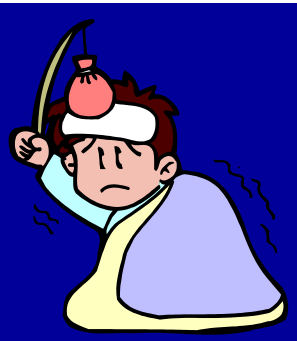
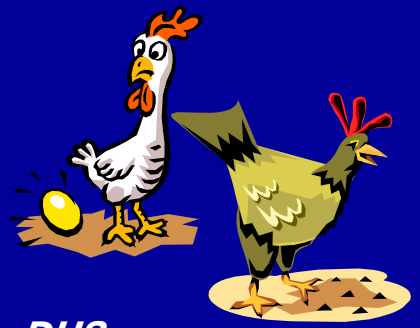


AVIAN INFLUENZA

"The pandemic influenza clock is ticking. We just don't know what time it is."

Laurene Mascola, MD, MPH, FAAP

Acute Communicable Disease Control Program



OUTLINE

- Background on Influenza A
- Impact of influenza
- Pandemics
- Avian influenza A viruses
- Human infections with avian influenza A viruses since 1997
- H5N1 Asia 2005

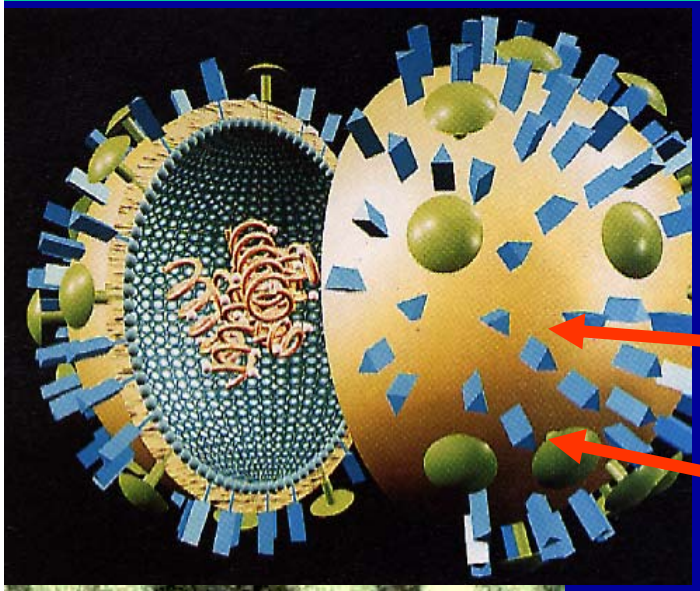
BACKGROUND: HUMAN INFLUENZA

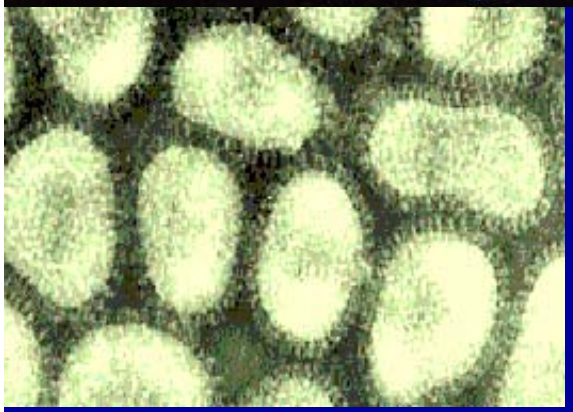
- Acute febrile respiratory illness
  - ✓ Symptoms, signs may differ by age
- Etiology: infection with human influenza viruses (infect upper respiratory tract epithelial cells)
  - ✓ 2 major surface glycoproteins
    - Hemagglutinin, Neuraminadase
    - 8 gene segments code for 10 proteins
- Types A and B viruses cause substantial illness and death among humans yearly

EPIDEMIOLOGY

- Short incubation period, usually 1-4 days.
- Spread by respiratory droplets—person-to-person, direct contact, rare aerosol
- Highly contagious; infectious period:
  - ✓ Adults: 1 day prior to symptoms thru 5 days post illness
  - ✓ Children: >10 days
  - ✓ Immune compromised shed virus for weeks to months
- Virus 1st detectable just before symptom onset. Usually not detectable after 5-10 days

KEY INFLUENZA VIRAL FEATURES





Surface proteins (major antigens)

- Hemagglutinin (HA)
  - ✓ Site of attachment to host cells
  - ✓ Antibody to HA is protective
- Neuraminadase (NA)
  - ✓ Helps to release virions from cells-oseltamavir works here
  - ✓ Antibody to NA can help modify disease severity

CDC

Tim Uyeki, MD

IMPACT OF INFLUENZA

- Seasonal epidemics in temperate regions
  - ✓ U.S., Canada, Europe, Russia, China, Japan, Australia, Brazil, Argentina
- Year-round activity in tropical climates
  - ✓ Equatorial Africa, Southeast Asia
- U.S. impact
  - ✓ Average of >200,000 influenza-related hospitalizations/year
  - ✓ Average of >36,000 influenza-related deaths/year
- 3 global pandemics in the 20th century

INFLUENZA PANDEMICS
20TH CENTURY

Credit: US National Museum of Health and Medicine

1918: "Spanish Flu"
A(H1N1)
20-40 m deaths
675,000 US deaths

1957: "Asian Flu"
A(H2N2)
1-4 m deaths
70,000 US deaths

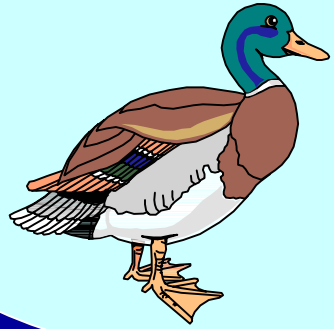
1968: "Hong Kong Flu"
A(H3N2)
1-4 m deaths
34,000 US deaths

INFLUENZA A VIRUSES

- Subtypes based on surface glycoproteins
  - ✓ Hemagglutinin (HA) and Neuraminidase (NA)
  - ✓ Current human influenza A virus subtypes:
    - H1 (H1N1, H1N2)
    - H3 (H3N2)
- Cause epidemics and pandemics
- Infect multiple species
  - ✓ Humans
  - ✓ Birds (wild birds, domestic poultry)
  - ✓ Other animals: pigs, horses, dogs, marine mammals (seals, whales)

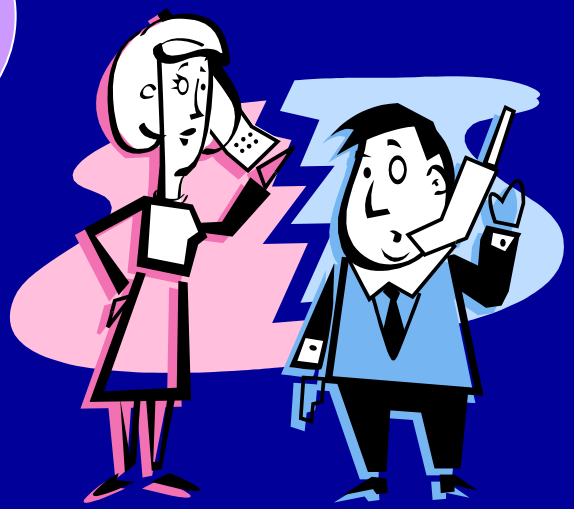
NATURAL RESERVOIR FOR NEW HUMAN INFLUENZA A VIRUS SUBTYPES: WATERFOWL (AQUATIC DUCKS)

