

Birds, Pigs and Kids, Oh My!

Update on Recent Swine Flu, Pertussis and West Nile Virus Outbreaks

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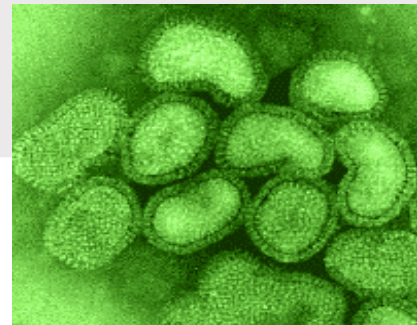
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Swine Influenza

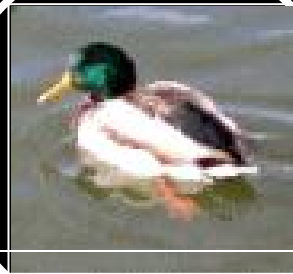
- Influenza strains circulate amongst birds, pigs, humans, and other species
- Usually avian and swine strains don't infect humans
- When they do, termed "variant virus"
- Current outbreak = variant H3N2
- Genes from avian, swine, and human flu viruses
- vH3N2 circulating in swine since 2010
- August – December 2011: 12 human cases
- July 2012 - present: 296 human cases



Aquatic Mammals



**Waterfowl
and Shorebirds
(Ducks, Geese, Swans,
Gulls, Terns)**



Horses



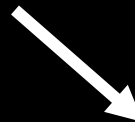
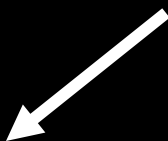
Domestic Poultry



Humans

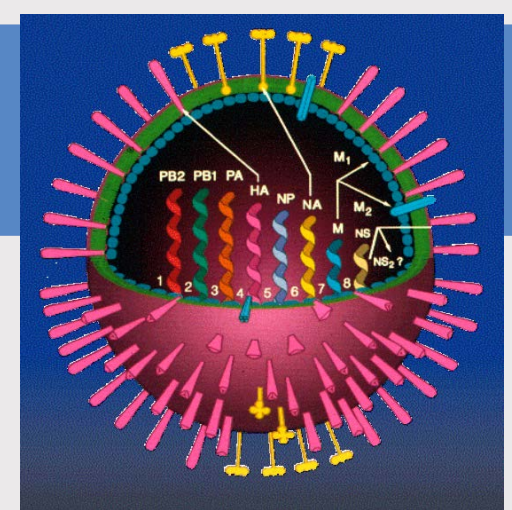


Pigs

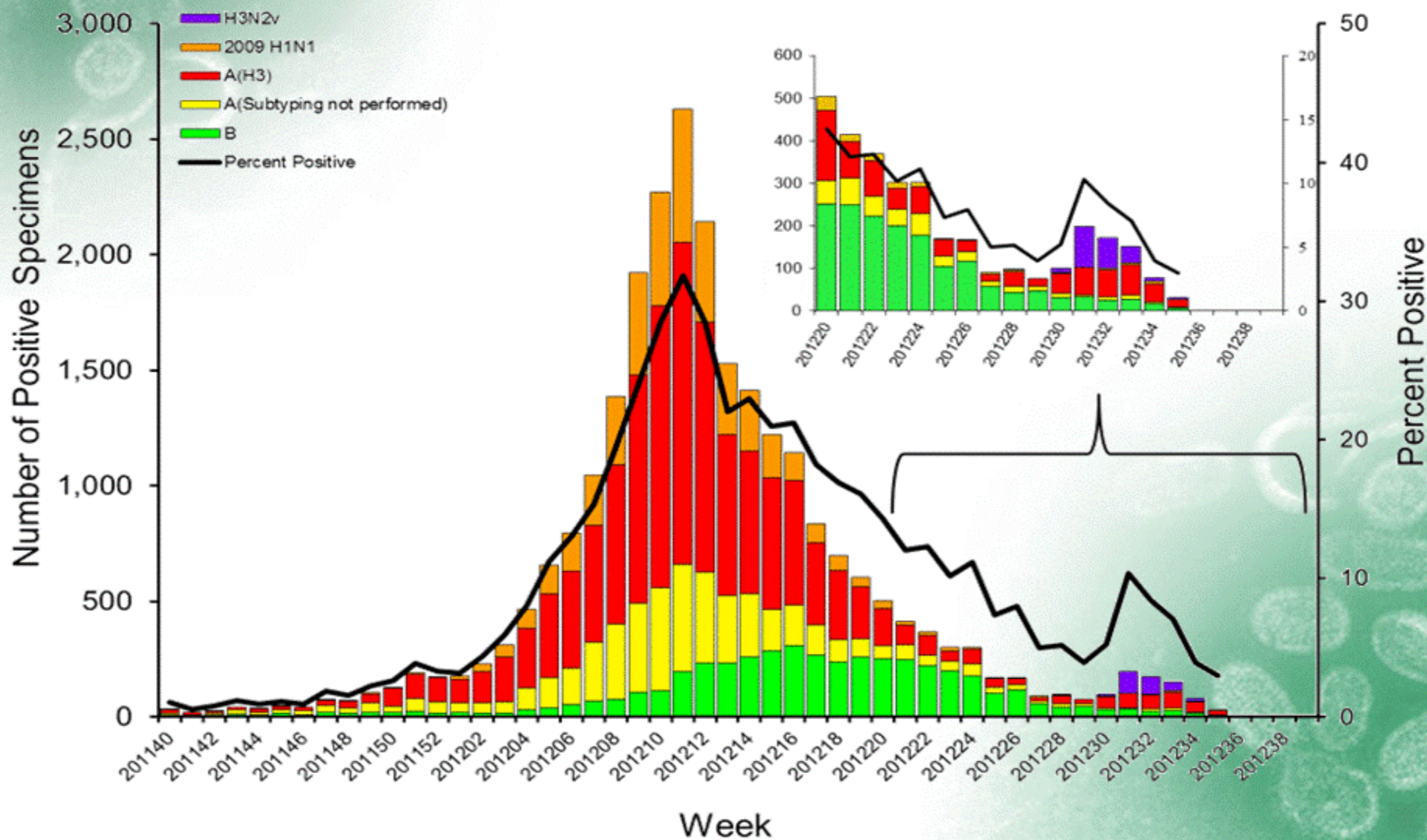


Swine Influenza

- Pigs can be infected with avian, human and swine strains
- The perfect mixing vessel for emergence of a novel strain that could be transmissible human to human: e.g. pandemic 2009 H1N1
- vH3N2 contains the M gene from pandemic 2009 H1N1 strain
- M gene encodes matrix proteins in viral shell
- Concern that this could potentially confer ability for better human to human transmission

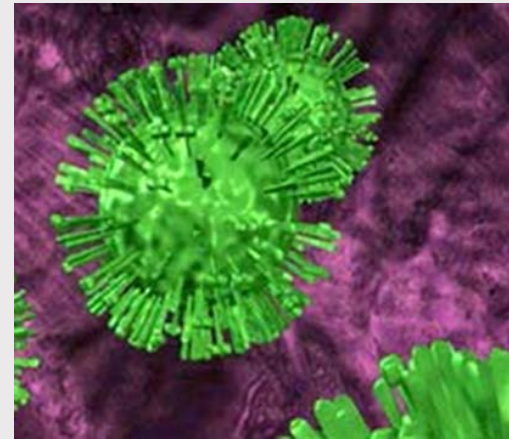


Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS
Collaborating Laboratories, National Summary, 2011-12



Swine Influenza – Case count Week Ending Sept 1, 2012

- 296 cases from 10 states
 - Hawaii [1], Illinois [4], **Indiana [138]**, Maryland [12], Michigan [5], Minnesota [2], **Ohio [102]**, Pennsylvania [11], West Virginia [3], and Wisconsin [18]
 - Vast majority of cases with identified pig exposure
 - 6 cases of human to human transmission
- 16 Hospitalizations
- 1 Death:
 - 61 y.o Ohio woman
 - Pig contact at county fair ; underlying medical condition



Swine Influenza – What's the Big Deal?

