United States Department of
Health & Human Services

Pandemic Influenza Preparedness: Focus on Pandemic Vaccines

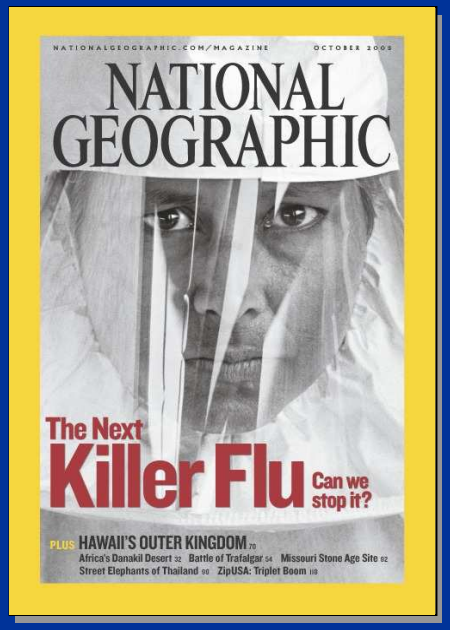
North Carolina Institute of Medicine

July 31, 2006

Bruce Gellin, MD, MPH

Director, National Vaccine Program Office

Department of Health and Human Services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The Next
Killer Flu
Can we stop it?
PLUS HAWAII'S OUTER KINGDOM 70
Africa's Danakil Desert 32 Battle of Trafalgar 54 Missouri Stone Age Site 82
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Cattle movements spread disease
SOLAR SYSTEM EVOLUTION
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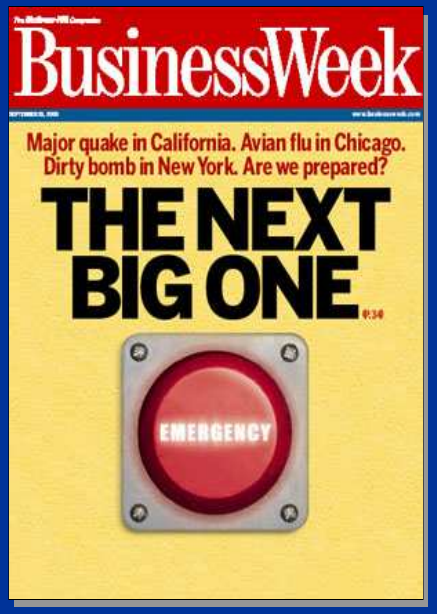
PLANT HORMONES
At last, an auxin receptor
VISUAL SEARCH
Can't see for looking?
AVIAN FLU
Ready for a pandemic?
Gene therapy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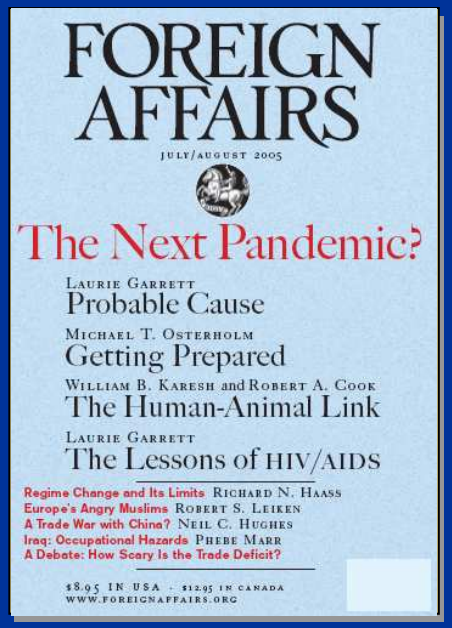
Major quake in California. Avian flu in Chicago.
Dirty bomb in New York. Are we prepared?
THE NEXT BIG ONE
EMERGENCY

TIME
AVIAN FLU
DEATH THREAT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The Next Pandemic?
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TIME
BIRD FLU

North Carolina Pandemic Flu Plan

Updated January 2006

N.C. Division of Public Health

North Carolina Public Health

THE NEWS&OBSERVER
newsobserver.com

Novartis chooses Holly Springs

The drug maker's vaccine plant would create hundreds of jobs.

JONATHAN B. COX, Staff Writer

July 18, 2006

Holly Springs will get hundreds of jobs and millions of dollars of investment from a new employer that could become the cornerstone for development in the town.

THE NEWS&OBSERVER
newsobserver.com

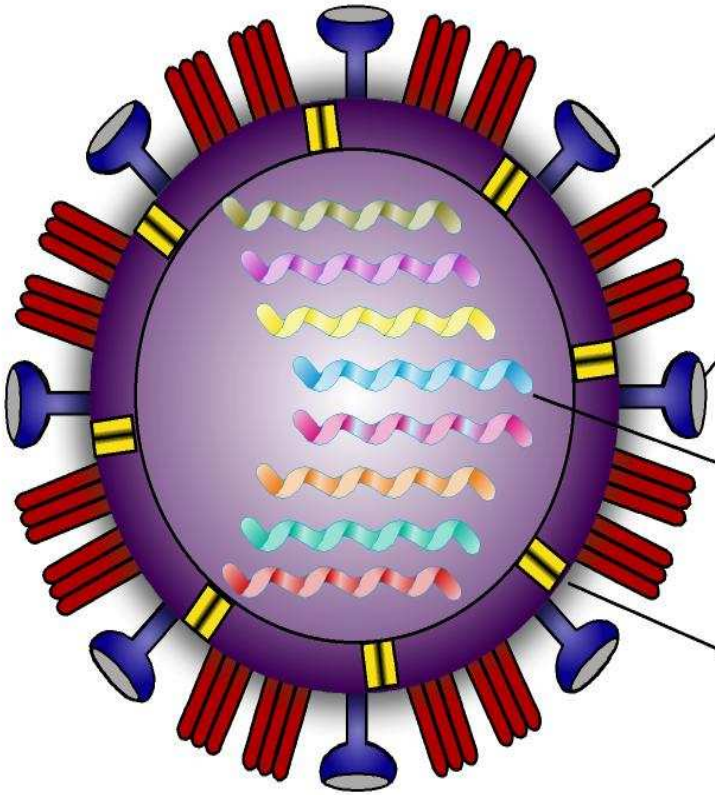
Business Wire -- July 26, 2006 -- Associated Press

GlaxoSmithKline PLC, announced Wednesday it might be able to produce a human vaccine for H5N1 bird flu in mass quantities by 2007, following encouraging results from a clinical trial, T

The prototype vaccine, which could potentially be used during a pandemic caused by H5N1, uses low doses of its active ingredient, meaning that greater quantities could be produced.

The company has its U.S. headquarters in Research Triangle Park, N.C., and Philadelphia.

Influenza A Virus



Hemagglutinin (H) - 16 subtypes
(attachment, penetration)

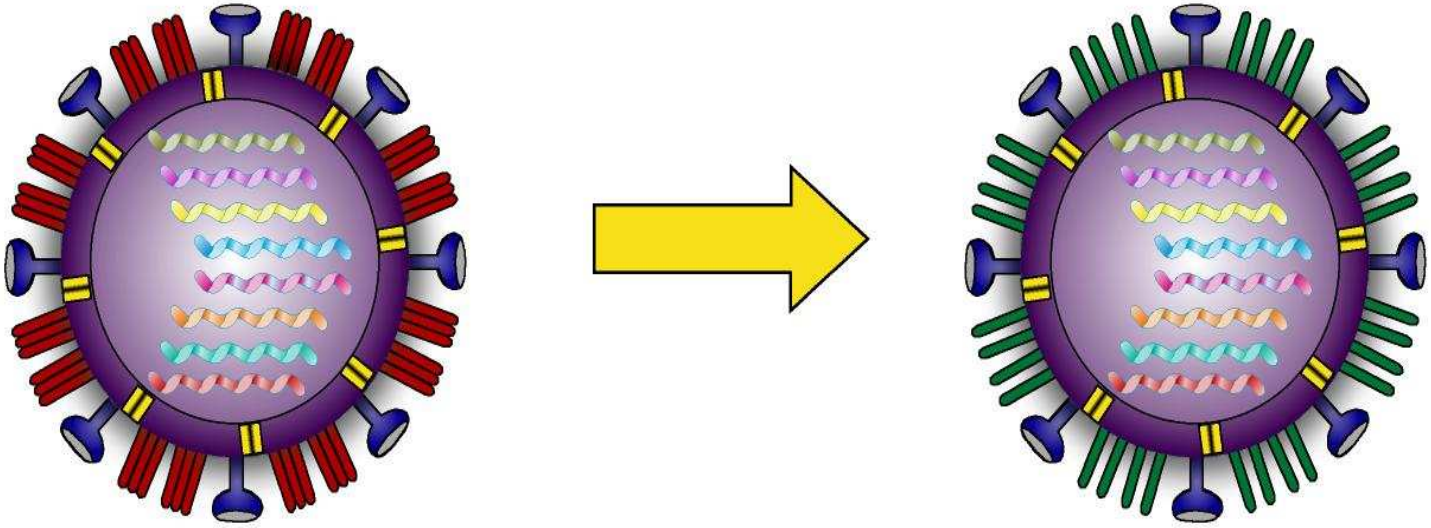
Neuraminidase (N) - 9 subtypes
(release)

8 viral genes
(assembly, replication, etc.)