Avian Influenza A Viruses
H1 - H16
N1 - N9



H1 - H3

Human Influenza A Viruses



Tim Uyeki, MD

DHS
Acute Communicable Disease Control Program

INFLUENZA A VIRUSES AND ANTIGENIC "DRIFT"

- Antigenic "drift": Point mutations in the hemagglutinin gene cause minor antigenic changes to HA
  - ✓ Continuous process
  - ✓ Immunity against one strain may be limited
  - ✓ Vaccine strains must be updated each year
    - 6-8 month process
    - Targeted at high-risk (inactivated); healthy (LAIV)
- Antigenic "drift" causes seasonal epidemics

INFLUENZA A VIRUSES AND ANTIGENIC "SHIFT" (1)

- Antigenic "shift": Emergence of a new human influenza A virus subtype (new HA subtype +/- NA) through:
  - ✓Genetic reassortment (human and animal viruses)
  - ✓Direct animal (poultry) to human transmission

INFLUENZA A VIRUSES AND ANTIGENIC "SHIFT" (2)

- Because there is little or no immunity to a novel virus, a pandemic can occur if:
  - ✓Efficient and sustained virus transmission occurs among humans (sustained person-to-person spread)
- A pandemic can result in:
  - ✓Widespread morbidity and mortality worldwide
  - ✓High proportion of deaths among young adults

DEFINITION OF PANDEMIC

- Isolation from humans of a novel influenza A virus
- Little or not immunity in the population
- Demonstrated ability of the virus to replicate and cause disease
- Efficient person to person transmission
- May have increased mortality with higher proportion in younger persons

WHO ALERT PHASES

PANDEMIC ALERT PERIOD
Where we are now

- Phase 3: Human infection(s) with a new subtype, but no human-to-human spread, or at most rare instances of spread to a close contact

www.dh.gov.uk/pandemicflu

DOES AVIAN FLU = PANDEMIC FLU

- NO!
- Current impact of highly pathogenic avian influenza (HPAI) viruses on human health is small
- Only since 1997, and in 2003 till present do we see human infections
- Current A/H5N1 viruses are poorly adapted to human species-rare human to human transmission, rare to no mild or asymptomatic infection

Antigenic "Shift" Pandemic

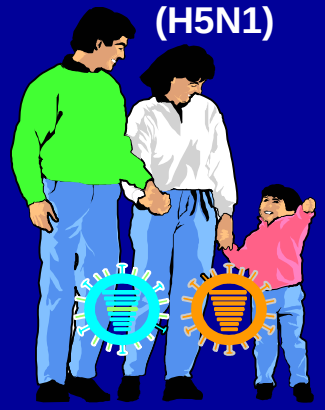
Avian virus

Avian reassortant virus

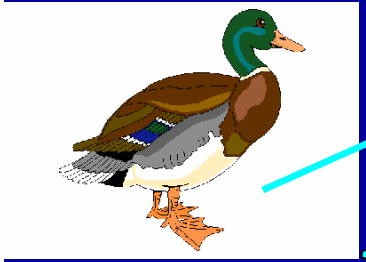
A/HK156/97 (H5N1)

Goose/Guangdong/1/96 (H5N1)

Quail/HK/G1/97 (H9N2)



Teal/HK/W312/97 (H6N1)

