



Pandemic Influenza – Where Are We??

W. Paul Glezen, MD
Department of Pediatrics
Baylor College of Medicine, Houston, TX

Goals

- Recognize that the occurrence of influenza pandemics is chaotic
- Learn the origin of influenza pandemics
- Follow the evolution of the 1968 A(H3N2) pandemic
- Recognize that the failure to control inter-pandemic influenza handicaps ability to confront a new pandemic
- Consider new strategies for influenza control






















Pandemic Influenza: The Pattern of Occurrence Is Chaotic

- It is not possible to predict the time of occurrence
- All pandemics are caused by influenza A viruses
- Influenza A viruses are basically avian viruses that mutate or reassort in nature to allow facile human-to-human transmission

Three Pandemics in the 20th Century

- 1918 – A(H1N1)
 - The most severe pandemic recorded in history
 - High mortality in young adults
 - (W-shaped)
- 1957 – A(H2N2)
 - Toll was 1/10th that of 1918
 - (U-shaped)
- 1968 – A(H3N2)
 - Toll was 1/20th that of 1918
 - (U-shaped)

Hemagglutinin Subtypes of Influenza A Virus

Subtype	Human	Swine	Horse	Bird
H1				
H2				
H3				
H4				
H5				
H6				
H7				
H8				
H9				
H10				
H11				
H12				
H13				
H14				
H15				

Adapted with permission from Levine AJ. *Viruses*. 1992;165.

Origin of 20th Century Pandemic Strains*

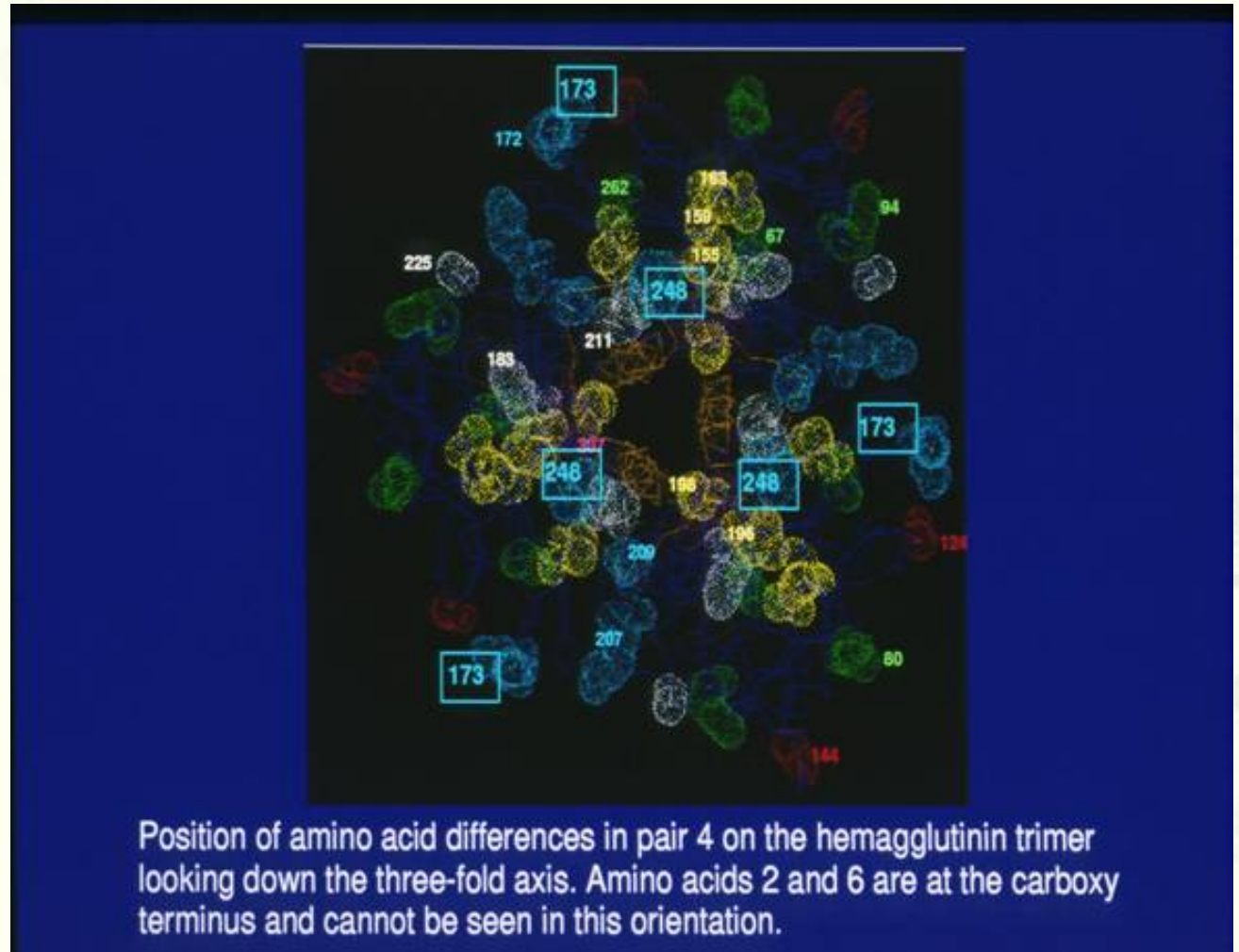
GENE SEGMENT	YEAR		
	1968	1957	1918
PB1	<i>Avian</i>	<i>Avian</i>	<i>Avian</i>
PB2	Human	Human	<i>Avian</i>
PA	Human	Human	<i>Avian</i>
HA	<i>Avian</i>	<i>Avian</i>	<i>Avian</i>
NA	Human	<i>Avian</i>	<i>Avian</i>
NP	Human	Human	<i>Avian</i>
M	Human	Human	<i>Avian</i>
NS	Human	Human	<i>Avian</i>

*1968 and 1957 viruses were reassortants of human and avian strains.