- Historically, reports of humans infected with swine viruses on average 1-2 every year
- More recently, increased reports
- Why?
 - Better surveillance due to pandemic preparedness
 - Avian Flu Outbreak SE Asia 2005
 - vH1N1 pandemic 2009
 - 100 countries/100 flu centers/ year round surveillance
 - Actual increase in pig to human transmission

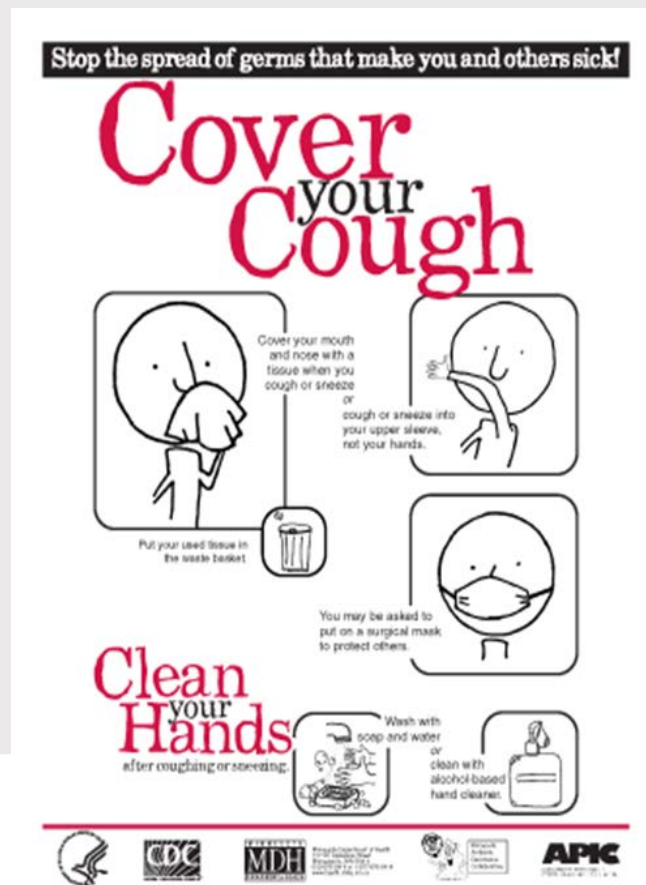


Swine Flu

- Symptoms
 - Same as for seasonal influenza
 - Fever, cough, sore throat, runny or stuffy nose, muscle aches, headache, and fatigue
 - GI (nausea, vomiting, diarrhea) symptoms not uncommon in children

Swine Flu - Guidance

- If at higher risk of complications from flu – avoid swine areas at county fairs
- If not high risk and visiting swine areas, do not:
 - Eat or drink
 - Carry toys, pacifiers, other objects
- **DO WASH HANDS**



2012-13 Influenza Season Vaccine Components

- One strain same as 2011 vaccine:
 - A/California/7/2009 (Pandemic 2009 strain)
- Two strains different from 2011 vaccine:
 - A/Victoria/361/2011 (H3N2)-like
 - B/Wisconsin/1/2010-like virus
- **NOT in vaccine:**
 - 2012 vH3N2
 - FDA testing prototype of vH3N2 in case it begins to spread on a widespread human-to-human basis



Who Should Receive Seasonal Flu Vaccine?

- **Anyone ≥ 6 months of age**
- Especially, those at high risk for complications from flu
 - < 5 years of age
 - > 65 years of age
 - Pregnant
 - Chronic Medical Condition (Asthma, DM, CV)
 - Immunocompromised
 - Neurologic/Neurodevelopmental disorder

Seasonal Flu Vaccine - Preparations

Type	Route	Population	Trade Name
Killed	Intramuscular	Anyone ≥ 6 months of age	Fluzone Fluvirin Afluria, FluLaval Fluarix Agriflu
Killed – High Dose	Intramuscular	>65 years of age	FluZone High Dose
Killed	Intradermal	18-64 years of age	Fluzone Intradermal
Live, attenuated, cold-adapted	Intranasal	2-49 years NOT pregnant or immunocompromised	FluMist



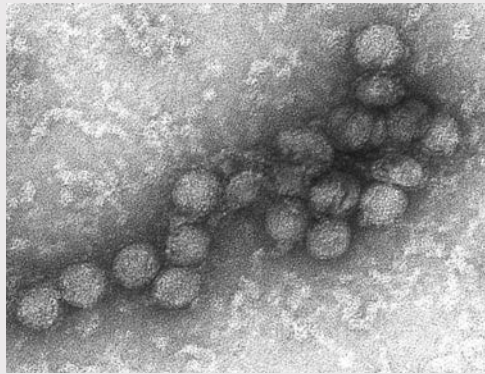
Influenza – diagnosis and treatment

- RT- PCR gold standard
- Rapid Flu Testing: Sensitivity 40-70%; Specificity 85-100%
- Confirmation at STATE Health Dept
 - no longer sending to CDC
- Resistant to M2 Inhibitors:
 - Do not use amantadine/rimantadine
- Susceptible to Neuraminidase Inhibitors:
 - oseltamivir (Tamiflu) or zanamivir (Relenza)
- Severe hospitalized influenza: I
 - Intravenous zanamivir multicenter trial (at CNMC)

Recommended Dosage and Duration of Treatment or Chemoprophylaxis for Influenza Antiviral Medications

Antiviral Agent	Use	Children	Adults
Oseltamivir (Tamiflu®)	Treatment	(Not FDA approved for use in children <1 yr old, but was approved under EUA during the 2009 pandemic) If <1 yr old, the dose is 3 mg/kg/dose twice daily	75 mg twice daily
		(Dose varies by child's weight) If ≥1 yr old and weigh 15 kg or less, the dose is 30 mg twice a day.	
		If ≥1 yr old and weigh >15 to 23 kg, the dose is 45 mg twice a day.	
		If ≥1 yr old and weigh >23 to 40 kg, the dose is 60 mg twice a day.	
		If ≥1 yr old and weigh more than 40 kg, the dose is 75 mg twice a day.	
	Chemo prophylaxis	(Not FDA approved for use in children <1 yr old) If child is <3 months old, chemoprophylactic use is not recommended unless situation is judged critical due to limited data on use in this age group.	75 mg once daily
		(Not FDA approved for children <1 yr old, but use in children ≥3 months and <1 yr old was approved under EUA during the 2009 H1N1 pandemic) If child ≥3 months and <1 yr old, dose is 3 mg/kg/dose once per day	
		(Dose varies by child's weight) If ≥1 yr old, and weigh 15 kg or less, the dose is 30 mg once a day.	
		If ≥1 yr old and weigh >15 to 23 kg, the dose is 45 mg once a day.	
		If ≥1 yr old and weigh >23 to 40 kg, the dose is 60 mg once a day.	
		If ≥1 yr old and weigh more than 40 kg, the dose is 75 mg once a day.	
Zanamivir (Relenza®)	Treatment	10 mg (2 inhalations) twice daily (Not FDA approved for use in children <7 yrs old)	10 mg (2 inhalations) twice daily
	Chemo prophylaxis	10 mg (2 inhalations) once daily (Not FDA approved for use in children <5 yrs old)	10 mg (2 inhalations) once daily

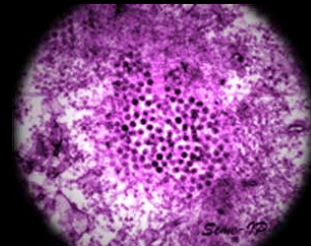
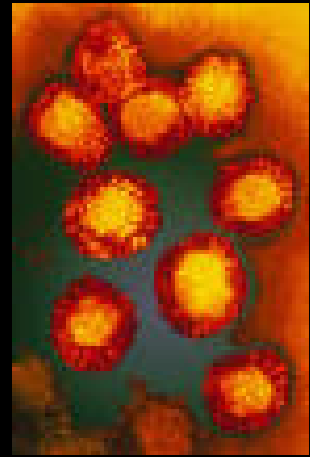




