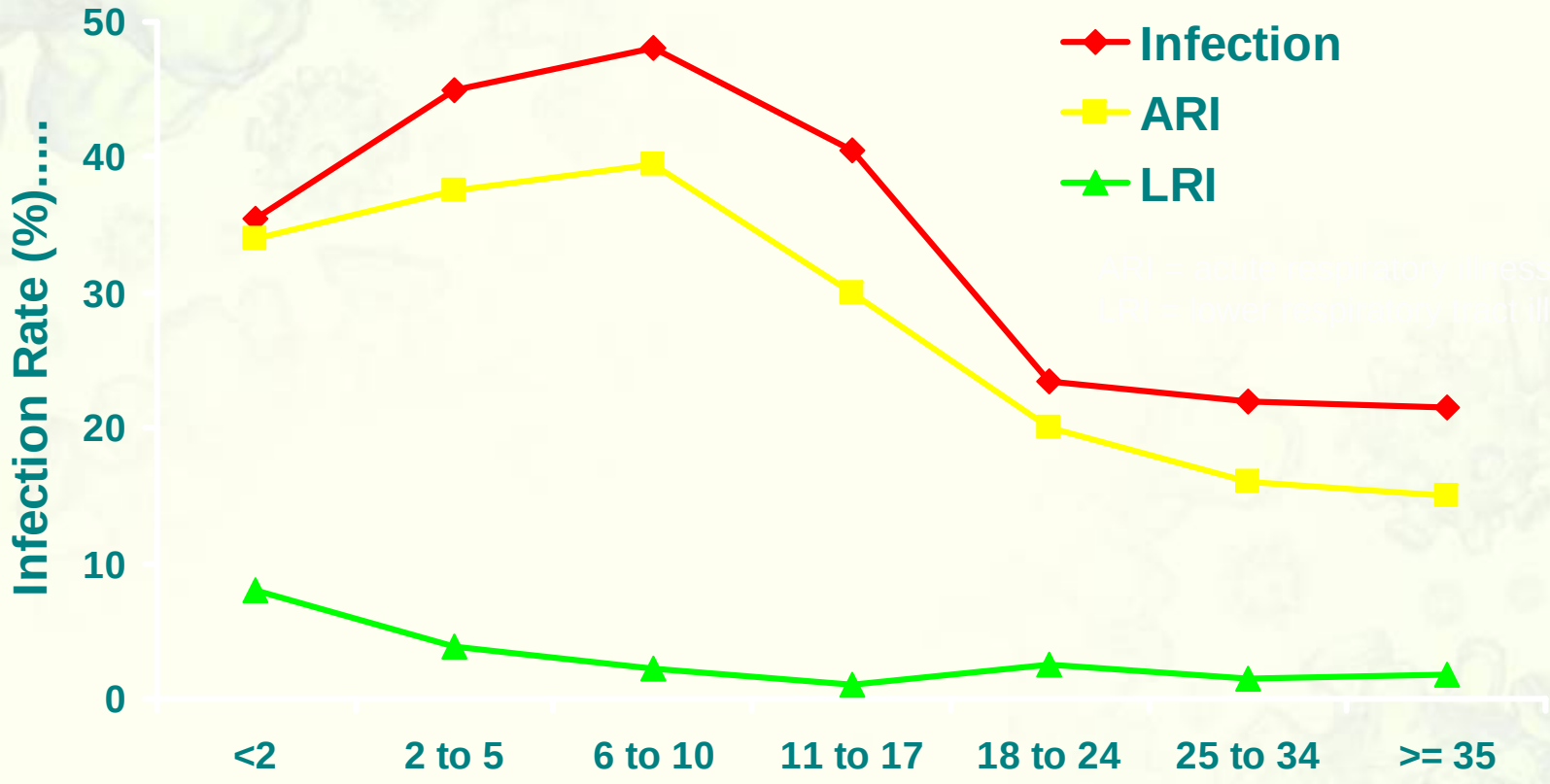
CDC. Influenza (The Pink Book, 8th ed; www.cdc.gov/nip/publications/pink)

Transmission of Influenza

* Droplet
* Aerosol
* Contact

Influenza Is Everyone's Illness

Influenza Virus Infection and Illness Rates: Houston Family Study, 1976-1984



Glezen WP. *Pediatr Infect Dis J*. 1997;16:1065.

Morbidity Associated With Influenza Episodes

Restricted Activity	5 – 6 days
10% to 20%	10 + days
Bed Disability	3 – 4 days
Absenteeism	3 days
Medically Attended	50%

Kavet J. *Am J Public Health*. 1977;67:1063.

Influenza Morbidity in Adults

Symptom	Time to resolution
All symptoms	6.7 days
Normal activity	8.4 days
Normal sleep scores	7.3 days
Fever	2.9 days
Cough	3.8 days
Headache	1.2 days
Myalgia	1.4 days

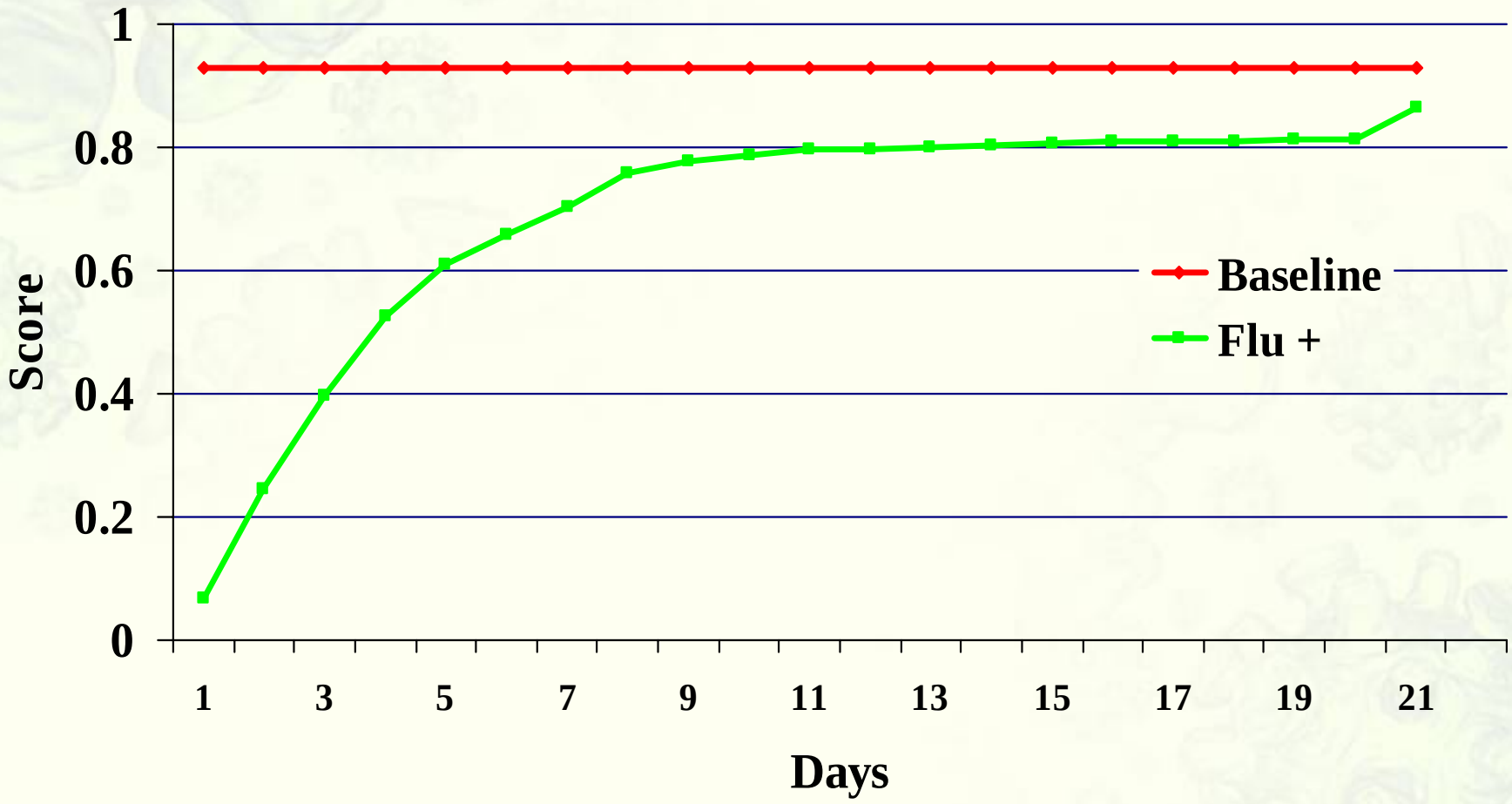
Singh S. *Clin Drug Invest*. 2003;23:561.

