TB, West Nile Disease, and Influenza A

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Disclosures
Edward A. Dominguez, MD

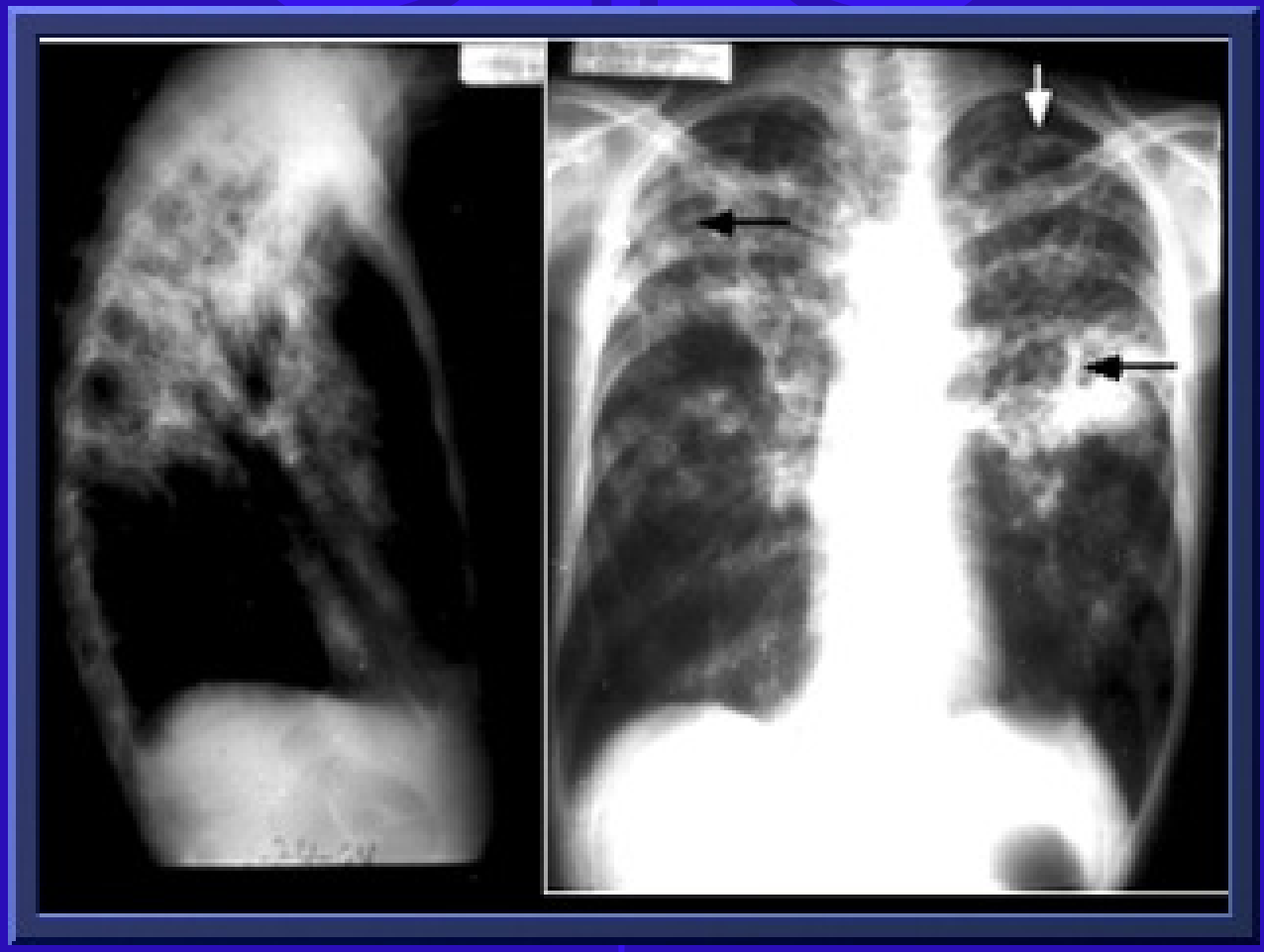
- Research
  - Cubist
- Consultancy
  - Pfizer
  - Celgene
- Speaker Bureau
  - Astellas
  - Cubist
  - Pfizer

What I hope to achieve…

- Tuberculosis update
  - Epidemiology
  - Quantiferon vs. PPD
  - Therapy
- West Nile update
  - What we learned from 2012
- Influenza A update
  - Seasonal and pandemic
  - Treatment
  - Vaccines

What I Hope to Avoid!!!!

Tuberculosis



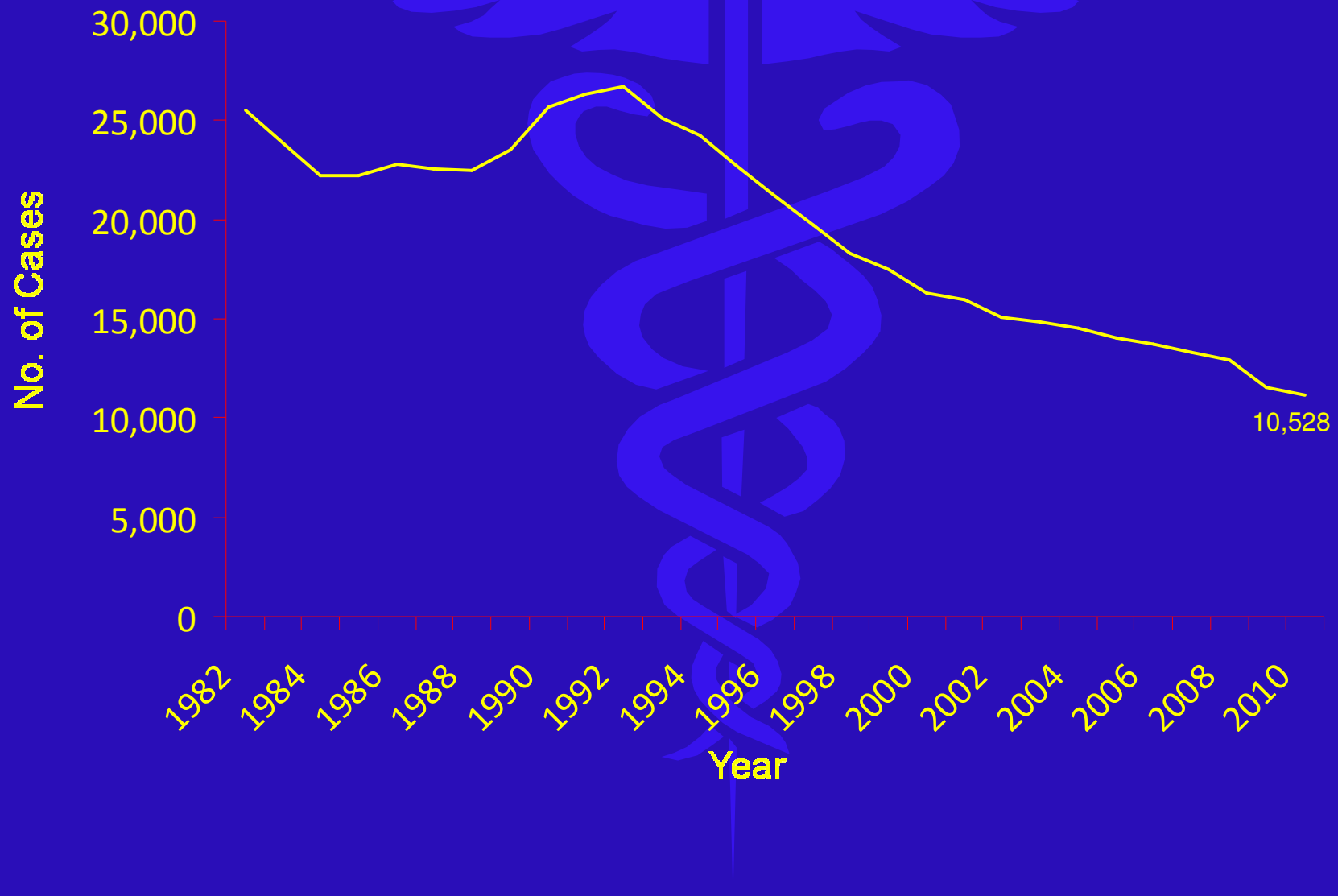
Epidemiology of Tuberculosis

- One-third of the world population is infected with TB
- 9 million new cases and 1.4 million deaths annually worldwide
- Most U.S. cases are in urban and immigrant communities
- Among immigrants to US, TB is largely caused by reactivation of latent infection.
- Among US natives, many cases result from recent transmission.