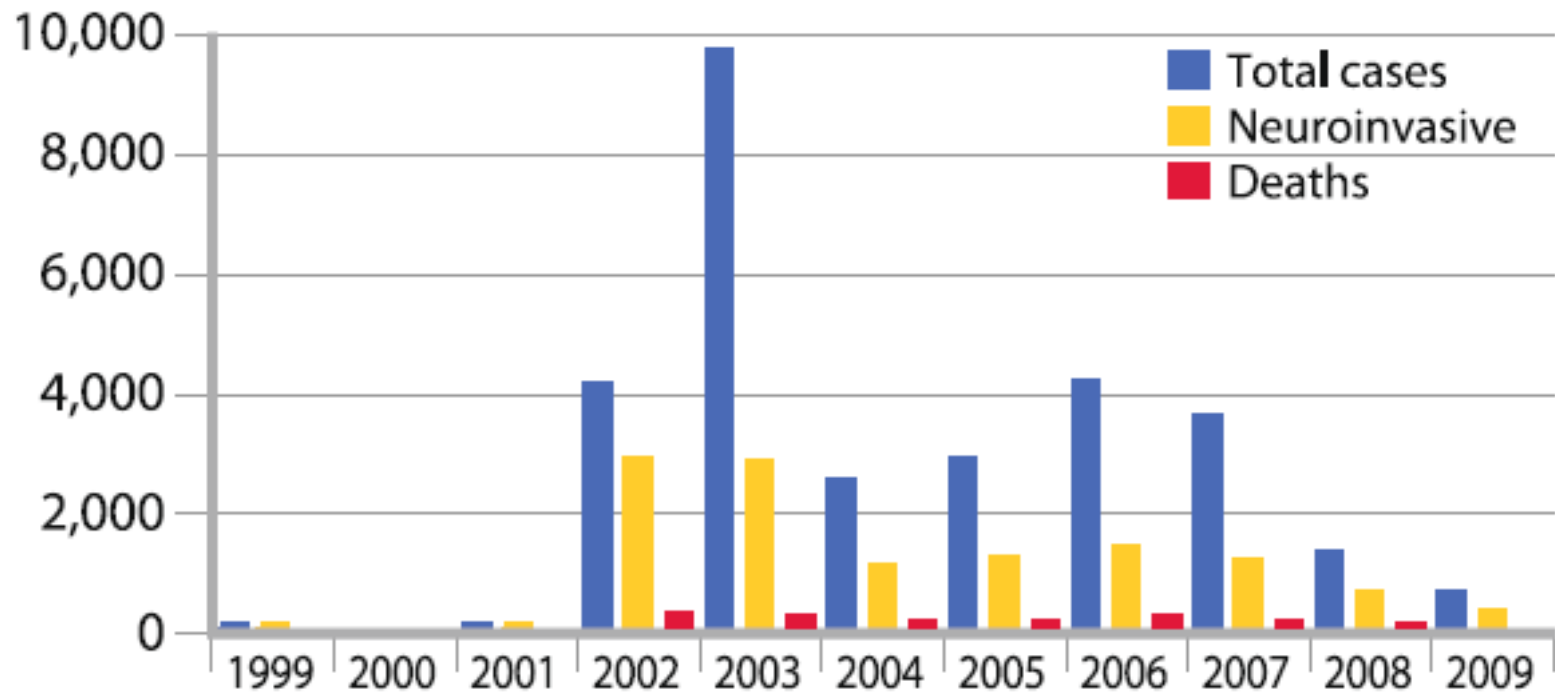
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West Nile Virus

- SS, +sense, RNA Virus
- Widely distributed virus worldwide.....
 - Endemic in Sudanese children 1950's
 - Worldwide Epidemics throughout 1990's
- NEVER in Western Hemisphere until 1999:
 - **US (1999-2003)**
 - **Western hemisphere's largest arboviral ME epidemic**
 - **Largest WNME epidemic *EVER***
- Shift in **NEUROVIRULENCE** of the virus:
 - Increased viremia and mortality in birds
 - Increased frequency of severe neurological disease in humans



West Nile Virus Cases reported to CDC US 1999-2009



Total cases	62	21	66	4156	9862	2539	2949	4261	3630	1356	720
Neuroinvasive	59	19	64	2946	2860	1142	1272	1491	1227	689	386
Deaths	7	2	9	284	264	100	111	161	117	44	20

WNV Outbreak 2012: National Data

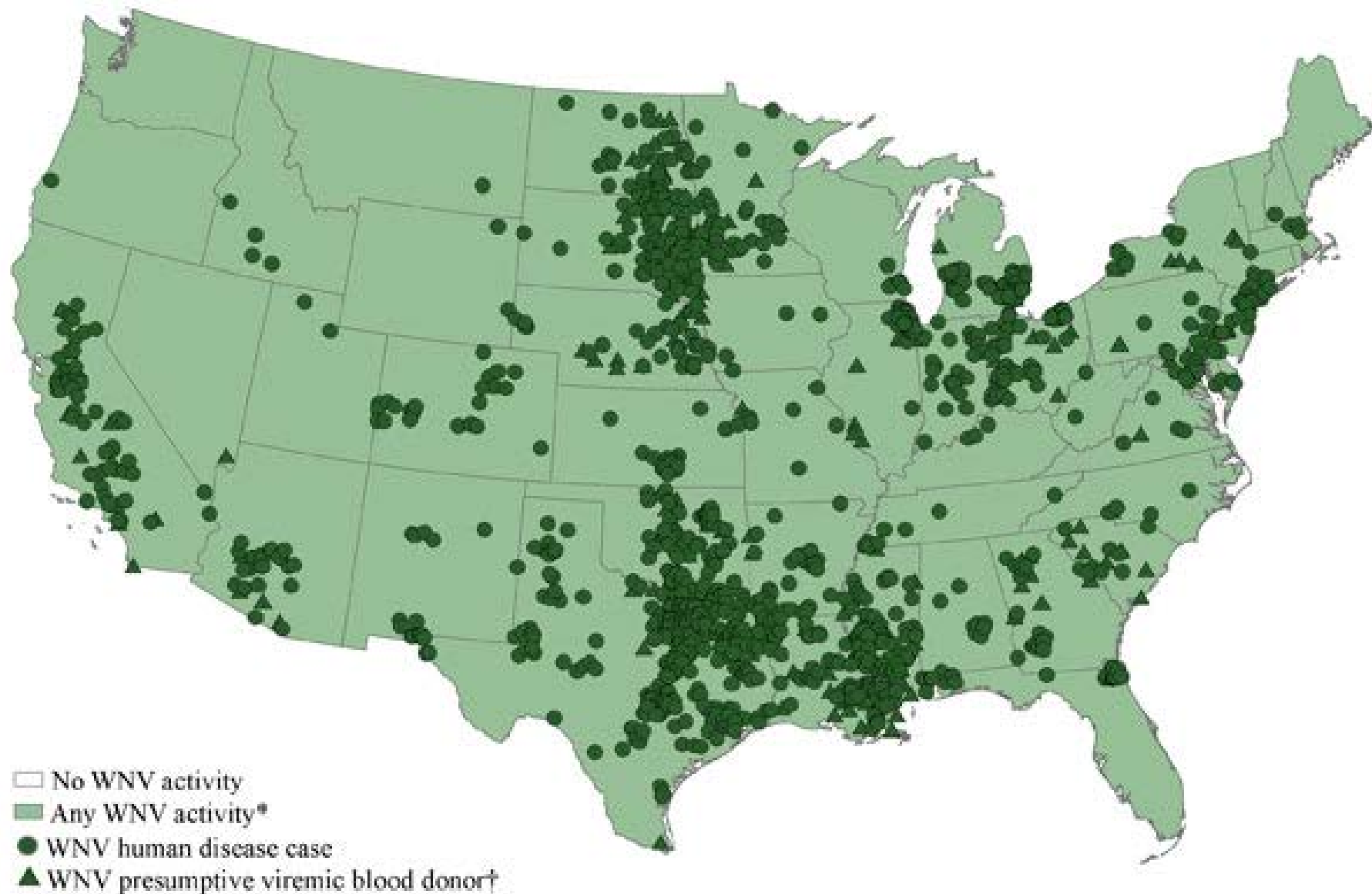
As of Sept 4, 2012

- Most cases reported through first week of September since first detected in US in 1999
- 1993 cases
 - 1069 (54%) Neuroinvasive Disease
 - 924 (66%) Non Neuroinvasive
- 87 deaths
- > 70% cases reported from 6 states
 - Texas, South Dakota, Mississippi, Oklahoma, Louisiana, and Michigan
- 45% cases from Texas (Dallas)

WNV Outbreak 2012 - Local Data

(As of Sept 4, 2012)

Location	WNND	WNF	Total Cases	Deaths
DC	1	0	1	1
Maryland	8	6	14	1
Virginia	2	3	5	1
West Virginia	2	0	2	0
Pennsylvania	10	4	14	1