M2 Protein
(penetration)

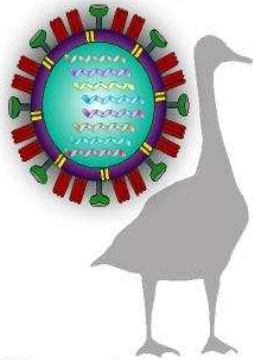
Emergence of New Human Influenza Subtypes

Drift (minor mutations)



Emergence of New Human Influenza Subtypes (continued)

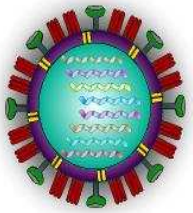
Shift (major change)



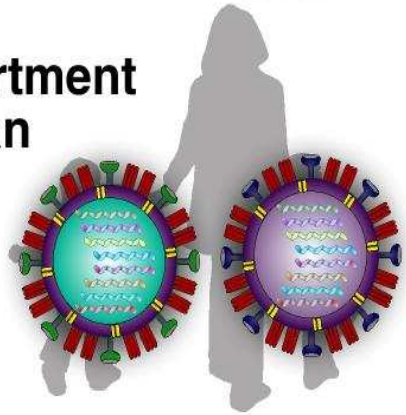
Non-human virus

Human virus

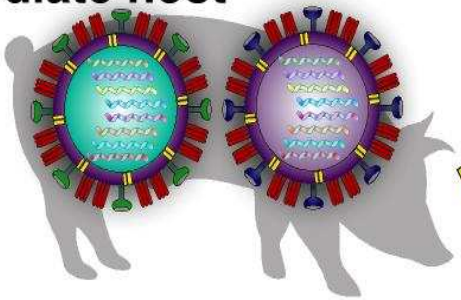
Direct infection



Reassortment in human



Reassortment in an intermediate host

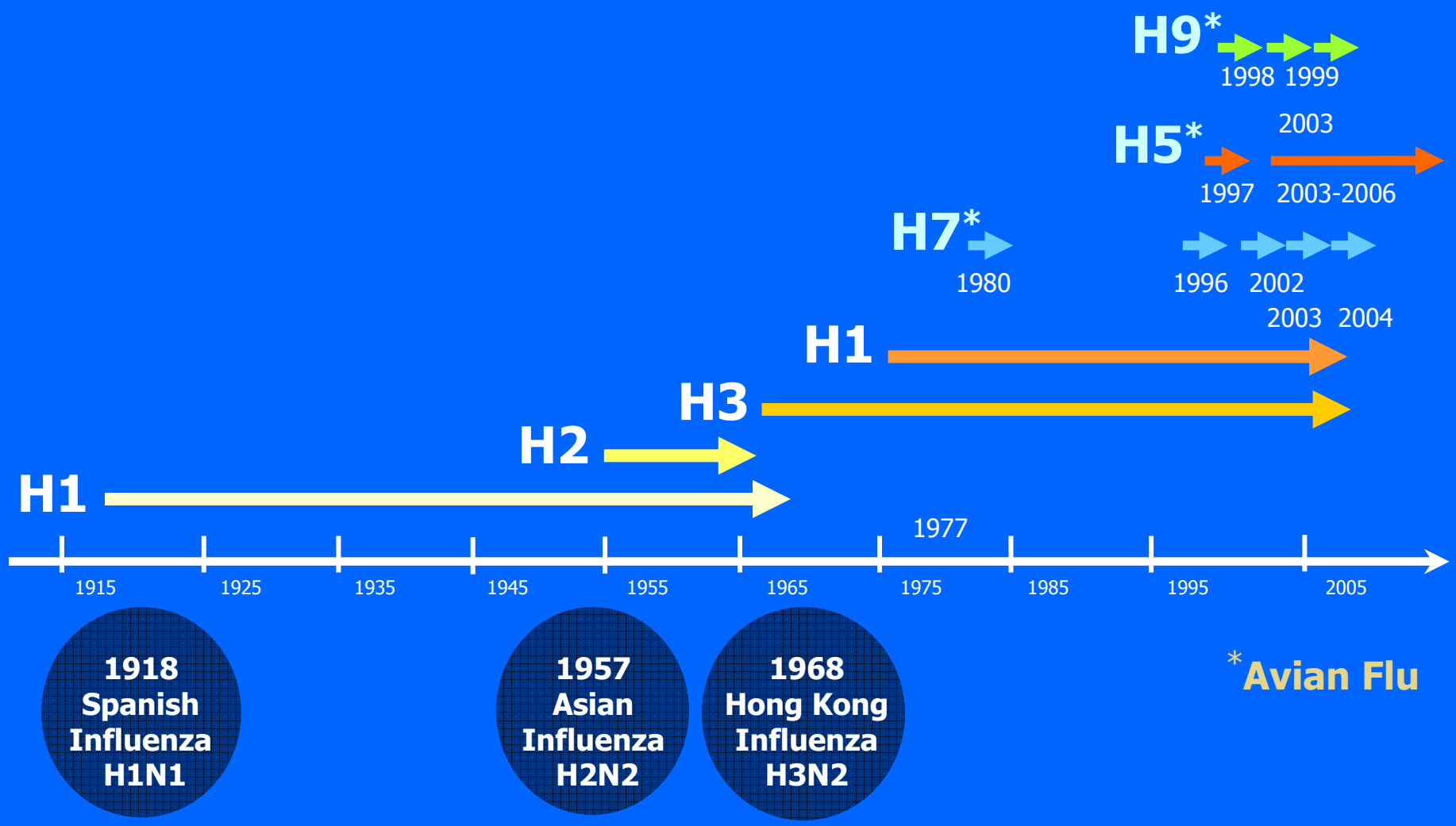


Annual and Pandemic Influenza

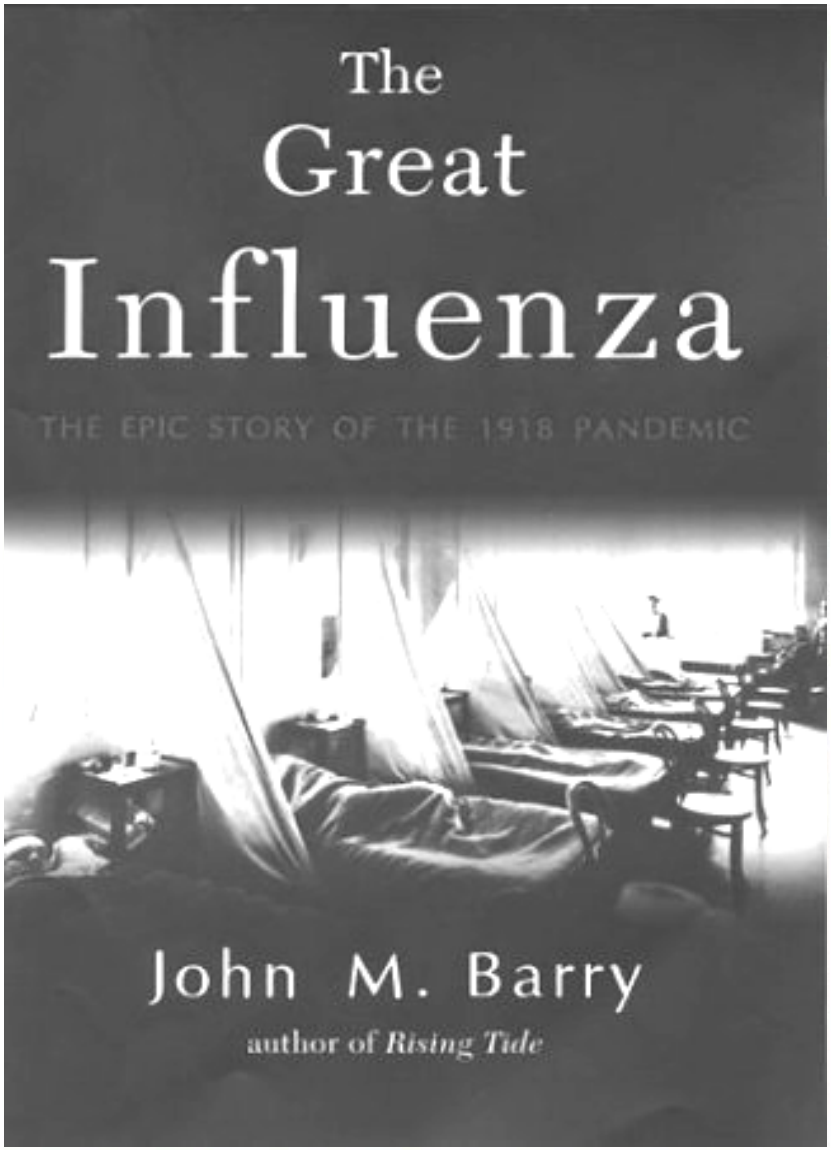
- **Annual influenza**
  - Average 5-15% become ill and 36,000 die in U.S.
  - New vaccine needed annually because of mutations in viral strains (“antigenic drift”)

- **Pandemic influenza**
  - Emergence and spread of a new influenza A subtype (“antigenic shift”)
    - Subtypes defined by hemagglutinin and neuraminidase antigens
    - All 16 HA and 9 NA types are found in birds but only H1N1 and H3N2 currently circulate in humans
  - Efficient and sustained transmission from person to person
  - Universal susceptibility

Pandemic and Seasonal Influenza: An Evolutionary History



The Influenza Pandemic of 1918-1919



- 25-30% of world's population (~500 million people) fell ill
- >40 million deaths worldwide; ~60 percent in people ages 20-45
- >500,000 deaths in United States; 196,000 in October, 1918 alone

Source: WHO, 1/2005

FAONEWSROOM

31 August 2005

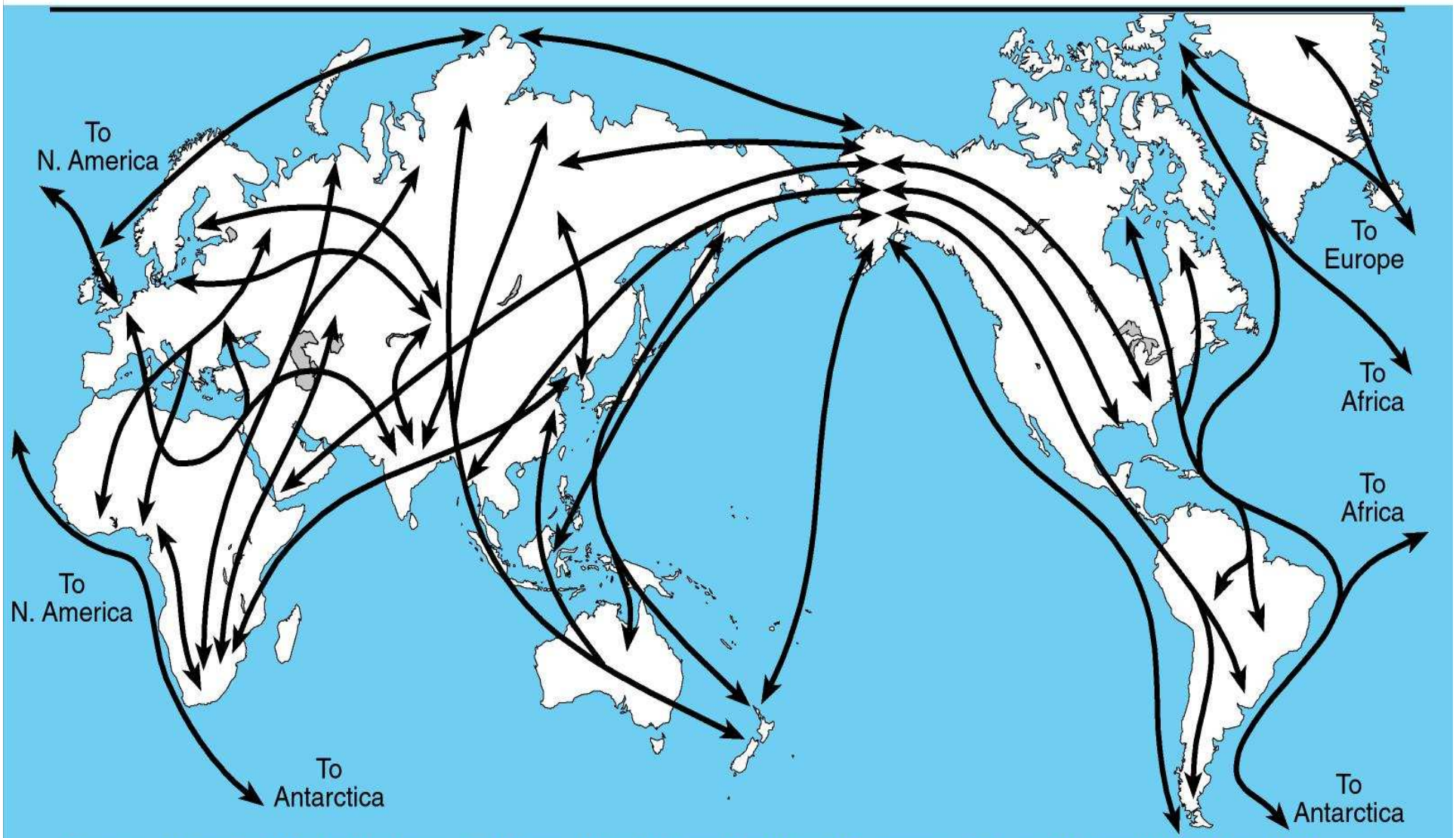
Wild Birds Expected to Spread Bird Flu Virus Further