Some Complications Are Common in Low-Risk Groups

Group and Complication	Incidence
Young children -- Otitis media[1]	30% to 45%
Healthy adolescents and adults	
Resp w/antibiotics[2]	17%
upper resp:	8%
lower resp:	9%
Any Lower Resp Tract[3]	5.3%

1. Belshe RB, et al. *Pediatr Infect Dis J*. 2000;19:S66;
2. Kaiser L, et al. *Arch Intern Med*. 2000;160:3234.
3. Kaiser L, et al. *Arch Intern Med*. 2003;163:1667.

QALD Scores for Healthy Adults With Influenza



Turner D. *Health Technol Assess*. 2003:7(35):122.
Gold MR. *Med Care*. 1998;36:778.

ILI Interferes With Work and Leisure Time Activities

Morbidity Associated With ILI in Workers	
Work Loss	2.8 days
Effectiveness at Work	4.6 (scale of 1 to 10)
Confined to Bed	2.4 days
Caregiver Assistance	0.4 days
Interference with Activities at Home	73%
Interference With Leisure Activities	84%

Keech M, et al. *Occup Med*. 1998;48:85.

ILI Among Adults: 2004

ILI during 2003-04 season	**17.8%**
HCW visit	**43.3%**
Received antibiotics	**33.1%**
Received antiviral	**14.7%**
Hospitalized due to ILI	**0.1%**
Missed work/school due to ILI in self /family member	**15.9%**
Attended work or school while ill with ILI	**82.7%**

Believe that vaccine is somewhat or very effective:	71%
Believe that vaccine can cause influenza:	33%

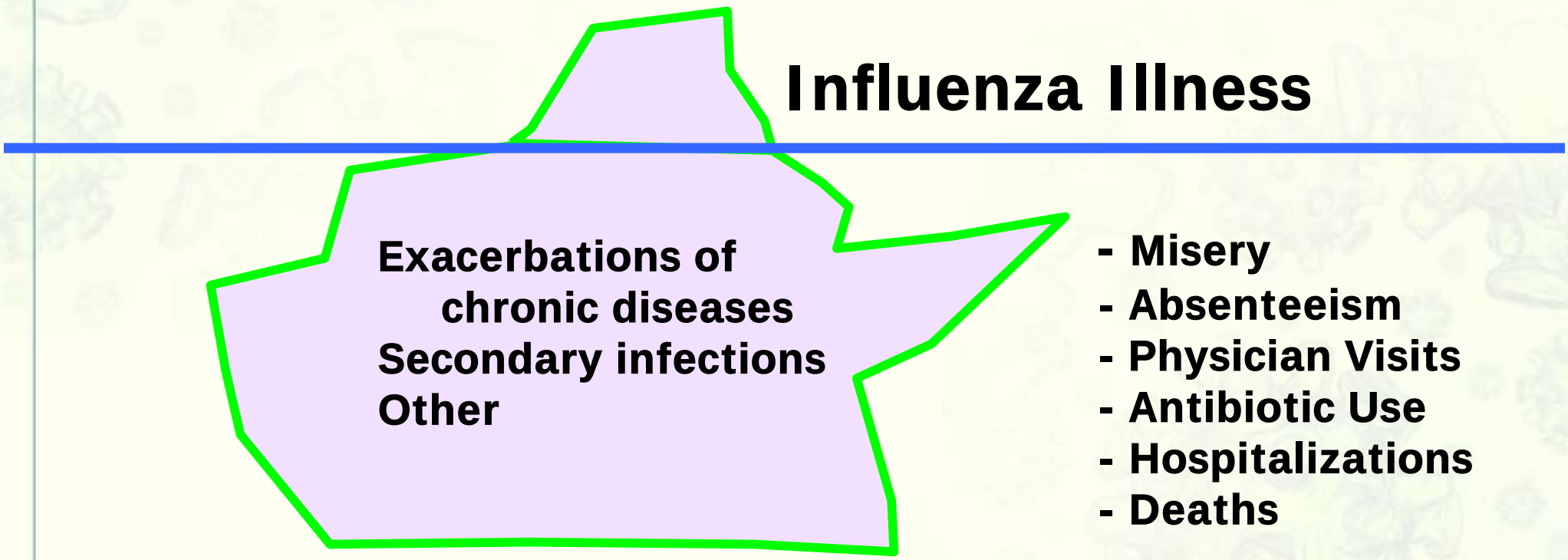
MMWR. 2004;53:1156-8.

Morbidity Associated With Influenza in Adults Ages 18 to 64: Population Perspective, 1996

Restricted Activity	**167 million days**
Bed Disability	**95 million days**
Work Loss	**69 million days**
Medically Attended	**18 million**