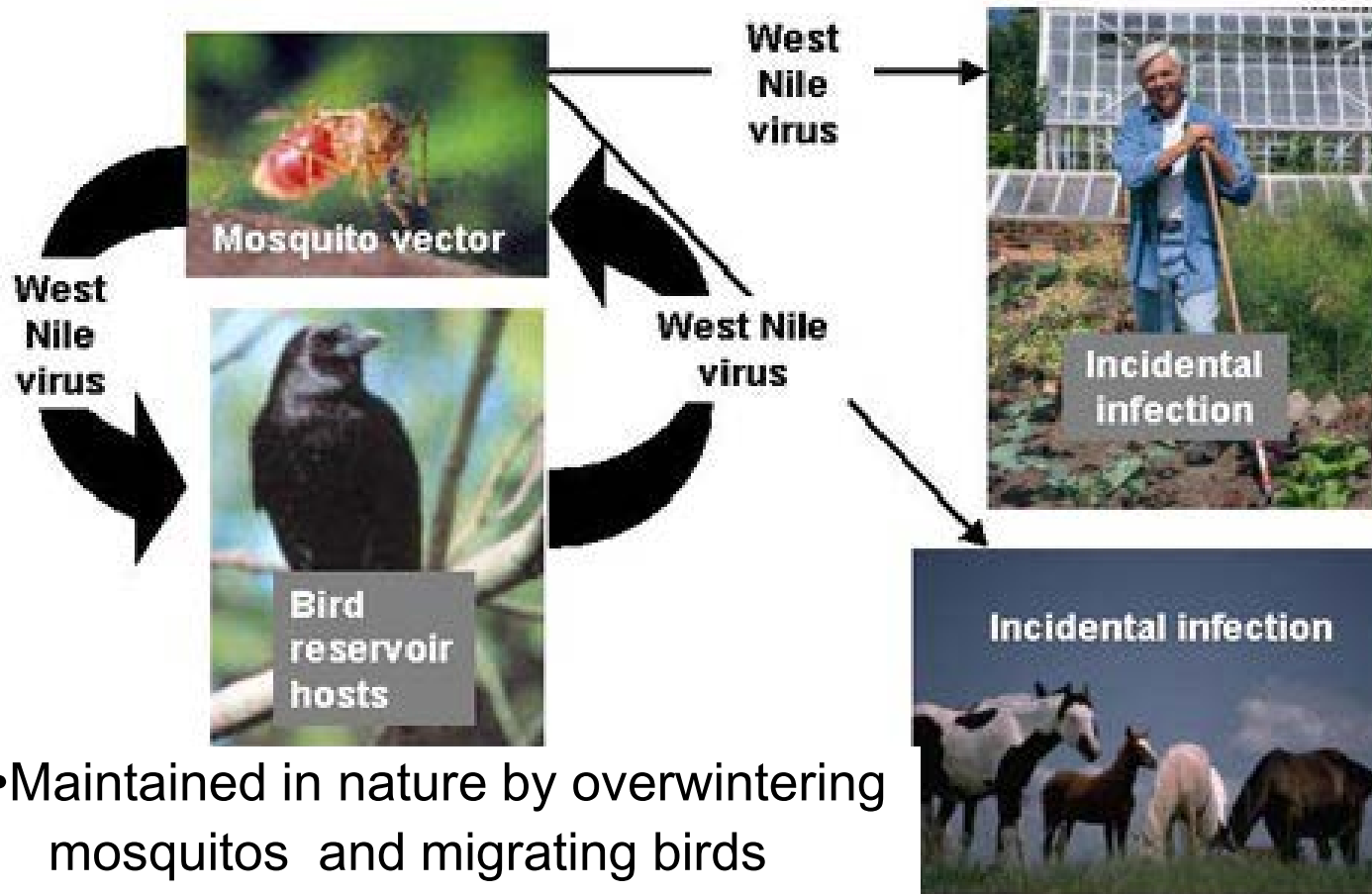
Arboviruses

- Arthropod-borne viruses
 - Mosquito & Tick Vectors
- Complex Natural Cycles
 - Natural Reservoirs: Insects, Birds, Small Mammals
 - Epizootics: Humans, Horses, Birds

Major Arboviruses Causing Worldwide Disease

- **Flaviviruses:**
 - Japanese Encephalitis (JE)
 - West Nile (WN)
 - Kunjin
 - St. Louis Encephalitis (SLE)
 - Murray Valley Encephalitis (MV)
 - Powassan
 - Tick-borne Encephalitis (TBE)
- **Alphaviruses:**
 - Eastern Equine Encephalitis (EEE)
 - Western Equine Encephalitis (WEE)
 - Venezuelan Equine Encephalitis (VEE)
- **Bunyaviruses:**
 - California/LaCrosse (LAC)

West Nile Virus Transmission Cycle

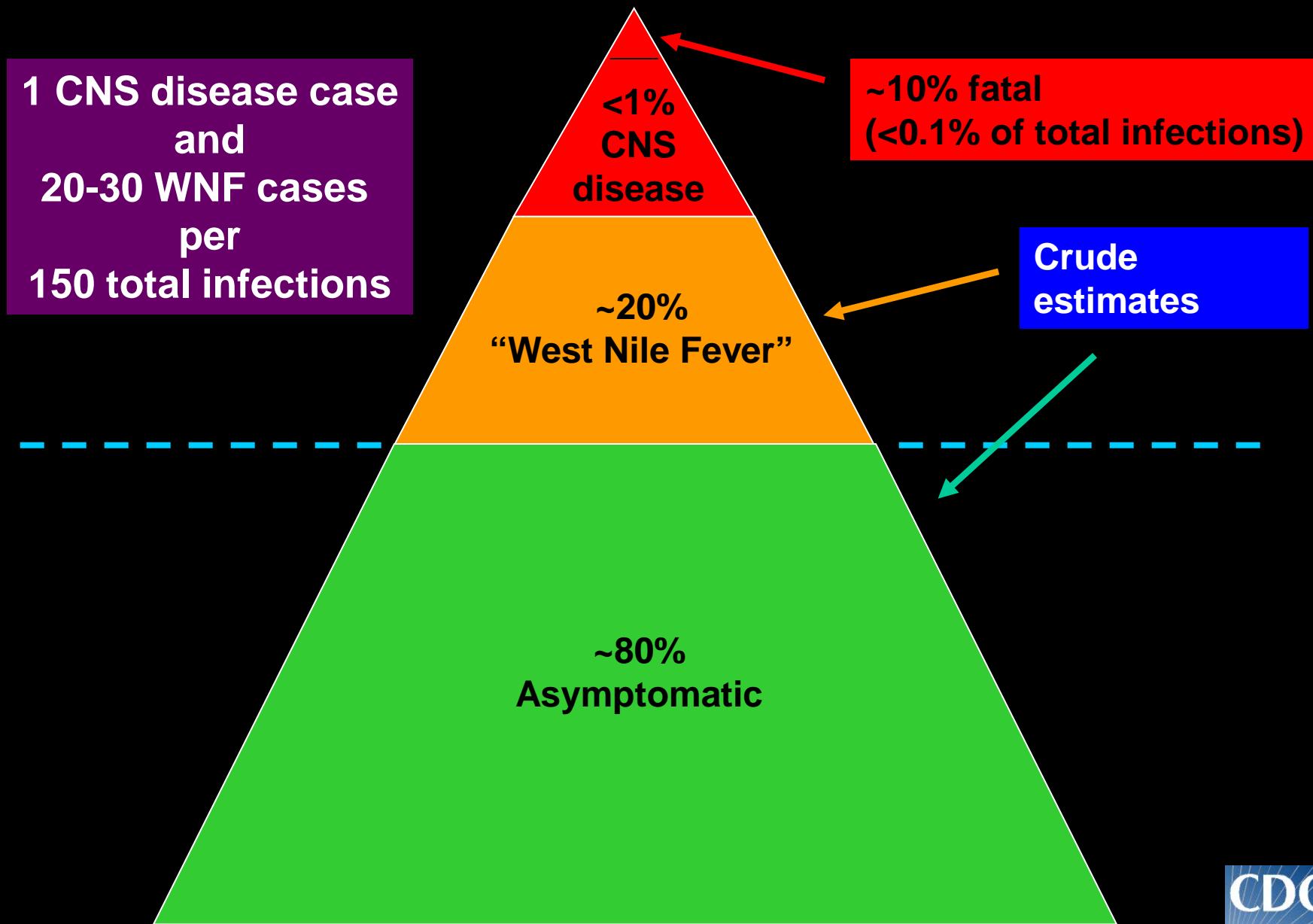


- Maintained in nature by overwintering mosquitos and migrating birds
- No “carrier” or “chronic” state