Countries along migratory routes of wild birds should be on alert - emergency preparedness essential

"FAO urged countries at risk, especially along the routes of migrating birds, to step up surveillance of domestic poultry and wild birds."

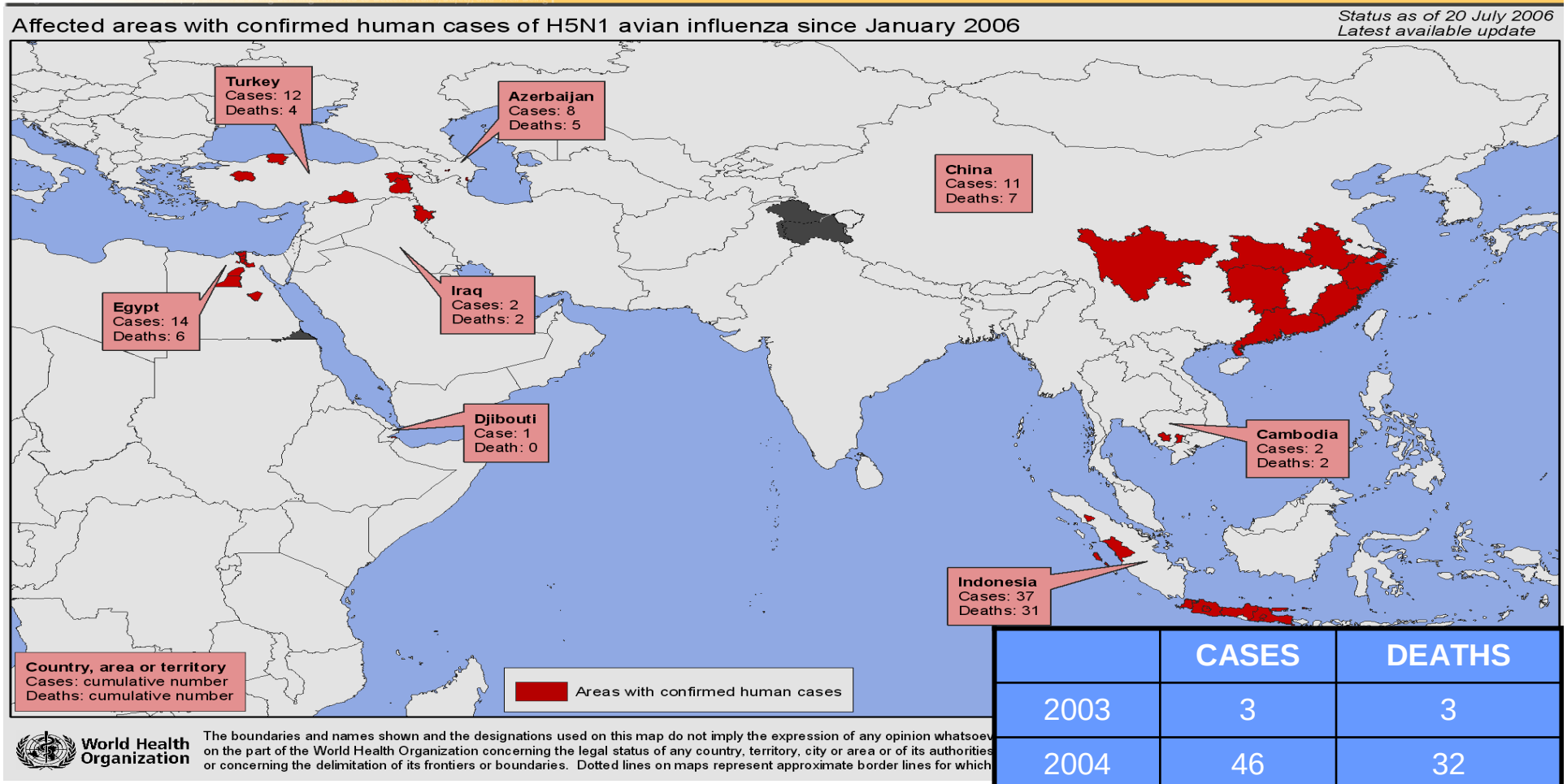
Source: Food and Agriculture Organization of the United Nations

Migratory Bird Flyways



Sources: University of Alaska/Anchorage Daily News; United Nations World Food Programme; Tracey et al. *Emu*, Vol. 104 June 2004; Random House Atlas of Bird Migration© 1995.

Human Cases of H5N1: Situation Report



	CASES	DEATHS
2003	3	3
2004	46	32
2005	94	41
2006	89	58
TOTAL	**232**	**134**

WHO: July 26, 2006

World Health Organization: Phases of a Pandemic

Inter-pandemic phase	Low risk of human cases	1
New virus in animals, no human cases	Higher risk of human cases	2
Pandemic alert	No or very limited human-to-human transmission	3
New virus causes human cases	Evidence of increased human-to-human transmission	4
	Evidence of significant human-to-human transmission	5
Pandemic	Efficient and sustained human-to-human transmission	6

Will H5N1 Cause the Next Pandemic?

- **Likelihood of mutation or reassortment leading to efficient person-to-person transmission unknown**
- **Spread of avian H5N1 infections increases risk**
  - **Recent evolutionary changes in the virus make control among birds more difficult and continued spread likely**
- **Other avian influenza A subtypes (H7N3, H7N7, H9N2) also have caused human infections**

Compounding Probabilities

- ☑ Virus appears in birds in a restricted geographic setting
- ☑ Virus spreads to birds in a wider geographic setting
- ☑ Virus infects other mammals
- ☑ Virus jumps from bird to human inefficiently
- ☑ Virus more efficiently spreads from bird to human
- ☑ Inefficient human to human transmission of virus
- ☐ Efficient human to human transmission of virus

Planning Assumptions: Health Care

	Moderate (1957-like)	Severe (1918-like)
Illness	**90 million (30%)**	**90 million (30%)**
Outpatient medical care	**45 million (50%)**	**45 million (50%)**
Hospitalization	**865,000**	**9, 900,000**
ICU care	**128,750**	**1,485,000**
Mechanical ventilation	**64,875**	**745,500**
Deaths	**209,000**	**1,903,000**

- **50% or more of those who become ill will seek medical care**
- **Number of hospitalizations and deaths will depend on the virulence of the pandemic virus**

Pandemic Planning Assumption: Illness & Transmission

- **Universal susceptibility**
- **Illness rate during the first disease wave ~30%**
  - **Rates of hospitalization and death vary with virulence**
- **Transmission by contact with respiratory secretions**
  - **Children best transmitters because of a higher infection rate, more viral shedding, and closer contact with others**
- **Average time between infection and illness ~2 days**
  - **Viral shedding and transmission risk during last ½ to 1 day of this period**

Public Health: More than a One-Shot Deal

A one-shot infusion of money or a single focus on stockpiling drugs and vaccines is not enough to protect Americans from biological and chemical threats, let alone diseases like asthma and cancer.

Congress and the Administration must also make a long-term commitment to strengthen the fundamentals of our public health system:

- more and better-trained public health professionals
- a state-of-the-art early warning system and communications network
- better-equipped laboratories
- and tracking of diseases and monitoring of environmental exposures.