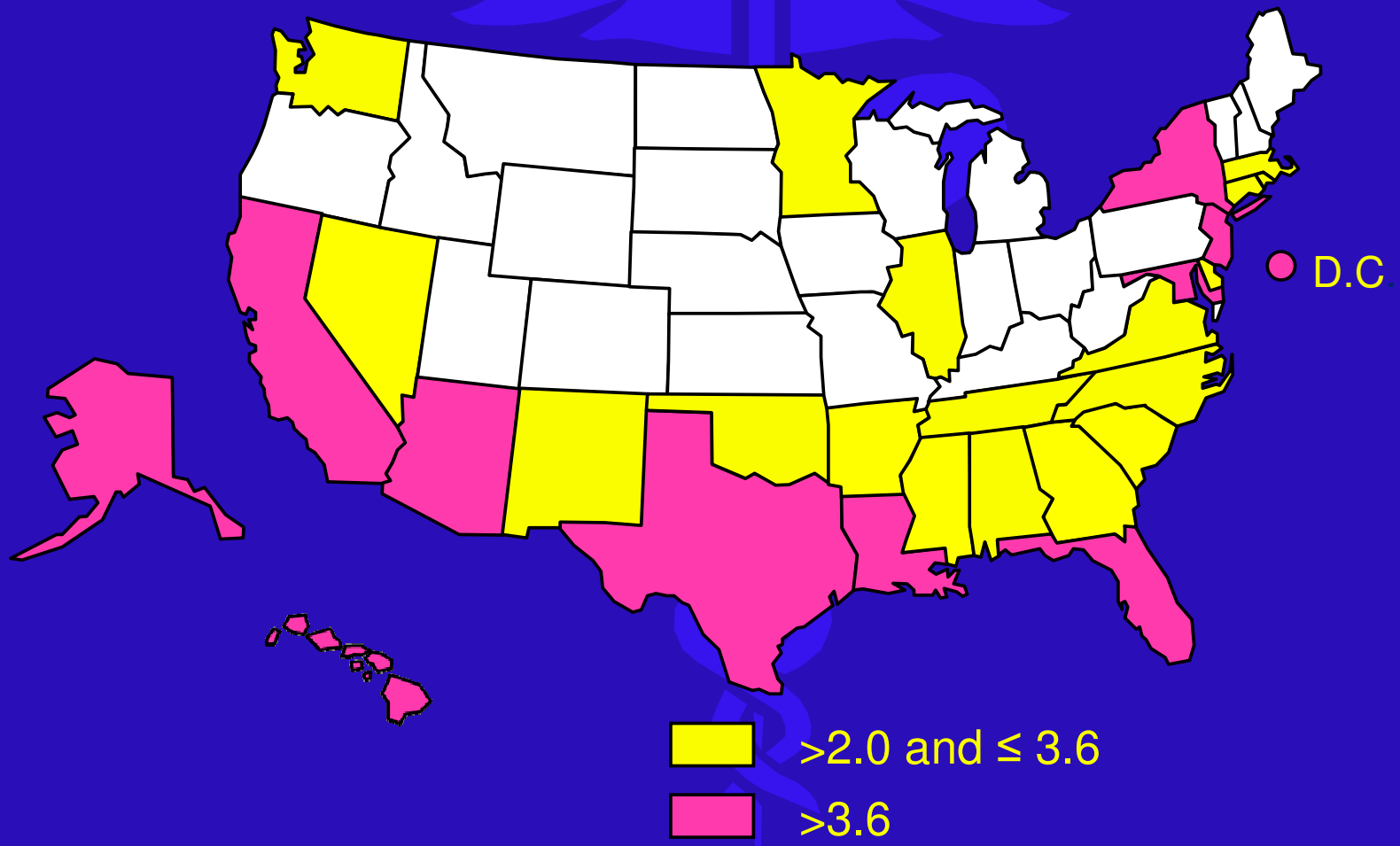
Primary Tuberculosis and Sequelae

- Primary TB usually a self-limited, mild pneumonic illness; often undiagnosed
- The incidence of progression from latent to active infection is ~5% in the first 5 years, plus an additional 5% lifetime risk thereafter

Reported TB Cases
United States, 1982–2011



TB Case Rates,* United States, 2011



*Cases per 100,000.

Conditions That Increase Risk of Progression to TB

- HIV (risk of TB disease is ~10% each year)
- CXR suggestive of previous untreated TB
- Diabetes mellitus
- Silicosis
- Prolonged immunosuppressive therapy
- Cancer of the head and neck
- Hematologic and RES diseases
- End-stage renal disease
- Intestinal bypass or gastrectomy
- Malabsorption syndromes
- Low body weight (10% or more below the ideal)

Risk Factors for Drug-Resistant TB

- History of treatment with TB drugs
- Contacts of persons with drug-resistant TB
- Foreign-born persons from high prevalence drug- resistant areas
- Smears or cultures remain positive despite 2 months of TB treatment
- Received inadequate treatment regimens for >2 weeks

MTB: Diagnosis of LTBI

Testing methods

- Tuberculin skin test (TST):
  - 0.1 mL purified protein derivative (PPD)
  - In HIV-infection, positive is induration ≥5 mm at 48-72 hours
  - Specificity 56-95%
- Interferon-gamma release assay (IGRA):
  - IFN-γ release in response to MTB-specific peptides
  - Sensitivity: 0.70 to 0.90 (T-Spot more sensitive)
    - PPD test is about 0.76
  - Specificity:
    - Non-BCG vaccinated: 0.99
    - BCG-vaccinated: 0.93 to 0.96
    - PPD is only 0.56
  - Advanced immunosuppression may cause false-negative results to both tests

MTB: Treatment of TB Disease

For drug-susceptible pulmonary TB

- Two phases:
  - Initial: 2 months
    - Isoniazid (INH), rifampin (RIF) or rifabutin (RFB), pyrazinamide (PZA), ethambutol (EMB)
    - If organism is susceptible to INH, RIF, and PZA, may discontinue EMB
  - Continuation: 4 months
    - INH + RIF (or RFB)

MTB: Monitoring

- Close follow-up is essential to ensure treatment success
- Pulmonary TB: ≥1 sputum smear and culture monthly until 2 consecutive specimens are negative on culture
  - Positive cultures after 3 months of treatment: repeat drug susceptibility tests
  - Positive cultures after 4 months: consider as treatment failure; manage accordingly
- Extrapulmonary TB: follow-up evaluation depends on sites involved

Treatment of Multi-drug Resistant TB

- Best regimens include all of the following:
  - Aminoglycoside (streptomycin or amikacin) or capreomycin
  - Fluoroquinolone
  - Four other agents to which the isolate is sensitive
- Treat for 24 months after culture conversion
- Always use observed therapy
- Delamanid (not yet approved)
- Linezolid (not FDA-approved for this)

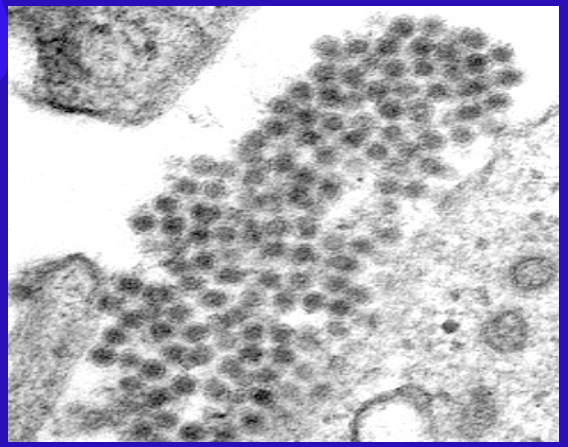
Gler MT, et al. *N Engl J Med* 2012; 366:2151-2160
Lee M, et al. *N Engl J Med* 2012; 367:1508-1518

West Nile Virus, 2012

- Virology
- Epidemiology
  - Transmission
  - 2012 Epidemic
  - MHS experience
- Clinical syndromes
- Management and Prevention

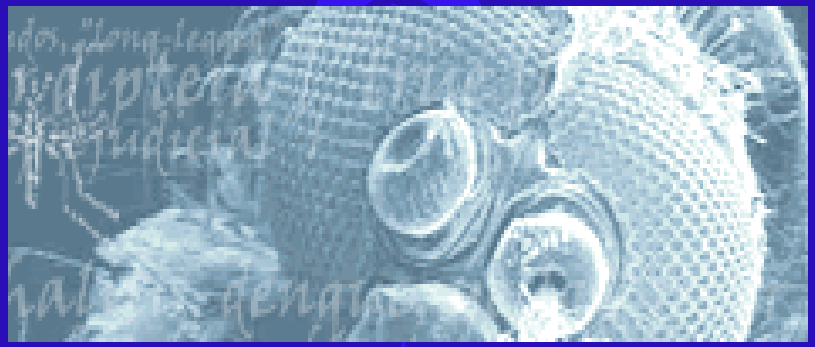
West Nile Virus

- Family: *Flaviviridae*
- Genus: *Flavivirus*
- Japanese encephalitis group
  - ***Japanese encephalitis virus***
  - ***Murray Valley encephalitis virus***
  - ***St. Louis encephalitis virus***
  - ***Usutu virus***
  - ***West Nile virus*** (Kunjin virus)
- Arboviruses (arbo = arthropod borne)



Potential Hosts of West Nile Virus

- At least 225 species of birds
- At least 49 species of mosquito
- At least 28 species of mammals, inc. cats, dogs, sheep, llama, wolf, goats, squirrels, skunks, etc...
- Alligators…..