The 1918 virus was an avian strain that mutated to allow human-to-human transmission.

Antigenic Variants of Influenza A (H3N2) and Changing Hemagglutinin Amino Acid Positions

<u>Year</u>	<u>Variant</u>
1968-72	A/Hong Kong/68
1972-73	A/England/72
1974-75	A/Port Chalmers/73
1975-76	A/Victoria/75
1977-78	A/Texas/77
1980-83	A/Bangkok/79
1984-85	A/Philippines/73
1985-86	A/Stockholm/85
1987-88	A/Sichuan/87
1989-90	A/Shanghai/87
1991-92	A/Beijing/89
1993-94	A/Beijing/92
1994-95	A/Shangdong/93
1995-96	A/Johannesburg/94
1996-97	A/Wuhan/95
1997-00	A/Sydney/97
2001-02	A/Panama/99
2003-04	A/Fujian/02
2004-05	A/California/04
2005-06	A/Wisconsin/05



Estimated Annual Influenza-Associated Deaths for 1990-1991 Through 1998-1999 Seasons Using the Influenza Model

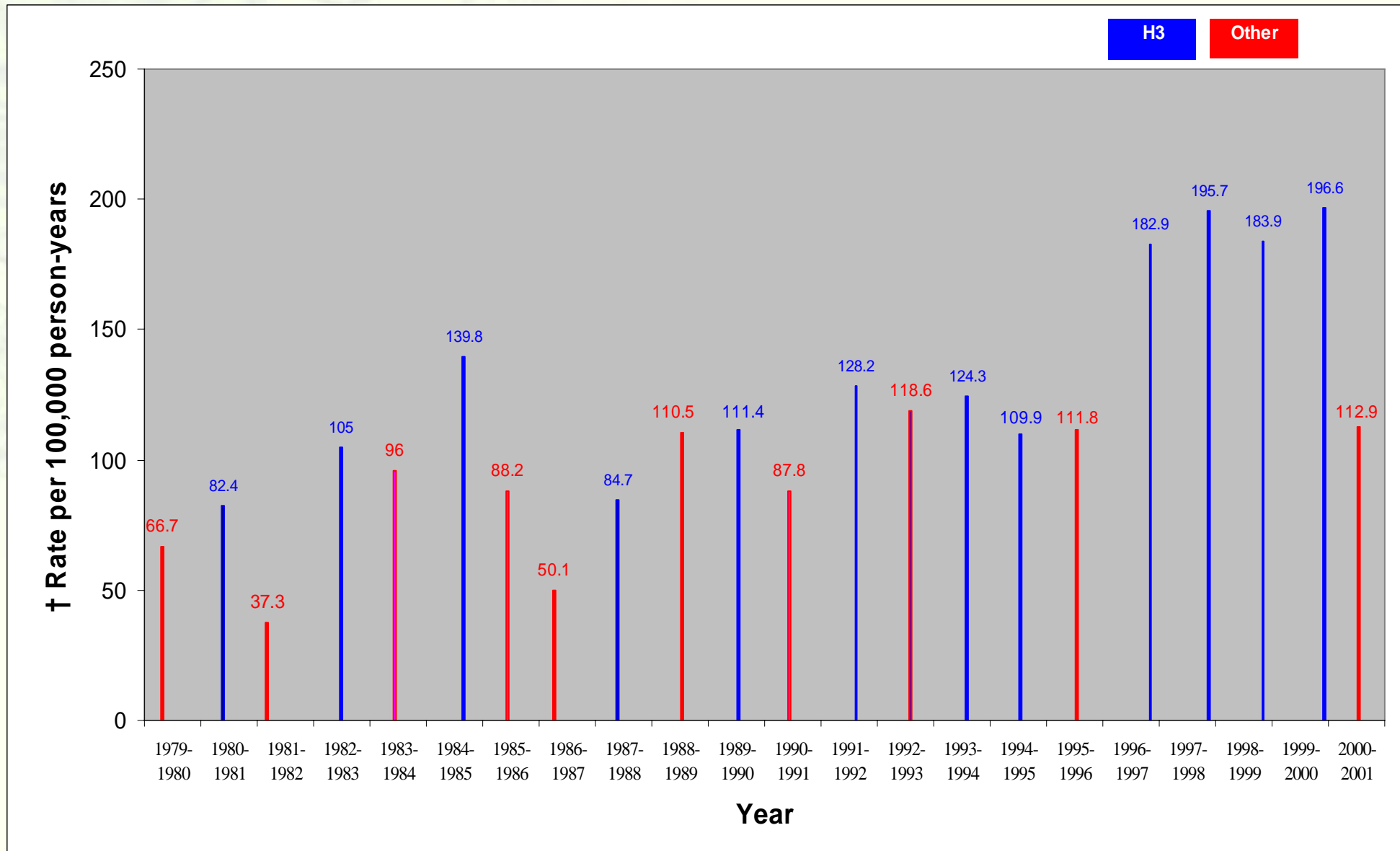
All-Cause Deaths

Season	No. of Influenza Deaths			
	A(H1N1)	A(H3N2)	B	Total
1990-1991	1,988	6,033	17,549	25,570
1991-1992	6,518	45,928	566	53,012
1992-1993	1,190	19,892	19,030	40,112
1993-1994	173	48,923	404	49,500
1994-1995	572	33,767	7,129	41,468
1995-1996	14,727	23,605	7,509	45,841
1996-1997	0	55,937	12,609	68,546
1997-1998	66	70,701	649	71,416
1998-1999	293	55,367	9,698	65,358
Mean (SD)	2,836 (4,909)	40,017 (20,656)	8,349 (7,105)	51,203 (15,081)

Abbreviations: NA, not applicable.

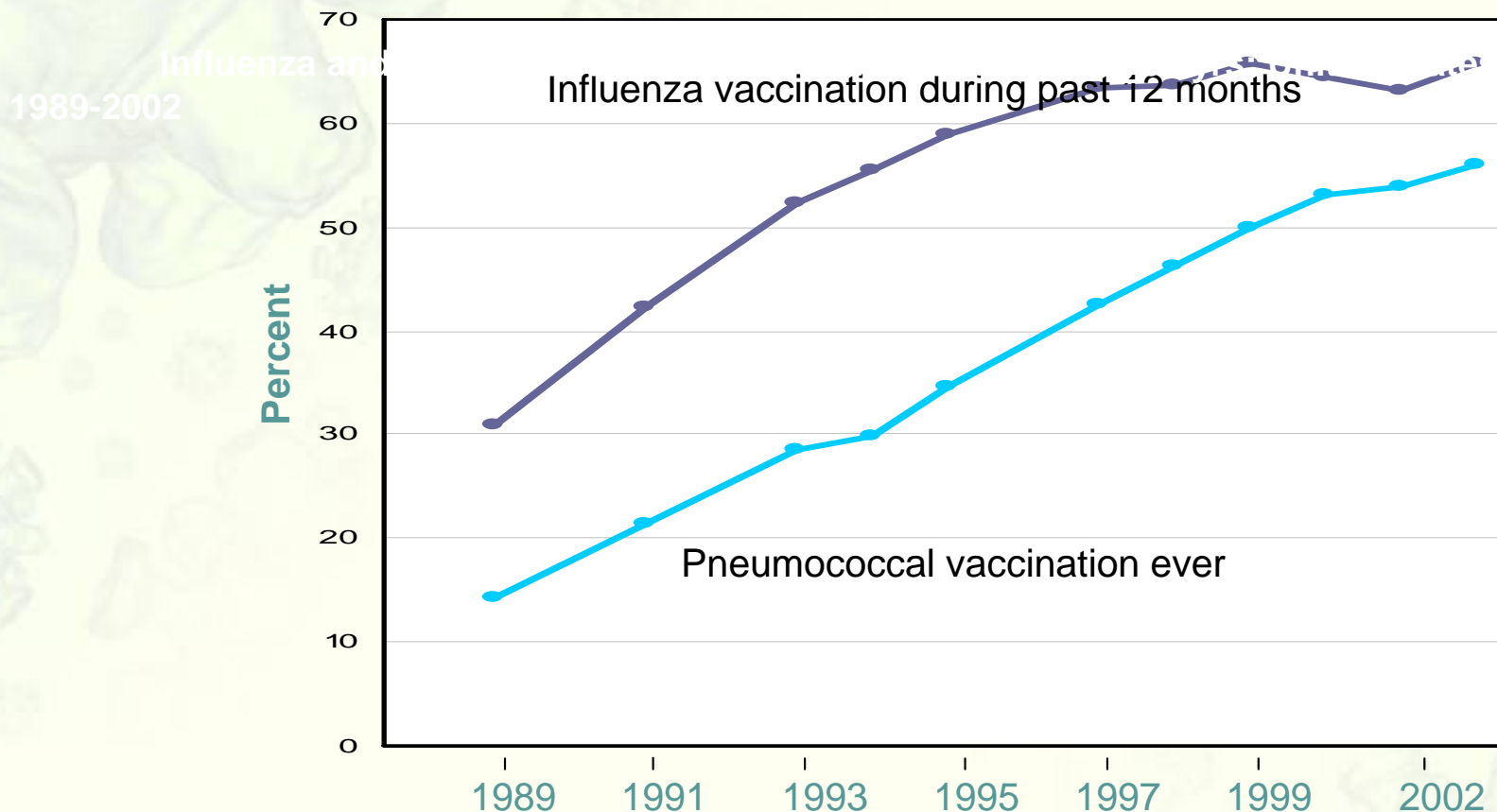
*Pneumonia and influenza estimates are based on the 1990-1991 through 1997-1998 seasons.