Long neglected, America's public health system is vital to our defense against biological and chemical attacks, as well as on-going serious health concerns such as asthma and cancer, and the unforeseen emergencies of tomorrow. ***We cannot afford to do less.***

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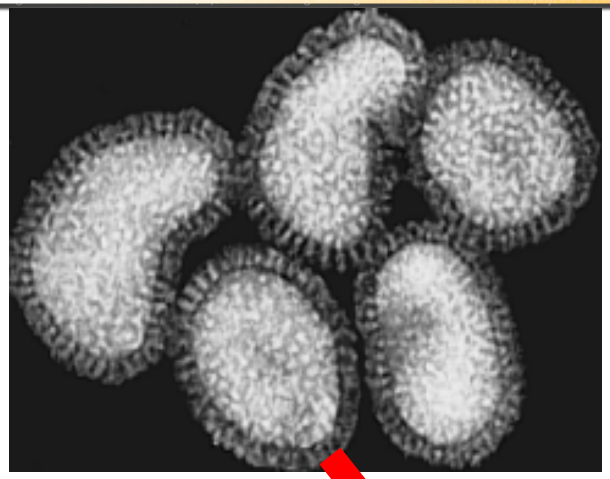
The Trust for America's Health

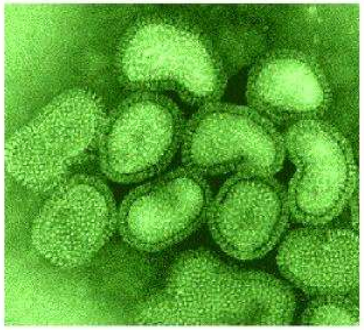
www.healthyamericans.org

Influenza Vaccine Production



Annual Influenza Vaccine Production Timeline

Jan – May → Jun - Jul → Aug → Sep → Oct - Nov



Virus Selection

- FDA advisory panel selects 3 strains
- CDC provides new strains of the seed virus to the FDA
- FDA distributes the 3 seed viruses to manufacturers

Production Begins

FDA Testing, Licensure

Filling/ Packaging

- Vaccine is filled into vials and syringes; packaged for distribution

Product Release/ Shipping

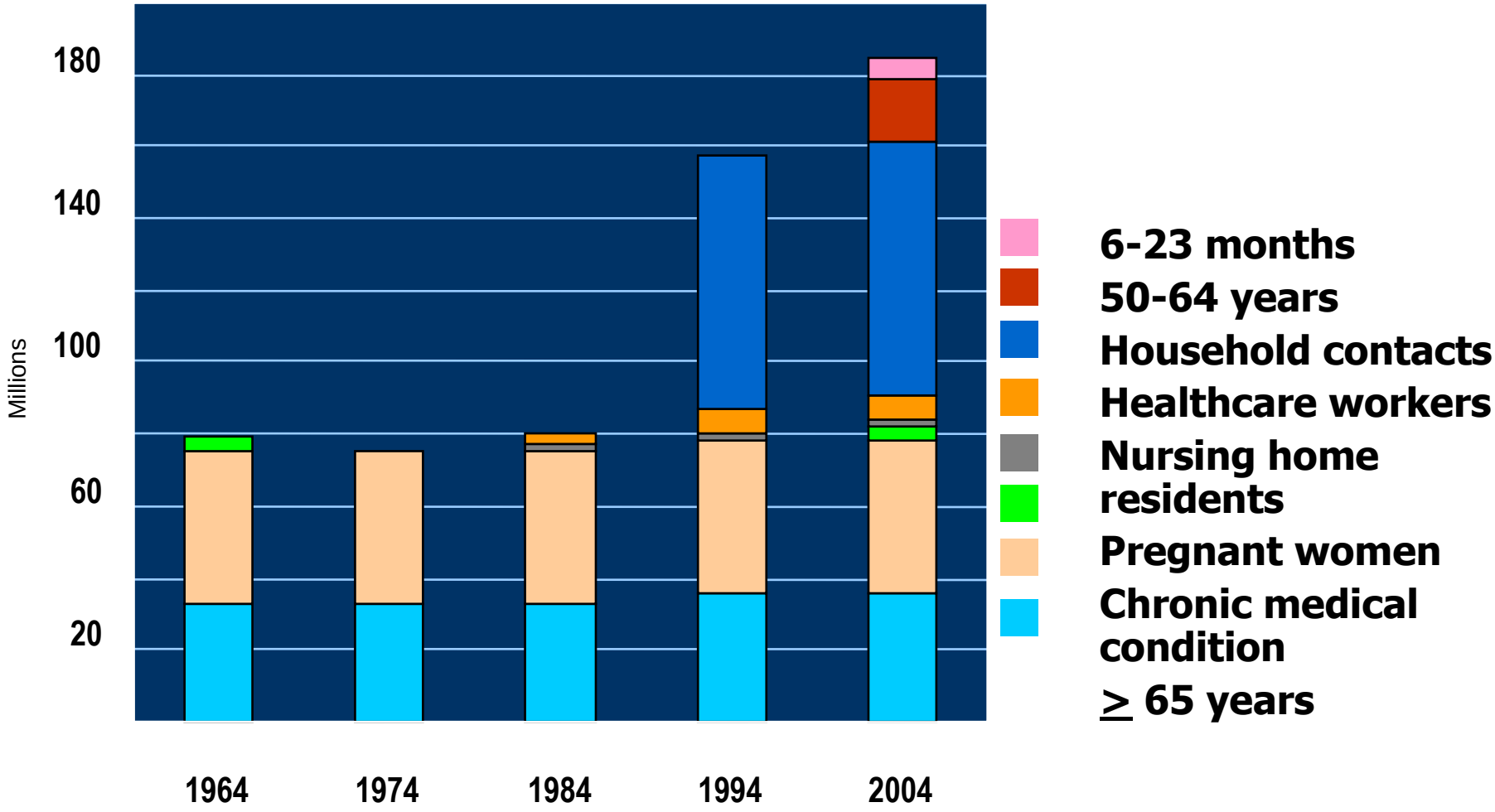
Vaccination Begins

- Immunity develops approximately 2 weeks after vaccination

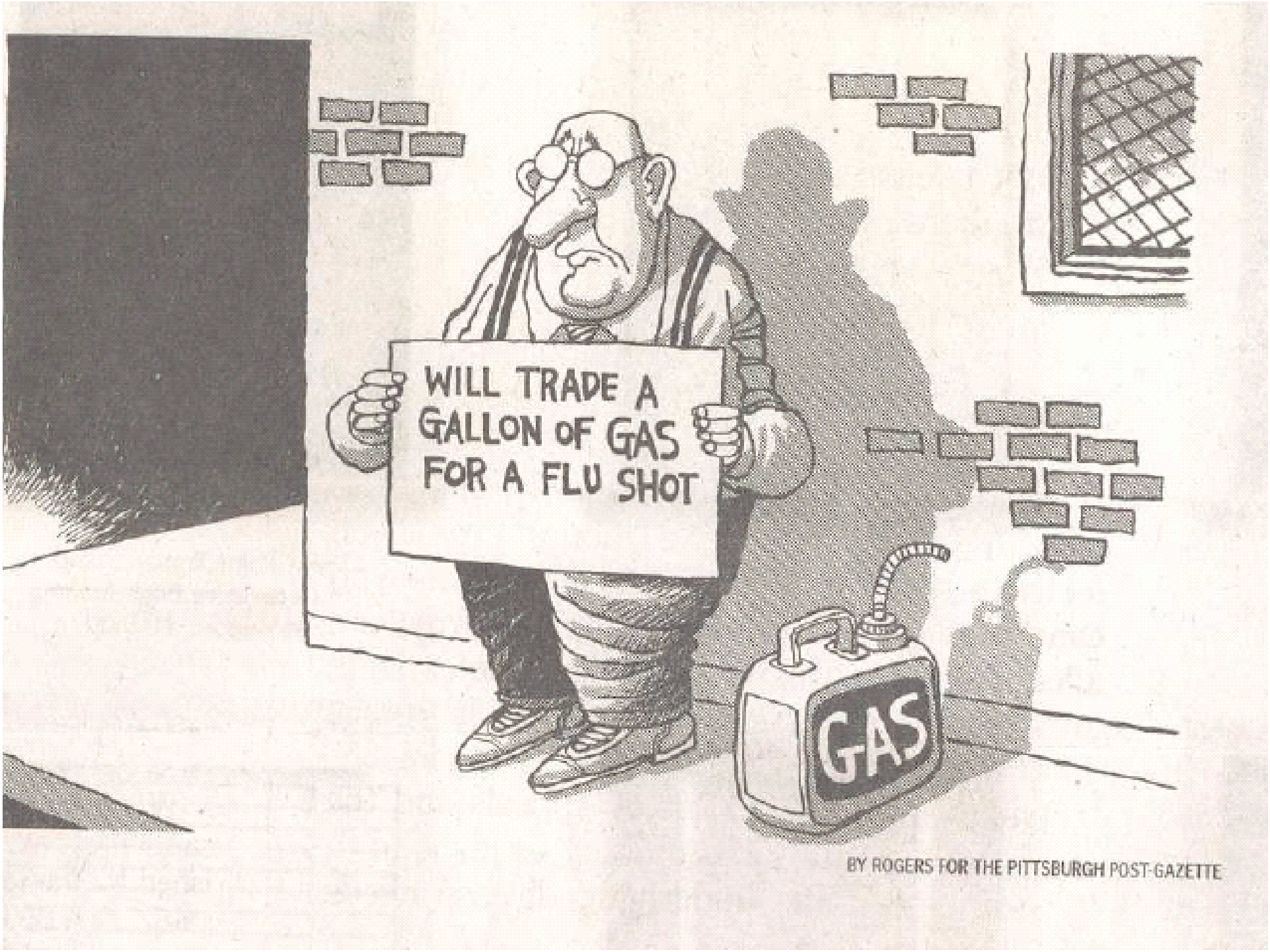
Seasonal Influenza Vaccine: Supply and Demand

	Doses Produced (millions)	Doses Distributed (millions)
1980	15.7	12.4
1985	23.1	20.1
1990	32.3	28.3
1995	71.5	54.9
1999	77.2	76.8
2000	77.9	70.4
2001	87.7	77.7
2002	95.0	83.0
2003	86.9	83.1
2004	61.0	56.5
2005	86.0	> 81

Expanding Use of Seasonal Vaccine



Seasonal Influenza Vaccine: Supply and Demand


WILL TRADE A
GALLON OF GAS
FOR A FLU SHOT
GAS
BY ROGERS FOR THE PITTSBURGH POST-GAZETTE

The Public Health Challenge

Flu Vaccine Makers Plan Sharp Increase in Output

January 25, 2006

(Associated Press) – ATLANTA - Expecting rising demand for flu shots, pharmaceutical companies are gearing up to produce as many as 120 million doses of vaccine for next flu season, far surpassing the record of 95 million doses produced in 2002.