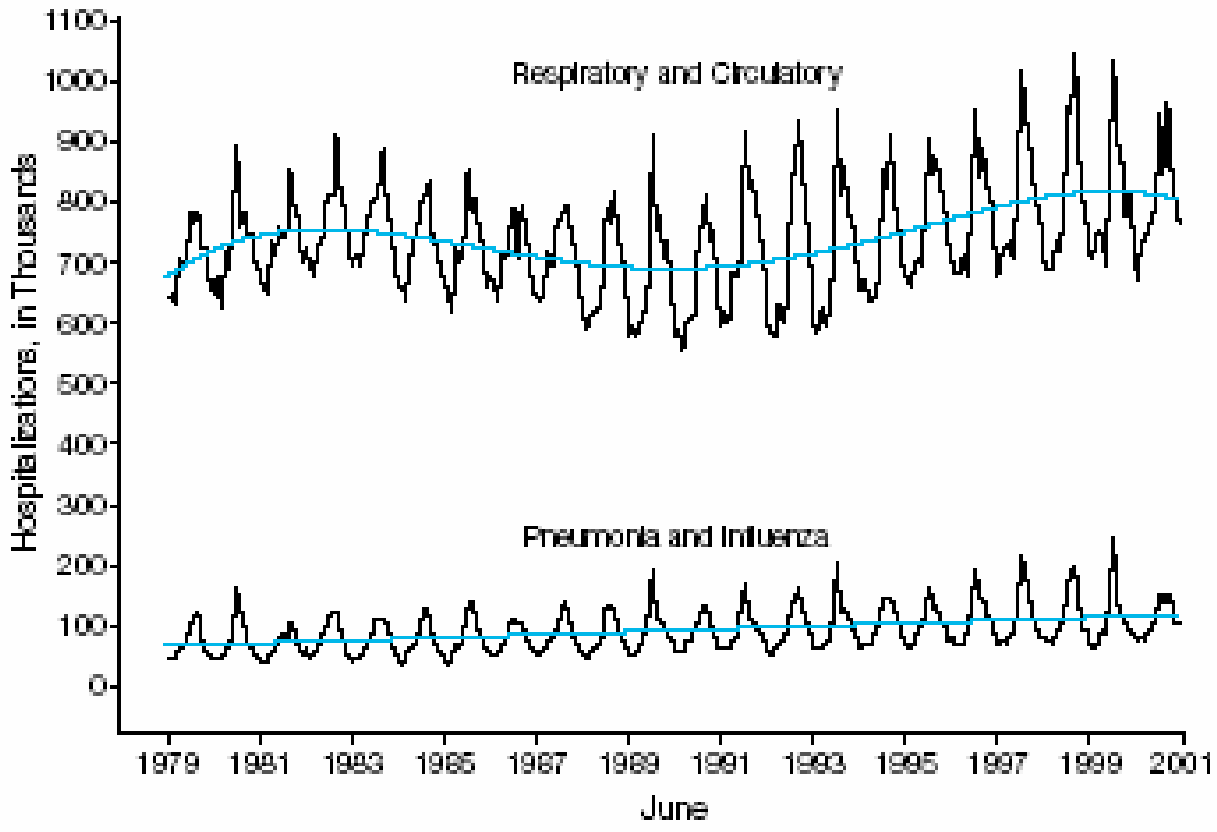
Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. National Center for Health Statistics. *Vital Health Stat*. 1999;10(200).

Influenza Illness:
The Tip of the Iceberg



Influenza Epidemics Cause Seasonal Increases in Hospitalizations

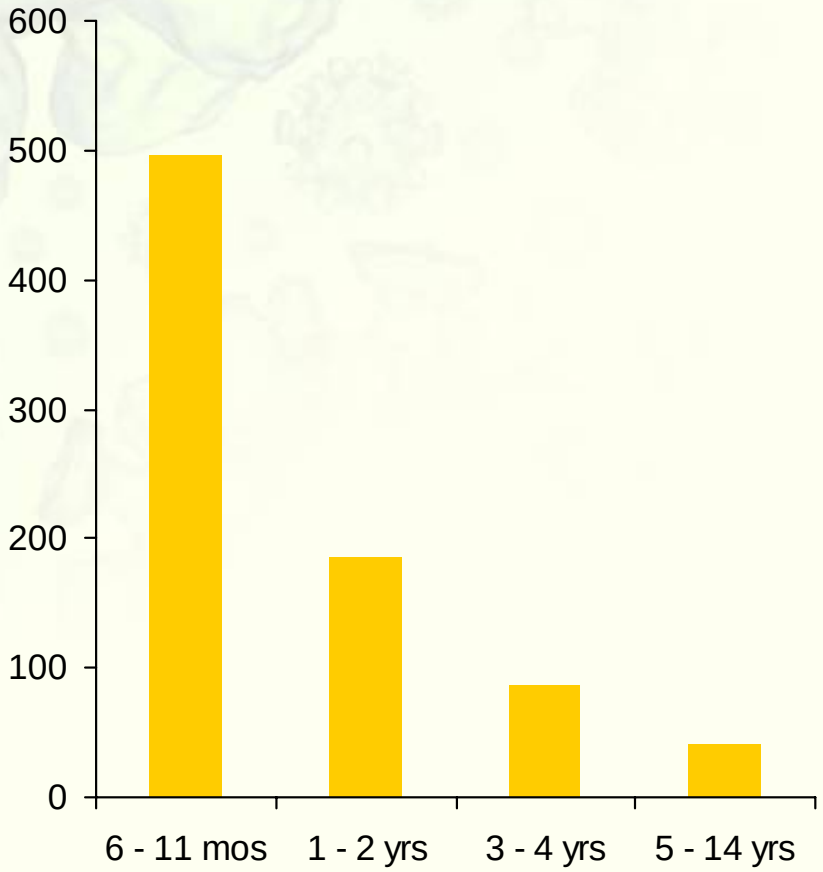
Figure. Monthly Numbers of Hospitalizations by Primary Discharge Type From the 1979-1980 Through 2000-2001 Respiratory Seasons

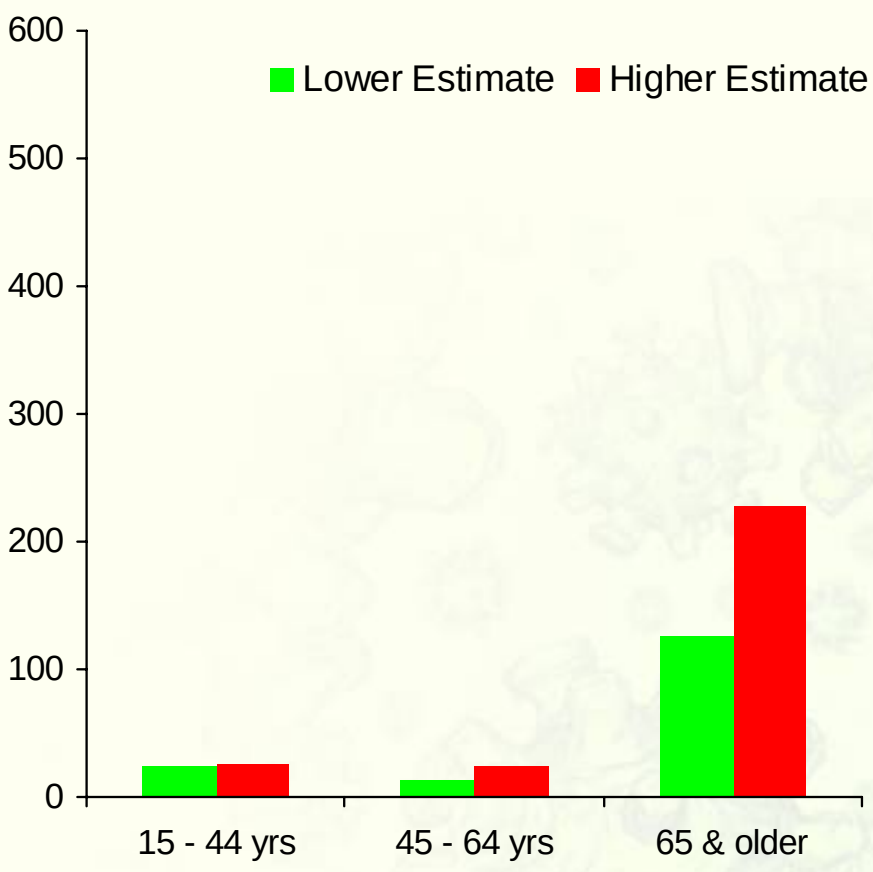


Thompson et al. *JAMA*. 2004;292:1333.