West Nile Virus Transmission Cycle

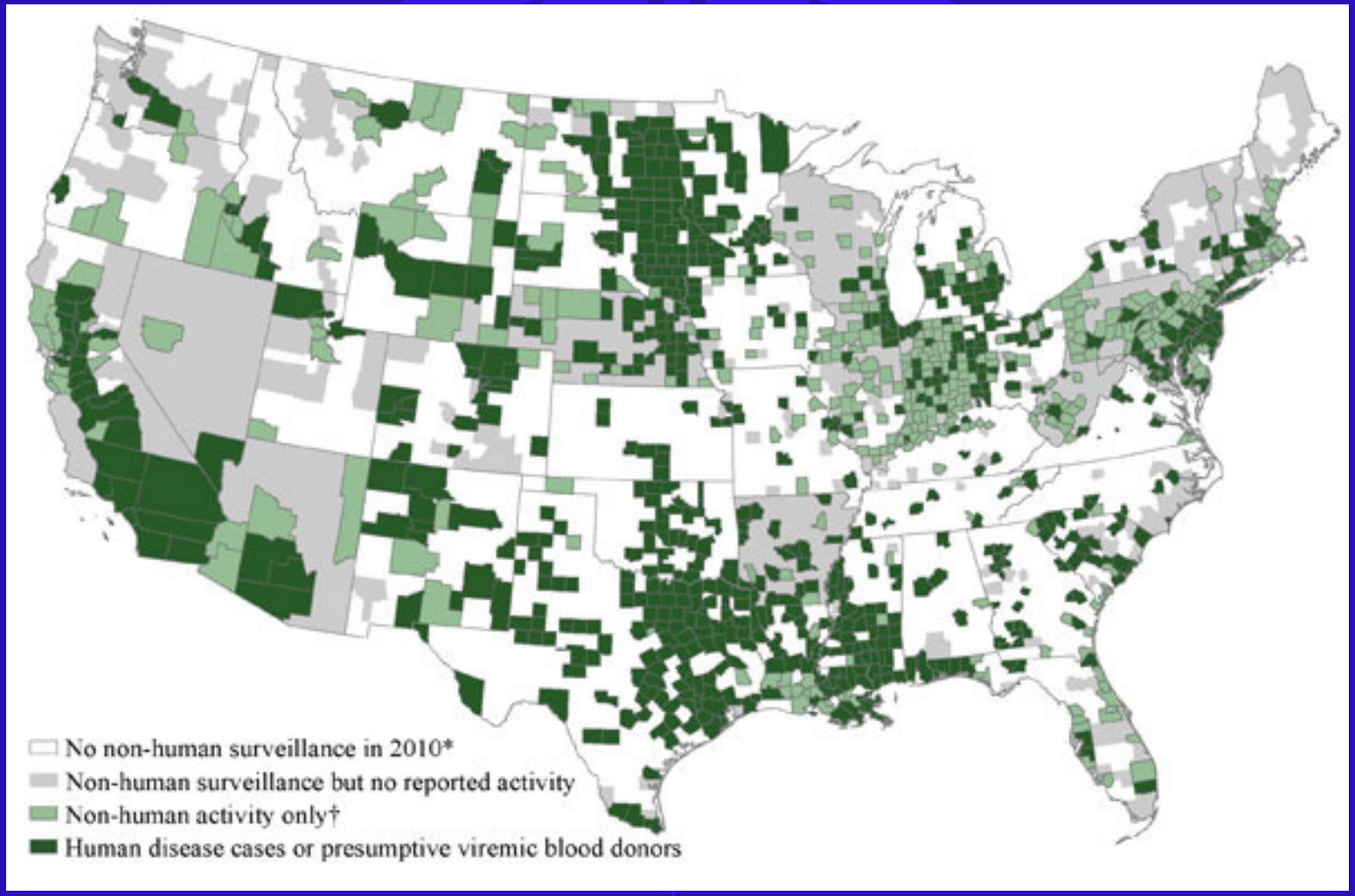
West Nile virus

West Nile virus

WNV: Novel Modes of Transmission

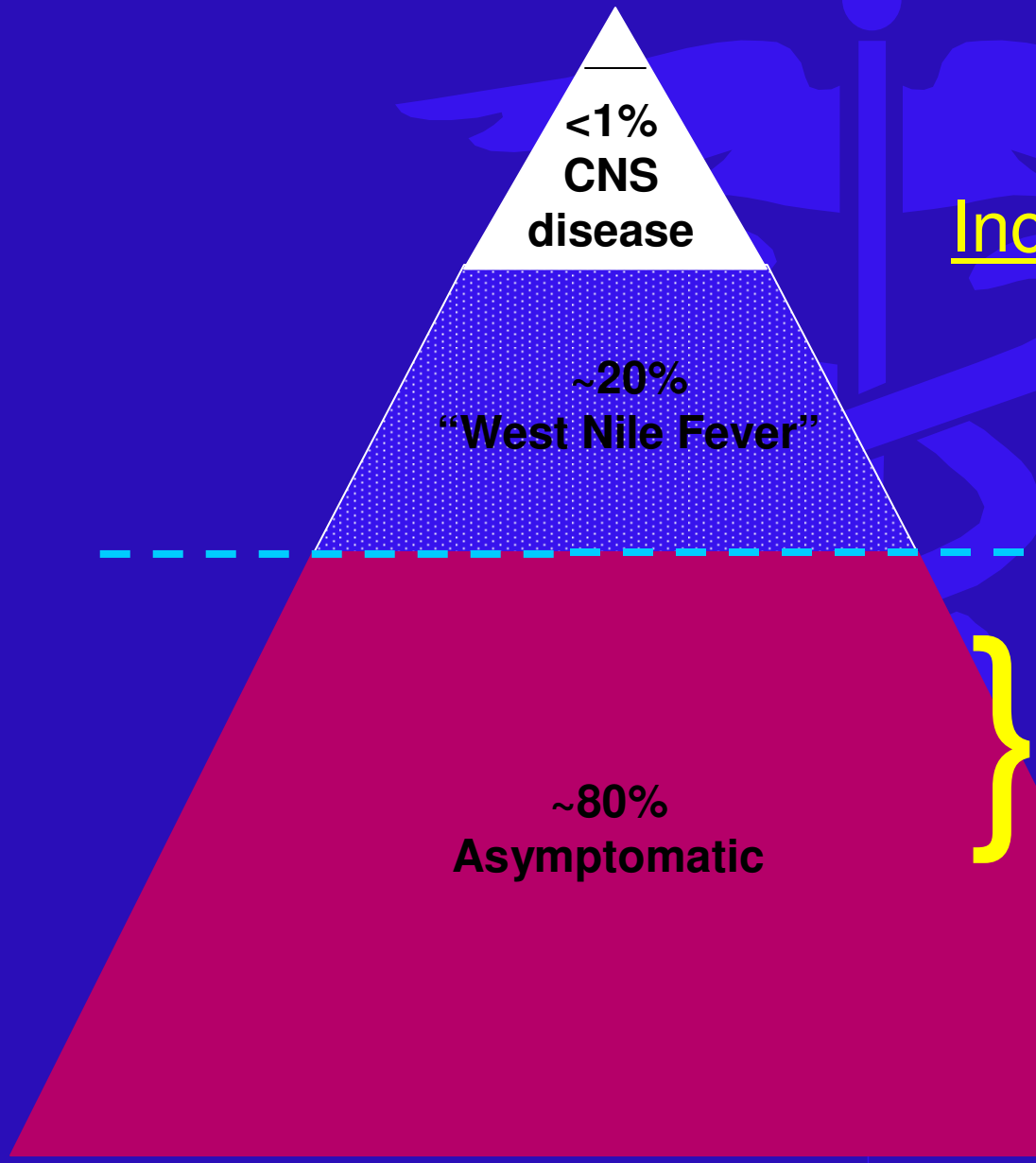
- Blood transfusion-associated transmission
  - As of July 2003, US blood donors screened for WNV using nucleic acid amplification testing (NAT)
- Solid organ transplant transmission
  - 7 cases as of 2009
- Intrauterine transmission
  - Ongoing CDC registry; only 1 proven case
- Transmission through breast milk
  - Only 1 proven case

WNV Activity Reported To ArboNET
(as of September 18, 2012)



www.cdc.gov/ncidod/dvbid/westnile/Mapsactivity/surv&control12MapsAnybyState.htm

WNV Human Infection "Iceberg"

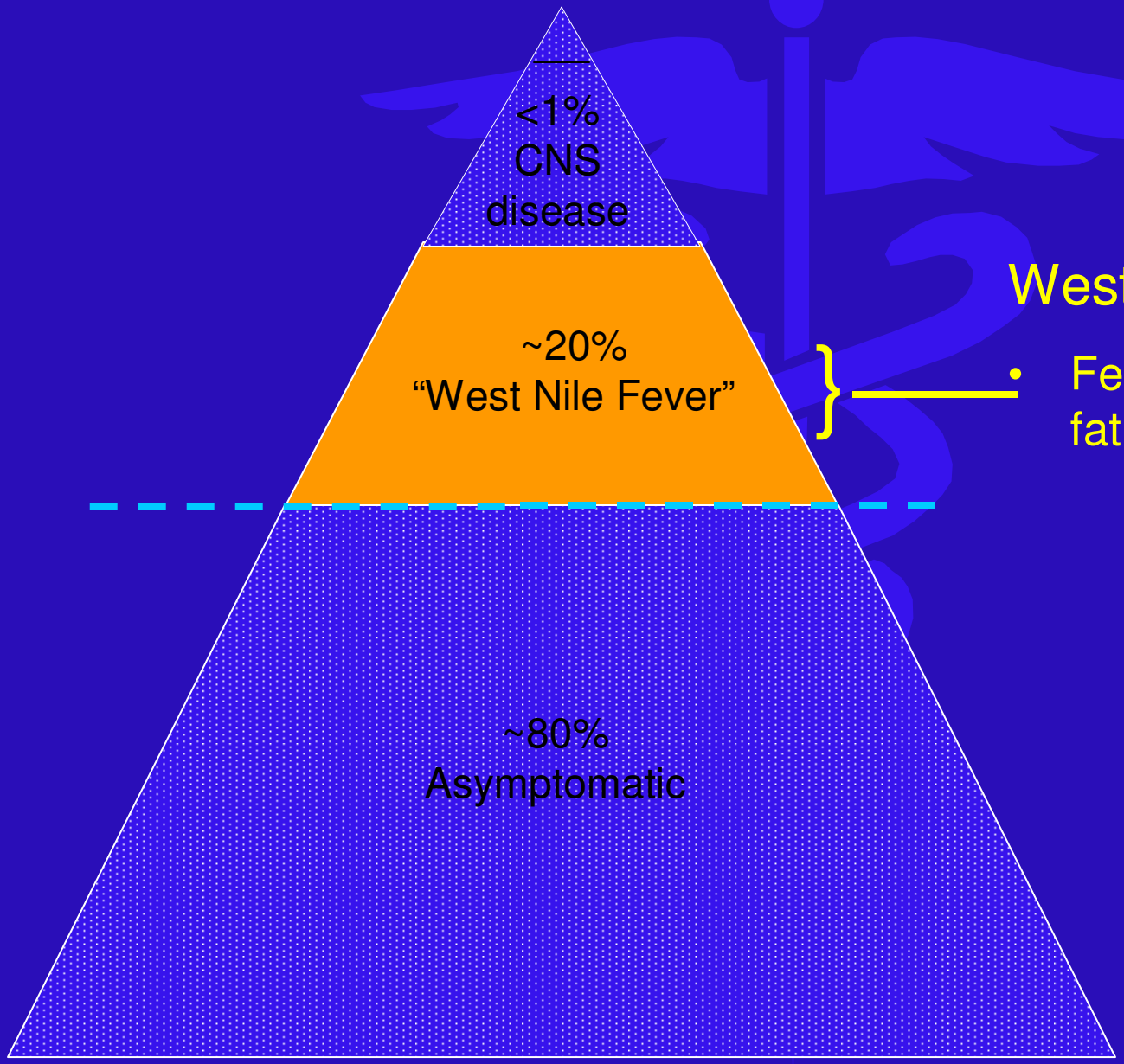


Incubation: 3-14 days

Asymptomatic Infection

- Generation of life-long immunity (presumed)