Annual Rates of Influenza-Associated Hospitalizations in the US†



Thompson et al. *JAMA*. September 15, 2004;292:11:1337.

Influenza and Pneumococcal Vaccination Among Adults ≥ 65 Years: United States, 1989-2002

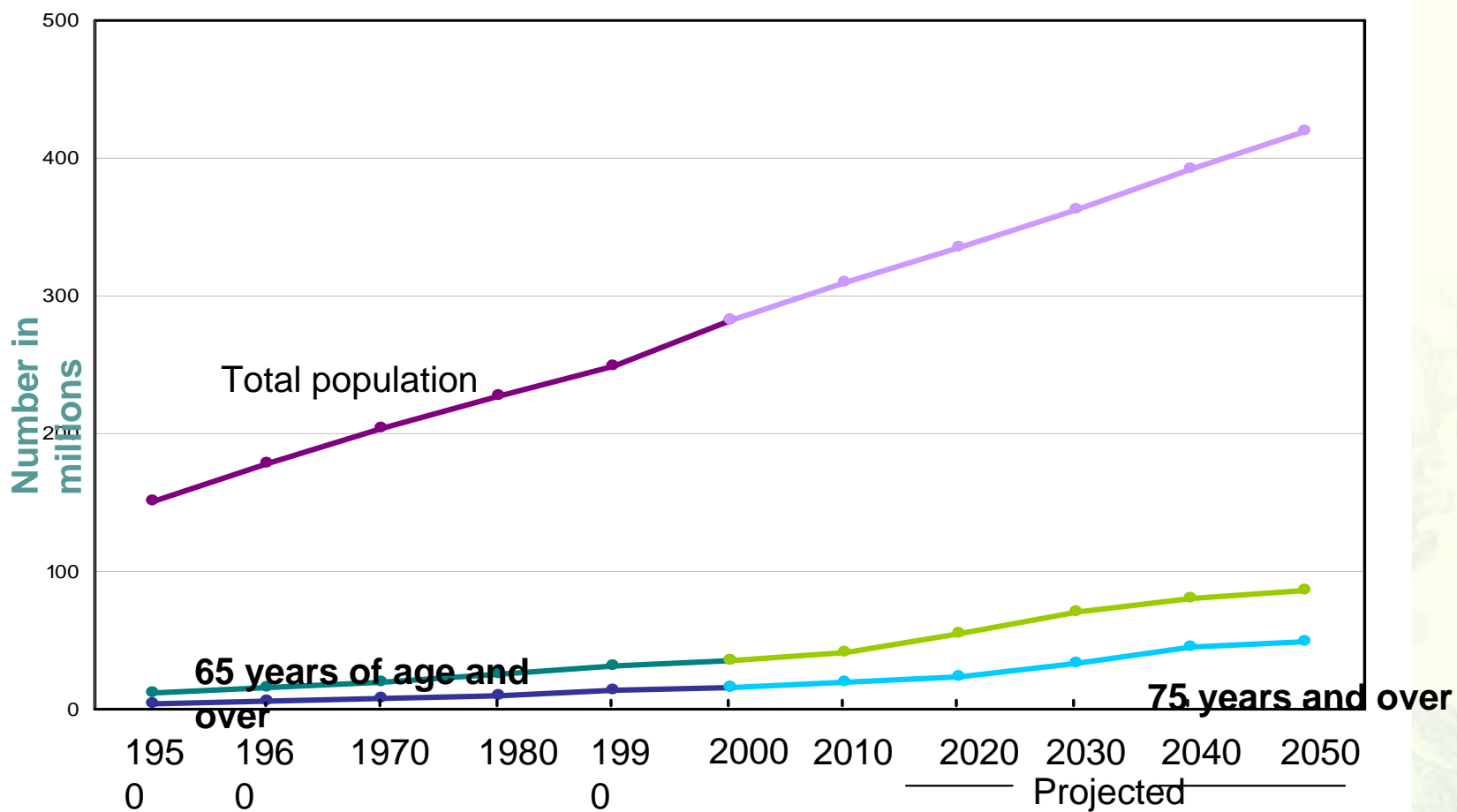


NOTE: Data are for the civilian noninstitutionalized population and are age adjusted. See Data Table for data points graphed and additional notes.

Year
SOURCES: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey.

Centers for Disease Control and Prevention, National Center for Health Statistics. *Health, United States, 2004.*

Total Population – Population >65 Years, and >75 Years: United States, 1950-2050



NOTE: See Data Table for data points graphed and additional notes.

Year

SOURCES: US Census Bureau, 1950-2000 decennial censuses, and 2010-50 interim population projections.

Centers for Disease Control and Prevention, National Center for Health Statistics. *Health, United States, 2004.*

Problems With Targeting High-Risk Patients

- High-risk patients are not easily accessible for vaccination
- Many high-risk patients are debilitated or immunocompromised and fail to respond optimally to vaccine

Herd Protection Against Influenza

“...it is apparent that progress in the control of influenza has not been impressive.