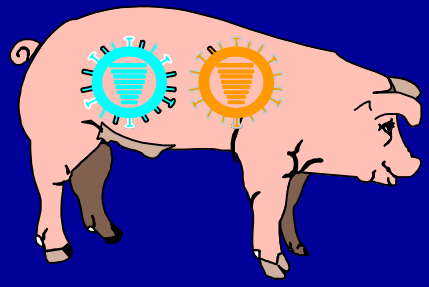


Reassortment in humans

Avian virus

Human virus

Model of the emergence of a pandemic influenza virus

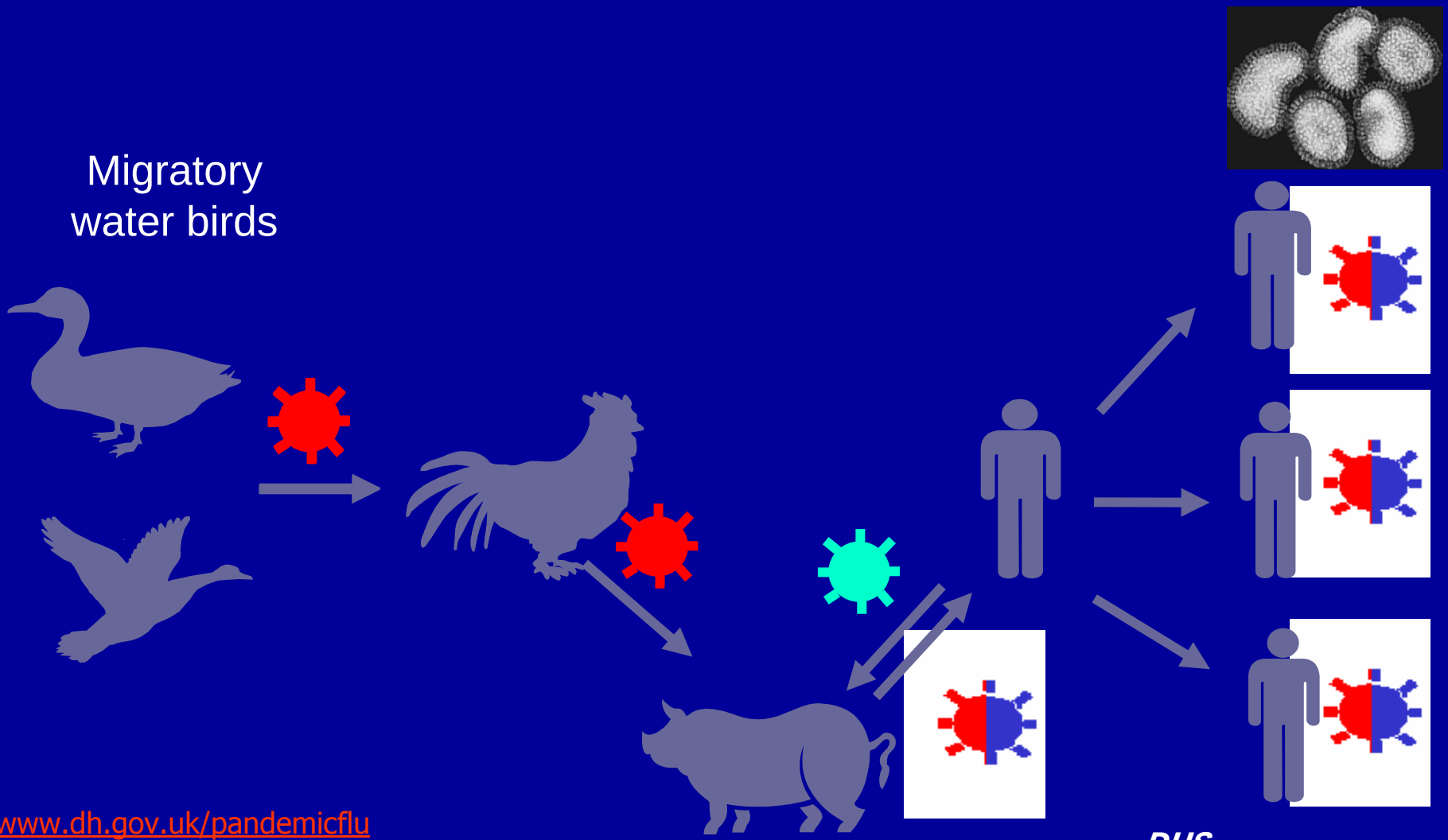


Reassortment in swine

Avian-human pandemic reassortant virus

CDC Tim Uyeki, MD

PANDEMIC STRAIN REASSORTMENT IN PIG



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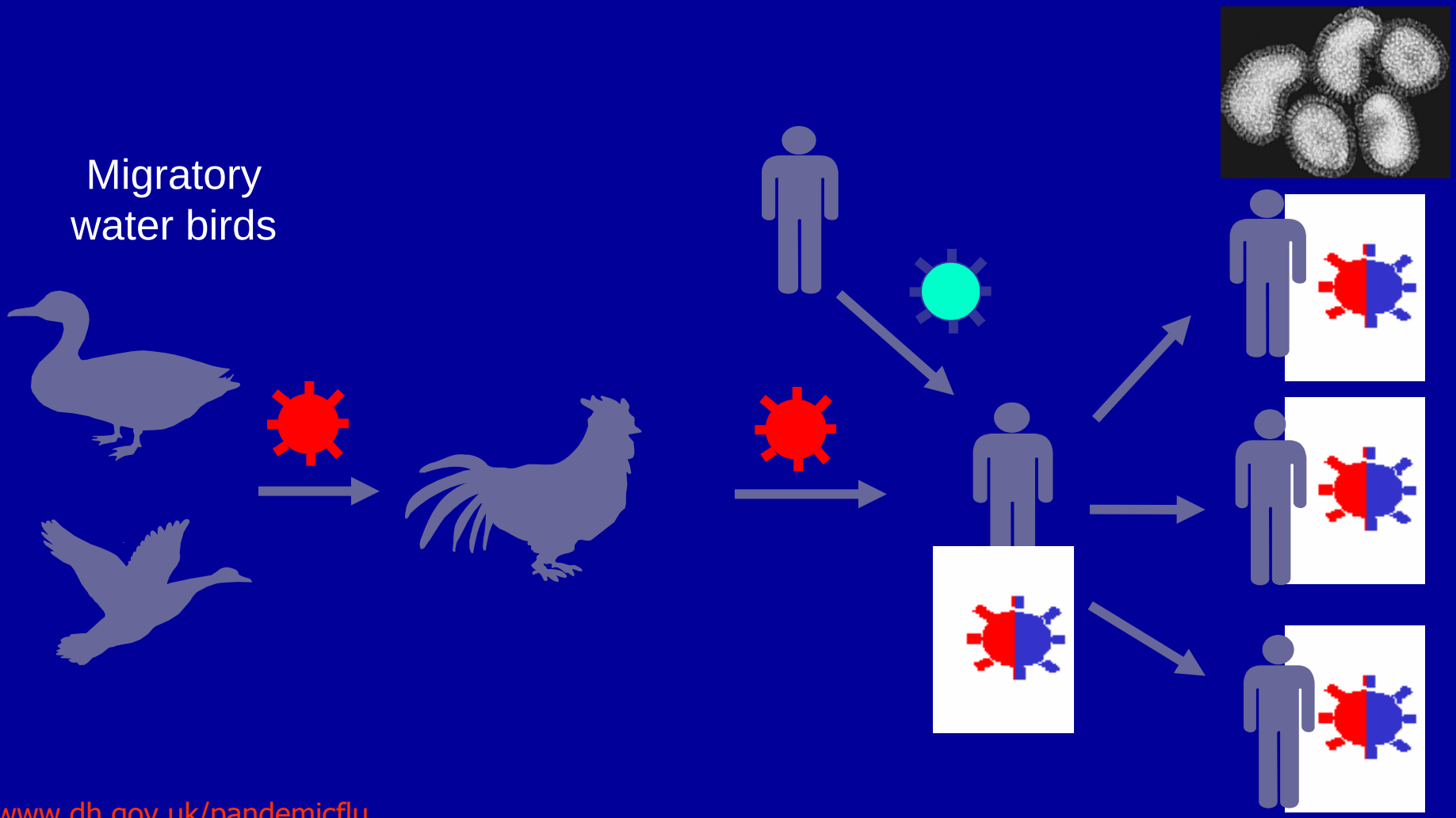
PANDEMIC STRAIN REASSORTMENT IN HUMANS



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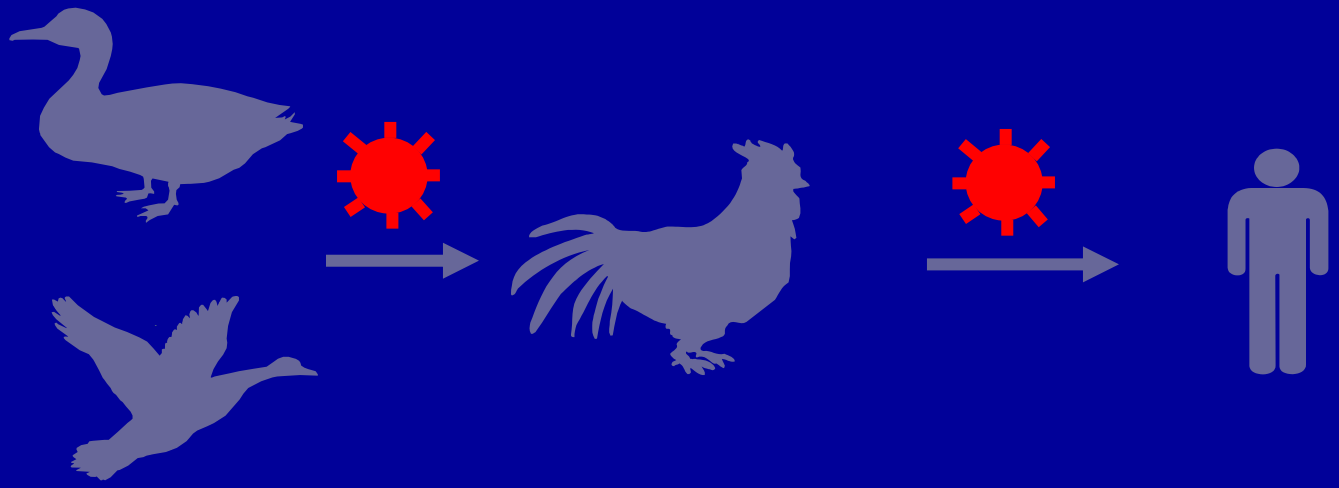
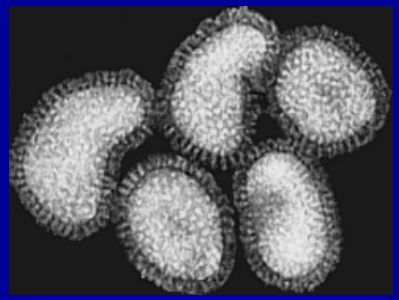
AVIAN INFLUENZA FROM BIRDS TO HUMANS

Migratory water birds

Domestic birds





- **Hong Kong 1997, H5N1**
- **HK, China 1999, H9N2**
- **Netherlands 2003, H7N7**
- **Hong Kong 2003, H5N1**
- **Viet Nam and Thailand, 2004 H5N1**

www.dh.gov.uk/pandemicflu

ESTIMATED IMPACT OF A FUTURE INFLUENZA PANDEMIC IN THE U.S.