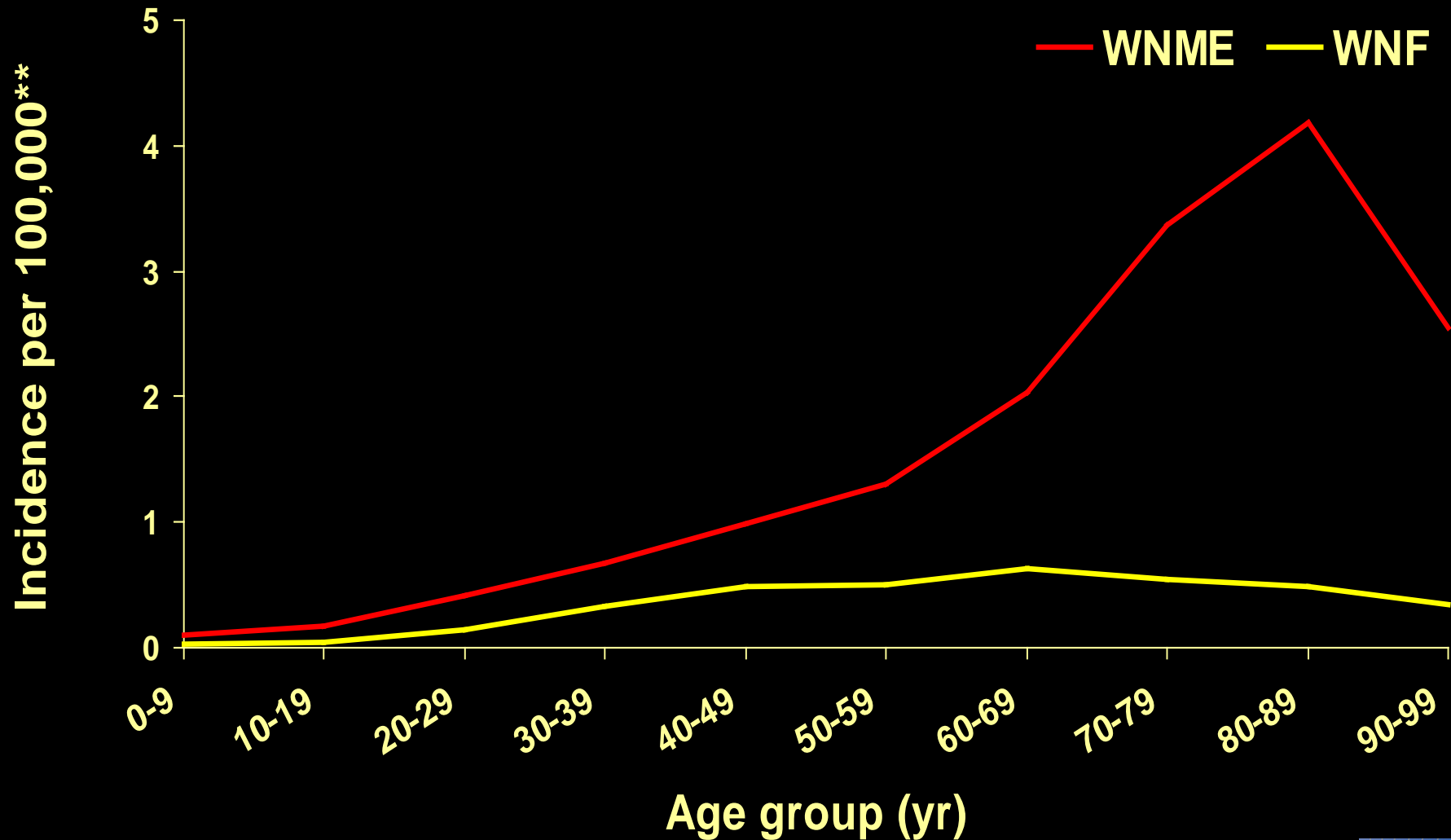
**Dead End Hosts
No High Level Viremia**

<1% mosquitoes carry virus, even in areas where virus is circulating

WNV Human Infection “Iceberg”



Human WNV Disease Incidence, by Age Group and Clinical Category, United States, 2002*



* Reported as of 01/21/2003

* *Entire US population

Pediatric WNV

- Incidence of neuroinvasive disease (WNND) increases with age
 - Highest in people > 70 years of age
- Children accounted for only 4% of all WNND cases reported 1999-2007
 - Median annual incidence of 0.07/100,000 children
- During US epidemic 2002 – 2004
 - CDC confirmed only 317 cases of WNND in children <19 years of age
- Pediatric WNND most commonly manifests as aseptic meningitis
- However, pediatric WNV poliomyelitis and encephalitis are reported

WNV Clinical Syndromes: West Nile Fever

- **NONSPECIFIC FEBRILE ILLNESS!!**
 - Fever (usually $> 39^{\circ}\text{C}$)
 - HA< Body ache
 - Nausea, vomiting
 - Rash (maculopapular) on chest /stomach/back – 30-60%
 - Swollen lymph nodes (generalized)
 - Duration 3-4 days
 - Prolonged fatigue common

Neurological Presentations of WNV

Previously Appreciated

- Meningitis
 - Fever, nuchal rigidity, CSF pleocytosis
- Encephalitis
 - Altered mental status
 - Weakness (50-80%)
 - Focal CNS Signs
 - Less common

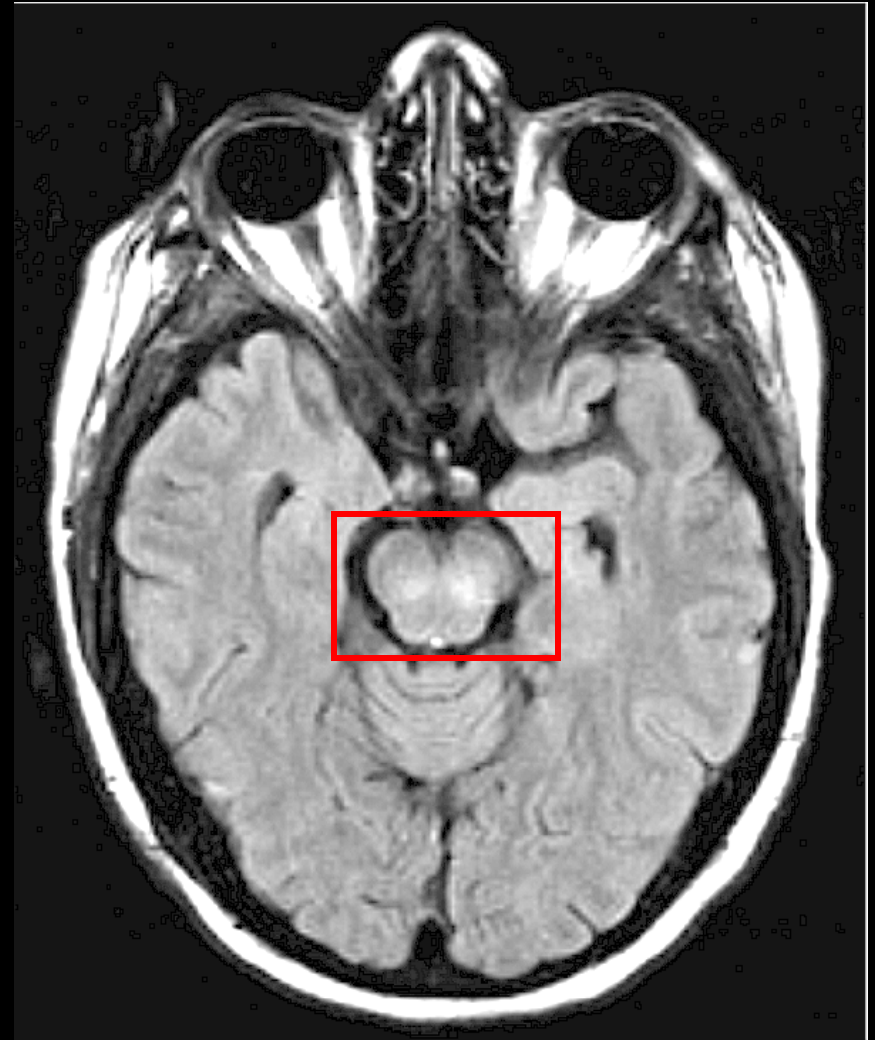
New/More Prominent

- Poliomyelitis-like:
 - Acute Flaccid Paralysis
- Movement disorders
 - Parkinsonism
 - Tremor (Resting & Action)
 - Myoclonus
- Brainstem Encephalitis
- Other
 - Rhabdomyolysis
 - Polyneuropathy/radiculopathy
 - Optic Neuritis
 - ADEM
 - Congenital CNS Abnormalities

West Nile Virus Encephalitis: MRI Usually Normal, but if Abnormal...