A reassessment of the basic assumptions upon which the program was developed is warranted.”

Risk-Based Strategies Have Failed

Universal recommendations generally are more successful

eg: age >65 years; 6-23 months – Ontario program

The most vulnerable persons – elderly and infants – have poor immune responses to vaccines and are at the end of the transmission chain = inefficient use of vaccine.

School Children, Preschool Children, and Working Adults Have the:

- Highest attack rates for influenza
- Are the spreaders in the community
- Introducers into the household
- Most accessible for rapid deployment of vaccine

Influenza Vaccines Generate Optimal Immune Responses in Healthy School Children and Working Adults

- Immunization of these groups has the potential for establishing indirect protection of the vulnerable [HERD IMMUNITY or HERD PROTECTION] = efficient use of influenza vaccine

Examples of Herd Protection by Currently Used Vaccines

- Rubella vaccine – infant immunization protects pregnant women
- Haemophilus influenzae type b (Hib) vaccines – in The Gambia¹
- Pneumococcal conjugate vaccine (7-valent) – in infants²; in adults^{3,4,5}
- Hepatitis A vaccine – in US adults⁶; in Israel⁷

1. Adegbola et al. *Lancet*. 2005;366:144.

2. Poehling et al. *JAMA*. 2006;295:1668.

3. Metlay et al. *Vaccine*. 2006; 24:468.

4. Hammitt et al. *JID*. 2006;193:1487.

5. Flannery et al. *Ann Int Med*. 2006;144:1-9.

6. Wasley et al. *JAMA*. 2005;294:194.

7. Dagan et al. *JAMA*. 2005;294:202.

Herd Protection by Influenza Vaccines

- Tecumseh MI study¹– 67% reduction in adult illness rates by single dose of TIV in school children
- Northern Territory, Australia²– reduction in attack rate in communities with variable vaccine coverage compared to those with no vaccine
- Novgorod, Russia school children study³– reduction in attack rate in staff where LAIV given to students
- San Diego⁴– TIV for daycare toddlers reduced ILI in older siblings and parents
- Moscow, Russia⁵– TIV in 57% of preschool and 72% of school children reduced illness and complications in unvaccinated, non-institutionalized adults

1. Monto et al. *Bull WHO*. 1969;41:537.

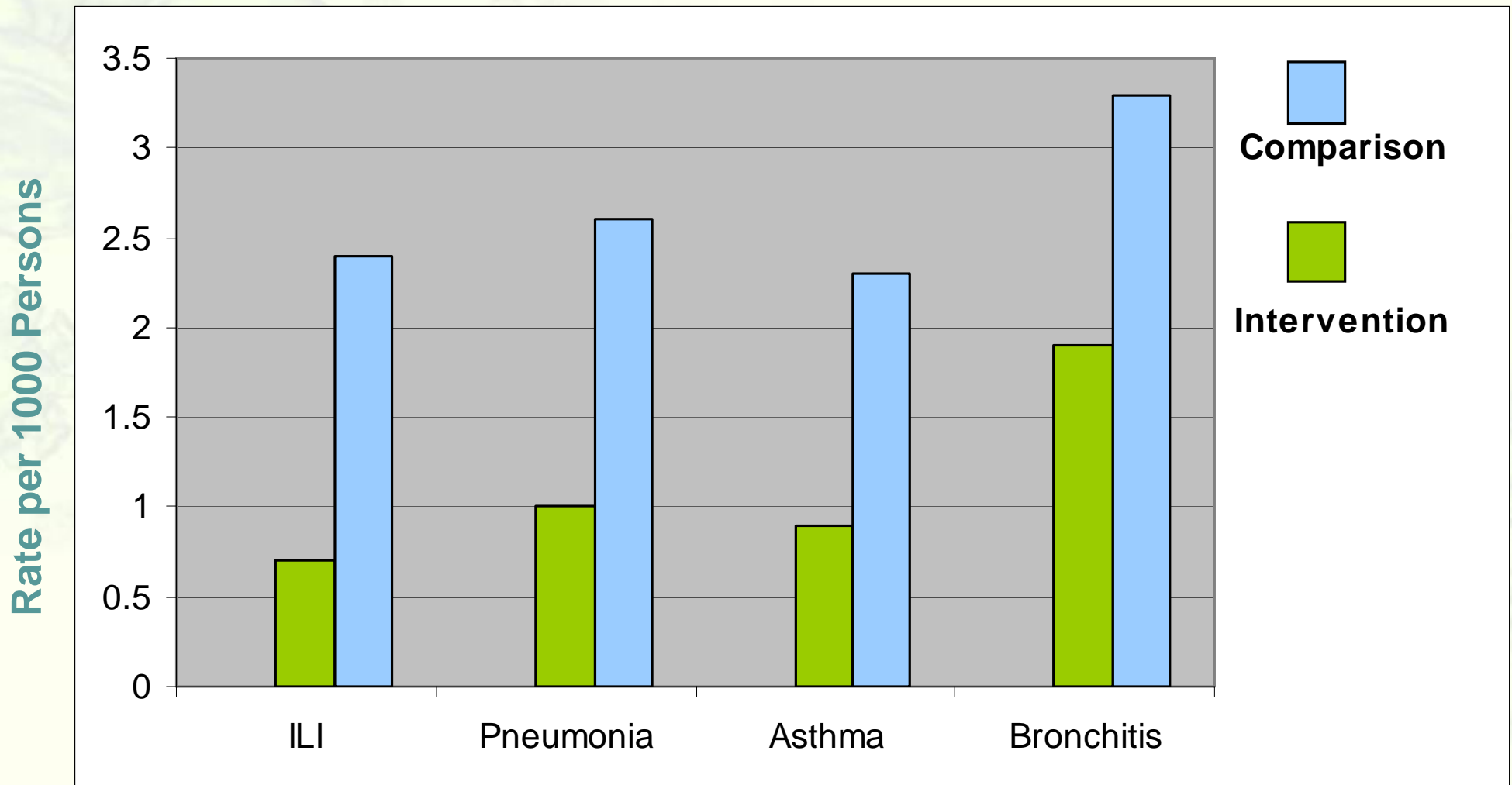
2. Warburton et al. *Med J Aust*. 1972;2:67.