- Deaths: 89,000-207,000
- Hospitalizations: 314,000-734,000
- Outpatient visits: 18-42 million
- Additional illnesses: 20-47 million
- Economic impact: $71.3-166.5 billion
- Population affected: 15-35%
- U.S. population: 290 million

Meltzer M, et al. Emerging Infectious Diseases 1999;5:659-671

IMPACT ON HEALTH SERVICES

- Likely to place great pressure on health and social services
- Increased numbers of patients requiring treatment
- Depletion of the workforce due to illness and other disruption

IMPACT ON BUSINESS

- 25% of the UK workforce will take 5-8 working days off over a three-month period
- Estimates suggest that during the peak absenteeism will double in the private sector and increase by two-thirds in the public sector

www.dh.gov.uk/pandemicflu

IMPACT ON SCHOOLS AND SERVICES

- Likely to spread rapidly in schools and other closed communities
- Impact on all services including police, fire, the military, duel supply, food production, distribution and transport, prisons, education and business

PANDEMIC WAVES

- Past experience teaches us that following the emergence of a new pandemic virus:
- More than one wave of influenza is likely
- The gaps between the waves may be weeks or months
- A subsequent wave could be worse than the first

www.dh.gov.uk/pandemicflu


www.timeasia.com
FEBRUARY 9, 2004
TIME
BIRD FLU
Is Asia hatching the next human pandemic?

D1

AVIAN INFLUENZA A VIRUSES

- Infect respiratory and gastrointestinal tracts of birds
  - ✓Usually do not cause disease in wild waterfowl
  - ✓Genetic re-assortment occurs frequently
  - ✓Can cause morbidity and mortality in domestic poultry
  - ✓Is a vet problem

THE CURRENT WORD ON AI AND FOOD SAFETY…

"There is no evidence that any human cases of avian influenza have been acquired by eating poultry products." CDC, February 24, 2004

"To date there is no epidemiological information to suggest that the disease can be transmitted through contaminated food or that products shipped from affected areas have been the source of infection in humans." WHO, January 24, 2004

AVIAN INFLUENZA A VIRUSES

- Highly Pathogenic Avian Influenza viruses (HPAI)
  - ✓May not cause illness in wild birds
  - ✓High mortality in domestic poultry
  - ✓Subtypes: H5, H7
  - ✓Molecular and pathogenicity criteria for determining HPAI

INTER-SPECIES TRANSMISSION AND PANDEMICS

- Many reports of transmission animal influenza viruses to humans that do not result in pandemic
  - ✓E.g. Swine Flu 1976
    - 230 infected, 13 hospitalized, 1 death
    - No sustained transmission
- But, because pandemics may be so devastating, vigilance and planning critical

HUMAN INFECTIONS WITH HPAI AVIAN INFLUENZA (1)

- H5N1, Asia
  - ✓1997: Hong Kong (18 cases, 6 deaths)
  - ✓Risk factor: visiting live poultry market
  - ✓2003: Hong Kong (2 cases, 1 death)
  - ✓2004: February 2, 2005, Vietnam, Thailand, Cambodia (55 cases, 42 deaths)
  - ✓Overall case fatality rate 65%

HUMAN INFECTIONS WITH HPAI AVIAN INFLUENZA (2)

- H9N2, 1999 and 2003
  - ✓3 cases Hong Kong, 6 cases China, no deaths
- H7N7, 2003 Netherlands (89 cases, 1 death)
- H7N3 2004 Canada (2 cases, 0 deaths)
- H7N2 2003, US
  - ✓Virginia (1 case, no deaths)
  - ✓New York (1 case, no deaths)

NORTH AMERICA HUMAN INFECTIONS WITH HPAI

H7N3 (British Columbia, Canada, Feb.- Apr. 2004)

- Highly pathogenic H7N3 detected in chicken farms
- 2 persons involved in H7N3 poultry outbreak culling activities (mild illness and conjunctivitis; conjunctivitis and headache)
  - ✓ H7N3 isolated
  - ✓ One worker was not wearing eye protection
  - ✓ One worker was wearing glasses
  - ✓ Oseltamivir treatment given, full recovery
- Highly pathogenic H7N3 detected in chicken farms

Tweed SA et al. EID Dec. 2004

Human Cases of H5N1 (2003 - 2006*)

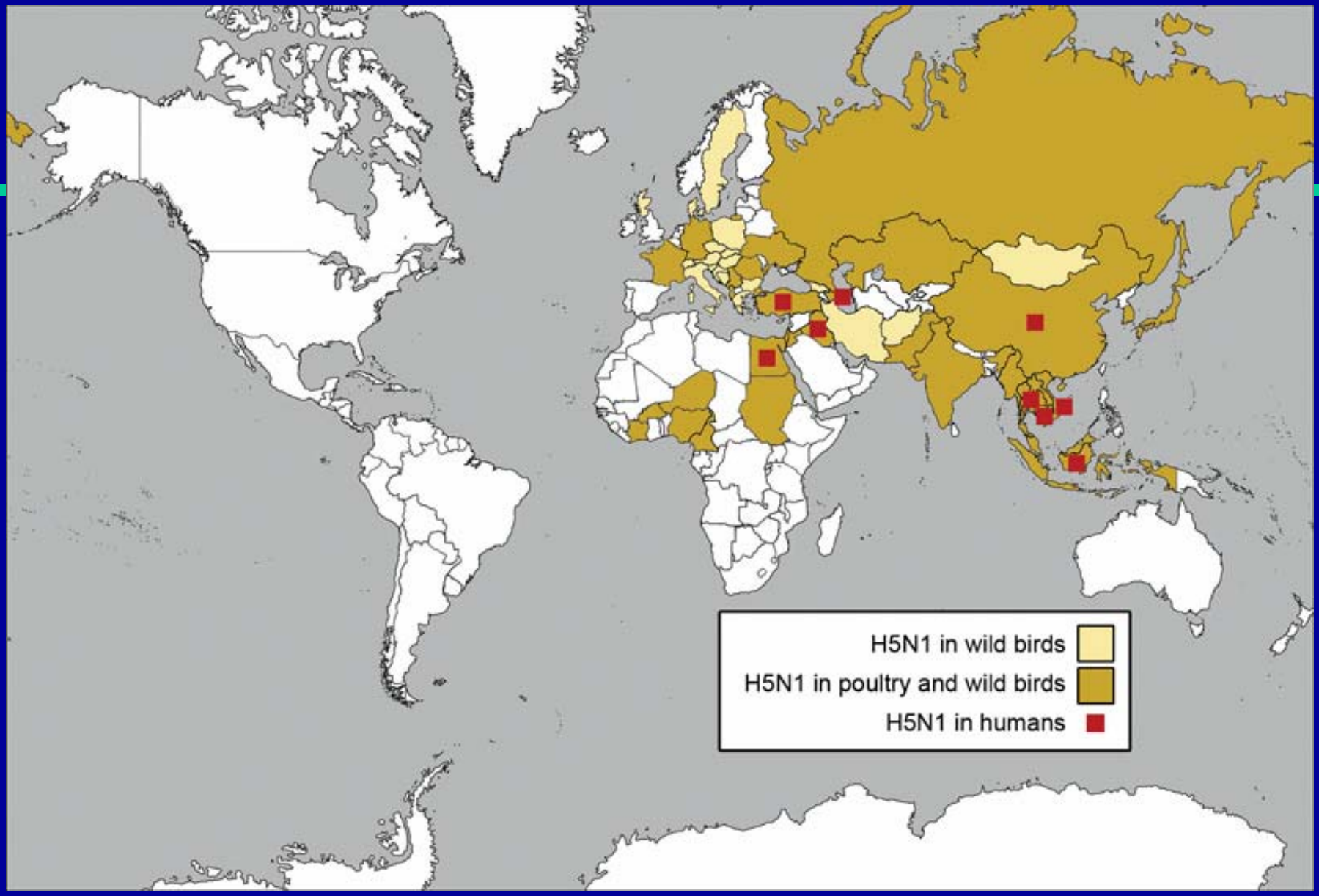
Country	Total cases	Deaths
Indonesia	33	25
Viet Nam	93	42
Thailand	22	14
Cambodia	6	6
China	18	12
Turkey	12	4
Iraq	2	2
Azerbaijan	8	5
Egypt	13	5
Total	**207**	**115**