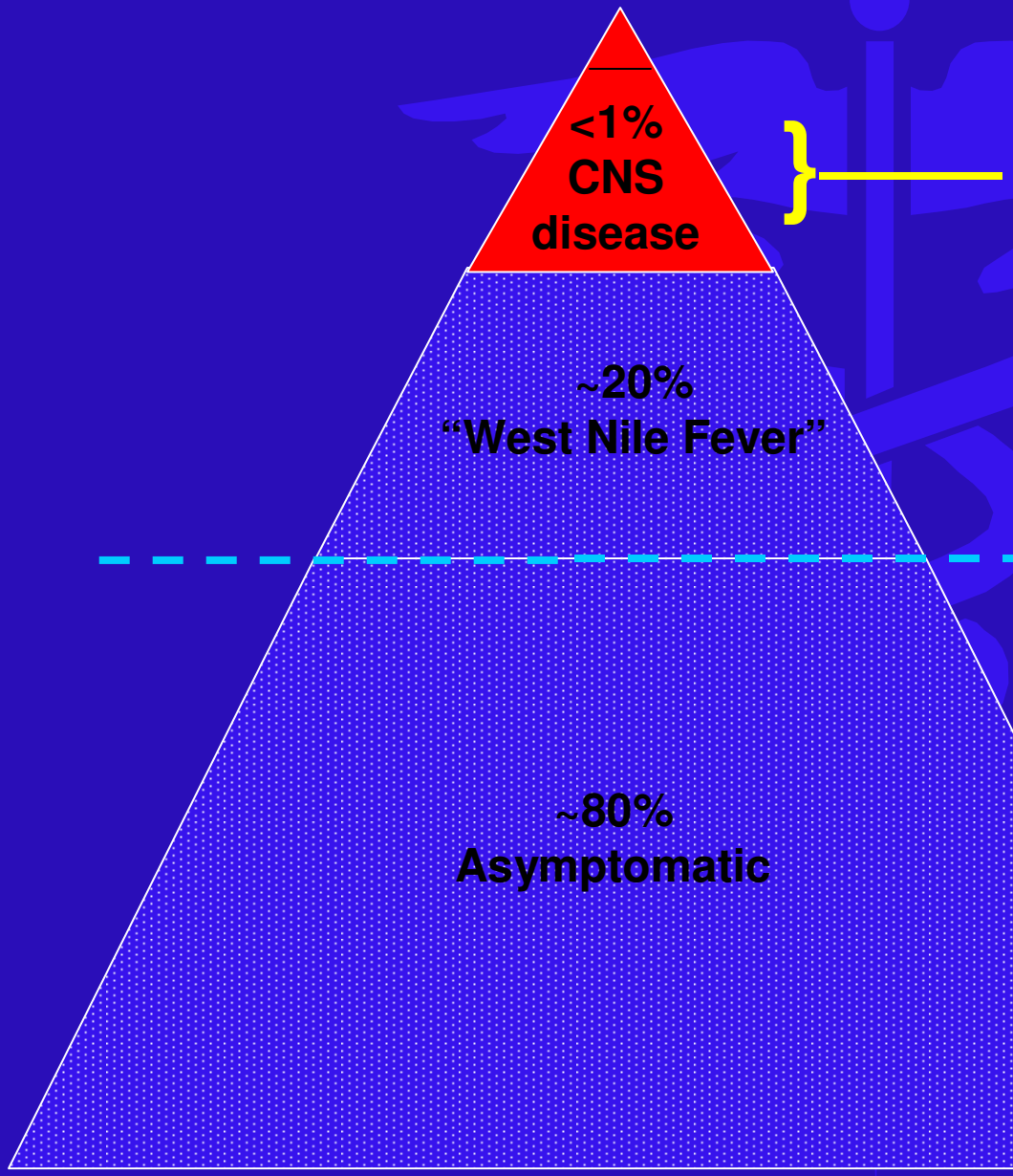
WNV Human Infection "Iceberg"



West Nile Fever

- Fever, headache, rash, fatigue

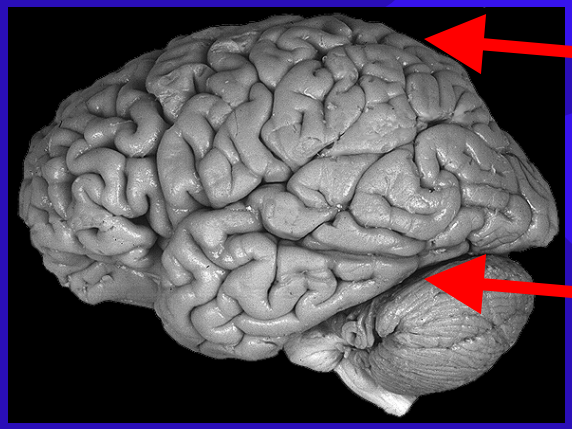
WNV Human Infection "Iceberg"



WNV Neuroinvasive Disease (WNND)

- Meningitis, encephalitis, poliomyelitis, Parkinson's

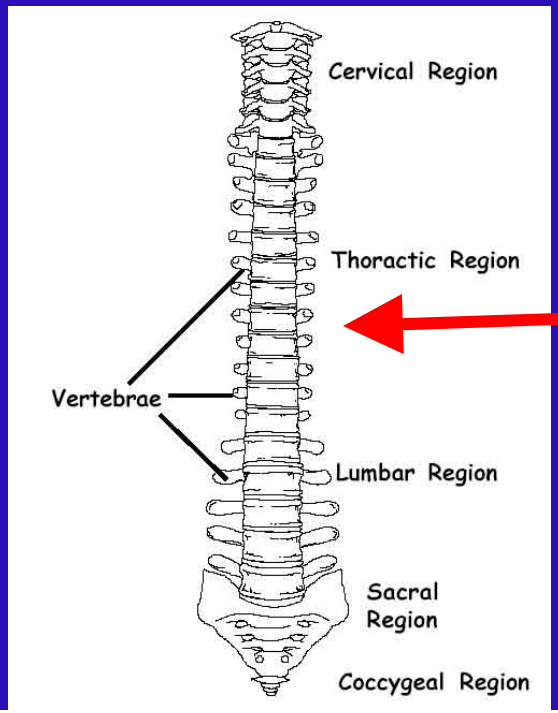
West Nile Neuroinvasive Disease



"Meningitis": Inflammation of the covering of the brain

"Encephalitis": Inflammation of the brain itself

"Meningoencephalitis"



"(Polio)Myelitis": Inflammation of the spinal cord

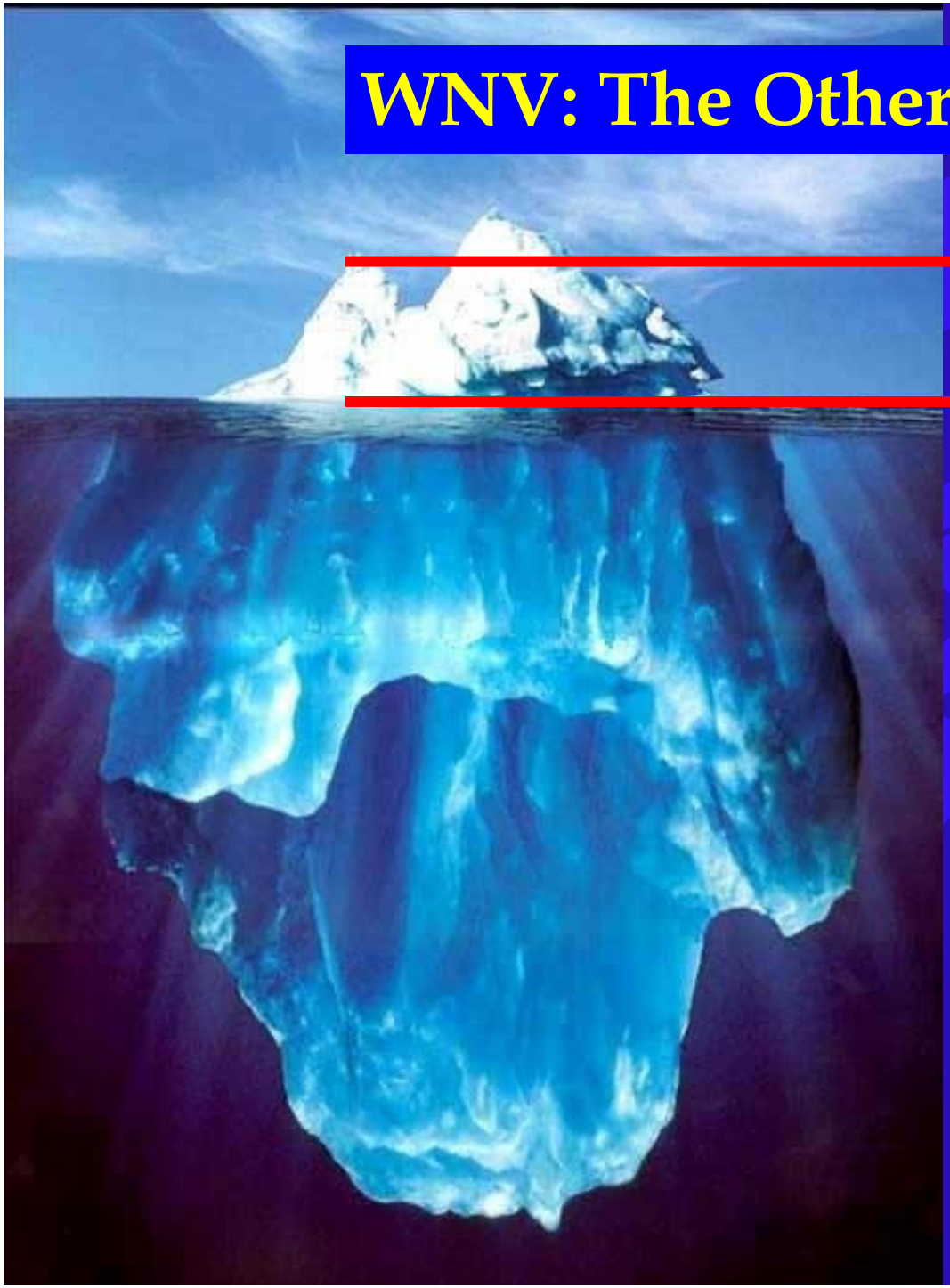
Methodist Health System 2012 WNV Experience

- Dallas: 8
- Charlton: 10*
- Mansfield: 16
- Richardson: 7

- Most cases: fever; meningitis

* One death: encephalitis, 10-day stay in ICU
Source: Dr. Zakir Shaikh, Med Director Infection Control, MHS

WNV: The Other "Iceberg"