3. Rudenko et al. *J Infect Dis*. 1993;168:881.

4. Hurwitz et al. *JAMA*. 2000;284:1677.

5. Ghendon et al. *Epidemiol Infect*. 2006;134:71.

Herd Protection of Elderly by Mass Influenza Immunization of Children: Moscow, 2001-2002



Clinical Effectiveness of Influenza Vaccine: Moscow, 2001-2002

Direct protection

	# children	# vaccinated	% efficacy
Kindergarten	6,374	3,659 (57.4%)	60.9
School aged	34,237	24,651 (72%)	68.8
<hr/>			
Total	40,611	26,275 (64.7%)	63.7

Indirect (herd) protection

Achieved with only 28,310 vaccine doses – sufficient for 34.5% of 82,051 persons >60 years of age.

Herd Protection – Proof of Concept

- In Japan from 1977 to 1987 influenza vaccine was mandatory for school attendance
 - 2 doses of inactivated vaccine/year
 - Vaccine not recommended for elderly/high-risk
- School program reduced influenza-related excess mortality by 35,000 to 47,000 lives/year

Herd Protection – Proof of Concept (cont'd)

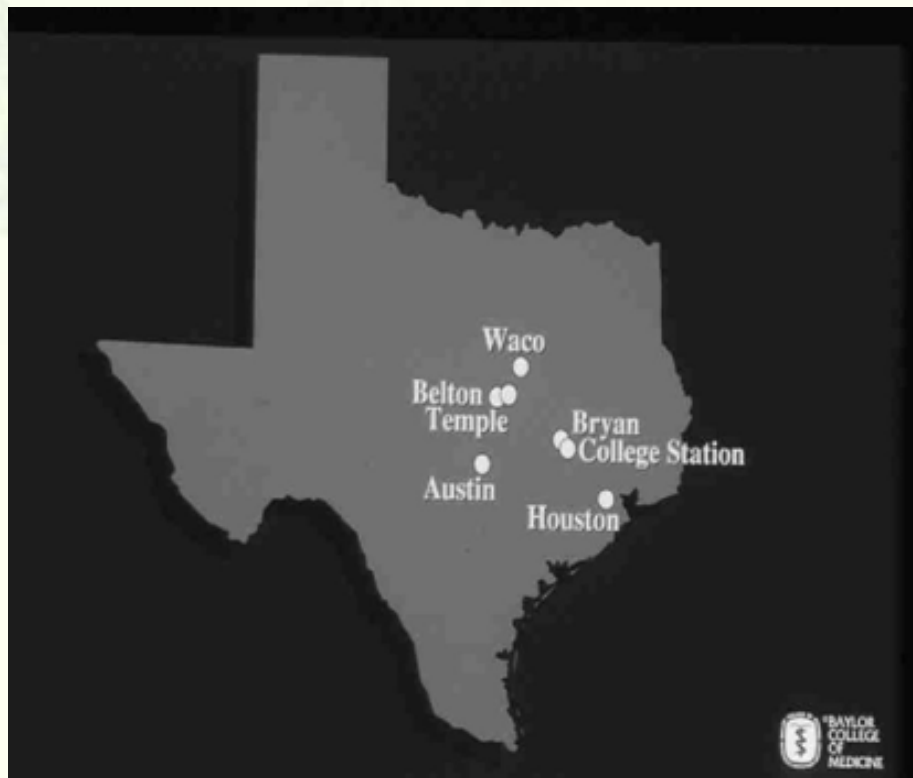
- Summertime baseline mortality trends for Japan very different than wintertime excess mortality
- Thus, herd immunity not due exclusively to economic recovery of Japan after WWII

Control of Epidemic Influenza: Objectives

- The primary objective is to determine the proportion of vaccinated school-age children needed to effect herd immunity (indirect effectiveness) against influenza
- The secondary objectives are to assess the direct effectiveness and safety of LAIV

Control of Epidemic Influenza: Study Design

- An open-label, non-randomized, community-based trial of annual influenza immunization of school-age children to effect herd immunity