Seasonal Influenza Vaccine: Supply and Demand

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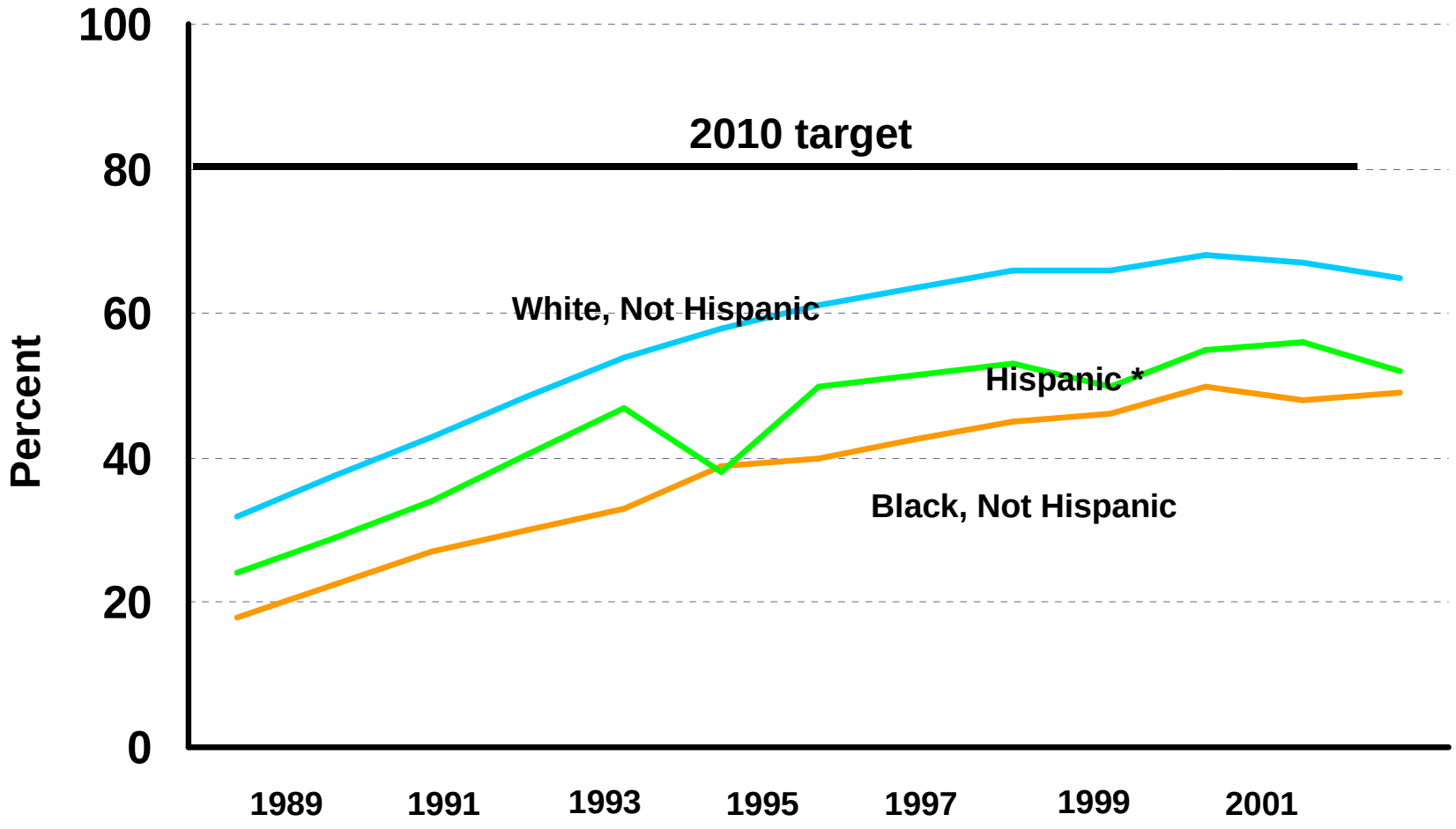
Influenza Vaccination
65 Years and Older, by Race/Ethnicity



* Can be of any race.

Source: National Health Interview Survey (NHIS), CDC, NCHS.

Influenza Vaccination: Recommendations vs. Use

TABLE 2. Influenza vaccination coverage rates among adult target* population groups — United States, National Health Interview Survey, 2002 (n =31,044 [crude] and 205,825,095 [weighted])

Population group	Crude sample size	Weighted sample size	Influenza vaccination rate (%)	(95% CI)†
All aged 50–64 years	8,424	42,946,096	34.0	(32.7–35.3)
Aged 50–64 years and not at high risk§	4,373	29,521,511	29.7	(28.2– 31.2)
All aged ≥65 years	5,757	32,524,974	65.6	(64.1–67.0)
Persons with high-risk conditions§				
Aged 18–49 years	2,428	16,983,876	23.1	(21.1–25.2)
Aged 50–64 years	1,969	12,925,647	43.6	(41.2–46.0)
Pregnant women¶	319	2,119,391	12.4	(8.5–16.3)
Health-care workers**	2,066	13,850,828	38.4	(35.9–40.9)
Household contacts of persons at high risk††				
Aged 18–64 years	3,127	24,298,165	18.1	(16.5–19.7)
Aged 18–49 years	2,654	20,450,993	14.6	(12.9–16.3)
Aged 50–64 years	473	3,847,172	36.3	(31.7–40.9)

* As recommended by the Advisory Committee on Immunization Practices

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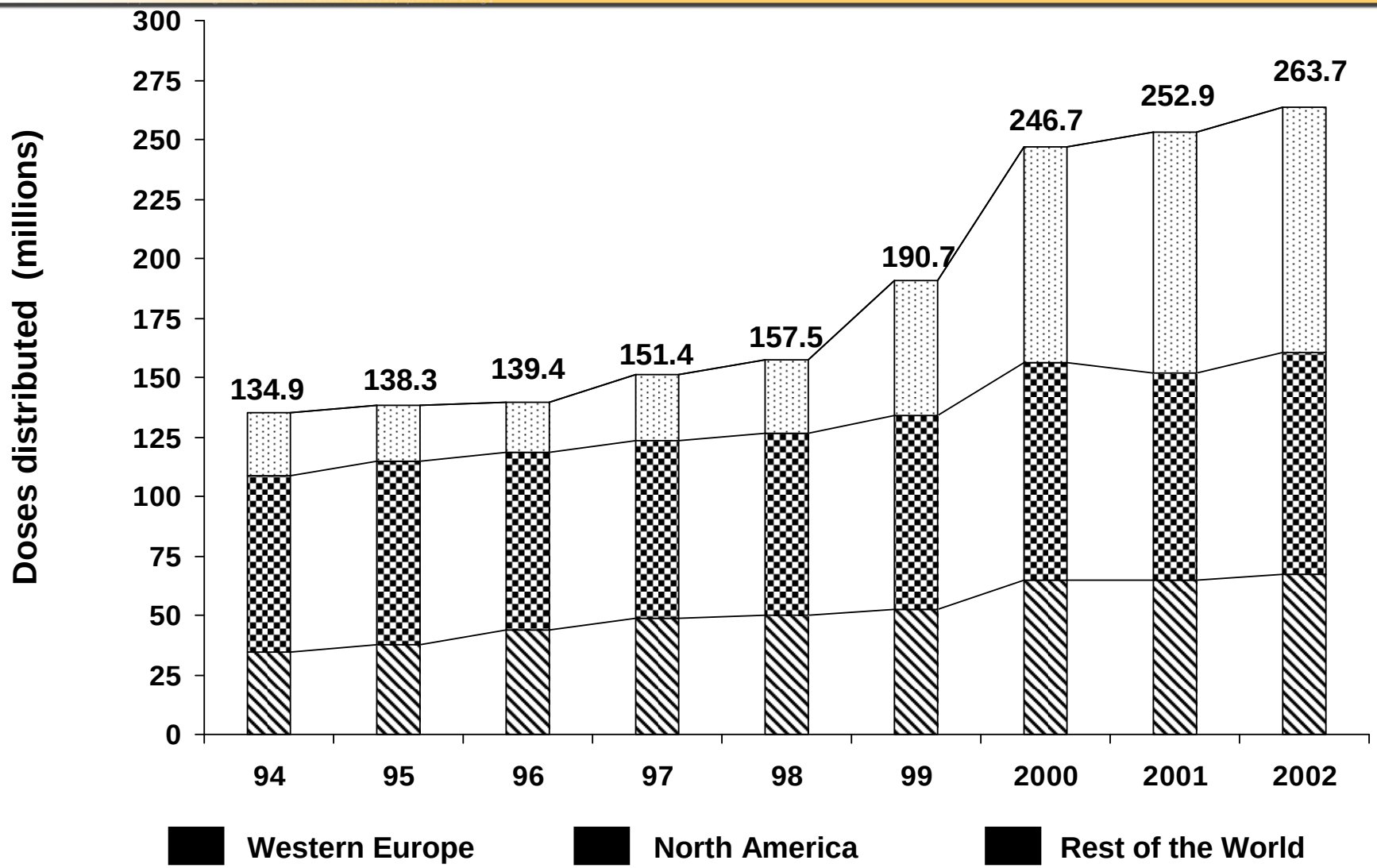
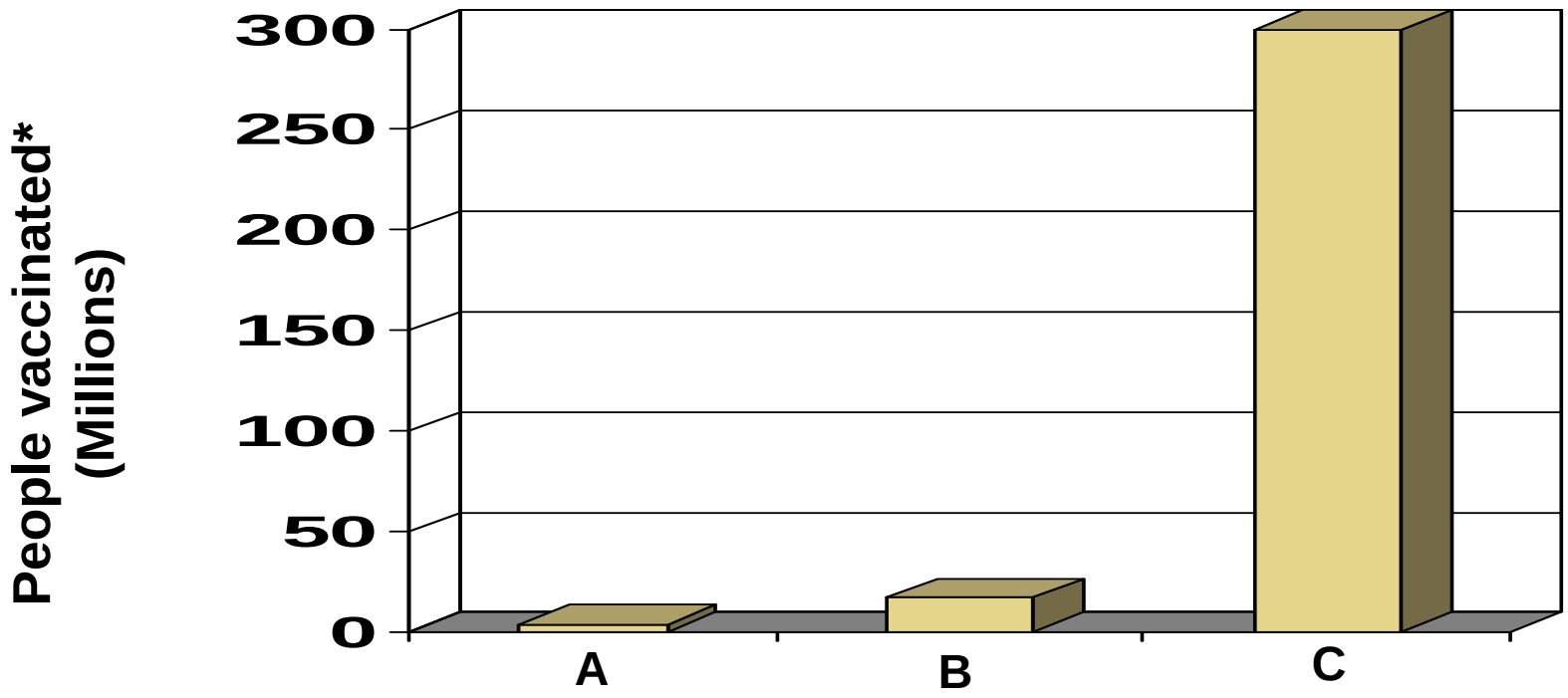
Global Influenza Vaccine Production 1994-2002