Excess Hospitalizations Are High in Young Children and the Elderly

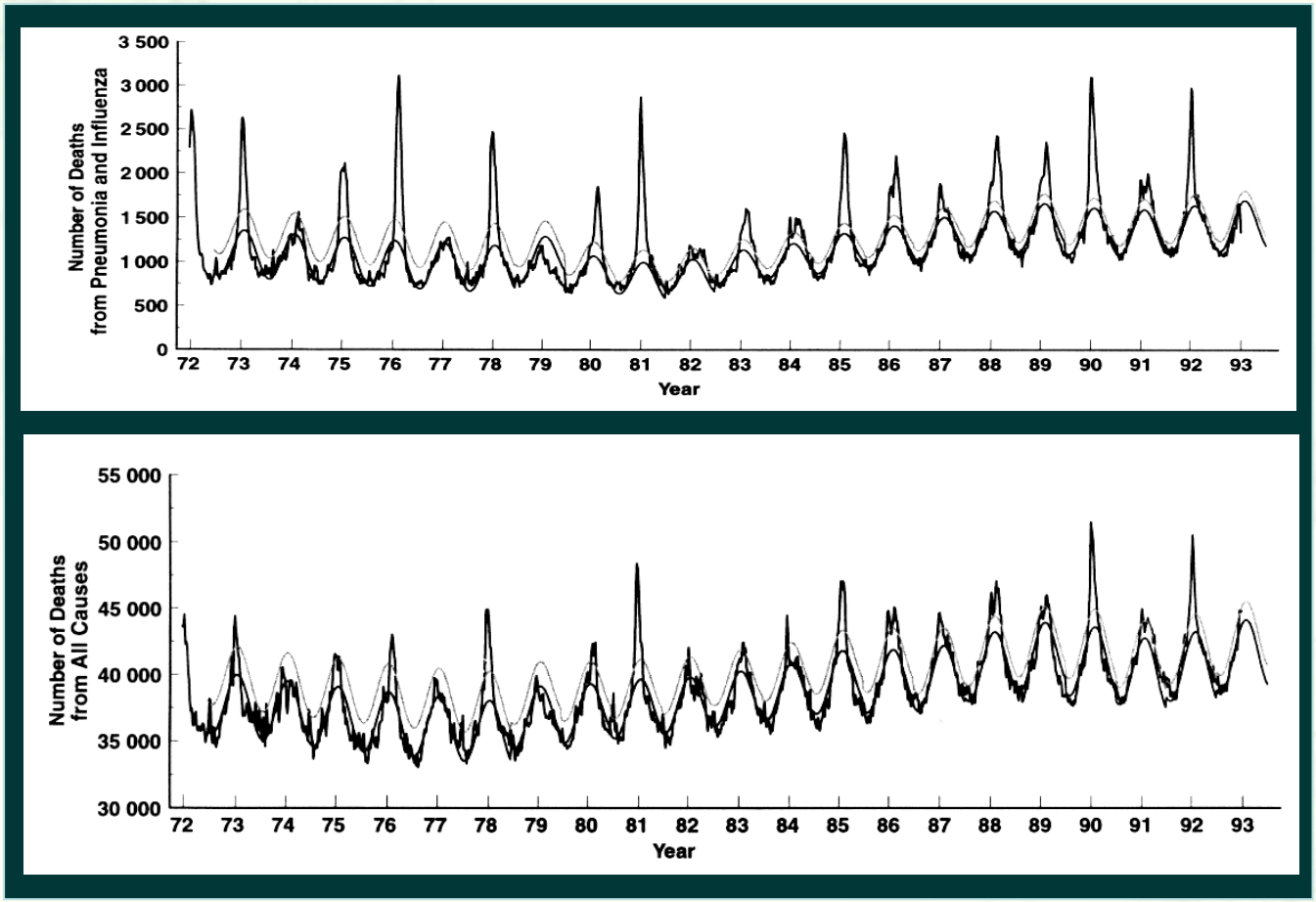
Excess Hospitalizations per 100,000 Healthy Persons





MMWR. 2003; 52 (RR-13).
Neuzil et al. *NEJM*. 2000;342:225.
Barker et al. *Am J Epidemiol*. 1980;112:798.

Influence of Influenza Epidemics on Seasonal Mortality



P & I Mortality

All-Cause Mortality

Simonsen L. *Am J Public Health*. 1997;87:1944.

Influenza Is the #1 Cause of Death Due to Vaccine- Preventable Diseases

Cases & Deaths, US 1989-1998

Disease	Cases	Deaths
Influenza	(millions)	> 500,000
Pneumococcal	(millions)	~ 120,000
Hepatitis A	282,650	1013
Hepatitis B	146,644	9694
Measles	60,189	132
Mumps	24,075	7
Rubella	4412	21
Pertussis	53,634	65
Tetanus	486	77

90% in the elderly

11K from 1989-98 (actual is 5x to 10x higher)

MMWR. 2001;48(RR-53).
Thompson et al. *JAMA*. 2003;289:179.
Feikin DR, et al. *Am J Public Health*. 2000;90:223-9.

Epidemic Influenza Continues to Have a Huge Annual Impact

Estimates for the US

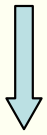
- Cases: 25 – 50+ million cases
- Days of illness: 100 – 200 million days
- Work and school loss: Tens of millions
- Hospitalizations: 85,000 – 550,000+
- Deaths: 34,000* – 51,000**
- Costs: Billions of dollars

\+ Ave respiratory and circulatory = 294,000 1979-80 thru 2000-01
* Ave all-cause, 1976-77 thru 1998-99.
**Ave all-cause 1990-91 thru 1998-99.

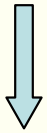
MMWR. 2003;52(RR-8).
Thompson et al. *JAMA*. 2003;289:179.
Thompson et al, *JAMA*. 2004;292:1333.
Adams PF et al. *Vital Health Stat*. 1999;10(200).

Influenza Transmission Within Households

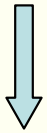
395 Index Cases (flu A pos)



817 Household Contacts



313 (38%) Secondary Cases



178 (57%) w/HC Visit

56% of households had at least 1 secondary case.