MAARI Rates in the Intervention and Comparison Sites During Influenza Outbreaks for SWHP Members >35 Years Old

Year	MAARI rates per 100 person-season		Overall effectiveness (1-RR)	95% CI
	Intervention site: T-B	Comparison site: W/B-CS		
1997-98; baseline	9.3	9.2	0	-0.03-0.05
1998-99; Year 1	12.0	13.1	0.08	0.04-0.13
1999-00; Year 2	12.2	15.0	0.18	0.14-0.22
2000-01; Year 3	15.1	17.8	0.15	0.12-0.19

CAIV-T Direct Effectiveness for all MAARI and Adjusted Efficacy for Culture-Positive MAARI With Both Influenza A(H1N1) and B: Temple-Belton, TX, 2000-2001

Age (years)	Direct (95% CI) Effectiveness	Adjusted (95% CI) Efficacy
1.5-4	0.20* (0.14,0.25)	0.91 (-0.34,0.99)
5-9	0.25 (0.15,0.34)	0.80 (0.26,0.95)
10-18	0.14 (0.01, 0.26)	0.70 (0.13,0.90)
Total	0.18 (0.11,0.24)	0.79 (0.51,0.91)
Subsets	Influenza A(H1N1)	0.92 (0.42,0.99)
	Influenza B	0.66 (0.09,0.87)

*Statistically significant results are in bold

Direct Effectiveness of LAIV Against MAARI for Year 2-Only Groups Compared With Age-Eligible Non-recipients From the Intervention Communities*, 2000-2001

Age Group	No. of Subjects	No. of MAARI Events	No. of Child-Days	MAARI Rate 10,000 Child-Days	Direct Effectiveness (95%, CI), %
LAIV			Year 2-Only Group		
2.5-4 yrs					
Yes	122	71	10,248	69.3	29(10 to 45)
No	1181	972	99,204	98.0	
5-9 yrs					
Yes	182	71	15,288	46.4	24(4 to 42)
No	2232	1156	187,488	61.7	
10-18 yrs					
Yes	312	75	26,208	28.6	11(-12 to 31)
No	5249	1421	440,916	32.2	
Total					22(11 to 32)

Effectiveness Measures for Working Adults Given Live Attenuated Influenza Vaccine (LAIV) or Trivalent Inactivated Influenza Vaccine (TIV) Before the Influenza A/Sydney(H3N2) Epidemics of 1997-1998 and 1998-1999

	% Reduction		
	LAIV*	TIV*	TIV+
	1997-98		1998-99
Flu-like	24	-0-	34
Days ill	23	-0-	34
Days lost	28	-0-	32
MD visits	41	-0-	42
*A/Wuhan(H3N2) in Vaccine		+A/Sydney(H3N2) in vaccine	

Nichol et al. *JAMA*. 1999;282:137-144.

Bridges et al. *JAMA*. 2000;284:1655-1663.

Table 4. Relative Risk of MAARI 0 to 14, and 15 to 42 Days After LAIV-T

Vaccine Year	Age groups	Pre-vaccination rate (reference) per 10,000 child-days	Relative Risk - post-vaccination/ pre-vaccination period (95%CI)	
			0-14 days post-vaccination	15-42 days post-vaccination
1 1998-99	18 mo - 4 yrs	68.5	0.85 (0.61-1.19)	0.86 (0.62-1.16)
	5 - 9 yrs	35.5	0.74 (0.50-1.09)	0.97 (0.71-1.33)
	10 - 18 yrs	21.4	1.04 (0.64-1.67)	1.10 (0.72-1.68)
2 1999-00	18 mo - 4 yrs	94.2	0.72 (0.54-0.96)	1.03 (0.80-1.33)
	5 - 9 yrs	45.9	1.18 (0.89-1.58)	1.09 (0.81-1.45)
	10 - 18 yrs	25.5	0.88 (0.59-1.33)	1.20 (0.84-1.70)
3 2000-01	18 mo - 4 yrs	104.6	0.72 (0.53-0.99)	1.02 (0.72-1.44)
	5 - 9 yrs	54.2	0.73 (0.52-1.02)	0.71 (0.49-1.05)
	10 - 18 yrs	29.3	0.73 (0.47-1.13)	0.97 (0.59-1.59)
4 2001-02	18 mo - 4 yrs	69.4	0.82 (0.55-1.24)	0.70 (0.45-1.09)
	5 - 9 yrs	50.1	0.62 (0.40-0.98)	0.82 (0.53-1.27)
	10 - 18 yrs	15.6	1.22 (0.67-2.24)	1.26 (0.67-2.37)

CAIV-T FIELD TRIAL Summary

1. Safe side effects do not increase direct medical costs
2. Direct Effectiveness
 - Protection inversely related to age (VE_{adj} 0.70-0.91)
 - Persists through 2 seasons
 - Heterovariant
 - Single dose is sufficient
 - Protection is effective soon after given
3. Indirect Effectiveness (Herd Immunity) – For proportion vaccinated compatible with Longini Model