Thalamus

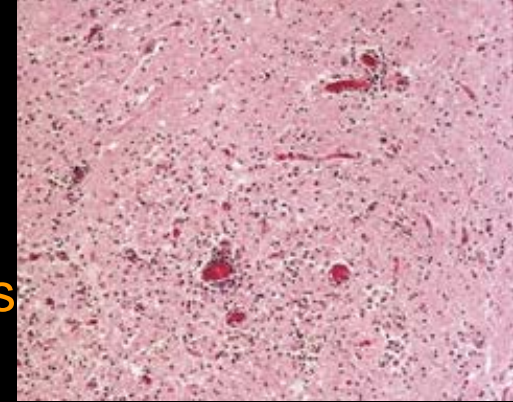


Midbrain (Substantia

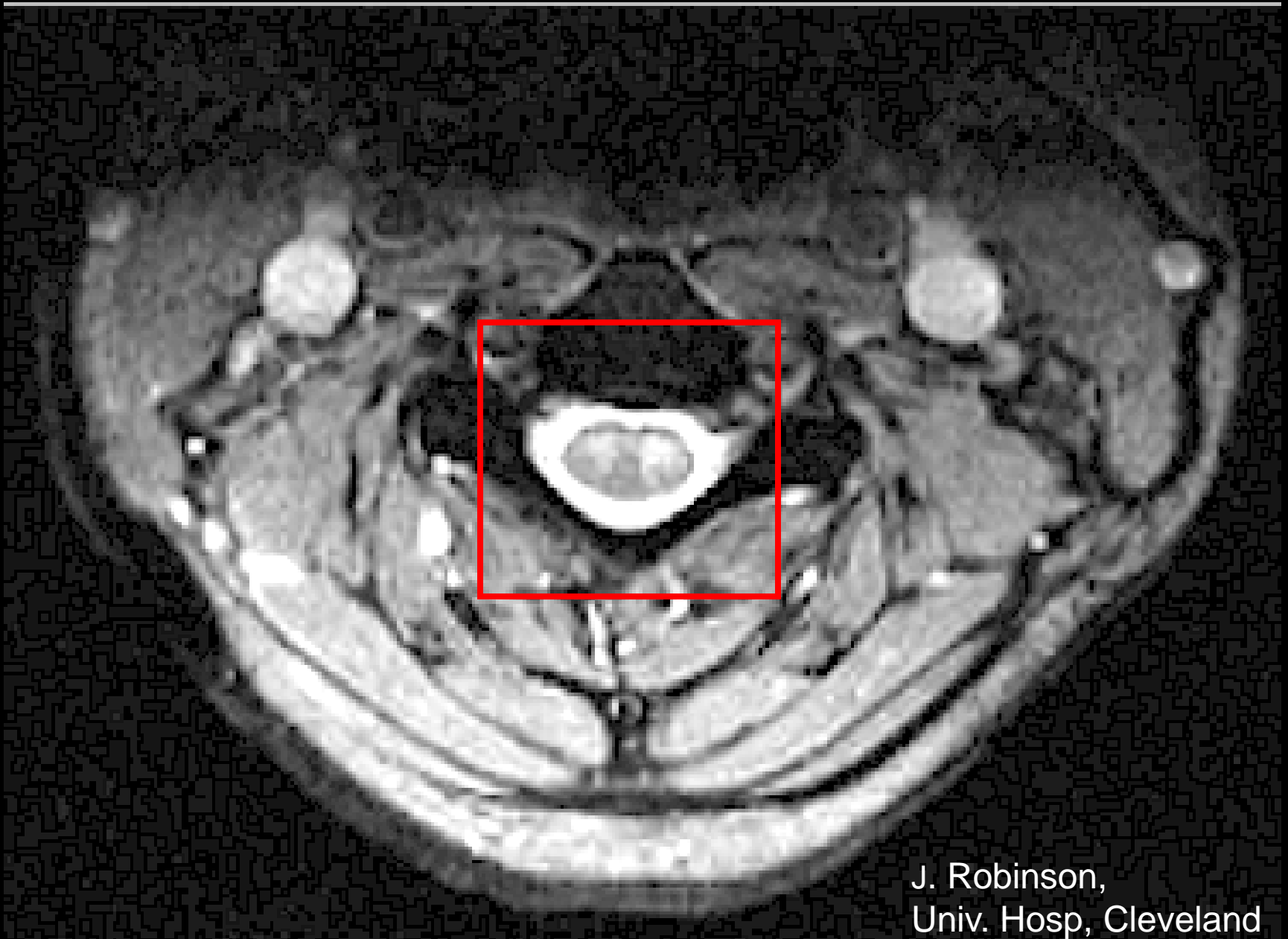
Nigra)

WNV: Acute Flaccid Paralysis = West Nile Poliomyelitis

- Younger group of patients: 40's
- Initially confused with Guillain-Barre Syndrome
- Later recognized as Poliomyelitis:
 - Loss of anterior horn spinal cord motor neurons
- Painless, asymmetric flaccid weakness
 - One or More Limbs
 - Generalized \pm Rapid Ascending Paralysis, Respiratory Failure
 - Bi-Facial weakness, Dysphagia, Urinary Incontinence
- Preserved Sensation
- Reduced or Absent DTRs
- Fever, HA, Malaise, Nausea & Vomiting
- Elevated ESR/CRP
- CSF: Lymphocytic Pleocytosis, Increased Protein
- MRI: Increased T₂ Signal in Gray Matter of Spinal Cord
- EMG/NCV: Axonal and demyelinating lesions



Spinal Cord Lesions on MRI in WNV Poliomyelitis



CSF and Serum Profile in WNND

- CSF

- Pleocytosis

- Mean = 225 WBC/cm³ [<10% >500]

- Polymorphonuclear or Lymphocytic,

- Mean = 40% polys

- Can include abnormal appearing reactive lymphocytes/monocytes - plasma cell-like

- Elevated Protein

- > 100 mg/dl in 50% (especially WNE)

- Normal Glucose

- Peripheral Blood

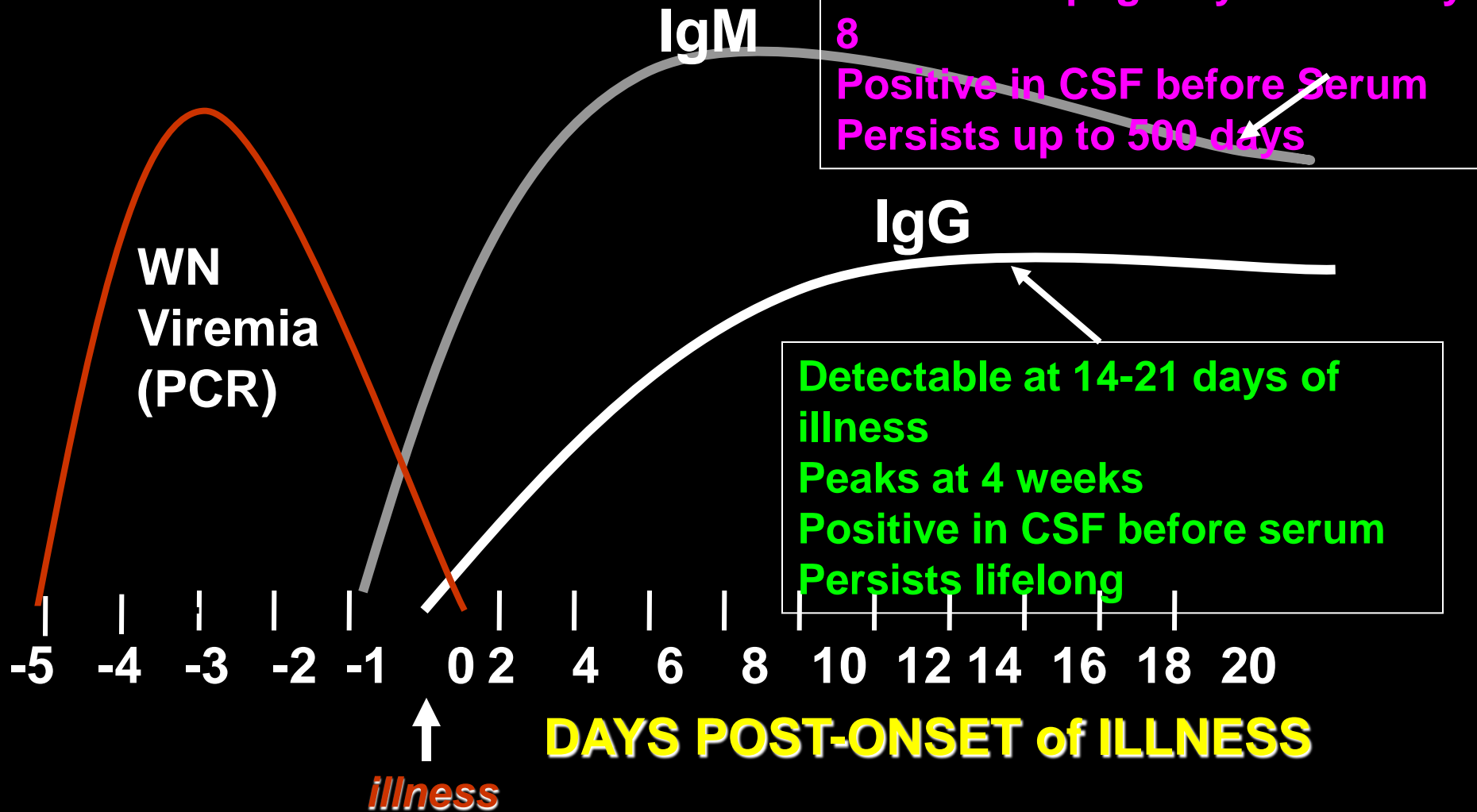
- Normal WBC count in 35-40%

- Leukocytosis in \leq 50% pts.