* 12/26/03 through 5/5/06

http://www.who.int/csr/disease/avian_influenza/country/en/index.html

HUMAN H5N1 CASES 2003-2006

- Most cases had direct contact with sick/dead poultry
- Majority of cases: children, young adults
- Reports of possible person to person spread, not sustained
  - ✓ Also seen during 1997 H5N1 Hong Kong outbreak and 2003 H7N2 Netherlands outbreak



As of 4/27/06

DHS

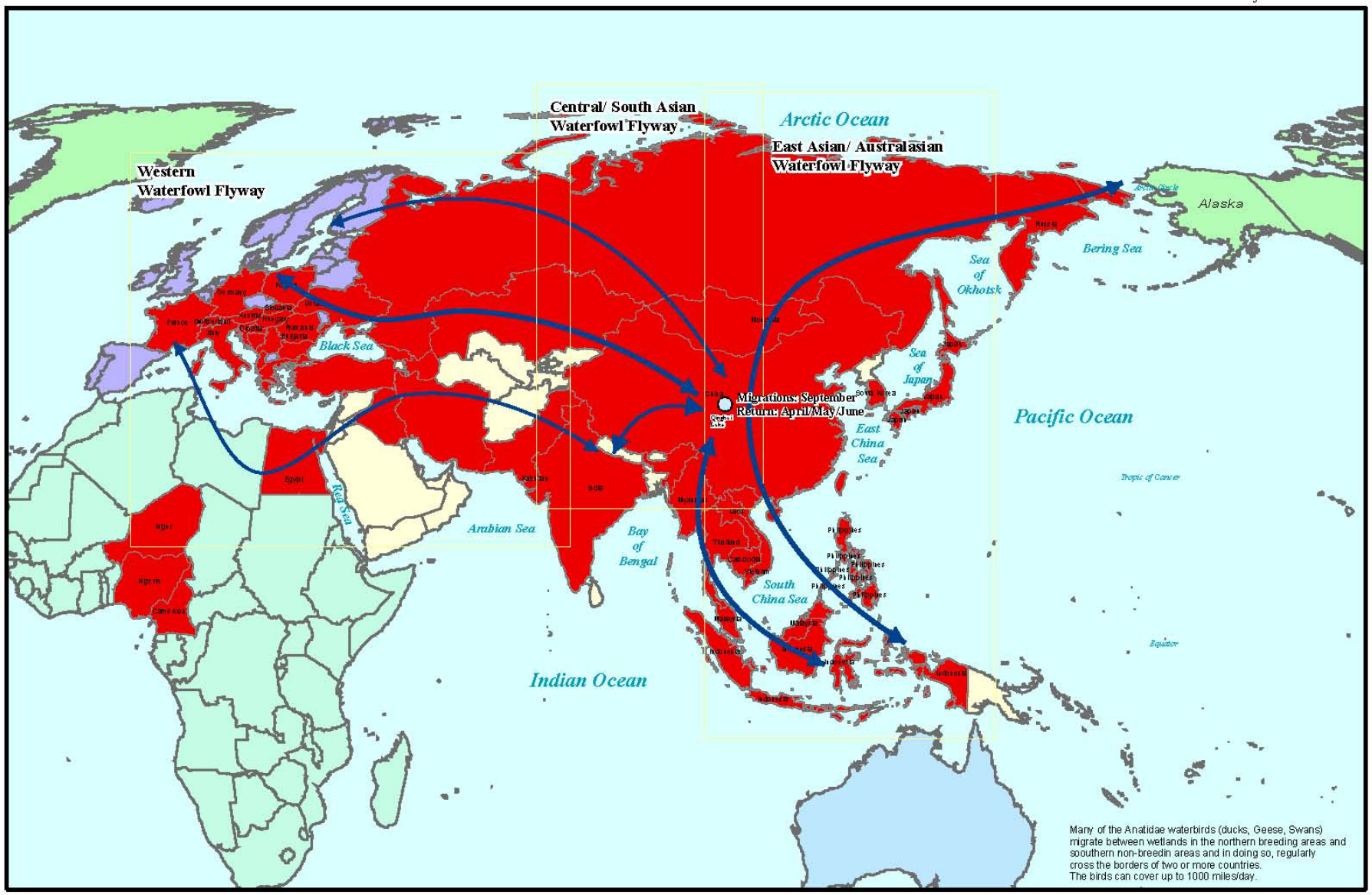
http://www.pandemicflu.gov/

H5N1 ISSUES

- Viruses circulating widely among poultry in several Asian countries, now Europe
  - ✓ Cannot be eradicated anytime soon
  - ✓ Activity may increase during cooler months
  - ✓ Viruses continue to evolve
- Can infect cats; has infected tigers, leopards (Thailand, China)
- Has infected pigs (China)
- Ducks may be infected without illness

Countries with Confirmed Poultry Cases (H5N1) Since 2003

Status as of 16 March 2006



Potential Migratory Routes for Avian Influenza (H5N1) via Waterfowl Flyways from Current Areas of Concern in SE Asia.