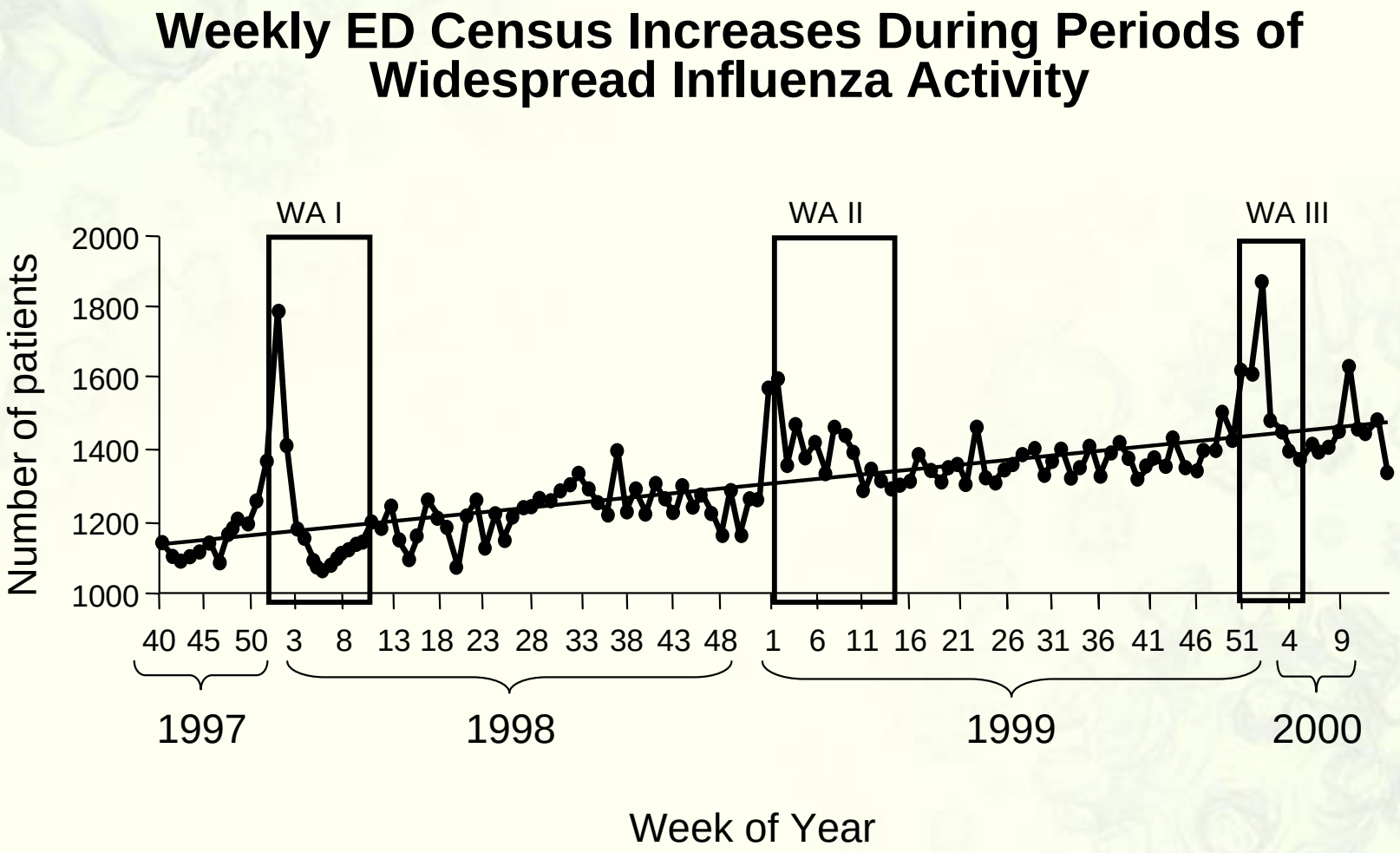
Carrat, et al. *Arch Intern Med*. 2002;162:1842.

Medical Care Capacity for Influenza Outbreaks: Los Angeles

- Setting
  - LA County, 1997-98 season
    - “worst flu epidemic in 2 decades”
- 7 flu seasons: 1991-1998 studied
  - Increasing hours of EMS diversion 1993-94 thru 1997-98
    - Peaks correspond with flu activity
  - Over study time period
    - 12% decrease in bed capacity over 7 seasons
    - 5% increase in population
- Conclusion
  - Influenza causes substantial upsurges in demand for care
  - Healthcare systems may have limited ability to respond

Glaser CA, et al. *Emerg Infect Dis*. 2002;8:569.

Influenza Can Strain the Capacity of the Healthcare System



Silka PA, et al. *Am J Emerg Med*. 2003;21:534.

Nosocomial Influenza Is Well Documented

- Nosocomial outbreaks documented on
  - Solid organ transplant units
  - Oncology units
  - Neonatal ICU
  - Pediatric units
  - LTCFs
  - General medical wards
- Results: morbidity for patients and staff, increased costs for institution
- Vectors for transmission include staff, visitors, patients

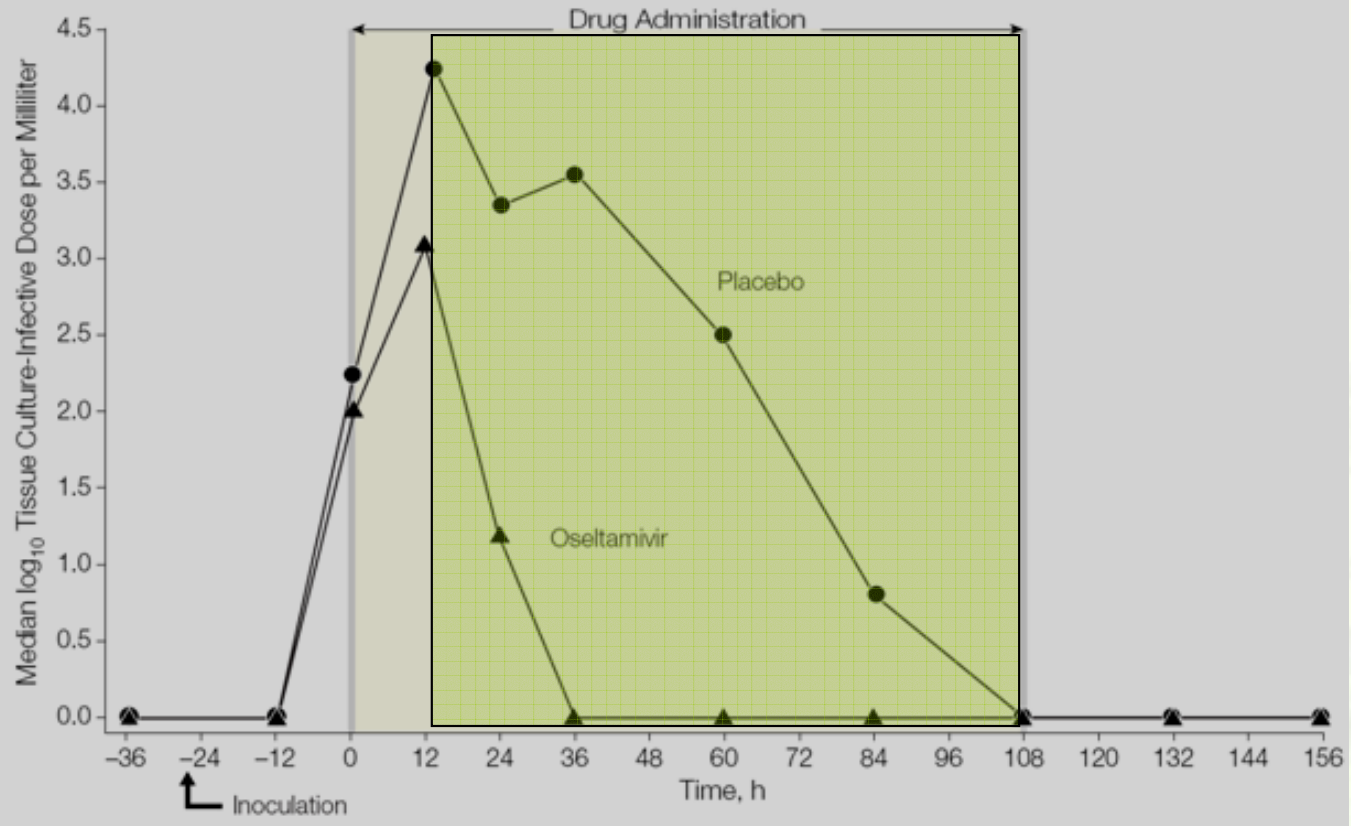
Stott DJ, Carman WF. *Occup Med*. 2002;52:249.