U.S. WHO/NREVSS Collaborating Laboratories Summary, 2005-06

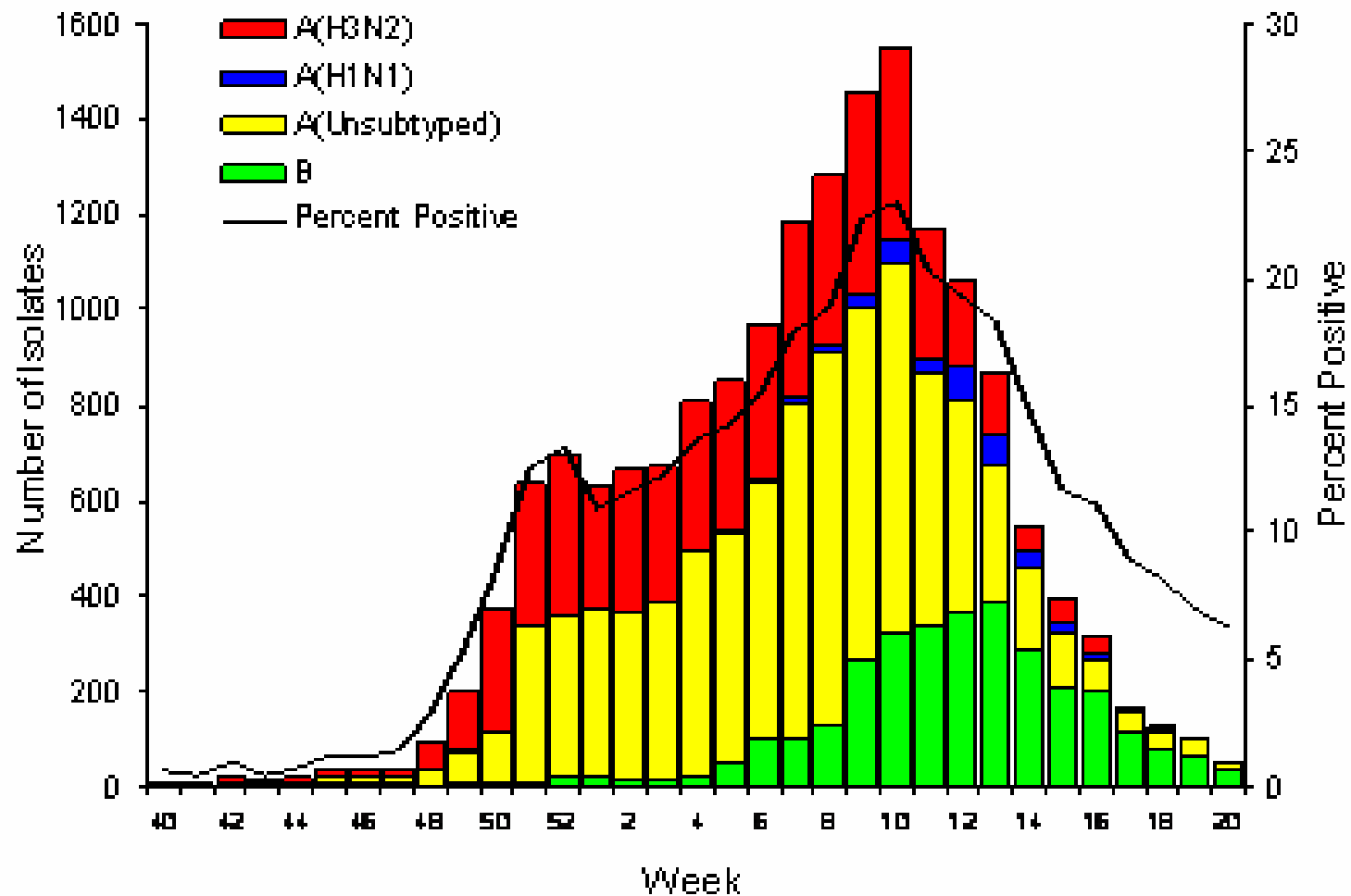


Table 3

**Influenza Antiviral Medications for Treatment and Prophylaxis
ACIP[†]**

Antiviral agent	Type of inhibition	Route of administration	Comments
Amantadine	M2 – A only	oral	Not used 2005-06
Rimantadine	M2 – A only	oral	Not used 2005-06
Oseltamivir	Neuraminidase	oral	Both A and B
Zanamivir	Neuraminidase	inhalation*	Both A and B

*** may be irritating to airways of persons with RAD; suggest close monitoring with short acting bronchodilators available**

Conclusions

1. Current ACIP recommendations give influenza immunization priority to 218 million people (72.7% of US population) including:
 - Children 6 – 59 months
 - Adults > 50 years
 - High-risk 5 – 49 years of age
 - Pregnant women
 - Healthcare workers/caretakers
 - Household contacts of children <5 years and all high-risk
2. The infrastructure does not exist to accomplish this
3. A practical complementary strategy is to utilize school-based and workplace-based clinics to systematically immunize all school children and working adults annually
4. This would provide time to access elderly and high-risk

Conclusions (cont'd)

5. Viral surveillance must be improved to facilitate efficient use of antivirals
6. Effective inter-pandemic control will increase demand for vaccines and antivirals to assure supplies and establish infrastructure for effective utilization of both during the pandemic