- Leukopenia (relative lymphopenia) in 10-15%

Tyler et al, Neurology. 2006;66:361–5.

WNV Serology



Remember: WNV Serology NOT part of CNMC Arboviral Panel

Sequelae of WNND

- Case fatality rates vary with presentation
 - WM Encephalitis: 10- 20%, possibly as high as 35% in elderly
 - WN Poliomyelitis (10%–50%)
 - WN meningitis < 1%
- ~50% Still Significantly Impaired @ 1year
 - Poliomyelitis patients most impaired with minimal recovery
 - Most improvement over first 6-8 months, then plateau
 - Headaches
 - Cognitive Impairment: Memory, Concentration
 - Disabling Fatigue
 - Tremor
 - Parkinsonism
 - Residual Weakness/Paralysis
 - Neuropsychiatric symptoms – New onset depression
- Prolonged and costly rehab often necessary

Treatment

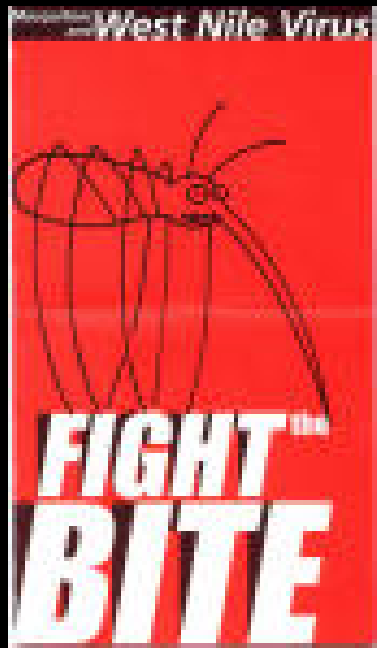
- Supportive Care
- Research: *In vitro*, animal and human clinical data
 - Ribavarin: Not likely to be of benefit
 - Interferon Alpha: Potential benefit
 - Randomized controlled clinical trial in progress
 - Hyperimmune WNV IVIG (High titer for WNV):
 - Animal data: 6 studies suggested protective effect
 - Human data
 - Multicenter, randomized, placebo-controlled human clinical trial performed in 2003 season – results still not published
 - Others:
 - Monoclonal E16 antibody – targets envelope protein
 - Phase I/II randomized trial completed – no results yet
 - Antisense Oligomers
 - Si RNA constructs

WNV Vaccine



- No vaccine for humans yet
- Equine vaccine available: 94% effective
 - Inactivated vaccine, USDA approved Feb 2003
- Ongoing primate studies
 - Most use chimeric constructs
 - Dengue virus or Yellow Fever backbone with WNV antigens genetically engineered
 - Safety and efficacy being evaluated carefully





Prevention



Fight West Nile Virus!



***Eliminate
Standing Water
(Mosquito Breeding Sites)***



***Repair
Screens***



***Protect
Yourself!***

***Questions? Call Your Local Health Department
State of New York • George E. Pataki, Governor***

Protective Measures

- EPA Registered Repellants:
 - DEET (not less than 2 mos of age)
 - 23.8% DEET 5 hours of protection
 - 20% DEET 4 hours
 - 6.65% DEET 2 hours
 - 4.75% DEET 1.5 hours
 - Picaridin
 - Oil of Lemon Eucalyptus* or PMD (the synthesized version of oil of lemon eucalyptus (not less than 3 years of age)
 - IR3535
- http://www.cdc.gov/ncidod/dvbid/westnile/qa/insect_repellent.htm

Pertussis – Burden of Disease

- Global:
 - 30-50 million cases/ 300,000 deaths/year
- Pre-vaccine Era in US:
 - 200,000 cases and 9,000 deaths/year
- 1940's DTP (inactivated) --90% effective
- US Cases decreased to 3000 cases and 20 deaths/year
- Endemic, with cyclical peaks every 3-5 years (10-25,000)
- Increasing number of cases noted since 1980s and especially in past 20 years
- 1991 shift to acellular vaccines; by 1998 exclusive (DTaP)
- 2000-2008: 181 deaths (166 <6 months of age)
- 2010: Nearly 30,000 cases; 27 deaths
- **Largest number of cases since 1950's.**



Annual Pertussis Cases in Past Decade

2001	7,580
2002	9,771
2003	11,647
2004	25,827
2005	25,616
2006	15,632
2007	10,454
2008	13,278
2009	16,858
2010	27,550

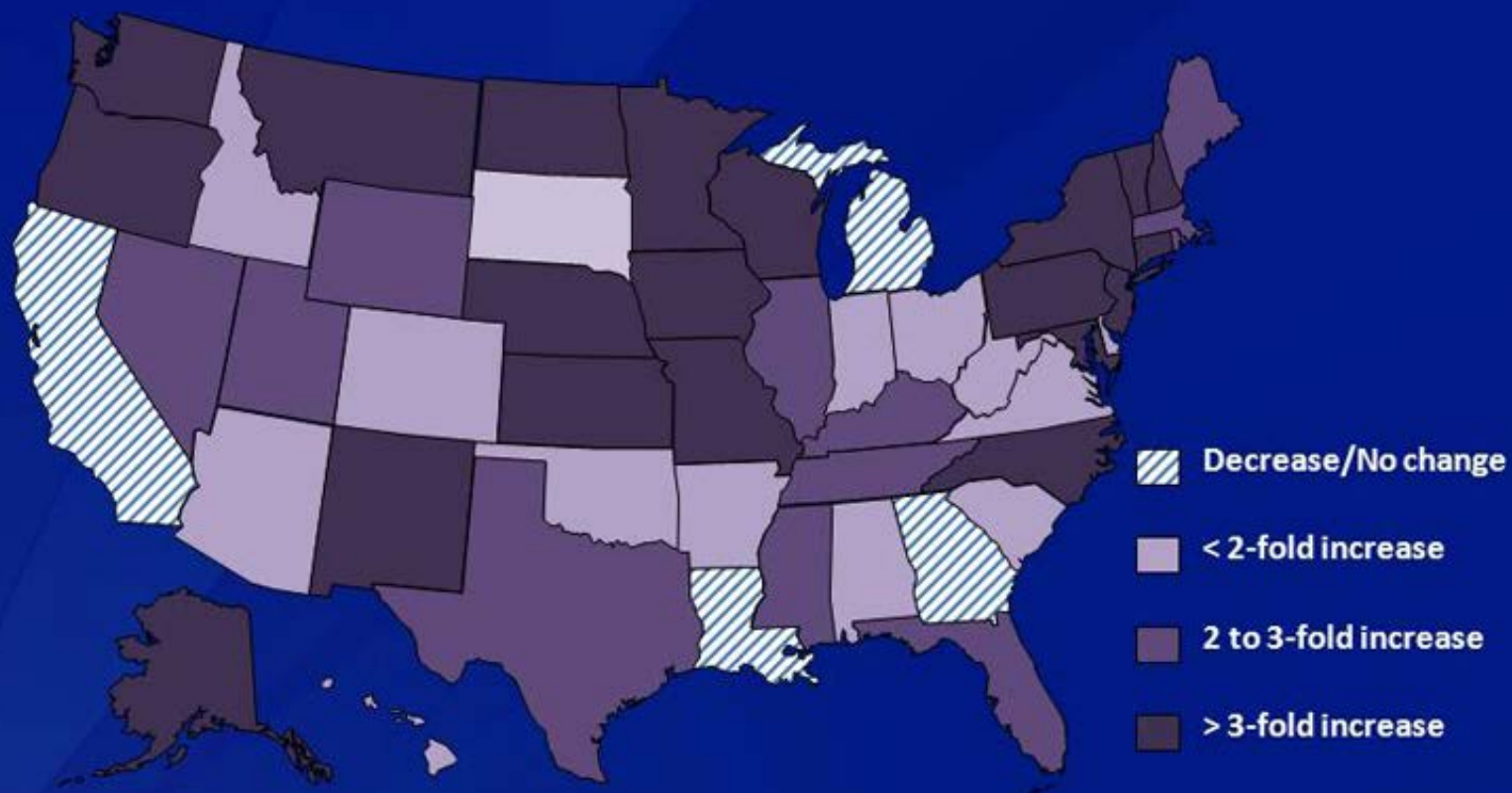


Pertussis Outbreak 2012 (As of August 25, 2012)