Rationale for Vaccinating Healthcare Workers

- “First, do no harm” – reduce the risk for nosocomial transmission from staff to patient
- Reduce staff absenteeism and preserve healthcare capacity
  - May be cost-saving for the healthcare organization
- Personal benefits to HCWs
- (? Increase awareness and likelihood of HCWs vaccinating patients)
- As of 1/1/2007, JCAHO requires HCW vaccination programs as part of accreditation process

Viral Shedding and Symptoms in Experimental Influenza

Figure 3. Effect of Oral Oseltamivir Treatment on Vital Titers in Nasal Lavages Following Experimental Influenza A/Texas/36/91(H1N1) Infection



The viral titer area under the curve value was lower in the combined oseltamivir group (n = 56) compared with placebo (n = 13); $P = .02$.

Viral Shedding (mean 107 hrs)

Hayden FG et al. *JAMA*. 1999;282:1240.

Disruption of Services in an Internal Medicine Unit Due to a Nosocomial Influenza A Outbreak

- Setting
  - Acute care hospital in Marseille, France
    - Feb/Mar 1999 outbreak of ARI
- Illness rates
  - Index case = patient sharing room with first nosocomial case
  - 41% (9/22) patients and 23% (5/22) staff
    - Vaccination rates were 43% for patients, and 36% for workers (VE of 63%, 95% CI 12%-100%)
- Implications for hospital:
  - 14 days of staff leave, 8 scheduled admits postponed, all emergency admits suspended for 11 days

Sartor C, et al. *Infect Control Hosp Epidemiol*. 2002;23:615.

An Outbreak of Influenza A in a Neonatal ICU

- 19/54 (35%) infants in NICU infected
  - 6 symptomatic cases, 1 death
    - 3/6 ➔ resp distress
- 33% of staff had ILI in preceding 4 months
  - Half had ILI during outbreak, and only 4/14 took off work while ill
- Only 15% of staff had been vaccinated

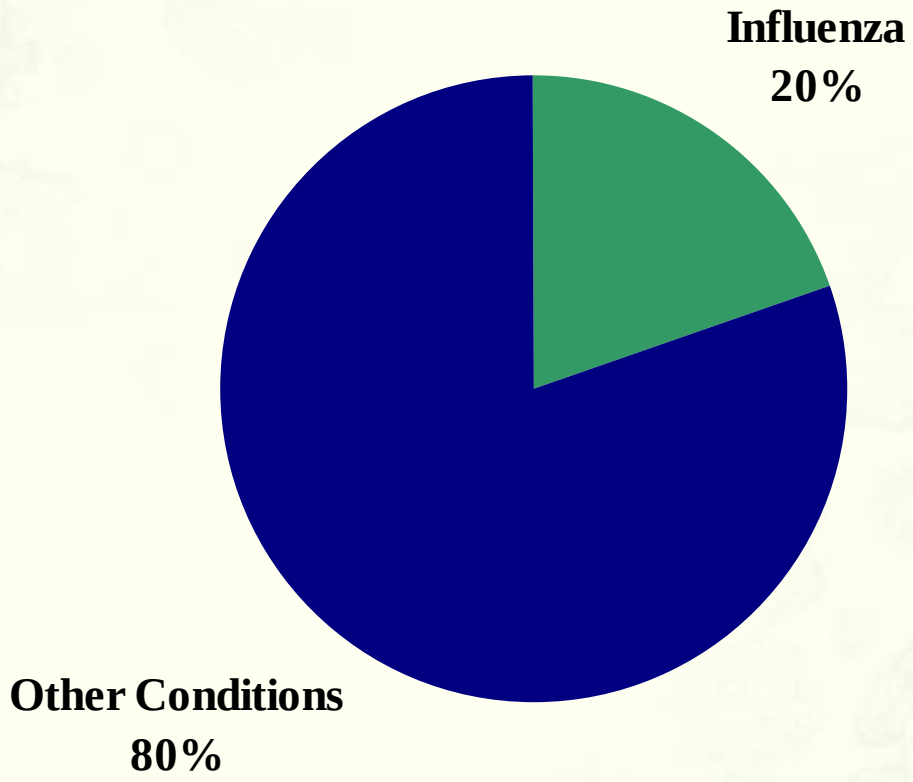
Cunney RJ, et al. *Infect Control Hosp Epidemiol*. 2000;21:449.

Rationale for Targeting the Workplace for Influenza Prevention and Control

- Influenza is a disease that can have a major impact on productivity
  - Influenza is common
  - Influenza is a major cause of
    - Absenteeism
    - Presenteeism
  - Ill workers also spread influenza to others
- Vaccinations at the worksite are consistent with other services provided by employers
  - Highly cost-effective if not cost-saving

Work Loss From Acute Conditions: US Adults Ages 18 to 64, 1996

(Influenza is the #1 Cause)



Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. National Center for Health Statistics. *Vital Health Stat*. 1999;10(200).

Influenza Virus Infection in Travelers to Tropical and Subtropical Countries

- 1450 Swiss travelers (1998-2000)
  - 19.9% had febrile illness during/after travel
    - 12.8% had seroconversion to influenza
  - 2.8% of all travelers had seroconversion (incidence of 1% per travel-month)
    - 62.5% acquired influenza outside of European flu season

Mutsch M et al. *CID*. 2005;40:1282-7.

Influenza and Air Travel

- Influenza outbreak related to air travel
  - Sep 1999: person with ILI boarded 75-seat jet (workers returning to mine in northwestern Australia)
    - Flight lasted 3.3 hours
    - Index case missed 4 days of work
    - Over next 4 days, 15 others developed ILI and saw MD
    - 5 other cases also identified
- Surveillance of influenza viruses isolated from travelers at Nagoya International Airport
  - 504 samples Aug 1996 – Mar 1999: travelers returning with respiratory symptoms
    - 30 influenza viruses isolated
      - 3 outside flu season

Marsden AG. *MJA*. 2003;179:172 [letter].
Sato K et al. *Epidemiol Infect*. 2000;124:507.

Options for Preventing and Controlling Influenza

- Hand hygiene
- Respiratory hygiene/cough etiquette
- Contact avoidance
- Antivirals
- Immunization

Trivalent Inactivated (TIV) and Live Attenuated Influenza Virus (LAIV) Vaccines

Category	TIV	LAIV
Administration & immune response	IM → Serum antibodies	Intranasal → Mucosal immunity
Formulation	Inactivated	Live attenuated
Efficacy children	50%–90%	70%–90%
Efficacy adults <65 y	70%–90%	70%–90%
Safety (side effects)	Sore arm	Runny nose
Growth medium	Chick embryos	Chick cells
Storage	Refrigerated	Frozen (refrigerated formulation now FDA approved)
Indication	≥6 mo (healthy & HR)	5–49 yrs (healthy)

MMWR. 2006;55(RR-10).