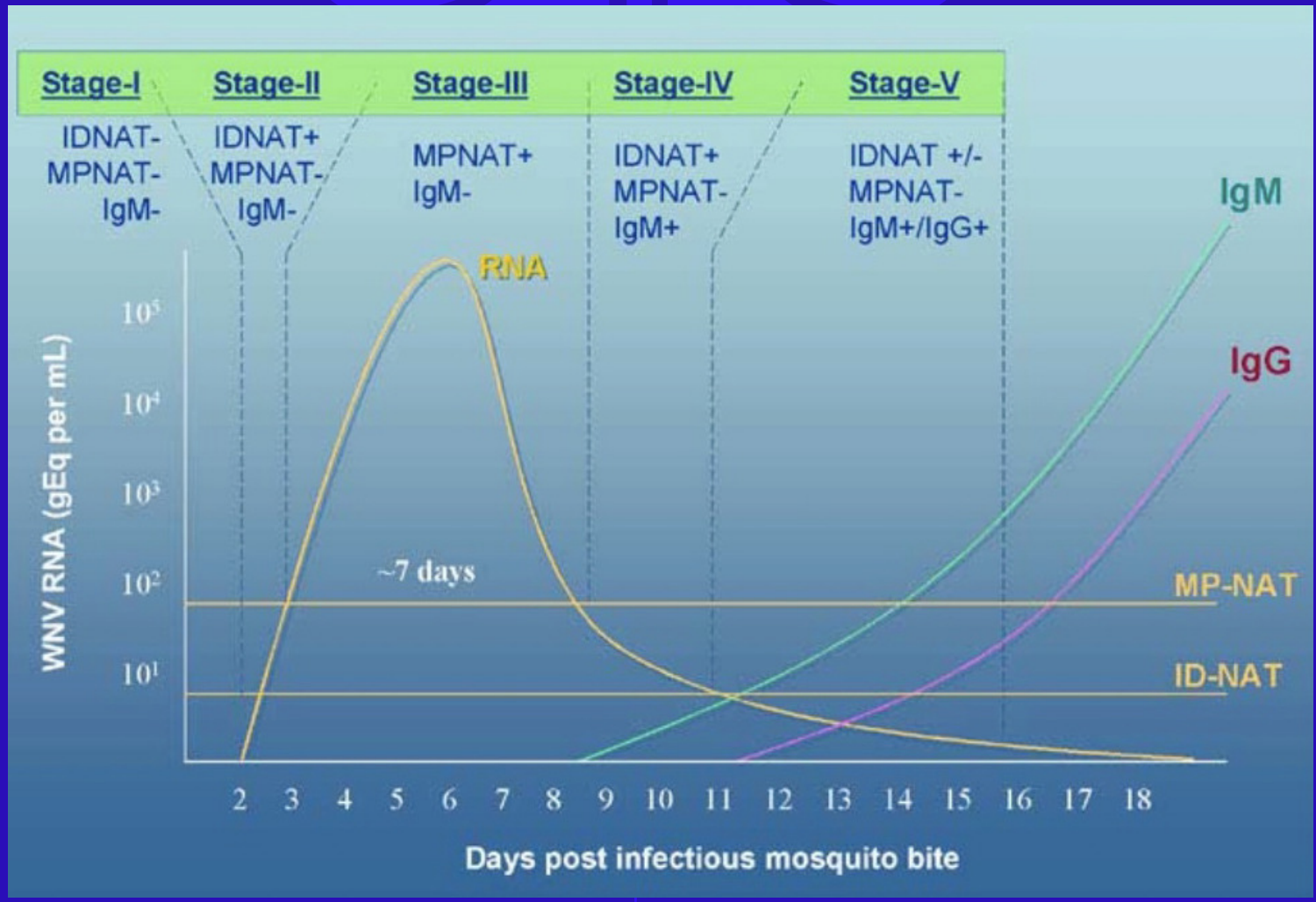


Acute WNV Illness

WNV Long-term effects:

- Neurologic
- Kidney

WNV Post-infection Time Table



WNV Treatment

- Treatment
  - Most cases: manage the symptoms
  - Severe cases:
    - Polyclonal IVIG
    - NIH-sponsored randomized, placebo-controlled trial of high-titer WNV intravenous immune globulin (IVIG)

Shimoni Z, et al. *Emerging Infect Dis* 2001;7:759
Beigel JH, et al. *Antimicrob Agents Chemo* 2010;54:2431-36
Beasley DW. *Immunotherapy* 2011;3:269-85

WNV Prevention

- WNV human vaccine
  - Phase I / II clinical trials
  - Promising safety, efficacy profiles
- Prevention
  - Avoid outdoors at dusk and dawn
  - Drain standing water
  - DEET

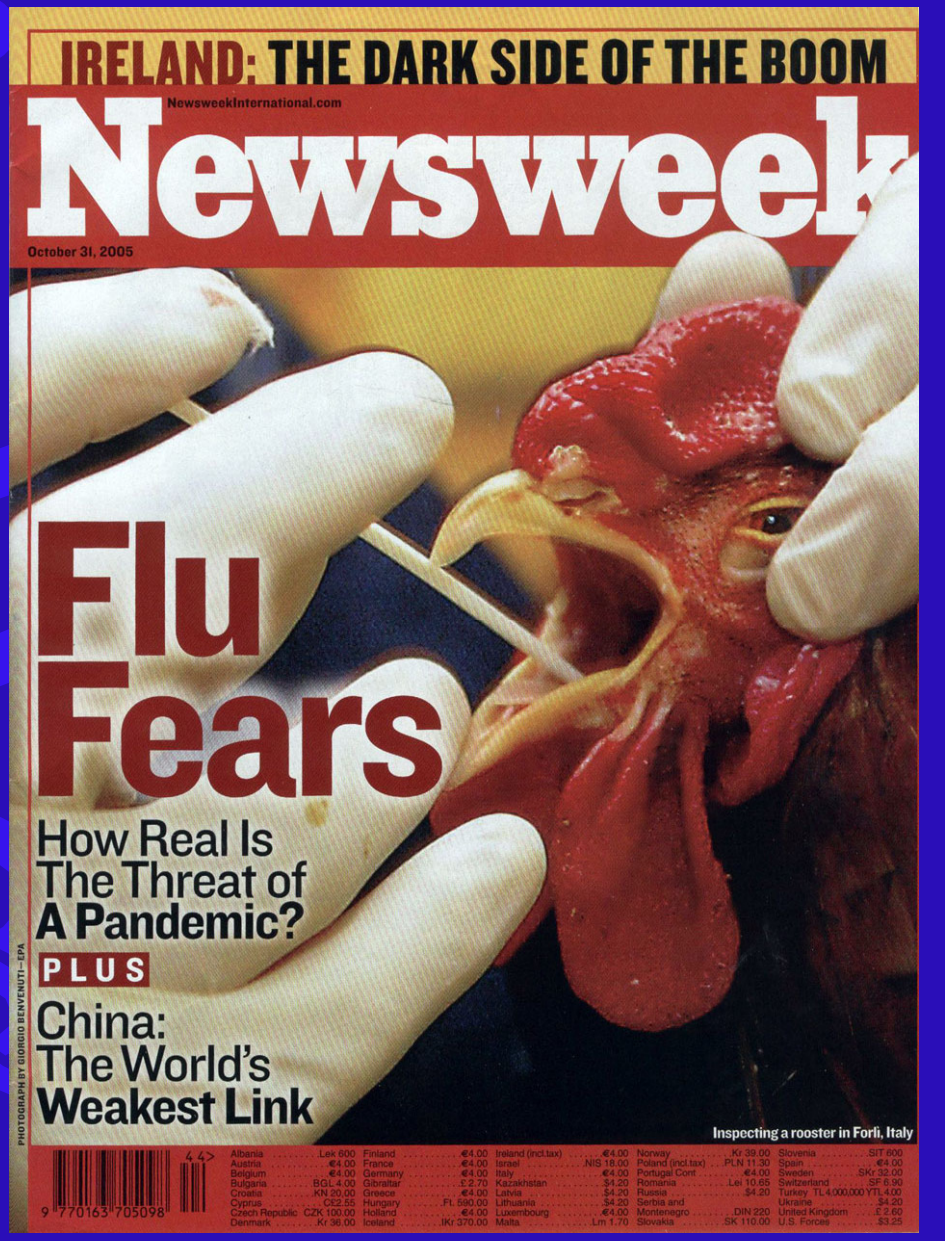
The Clinical Impact of WNV Infection 1999: What We Thought We Knew...

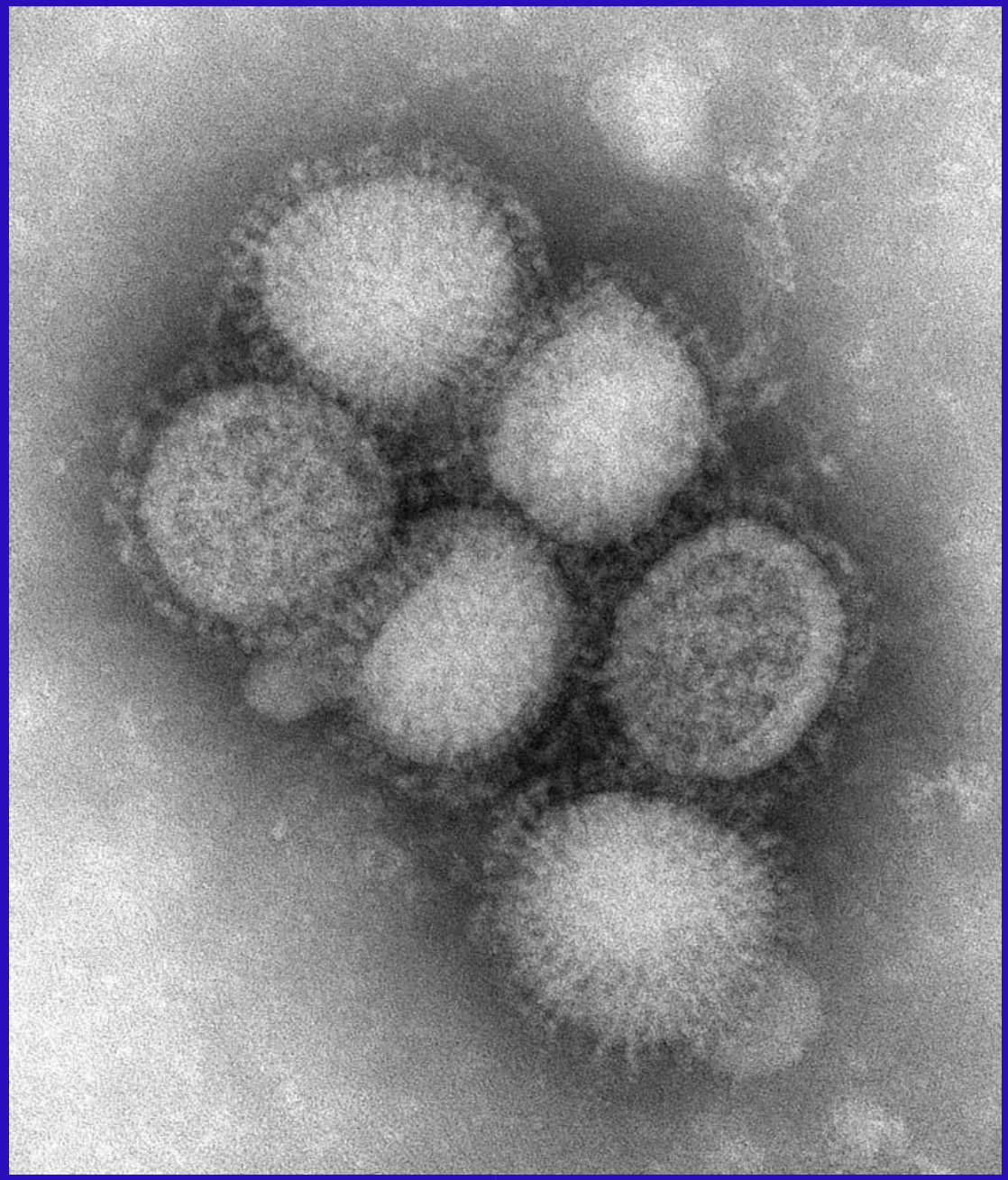
- Most WNV infections benign
- Febrile illness benign and mild
- Severe encephalitis associated with older age
- Infection acquired through bite of infected mosquitoes
- Neurologic illness from WNV: meningitis and encephalitis

The Clinical Impact of WNV Infection 2012: What We Know Now...