Estimated Current US Annual Domestic Production of Pandemic Influenza Vaccine: Supply, Capacity, and Need



A: Current stockpile
B: Current annual domestic capacity
- **Assumes all capacity dedicated to pandemic vaccine**
- **Assumes NO annual influenza vaccine**

C: National need

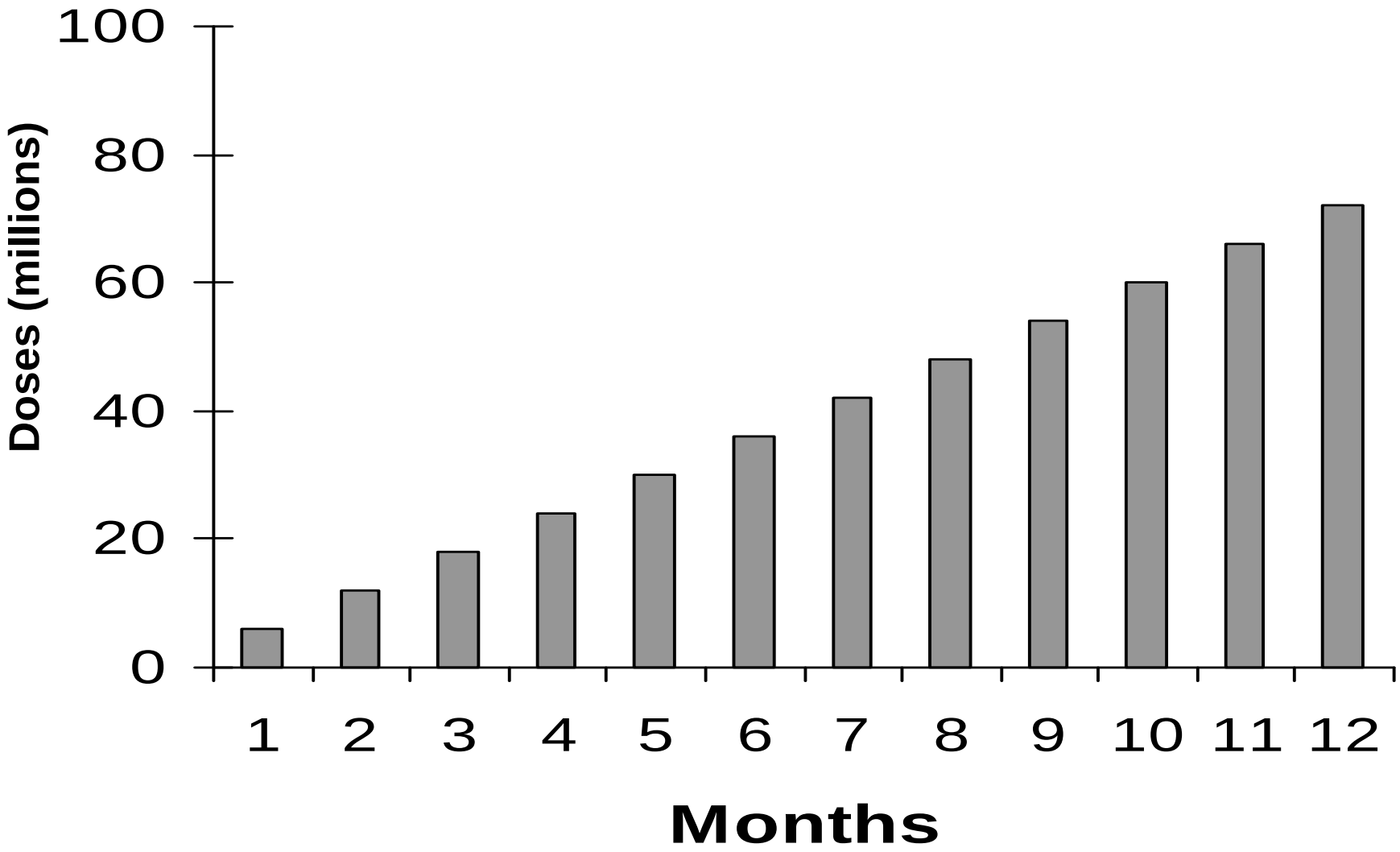
***Assumes 2 doses/person, 90 ug/dose**

Pandemic Vaccine: Recommended Priority Groups*

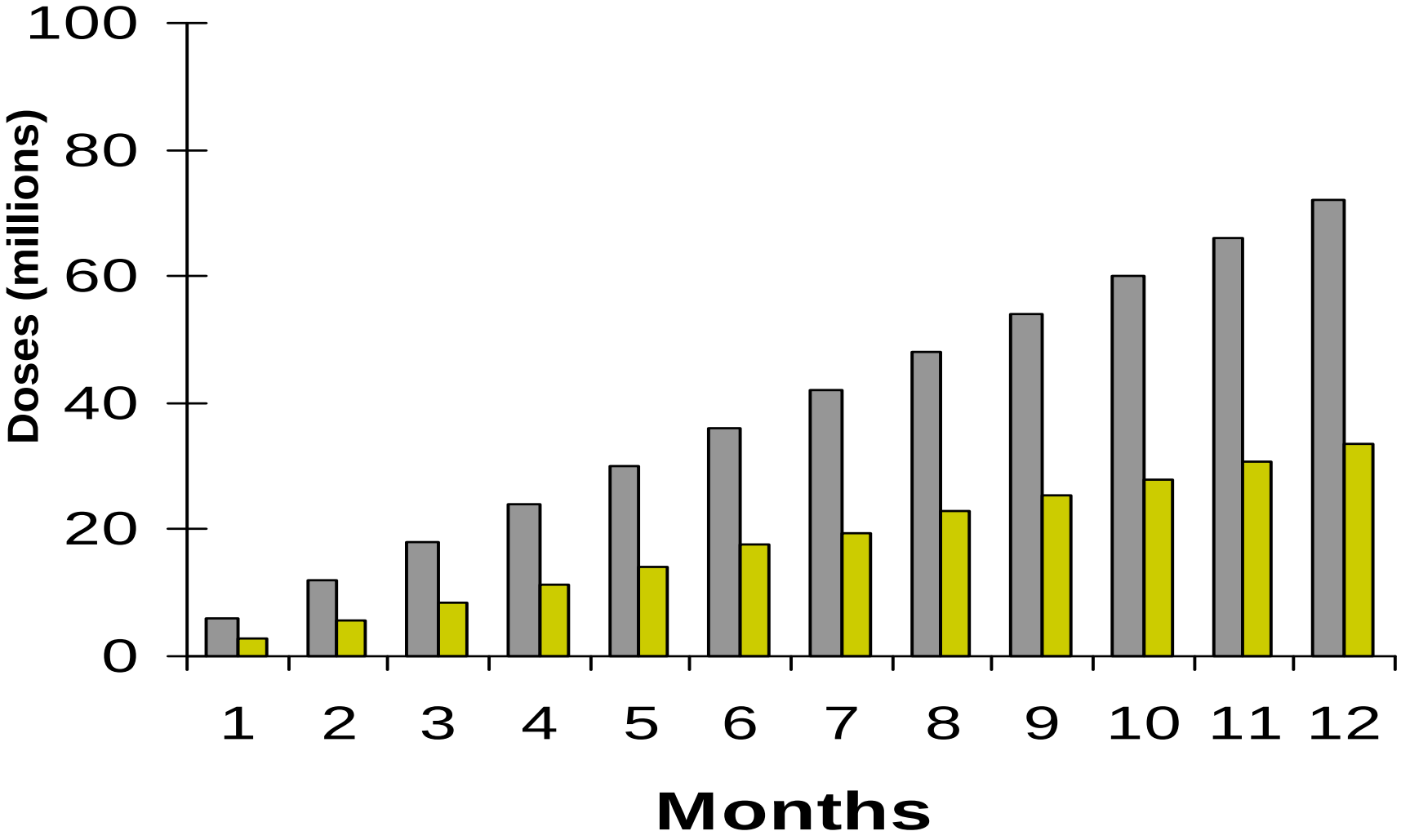
	Personnel (1,000's)	Cumulative total (1,000's)
FRONT LINE HEALTH CARE WORKERS	9,000	9,000
VACCINE/ANTICIRAL MANUFACTURERS	40	9,040
HIGH RISK PERSONS	25,840	34,880
HOUSEHOLD CONTACTS OF CHILDREN < 6 MONTHS	10,700	45,580
PREGNANT WOMEN/SEVERELY IMMUNOCOMPROMISED		
KEY GOVERNMENT LEADERS		
CRITICAL PUBLIC HEALTH PANDEMIC RESPONDERS	151	45,731
ADDITIONAL HIGH RISK	59,100	104,831
MOST CRITICAL INFRASTRUCTURE		
OTHER PUBLIC HEATLH RESPONDERS	8,500	113,331
OTHER KEY GOVERNMENT DECISIONMAKERS		
MORTUARY SERVICES	500	113,831
HEALTH 2-64 YEAR OLDS (NOT IN OTHER GROUPS)	179,260	293,091

Recommendations of National Vaccine Advisory Committee and Advisory Committee on Immunization Practices, July 2005