Legend

- Countries with Poultry Cases
- Asia
- North America
- Africa
- Australia
- South America
- Antarctica
- Europe

0 265 530 1,060 1,590 Miles

Source:
ESRI Data & Maps CD
World Health Organization
World Food Programme

Created in ArcGIS 9 using ArcMap
Created by Animal Health Branch

AVIAN INFLUENZA

- Highly pathogenic avian flu (A/H5N1) currently circulating in poultry in Asia
- Strain of avian flu has shown ability to transmit from poultry to people
- Fear that humans infected with avian flu could also be infected with "ordinary" flu
- Exchange of genes could lead to emergence of a potentially pandemic strain

www.dh.gov.uk/pandemicflu

AVIAN INFLUENZA

ALTERNATIVELY

- Avian flu strain could evolve into a potentially pandemic strain with greater affinity for people and acquire ability to pass easily from person to person

www.dh.gov.uk/pandemicflu

THE WORLD HAS CHANGED

- Global population in 18th century was <1 billion vs. 6 billion today
- Intercontinental travel is in hours rather than months and in millions rather than hundreds
- Human crowding has increased
- Population health has improved
- Animal husbandry has changed
- Interdependence had increased

www.dh.gov.uk/pandemicflu

OPPORTUNITIES FOR VIRUS EMERGENCE AND SPREAD

- Modern pig and poultry production create conditions for mass animal influenza outbreaks
- Proximity of humans and animals in many markets create potential of virus recombination
- Human crowding and travel present opportunities for virus spread

KEY H5N1 ISSUES

- Resistance to antivirals amantadine and rimatidine in many isolates
- Surveillance for disease in poultry, humans and virus changes critical
- Planning for H5N1-related pandemic and non-H5N1 pandemics essential to reduce impact
  - Including vaccine development

PANDEMIC SPREAD AND VACCINE AVAILABILITY

- Spread of a pandemic
  - ✓Months to reach U.S. for prior pandemic strains
    1918 – 0; 1957 – 4-5; 1968 – 2-3; 1977 – 3-4
  - ✓Next pandemic: earlier entry from air travel may be offset by international surveillance
- Availability of vaccine
  - ✓Optimally, first doses available ~4 months after reference strain is developed
  - ✓Weekly delivery of ~3-5 m doses from U.S. production

National Vaccine Program Office

SUMMARY OF THE PH IMPACT OF AVIAN INFLUENZA A VIRUSES

- No current evidence of sustained person-to-person transmission of avian influenza A viruses, all avian genes
- Avian influenza viruses continue to evolve and have the potential for genetic reassortment
- The key to preventing human infections with avian influenza A viruses is to control poultry outbreaks of avian influenza

ANTIVIRAL ISSUES (1)

- Single manufacturer for world supply
  - ✓US production expected 2006
- Limited courses in stockpile (2 million) and in pharmacies (1.5 million prior to 2005 season)
  - ✓Short shelf life 3-5 years

ANTIVIRAL ISSUES (2)

- Treatment vs. prophylaxis (>5 times as much)
  - ✓Treatment can reduce symptoms and complications
- Resistance may develop
  - ✓Current H5N1 strain resistant to adamantines

POSSIBLE PRIORITY GROUPS FOR VACCINE AND ANTIVIRAL DRUG USE

Define goals: Reduce health impacts or maintain infrastructure

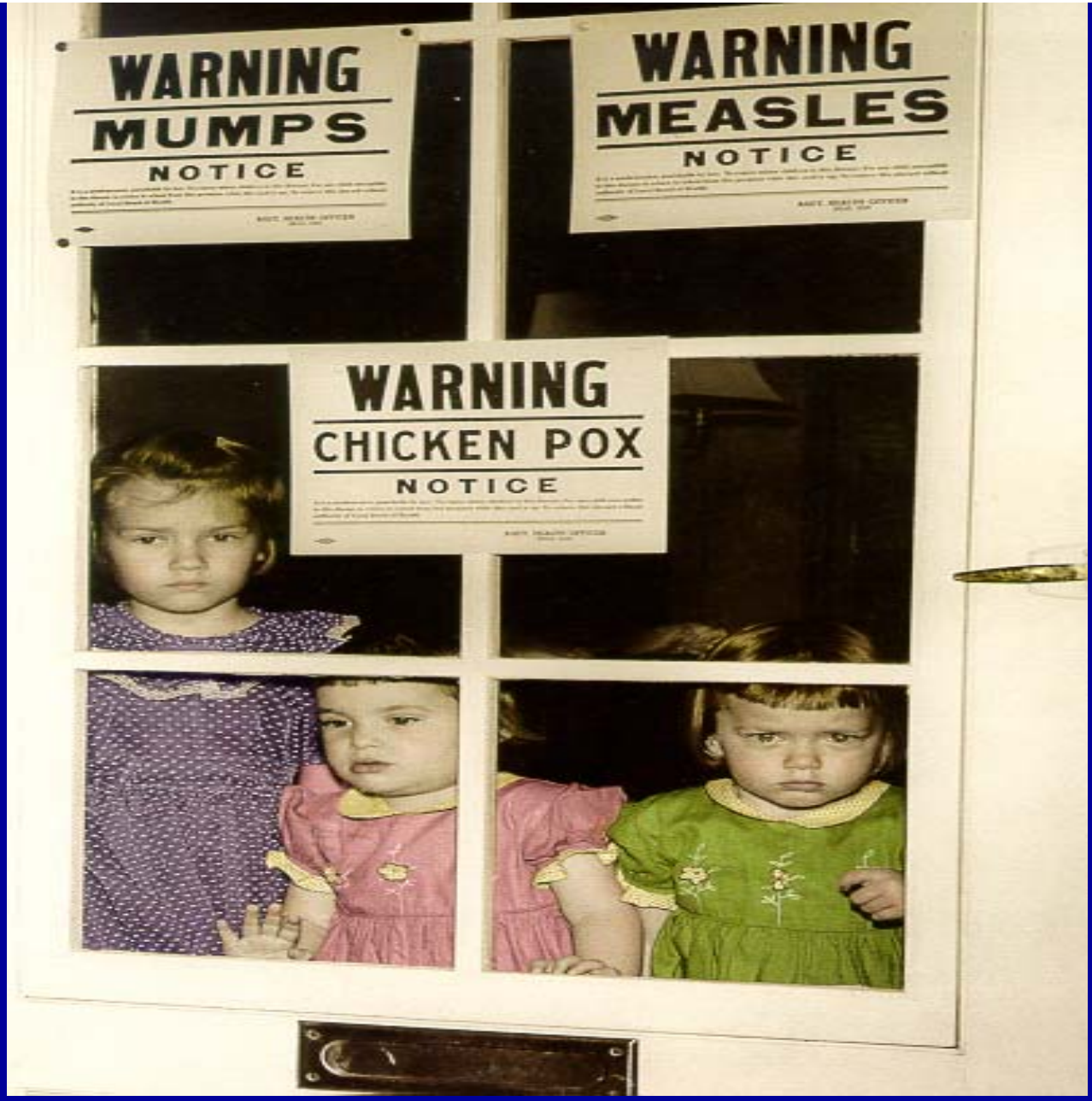
- Hospital health care workers
- Outpatient health care workers
- Public health and public safety workers
- Hospital in-patients
- Decision makers
- Persons admitted to hospital
- High-risk outpatients
- Long-term care facilities

PRIORITIZATION

- Optimally federal decision for consistency
- States or local jurisdiction will act in absence of federal leadership
- High degree of specificity is needed
  - ✓Clearly state objectives
  - ✓Definition of groups, e.g., direct patient care or essential service worker
  - ✓Sub-prioritization of "high risk"
- Cannot avoid ethical issues

ISOLATION AND QUARANTINE FOR PANDEMIC INFLUENZA

- Effectiveness doubtful
  - ✓Transmission characteristics not favorable
  - ✓Likely to be implemented early (public, political and professional pressures to "buy time")
  - ✓Lower impact as pandemic becomes more widespread