- Most WNV infections benign (fortunately)
- Febrile illness **generally** mild, **but may be associated with fatigue and cognitive problems**
- Severe encephalitis associated with older age, **but also immunosuppression**
- Infection acquired through bite of infected mosquitoes, **but also blood transfusion, solid organ transplantation, intrauterine (rarely)**
- Neurologic illness from WNV: meningitis and encephalitis, **poliomyelitis, parkinsonism**


www.timeeurope.com AOL Keyword: TIME
OCTOBER 17, 2005
GERMANY: THE GENERATION OF '68 BOWS OUT
TIME
AVIAN FLU
DEATH THREAT
SPECIAL REPORT: Inside the global race to avert a pandemic


IRELAND: THE DARK SIDE OF THE BOOM
NewsweekInternational.com
Newsweek
October 31, 2005
Flu Fears
How Real Is The Threat of A Pandemic?
PLUS
China: The World's Weakest Link
PHOTOGRAPH BY GIORGIO BENVENUTI—EPA
Inspecting a rooster in Forlì, Italy



Influenza Viruses

- RNA virus
- *Orthomyxoviridae* family
- Types A, B or C based on antigenic differences of their nucleo- and matrix proteins
- Avian influenza viruses (AIV) belong to type A
- On the basis of the antigenicity of these glycoproteins, influenza A viruses currently cluster into **sixteen H** (H1 - H16) and **nine N** (N1 - N9) subtypes.

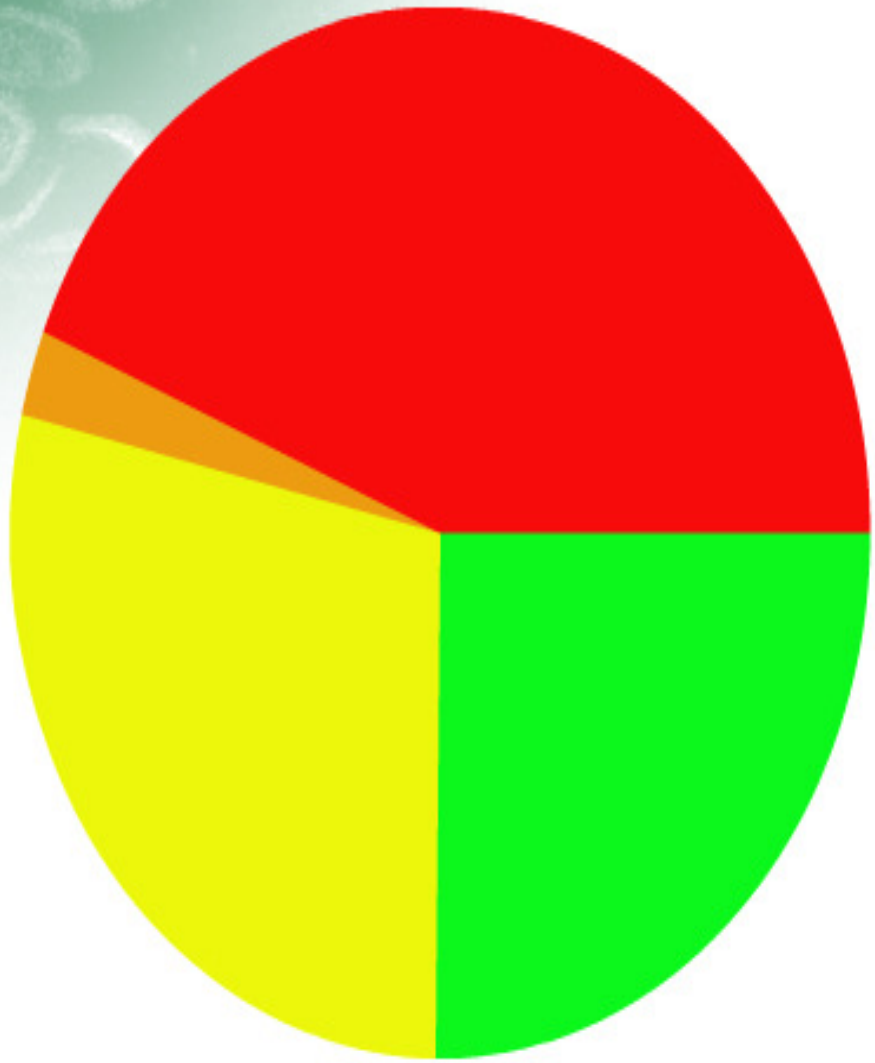
Circulating Influenza Viruses

- Seasonal influenza
  - A(H3N2), A(H1N1), B
- Avian influenza (‘bird flu’)
  - A(H5 and H7, e.g. HPAI H5N1)
- Swine influenza (‘swine flu’) -> variant flu
  - A(H1N1v) - 2009 pandemic strain
  - A(H3N2v) – 2011-2012 US strain

FluView

Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season, weeks ending Jan 19, 2013 - Feb 08, 2013

Reported by: U.S. WHO/NREVSS Collaborating Laboratories



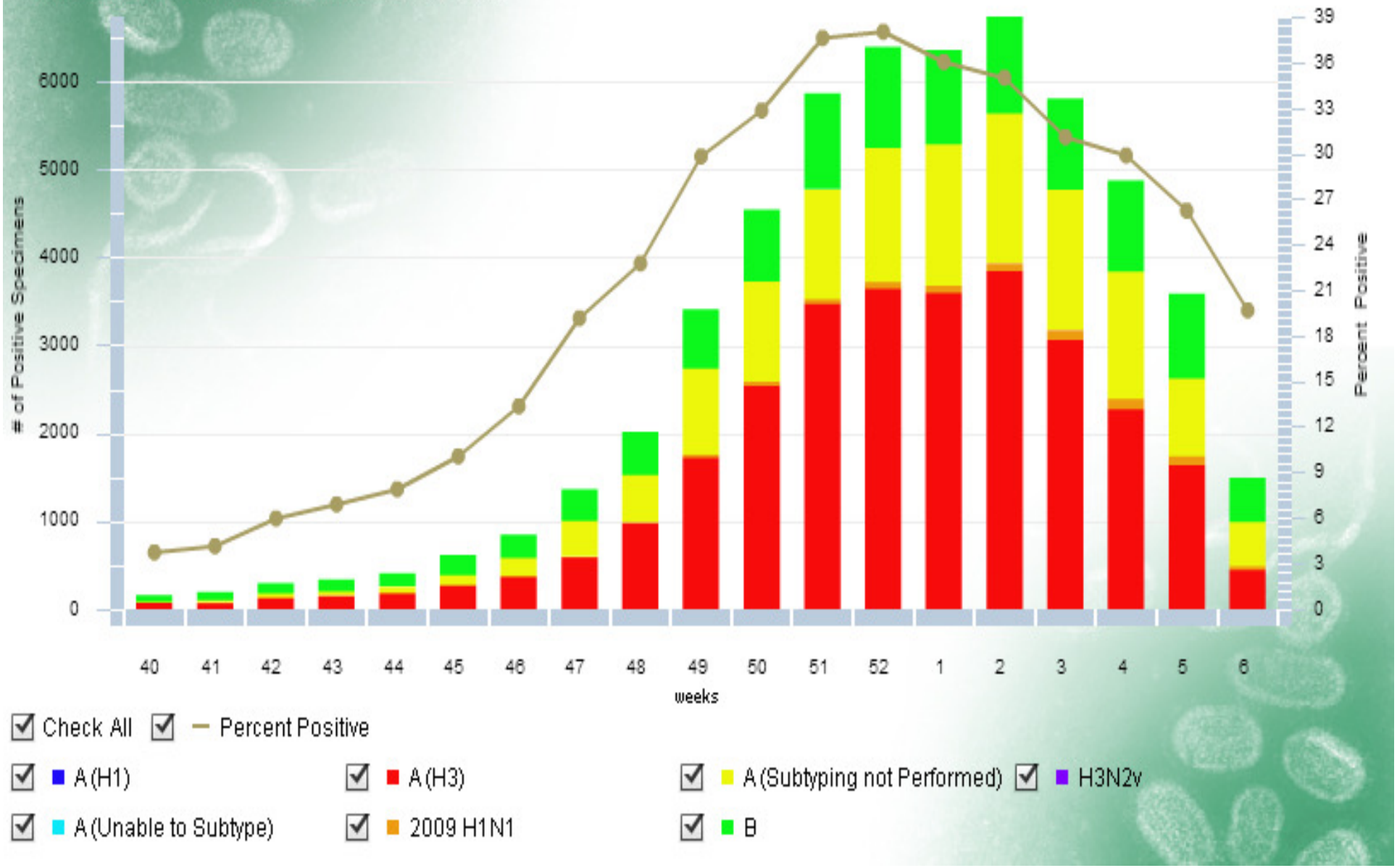
Number of Influenza Positive Tests

- A (H1) - **0**
- A (Unable to Subtype) - **0**
- A (H3) - **4366**
- 2009 H1N1 - **262**
- A (Subtyping not Performed) - **2841**
- B - **2513**
- H3N2v - **0**
- No Data