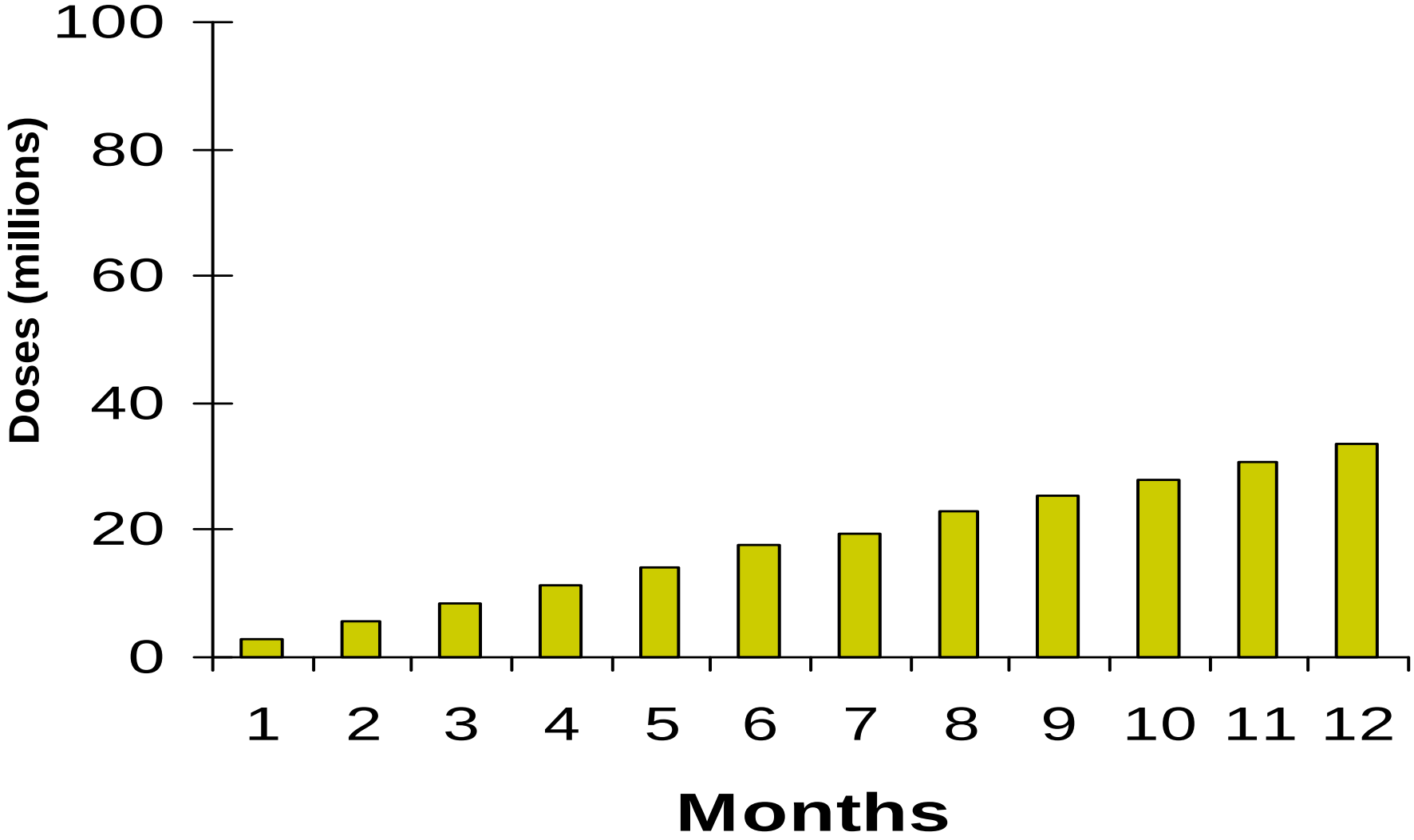
Influenza Vaccine:
Current US Domestic Production Capacity
Seasonal Influenza Vaccine



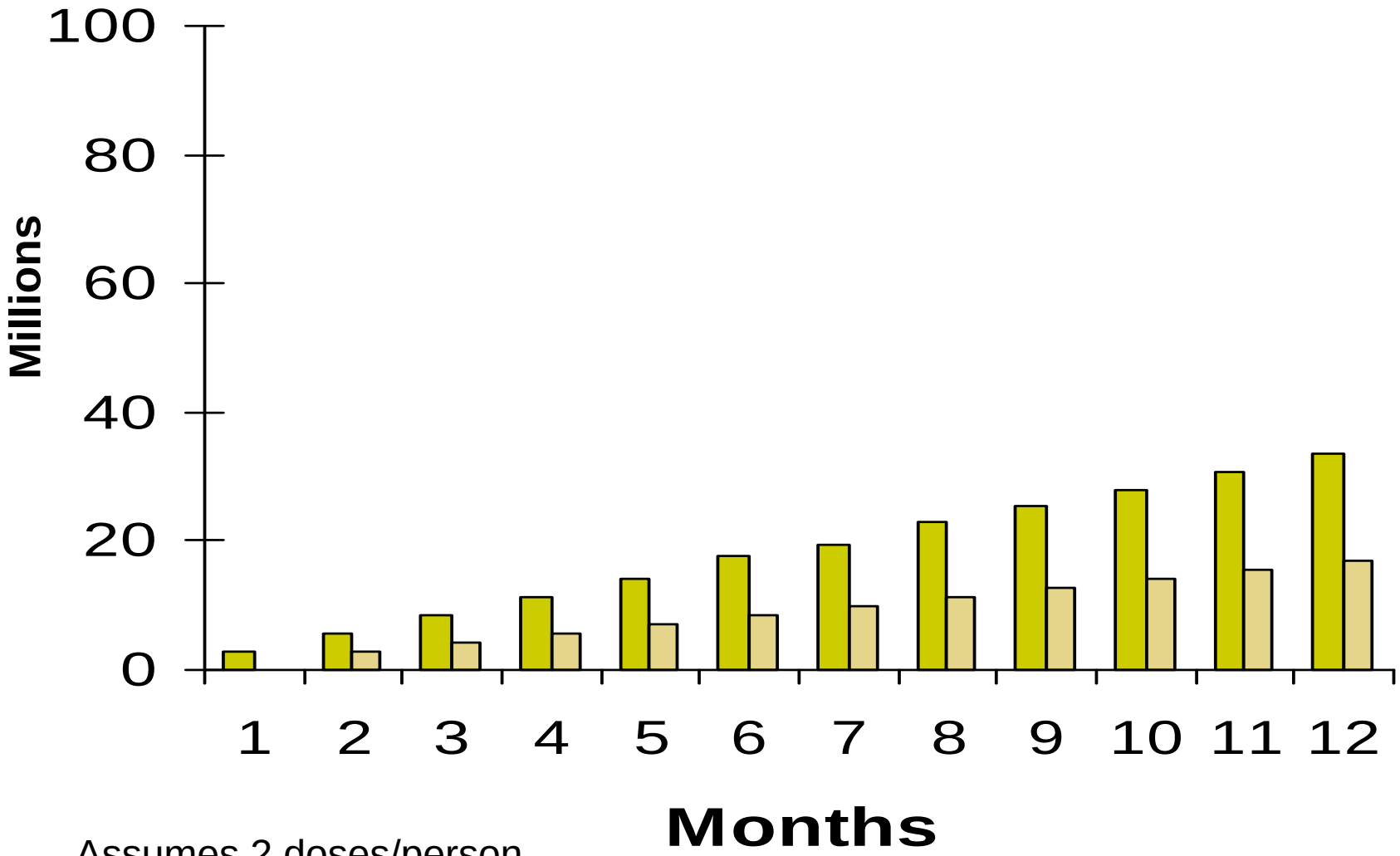
Influenza Vaccine: Current US Domestic Production Seasonal vs. Pandemic Vaccine



Influenza Vaccine: Current US Domestic Production Pandemic Vaccine

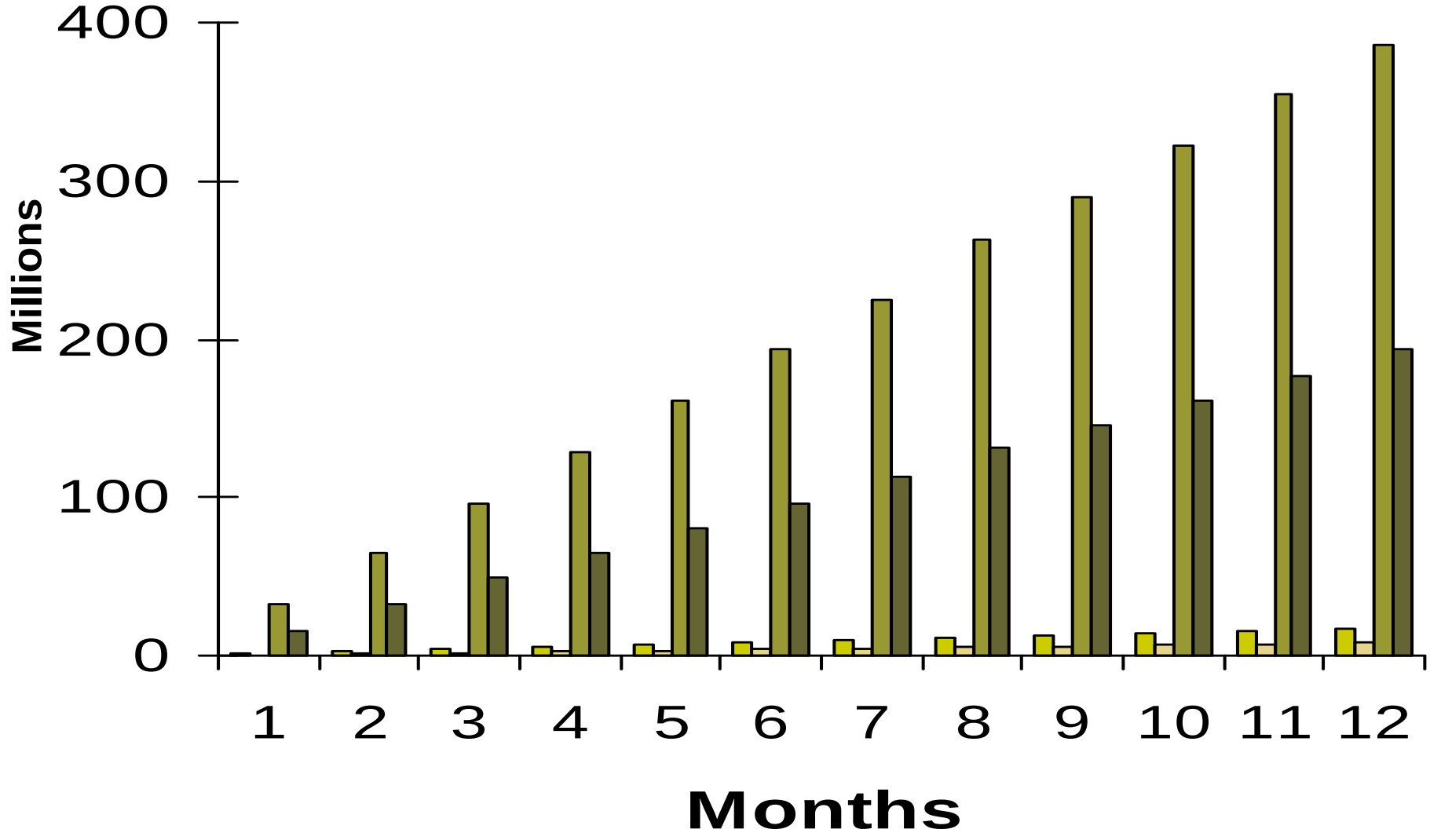


Pandemic Influenza Vaccine: Current US Domestic Production and Persons Fully Vaccinated