WARNING
MUMPS
NOTICE
WARNING
MEASLES
NOTICE
WARNING
CHICKEN POX
NOTICE

MEASURES TO CONTROL INFLUENZA PANDEMIC (1)

- Measures to reduce risk that cases transmit infection
  - ✓Confinement
  - ✓Face masks (symptomatic, exposed, seeking care)
- Measures to reduce risk that contacts transmit infection
  - ✓Follow-up of contacts
  - ✓Quarantine of healthy contacts
  - ✓Antiviral prophylaxis- only in specific situations

MEASURES TO CONTROL INFLUENZA PANDEMIC (2)

- Measures to increase social distance
  - ✓Isolation of ill
  - ✓Closures
  - ✓Masks—???CDC says unlikely to help

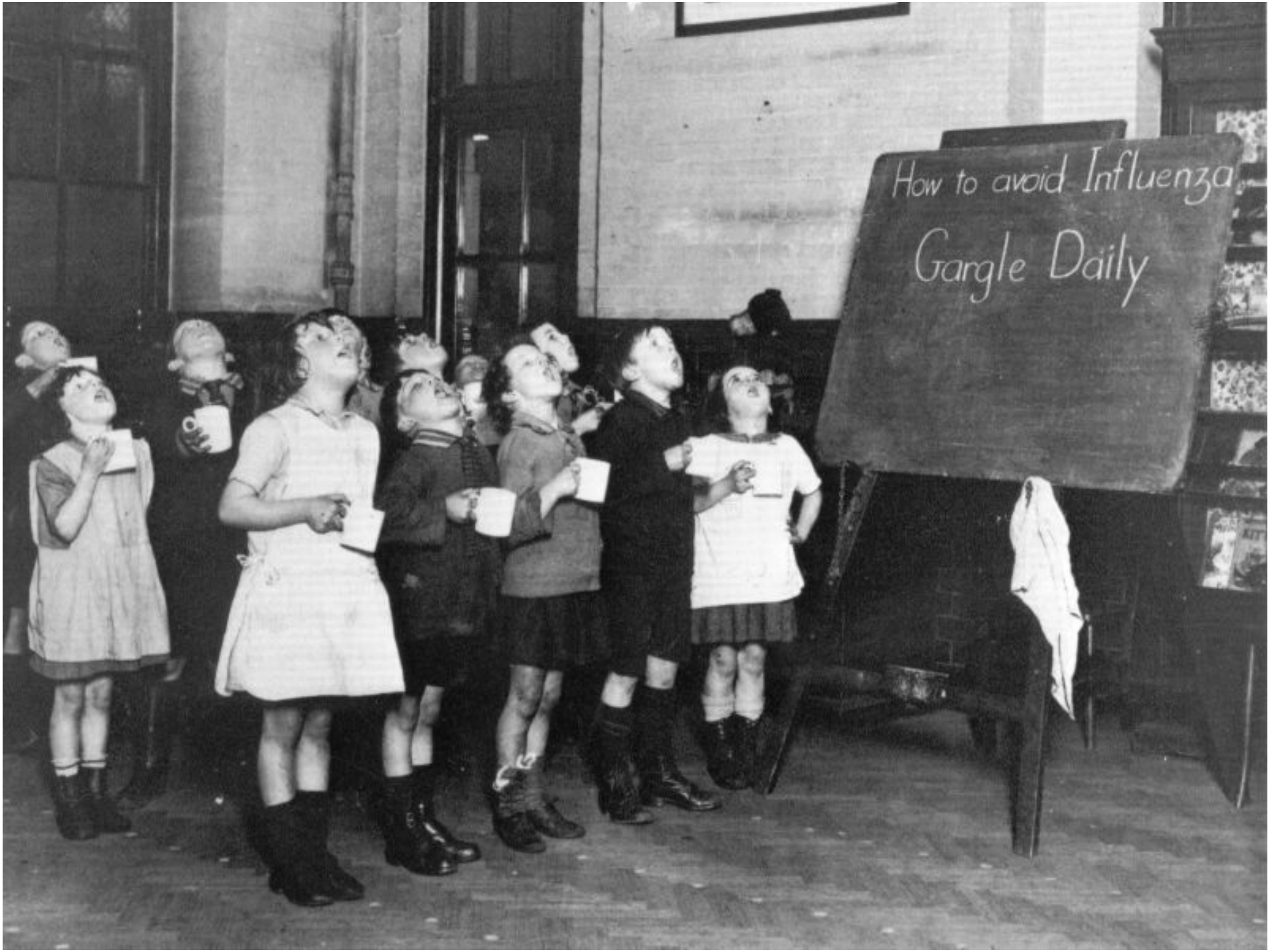
LESSONS FROM PAST PANDEMICS

- Occurs unpredictable, not always in winter
- Great variations in mortality, severity of illness and pattern of illness or age most severely affected
- Rapid surge in number of cases over brief period of time, often measured in weeks
- Tend to occur in waves – subsequent waves may be more or less severe

Key lesson - unpredictability

OTHER CONTAINMENT MEASURES

- Influenza more difficult than SARS or smallpox
- Measures would vary as pandemic develops
  - ✓ Isolation of ill persons (yes)
  - ✓ Quarantine of exposed persons (initially-avian)
  - ✓ Contact tracing (initially-avian)
  - ✓ Cancellation of events (school, public meetings, etc)
  - ✓ Steps to reduce individual exposure to virus (yes)
    - Masks
    - Hand washing
  - ✓ Public will adopt their own measures


How to avoid Influenza
Gargle Daily

PANDEMIC INFLUENZA ESTIMATES FOR CALIFORNIA

CDC Estimates of Percent of Population Affected by the Next Pandemic*	Number Affected in California (pop. 36,363,502)**
15% to 35% become ill with flu	5.4-12.7 Million
8% to 19% require out-patient visits	2.9-6.9 Million
0.2% to 0.4% require hospitalization	72-145 Thousand
0.04% to 0.1% die of flu-related causes	14-36 Thousand

*Estimates from FluAid 2.0, CDC www2.cdc.gov/od/fluaid/default.htm
**California Department of Finance Pop. Projections for 2003

Backer H, MD
DHS
Acute Communicable Disease Control Program

LAC PANDEMIC ESTIMATES*

Influenza Pandemic Impact / Weeks		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Hospital Admission	Weekly admission	458	1,834	3,209	4,585	5,960	6,877	6,877	5,960	4,585	3,209	1,834	458		
	Peak admission/day						1,072	1,072							
Hospital Capacity	# of flu patients in hospital	458	1,834	3,209	4,585	5,960	6,877	7,226	6,734	5,746	4,371	2,995	1,620		
	% of hospital capacity used	2%	7%	12%	17%	22%	25%	27%	25%	21%	16%	11%	6%		
ICU Capacity	# of flu patients in ICU	69	306	606	906	1,206	1,438	1,517	1,488	1,275	1,000	706	413		
	% of ICU capacity used	4%	18%	36%	54%	72%	86%	91%	89%	76%	60%	42%	25%		
Ventilator Capacity	# of flu patients on ventilators	34	153	303	453	603	719	758	744	637	500	353	207		
	% usage of ventilator	2%	8%	15%	23%	30%	36%	38%	37%	32%	25%	18%	10%		
Deaths	# of deaths from flu			88	351	615	878	1,142	1,317	1,317	1,142	878	615	351	88
	# of flu deaths in hospital			61	246	430	615	799	922	922	799	615	430	246	61