FluView

Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season through Feb 08, 2013

Reported by: U.S. WHO/NREVSS Collaborating Laboratories



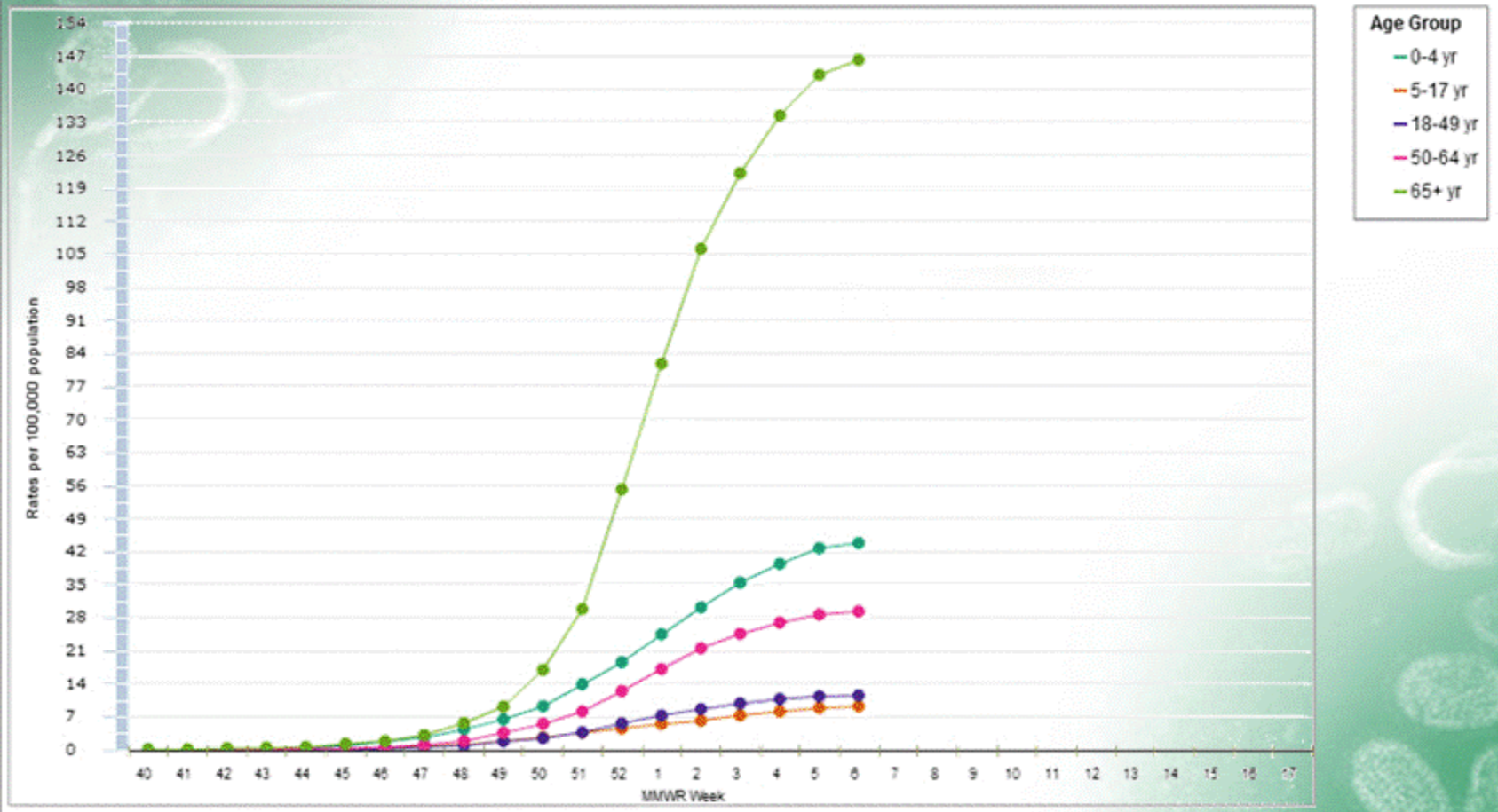
FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Laboratory-Confirmed Influenza Hospitalizations

Preliminary rates as of Feb 09, 2013



Data from the Influenza Hospitalization Surveillance Network (FluSurv-NET), a population-based surveillance for influenza related hospitalizations in children and adults in 15 US states. Incidence rates are calculated using the National Center for Health Statistics' (NCHS) population estimates for the counties included in the surveillance catchment area.

FLUVIEW

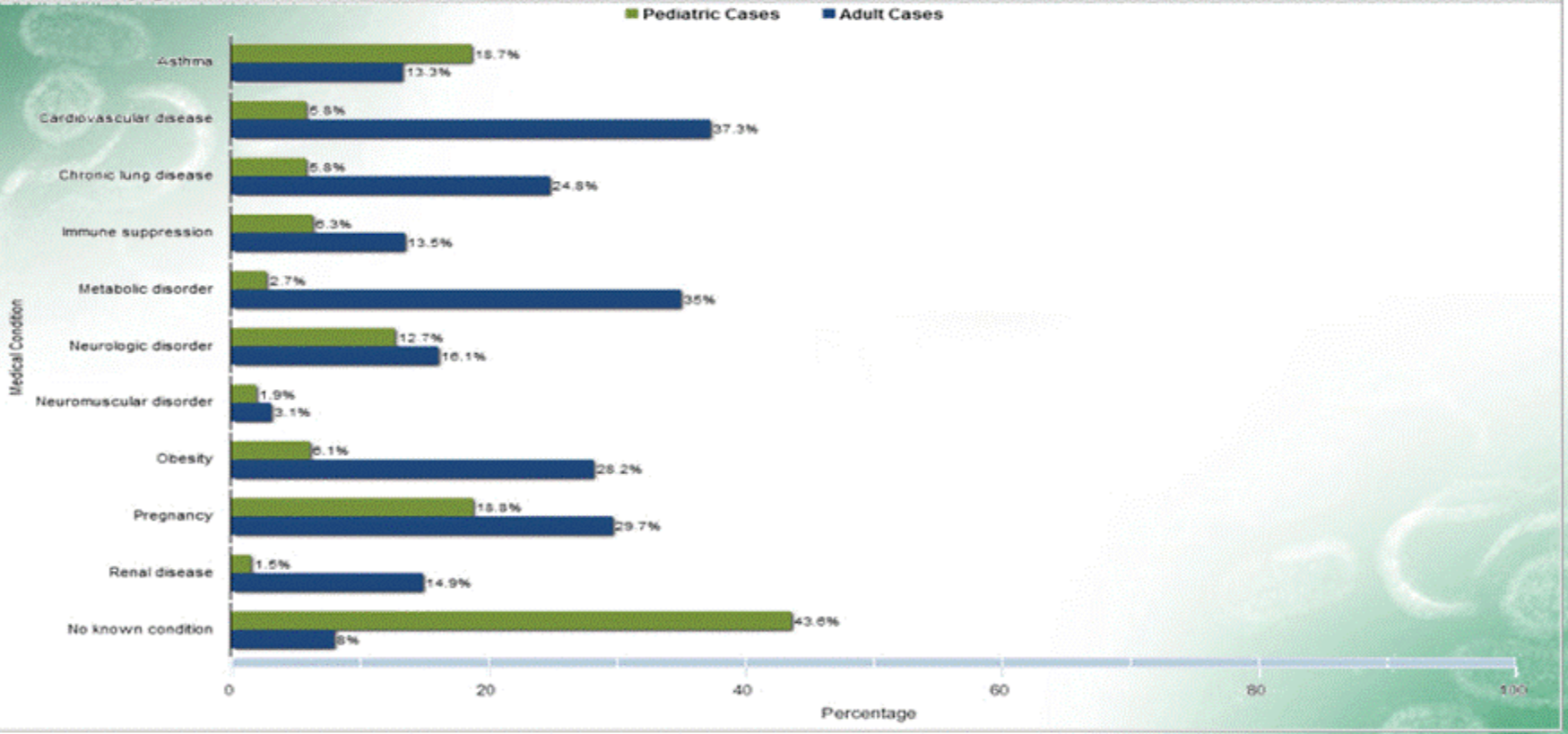
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC Centers for Disease Control and Prevention

Laboratory-Confirmed Influenza Hospitalizations

Preliminary data as of Feb 09, 2013

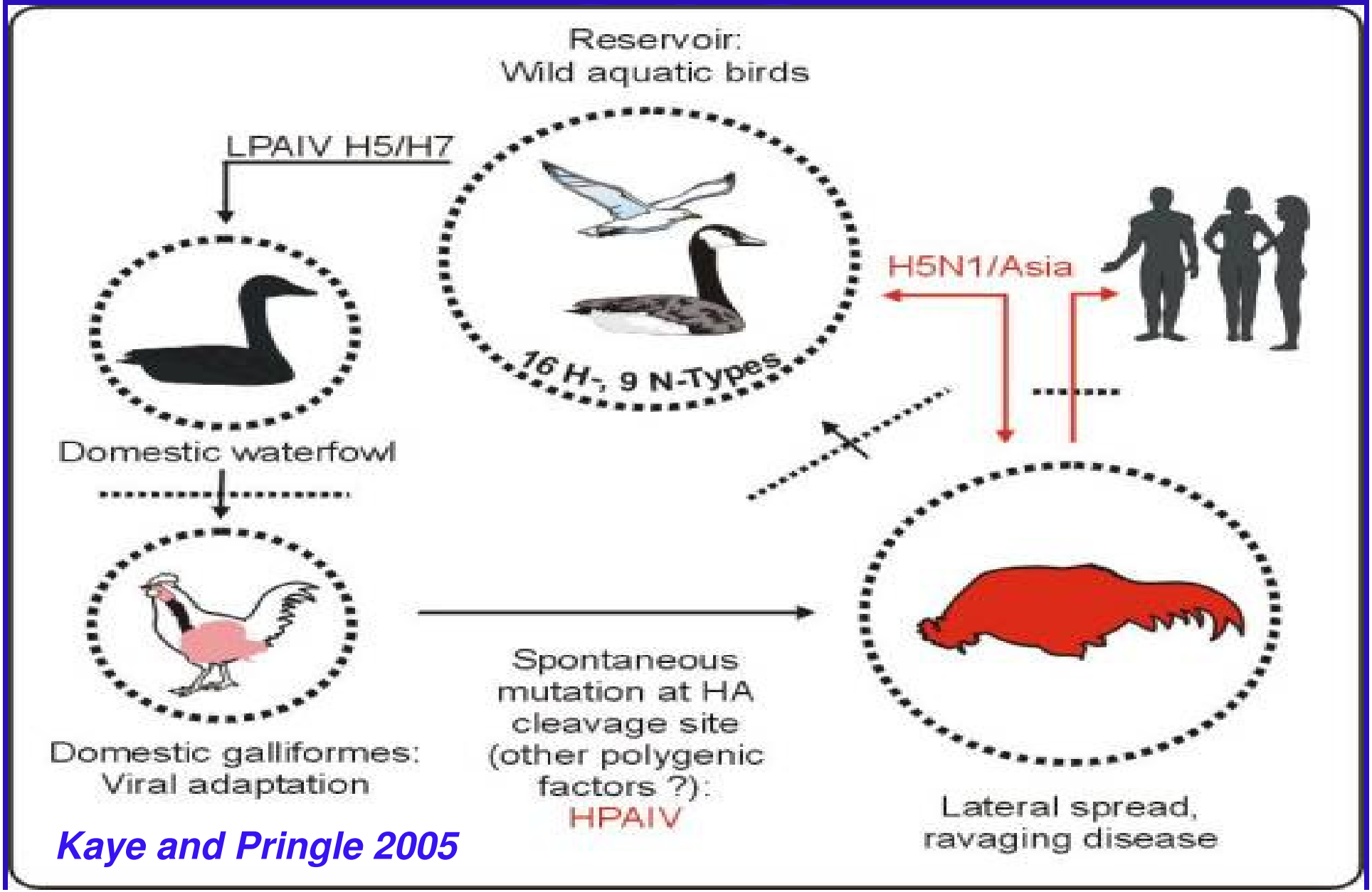
Selected Underlying Medical Conditions: 2012-13 Season