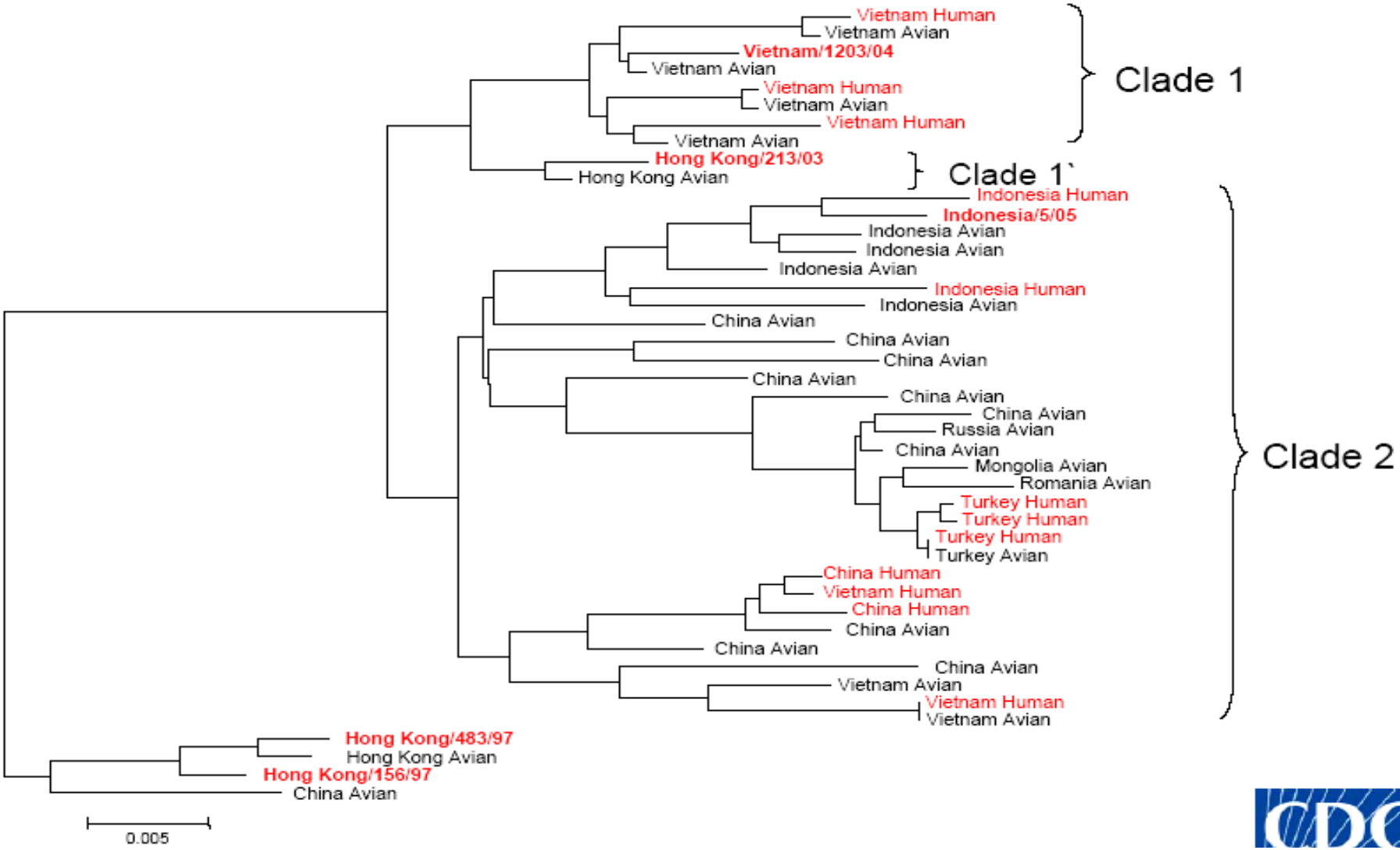
Assumes 2 doses/person
(90 ug/dose, unadjuvanted)

Pandemic Influenza Vaccine: The Promise of an Adjuvant



The (growing diversity) of H5N1 virus

Evolutionary Relationships Among Influenza A (H5N1) Hemagglutinin (HA1) Genes



HHS Pandemic Vaccine Goals

- **Goal #1: To provide pandemic vaccine to all U.S. citizens within six (6) months of a pandemic declaration**
- **Goal #2: To establish and maintain a dynamic pre-pandemic influenza vaccine stockpile available for 20 million persons**
- **Strategies:**
  - **Expand and diversify influenza vaccine production**
  - **Increase number of domestic manufacturers**
  - **Expand pandemic influenza vaccine manufacturing surge capacity**

HHS Cell Culture Influenza Vaccine Contracts

2005-2006

Company	Funding Amount
Sanofi Pasteur	$97,000,000
GSK (ID Biomed)	$274,752,168
MedImmune	$169,462,231
Novartis (Chiron)	$220,507,491
DynPort (Baxter)	$40,438,622
Solvay	$298,594,057

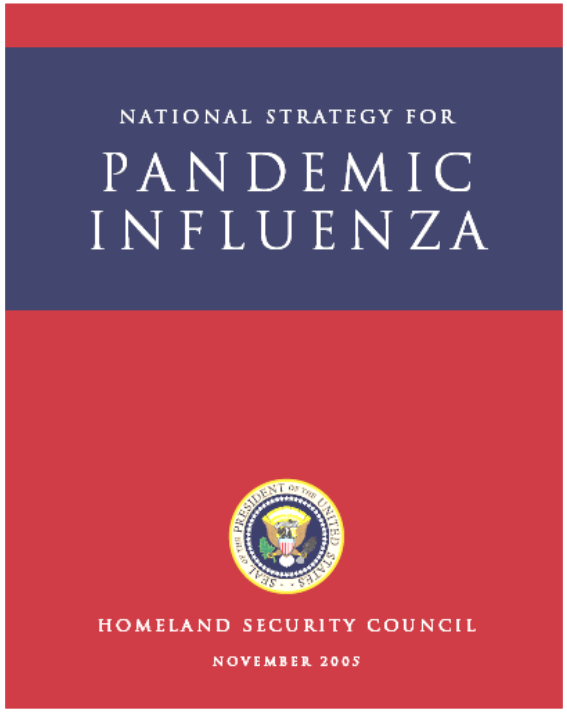
HHS Pandemic Influenza Vaccine Program

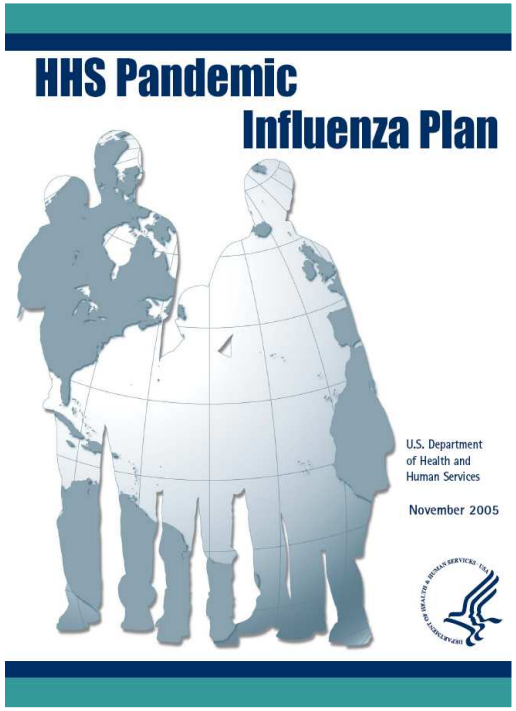
- Egg security
- Prepandemic vaccine stockpiles
- Increasing capacity
  - Egg-based
  - “Retrofit” existing biological facilities
  - Improved process manufacturing
  - Cell culture-based
- Dose sparing technology and techniques
- Pilot lot facilities
- Novel influenza vaccine approaches
  - DNA vaccines
  - Recombinant vaccines
- Broad spectrum, common antigen vaccines

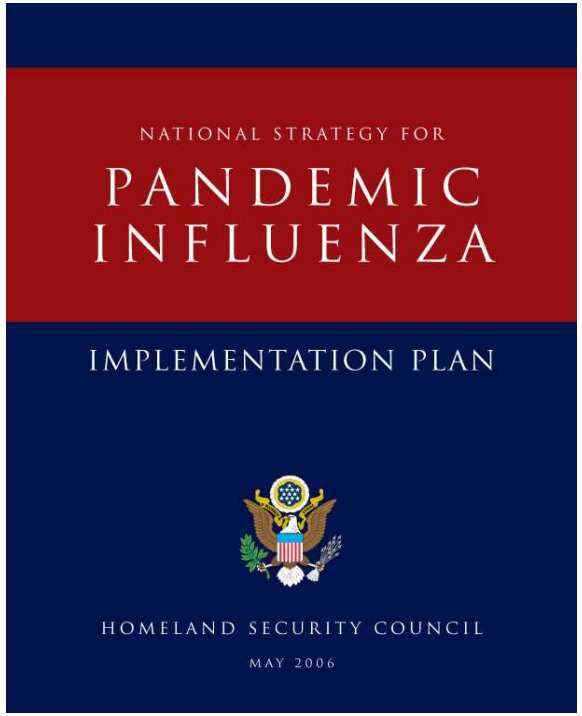
Seasonal Influenza Preparedness

Pandemic Influenza Preparedness

US Pandemic Preparedness Plans







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