D Bagwell: CDC FluSurge

*Assumes 35% attack rate

DHS

Acute Communicable Disease Control Program

MEDICAL CARE FOR SEVERE INFLUENZA INFECTIONS

- Supportive therapy
  - ✓Supplemental oxygen
  - ✓Intubation/ventilation
  - ✓Fluid management
  - ✓Nutrition
- Specific therapy
  - ✓Antiviral drugs
  - ✓Antibiotics for bacterial superinfection

CHALLENGES TO MAINTAINING QUALITY MEDICAL CARE

- Ability to effectively triage patients
- Ability to care for ill outpatients
  - ✓ Delivery of medical care, medications, and food
- High demand for inpatient services
  - ✓ Estimated >25% increase in demand for inpatient beds, ICU beds, & ventilators **for a mild pandemic**
  - ✓ Staff absenteeism
  - ✓ Limited availability of critical resources
- Surge capacity for inpatient care

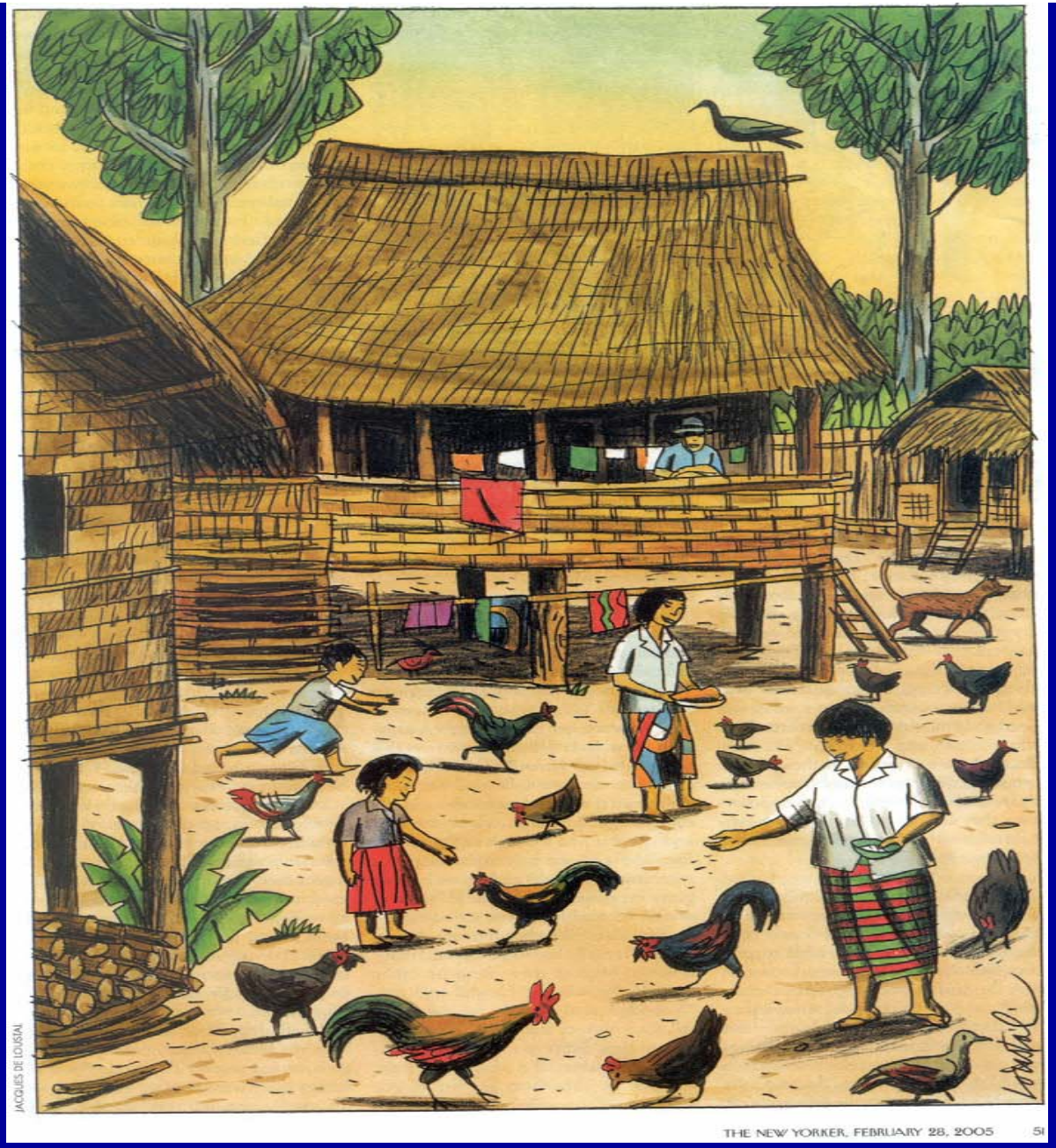
UNKNOWNS AND UNCERTAINTIES

- When will a pandemic occur?
- How bad will it be?
- Will there be major societal impacts beyond health?
- Who will be at greatest risk of disease and death?
- How much vaccine or antiviral drug will be available and who will get it?
- Will the health care system be able to cope with the increased demands?
- What control measures will be implemented to decrease spread in the community?

PANDEMIC INFLUENZA SUMMARY

- Limited antivirals
- Limited vaccine
- Limited benefit of isolation and quarantine
- Limited excess capacity in health care system

What are we supposed to do?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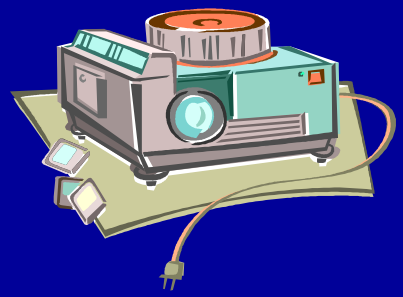

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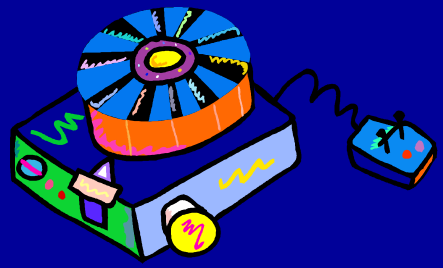
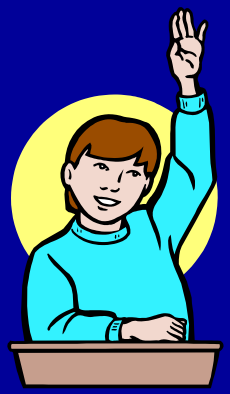
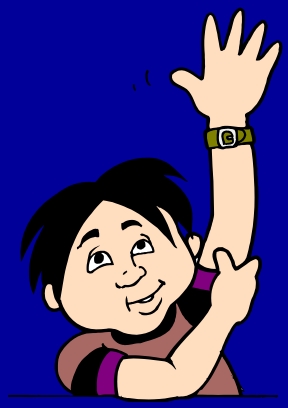


More information can be found at:

http://lapublichealth.org/acd/flu.htm

QUESTIONS AND ANSWERS






Good Bye


Have a Nice Day
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