- Nearly 25,000 cases/13 deaths reported
- Infants >>> 7-10 year olds > adolescents 13-14 years old
- 46 states + DC with increased disease compared to 2011
- 14 states with incidence rates > US average 7.36/100,000

Wisconsin	67.5	Utah	22.7	New York State	10.2
Washington	49.2	New Mexico	17.1	Kansas	9.4
Montana	39.5	Oregon	16.3	Pennsylvania	9.2
Minnesota	38.4*	North Dakota	15.9	Missouri	8.9
Iowa	31.4	Alaska	12.5	Illinois	8.2
Vermont	31.3	Colorado	10.5	Idaho	8.0
Maine	25.9	Arizona	10.3	New Hampshire	7.4

Changes in Pertussis Reporting by State from 2011 to 2012* †



*Data for 2012 are provisional and subject to change.

†Cases reported through Week 32 in 2011 were compared with cases reported through Week 32 in 2012; fold-changes were calculated for each state.



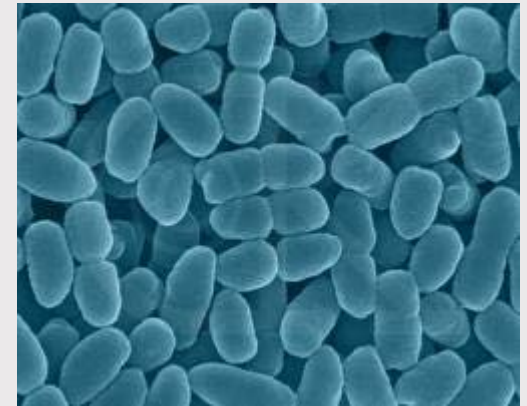
Pertussis – Key Disease Facts

- “The 100 Day Cough”
 - Catarrhal Phase: 1-2 week prodrome, URI – runny nose congestion, apnea, most contagious period
 - Paroxysmal Phase: Severe cough lasting 2-6 weeks; may have inspiratory whoop, post-tussive vomiting
 - Convalescent Phase: Residual cough weeks -months
- **20% of cough lasting >2 weeks in adults is pertussis**
- Severe Disease in Infants < 12 months of age:
 - 2 in 3 (66%) slowed or apneic breathing (< 2 mos of age)
 - 1 in 2 (50%) hospitalized
 - 1 in 4 (25%) develop pneumonia
 - 1 in 50-100 (1-2%) Fatal



Pertussis Outbreaks - Why

- Pertussis Epidemic — Washington, 2012
MMWR July 20, 2012; 61(28):517-22
- Washington State declared epidemic in April 2012
- Incidence highest in children <1 year of age followed by 7-10 year olds and 13-14 year olds.
- DESPITE overall 80% vaccination rate
 - 3mos-10 years: 76% UTD
 - 19-35 month olds: 93% UTD
 - 11-12 years olds: Only 43% UTD
 - 13-19 year olds: 77% UTD
- Suggests waning immunity potentiating circulation of disease



Pertussis Outbreaks: Waning Immunity

- Acellular preparations correlated with less long lasting immunity compared to DTP
- 49th IDSA Meeting, Boston
 - CA Dept Public Health Study: 2010 outbreak:
 - 600 children with Pertussis vs. 2000 without infection
 - Overall vaccine efficacy in 4-10 yr olds = 88.7%
 - Within one year of 5th dose = 98.1%
 - However, efficacy decreased annually to 71.2% by 5 years after 5th dose.
 - Highlights importance of booster at age 11-12
 - Adacel or Boostrix

Pertussis Outbreaks – Attempted Interventions

- DTaP: < 7 years age 5 doses: 2, 4, 6, 15 mos, 4-6 yrs
- 2005: Tdap booster for 11-12 year olds
- 2005: ACIP recommends Tdap for adults 19 to <65 years
- Oct 2010: ACIP expands Tdap rec to adults >65 years if close contact of child <12 months old
- Oct 2011: ACIP recommends Tdap vaccination of pregnant women (>20 weeks gestation or in 3rd trimester), as well as grandparents, childcare providers, and Health Care Workers : “Cocooning” approach
- February 2012: ACIP recommends Tdap for all including all adults >65 years of age.

Pertussis Outbreaks – Why?

- What about vaccine refusal?
- Children who have not had DTaP vaccines are ≥ 8 times more likely to get pertussis than children who received 5 doses
- Increased pockets of nonvaccination or delayed vaccination may potentiate epidemics
- However, vaccine refusal is NOT the driving force behind observed large scale outbreaks
- Bottom Line: We need a better vaccine

Pertussis - Diagnosis

- Clinical Case Definition
 - 2 weeks of cough or more
 - With one or more of:
 - Paroxysms ,Whoop, Post-tussive vomiting
- Laboratory Definition:
 - PCR is test of choice (DFA performs poorly)
 - Culture is also option - special media, dacron swab
- Contact Definition
 - Face to Face Contact within 3 feet
 - Direct contact with respiratory, oral, nasal secretions
 - Shared enclosed space >1 hour



Pertussis Prophylaxis and Treatment

- Prophylaxis of exposed individuals can prevent disease
- Treatment of symptomatic individuals will not have impact on clinical course but decreases infectivity
- Treat infants > 1 year and others up to 3 weeks into symptoms or post-exposure.
- Treat infants, pregnant women up to 6 weeks into symptoms or post-exposure
- Macrolides (Azithromycin, Clarithromycin, Erythromycin) preferred; Bactrim is alternative

Pertussis – Prophylaxis and Treatment

TABLE 4. Recommended antimicrobial treatment and postexposure prophylaxis for pertussis, by age group

Age group	Primary agents			Alternate agent*
	Azithromycin	Erythromycin	Clarithromycin	TMP-SMZ
<1 month	Recommended agent. 10 mg/kg per day in a single dose for 5 days (only limited safety data available.)	Not preferred. Erythromycin is associated with infantile hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40–50 mg/kg per day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants aged <2 months (risk for kernicterus)
1–5 months	10 mg/kg per day in a single dose for 5 days	40–50 mg/kg per day in 4 divided doses for 14 days	15 mg/kg per day in 2 divided doses for 7 days	Contraindicated at age <2 months. For infants aged ≥2 months, TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days
Infants (aged ≥6 months) and children	10 mg/kg in a single dose on day 1 then 5 mg/kg per day (maximum: 500 mg) on days 2–5	40–50 mg/kg per day (maximum: 2 g per day) in 4 divided doses for 14 days	15 mg/kg per day in 2 divided doses (maximum: 1 g per day) for 7 days	TMP 8 mg/kg per day, SMZ 40 mg/kg per day in 2 divided doses for 14 days
Adults	500 mg in a single dose on day 1 then 250 mg per day on days 2–5	2 g per day in 4 divided doses for 14 days	1 g per day in 2 divided doses for 7 days	TMP 320 mg per day, SMZ 1,600 mg per day in 2 divided doses for 14 days

* Trimethoprim sulfamethoxazole (TMP–SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 months who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.



Hantavirus Outbreak

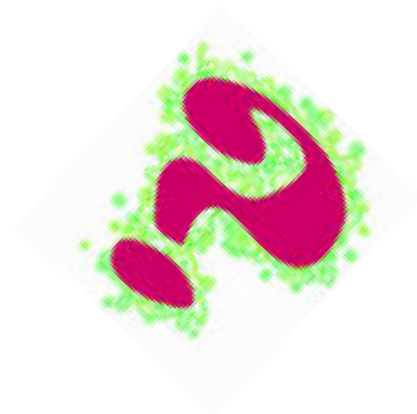
- Respiratory viral illness with high (40%) mortality rate
- Infection occurs following contact with rodent urine, droppings or saliva
- 2012 outbreak in exposed individuals visiting Yosemite National Park and staying in Signature Tent Cabins in Curry Village or High Sierra Camp
- Exposure period: Mid-June through end of August
- 8 confirmed cases to date
- 3 deaths
- Incubation period for Hantavirus Pulmonary Syndrome 1-5 weeks



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"You know, it wouldn't kill ya to go outside and get some exercise."



Questions???