Asthma includes a medical diagnosis of asthma or reactive airway disease; Cardiovascular diseases include conditions such as coronary heart disease, cardiac valve disorders, congestive heart failure, pulmonary hypertension, and aortic stenosis. Does not include hypertension disease only; Chronic lung diseases include conditions such as bronchiolitis obliterans, chronic aspiration pneumonia, and interstitial lung disease; Immune suppression includes conditions such as immunoglobulin deficiency, leukemia, lymphoma, HIV/AIDS, and individuals taking immunosuppressive medications; Metabolic disorders include conditions such as diabetes mellitus, thyroid dysfunction, adrenal insufficiency, and liver disease; Neurologic diseases include conditions such as seizure disorders, cerebral palsy, and cognitive dysfunction; Neuromuscular diseases include conditions such as multiple sclerosis and muscular dystrophy; Obesity was assigned if indicated in patient's medical chart or if body mass index (BMI) >30 kg/m^2; Pregnancy percentage calculated using number of female cases aged between 15 and 44 years of age as the denominator; Renal diseases include conditions such as acute or chronic renal failure, nephrotic syndrome, glomerulonephritis, and impaired creatinine clearance; No known condition indicates that the case did not have any known underlying medical condition indicated in medical chart at the time of hospitalization.

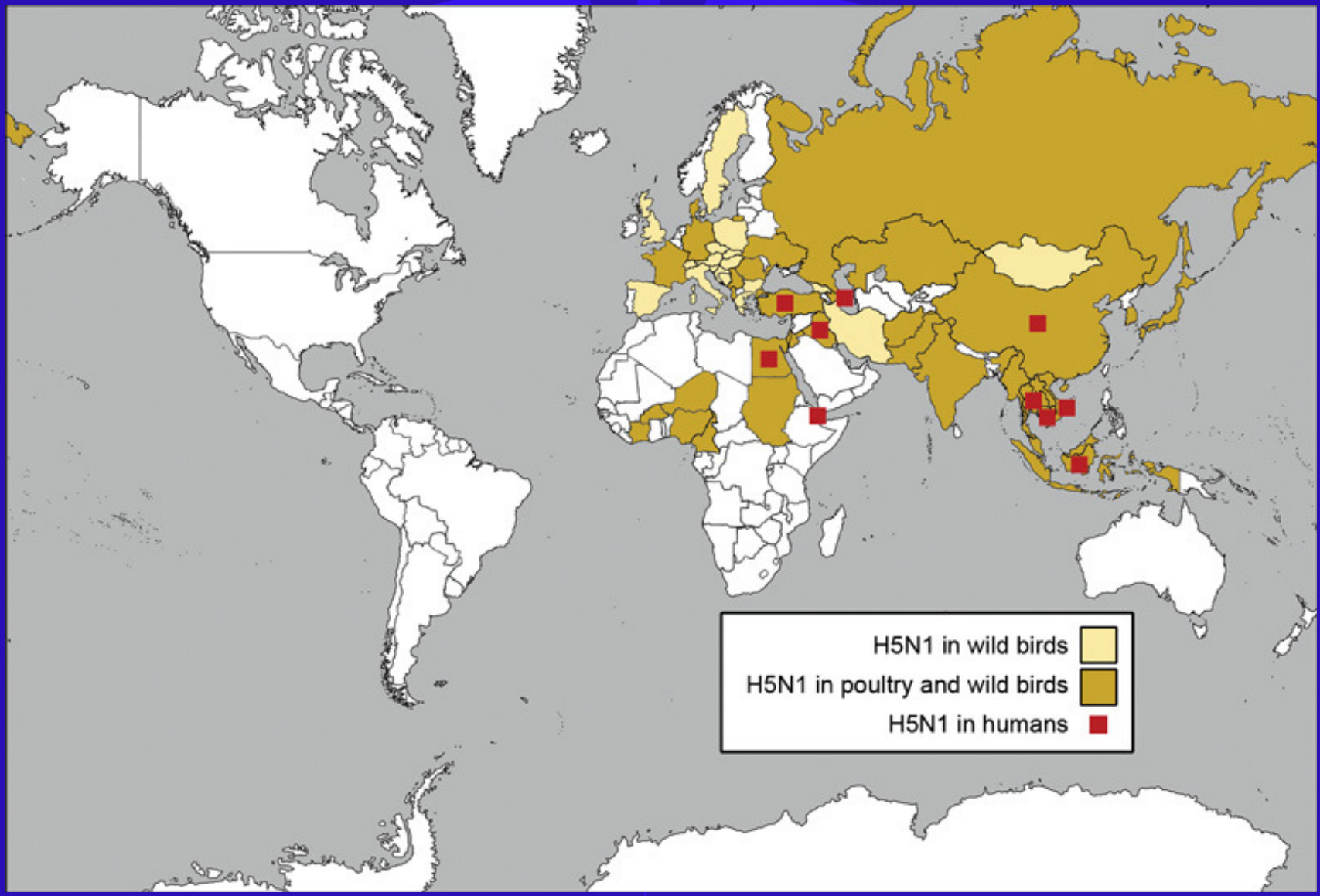
Only includes cases for which data collection has been completed through the medical chart review stage.

Avian Influenza Viruses



Kaye and Pringle 2005

Countries with H5N1 Human Cases



Virologic Diagnosis

- Culture
- Antigen detection (Rapid tests, ELISA, IFA)
- RT-PCR
- Serology
- All studies more likely to be positive if collected in first 3 days of illness

Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza

Antiviral Agent	Activity Against	Use	FDA Approved For	Not Recommended for Use in	Adverse Events
Oseltamivir (Tamiflu®)	**Influenza A and B**	**Treatment**	2 wks and older	N/A	**Adverse events:** nausea, vomiting. Sporadic, transient neuropsychiatric events (self injury or delirium) mainly reported among Japanese adolescents and adults.
		Chemo-prophylaxis	1 yr and older	N/A	
Zanamivir (Relenza®)	**Influenza A and B**	**Treatment**	7 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD)	**Allergic reactions:** oropharyngeal or facial edema. **Adverse events:** diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose and throat infections.
		Chemo-prophylaxis	5 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD)	

Influenza vaccine information, by age group --- United States, 2012--13 influenza season

TABLE. Influenza vaccine information, by age group — United States, 2012–13 influenza season*

Vaccine	Trade name	Manufacturer	Presentation	Mercury content (μg Hg per 0.5 mL dose)	Ovalbumin content (μg per 0.5mL dose)†	Age group	No. of doses	Route
TIV	Fluzone	Sanofi Pasteur	0.25 mL prefilled syringe	0.0	—§	6–35 mos	1 or 2¶	IM**
			0.5 mL prefilled syringe	0.0	—§	≥36 mos	1 or 2¶	IM**
			0.5 mL vial	0.0	—§	≥36 mos	1 or 2¶	IM**
			5.0 mL multidose vial	25.0	—§	≥6 mos	1 or 2¶	IM**
TIV	Agriflu****	Novartis Vaccines	0.5 mL prefilled syringe	0	<0.4	≥18 yrs	1	IM**
TIV	Fluvirin	Novartis Vaccines	0.5 mL prefilled syringe	≤1	≤1	≥4 yrs	1 or 2¶	IM**
			5.0 mL multidose vial	25.0	≤1			
TIV	Fluarix	GlaxoSmithKline	0.5 mL prefilled syringe	0	≤0.05	≥3 yrs	1 or 2¶	IM**
TIV	FluLaval	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	5.0 mL multidose vial	<25.0	≤0.3	≥18 yrs	1	IM**
TIV	Afluria	CSL Biotherapies (distributed by Merck)	0.5 mL prefilled syringe	0.0	≤1	≥9 yrs††	1	IM**
			5.0 mL multidose vial	24.5	≤1			
TIV high-dose§§	Fluzone High-Dose	Sanofi Pasteur	0.5 mL prefilled syringe	0.0	—§	≥65 yrs	1	IM**
TIV intradermal¶¶	Fluzone Intradermal	Sanofi Pasteur	0.1 mL prefilled microinjection system	0.0 (per 0.1 mL)	—§	18–64 yrs	1	ID
LAIV	FluMist***	MedImmune	0.2 mL prefilled intranasal sprayer	0.0 (per 0.2 mL)	<0.24 (per 0.2mL)†††	2–49 yrs§§§	1 or 2¶	IN

Re-Emerging Infectious Diseases

- Malaria
- Tuberculosis, drug resistant
- Cholera
- Invasive Group A streptococci
- Diphtheria
- Pertussis – ongoing epidemic in NY NOW!
- Syphilis – increasing rates in Bay Area
- Dengue fever

Resources for Emerging Infectious Diseases

- Emerging Infectious Diseases Journal, www.cdc.gov/ncidod/EID/index.htm
- Public Health 150: Contemporary Issues in Public Contemporary Issues in Public Health www.ph.ucla.edu/epi/faculty/detels/emerging_infecdis_10-03_RK-F.pdf
- Public Health Laboratories of the Ohio Department of Health www.odh.state.oh.us/Resources/MultiMedia/EI_Slide/EIMAIN.HTM

Only One Flight Away from a Global Microbial Threat

Behind Mask


Thank You!