ACIP Recommendations: 2005-2006

- High Priority
  - High-risk for serious complications
    - Age 65+
    - Chronic medical conditions
    - ***Conditions that compromise respiratory function or ability to handle secretions***
    - Residents of LTCFs
    - Pregnant women
    - Children/adolescents on chronic ASA Rx
    - Children 6 to 23 months of age
  - Likely to be high-risk (ages 50–64)
  - Persons who can transmit to high-risk groups
    - ***Special emphasis on HCWs***
- Others

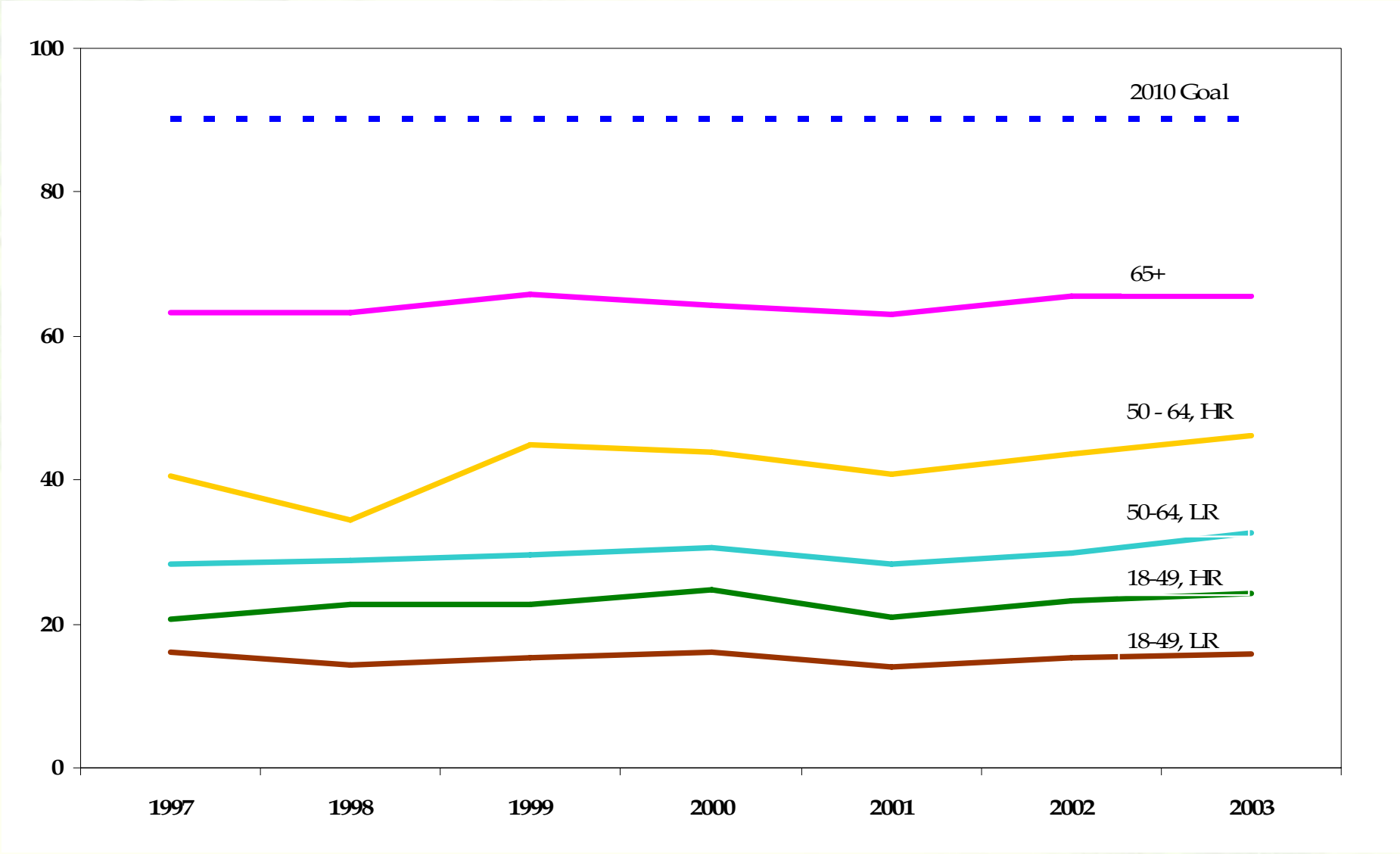
CDC. *MMWR.* 2005;54(RR-8).

What's New in ACIP Influenza Recommendations for 2006-2007

- Strain updates
- Avoid use of amantadine and rimantadine until US susceptibility re-established among circulating viruses
- Avoid tiering unless supply problems
- Routine vaccination of children 24-59 months + household contacts
- Universal vaccination strategy is being evaluated

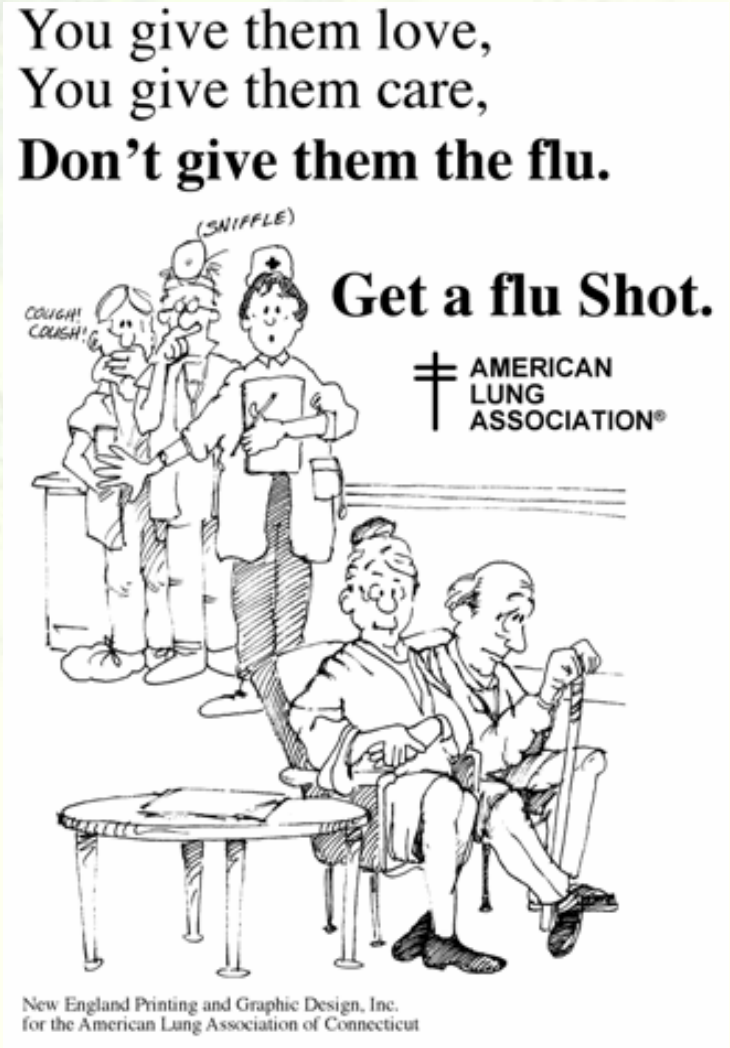
MMWR. July 28, 2006;55(RR10);1-42.

US Influenza Vaccination Rates: 1997-2003 NHIS

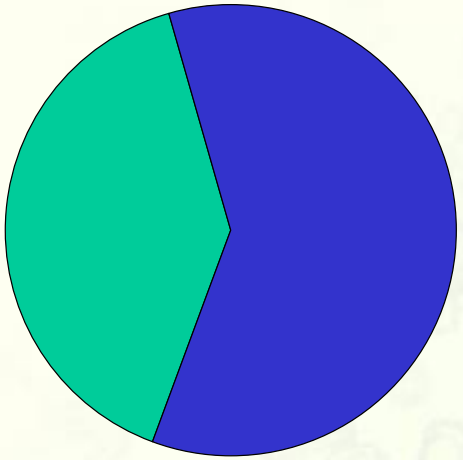


www.cdc.gov/flu/professionals/vaccination [accessed 8/23/06]

Healthcare Workers Should Be Immunized



HCW Influenza Vaccination Rates
NHIS: 2003



Diagnosis of Influenza

- Usually diagnosed clinically
  - PPV of ILI symptoms 30% to ~80% when influenza circulating in community
    - Depending on case definition used
  - Viral shedding persists through day ~5
  - Culture often negative when complications occur
- Lab confirmation important when it will affect treatment decisions
  - Rapid antigen tests
    - Positive tests can confirm influenza
    - Negative tests do not exclude influenza

Presentation of Clinical Influenza Differs by Age Group

Sign/Symptom	Children	Adults	Elderly
Cough (non-productive)	++	++++	+++
Fever	+++	+++	+
Myalgia	+	+	+
Headache	++	++	+
Malaise	+	+	+++
Sore throat	+	++	+
Rhinitis/nasal congestion	++	++	+
Abdominal pain/diarrhea	+	–	+
Nausea/vomiting	++	–	+

++++ Most frequent sign/symptom; + Least frequent; – Not found

Monto AS et al. *Arch Intern Med*. 2000;160:3243-3247.
Cox NJ, Subbarao K. *Lancet*. 1999;354:1277-1282.

Antivirals Complement Vaccination

Agent	Spectrum	Treatment	Prophylaxis
M2 Protein Inhibitors			
Amantadine	A	≥ 1 yr	≥ 1 yr
Rimantadine	A	adults	≥ 1 yr
Neuraminidase Inhibitors			
Zanamivir	A & B	≥ 7 yrs	≥ 5 yrs
Oseltamivir	A & B	≥ 1 yr	≥ 1 yrs

MMWR. 2006;55(RR-10).
http://www.cdc.gov/flu/professionals/treatment

Results of Influenza Treatment With Antiviral Drugs

- The 4 antivirals may have similar effects if used within 48 hours of onset of illness
- Antivirals reduce:
  - influenza symptoms by 1-2 days (all)[1]
  - duration of fever by 1-2 days (oseltamivir)[2,3]
  - antibiotic use by ~30% (zanamivir)[4]
  - acute otitis media by 44% (oseltamivir)[2]
  - secondary disease transmission in families (all)[5-7]

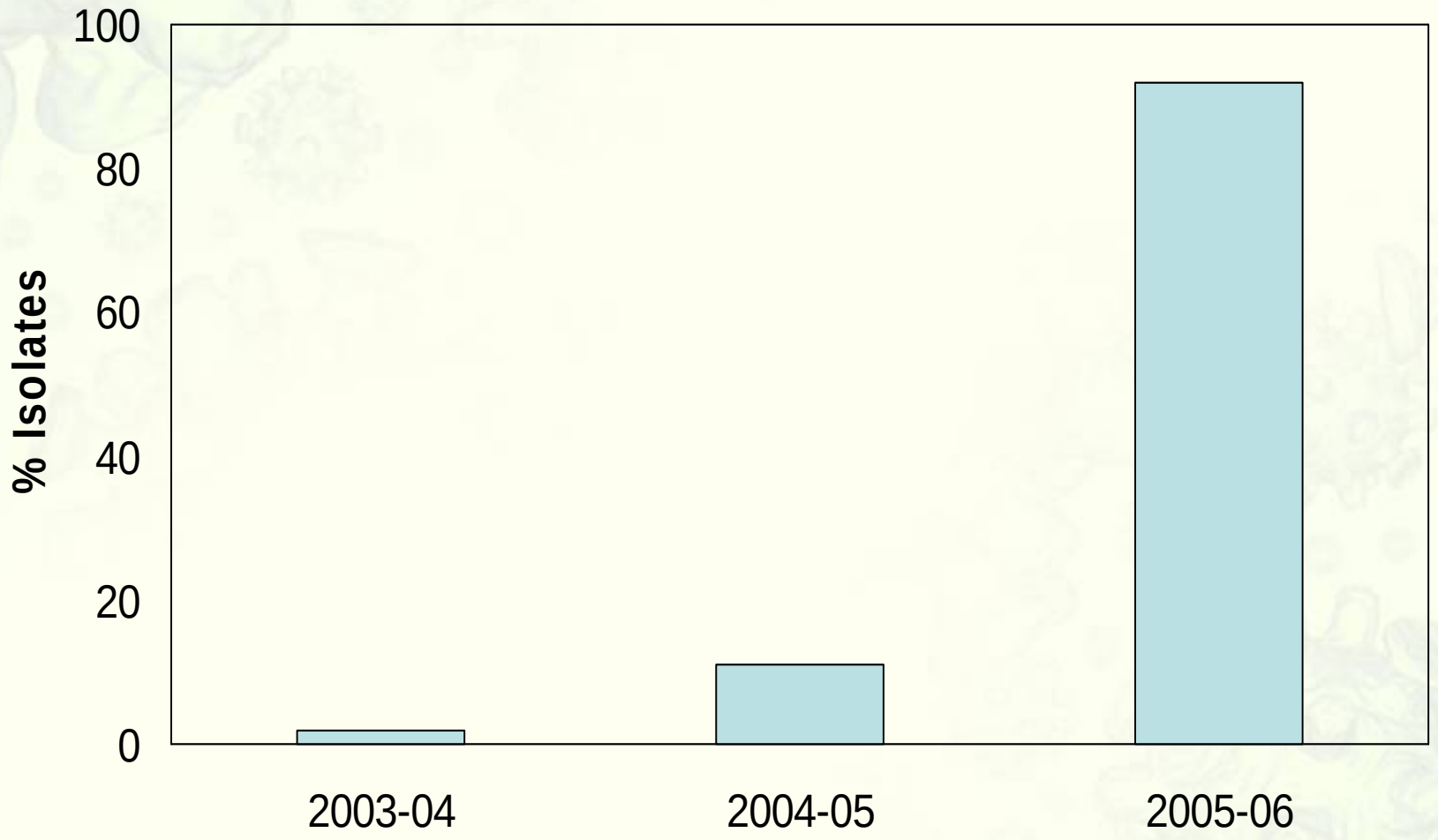
1. Couch RB. *N Engl J Med*. 2000;343:1778-1787.
2. Whitley RJ et al. *Pediatr Infect Dis J*. 2001;20:127-133.
3. Treanor JJ et al. *JAMA*. 2000;283:1016-1024.
4. Kaiser L et al. *Arch Intern Med*. 2000;160:3234-3240.
5. Couch RB et al. *J Infect Dis*. 1986;153:431-440.
6. Welliver R et al. *JAMA*. 2001;285:748-754.
7. Hayden FG et al. *N Engl J Med*. 2000;343:1282-1289.

Indications for Antiviral Prophylaxis

- Adjunct to vaccination of high-risk persons
- Unvaccinated persons caring for high-risk persons
- Immunodeficient persons (poor response to vaccine expected)
- Persons with contraindications to influenza vaccine (eg, severe egg allergy)
- Others if desired to prevent disease

MMWR. July 28, 2006;55(RR10);1-42.

Amantadine Resistance in the US



MMWR. July 28, 2006;55(RR10);1-42.

Conclusions

- Epidemiology and Disease Burden
  - Influenza is a common, miserable, and often serious illness
- Impact on specific settings
  - Influenza has a substantial impact in the workplace and in healthcare settings
- Options for prevention and control
  - Vaccination
    - Vaccination is the mainstay for influenza prevention and control
  - Antivirals
    - Important, complementary role for preventing and treating influenza

Internet Resources

- CDC's National Immunization Program
  - www.cdc.gov/nip
- CMS
  - www.cms.hhs.gov
- Immunization Action Coalition
  - www.immunize.org