

# Influenza-Related Mortality and Encephalopathy among Children in the United States

27 November 2007  
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## Influenza Morbidity and Mortality

- Influenza causes annual epidemics
  - Major cause of morbidity & mortality: children aged <24 months, those aged >65, and those with underlying pulmonary, cardiac, etc disease
- Nationally available data has limitations
  - Relatively few respiratory illness cases tested
  - Influenza generally not a reportable disease
- Estimates of U.S. deaths & hospitalizations made with statistical models for decades
  - With retrospective death certificate, hospital discharge data, and viral surveillance data



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## Hospitalizations & Deaths from Influenza

- Modeling studies estimate an average of
  - >200,000 influenza-associated hospitalizations/year
  - ~36,000 influenza-associated deaths/year
  - Average numbers 'hide' considerable variability
- Highest rates of complications are in:
  - Persons with pulmonary and cardiac disease
  - Persons  $\geq 65$  years
  - Children <5 years
- Mortality data for children limited
  - Estimated average of ~92 influenza-related deaths among children aged <5 years annually



Izurieta HS, NEJM 2000; Neuzil KM, NEJM 2000; Thompson WW, JAMA 2004; Neuzil K, JID 2002; Thompson WW, JAMA 2003

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## Pertinent Features of the 2003-04 Influenza Season

- Began as early as October in some states
- Influenza A (H3N2) predominant subtype
  - Historically associated with more severe seasons
- Vaccine mismatch for H3N2 strain
- CDC began receiving reports of influenza-related deaths in children in November 2003
  - No comparable historical data available
  - Public concern; spot vaccine shortages
- On December 12, 2003, request to state, territorial, and local health departments for reports of pediatric influenza-associated deaths



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## Enhanced Surveillance Methods

- **Surveillance period**
  - September 28, 2003 - May 22, 2004
- **Case definition**
  - U.S. resident
  - <18 years old
  - Death during surveillance period
  - Evidence of influenza virus infection by at least one laboratory test: rapid test, IFA, culture, RT-PCR, or immunohistochemistry on autopsy specimens



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## Results 2003-04 Season

- 153 deaths reported from 40 states
- Median age 3 years; range 2 weeks – 17 years
- 76 (50%) male
- **Race (n=146)**
  - White 67%
  - Black 22%
  - Asian 6%
- **Ethnicity (n=134)**
  - Hispanic 24%



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## Method of Diagnosis (n=153)

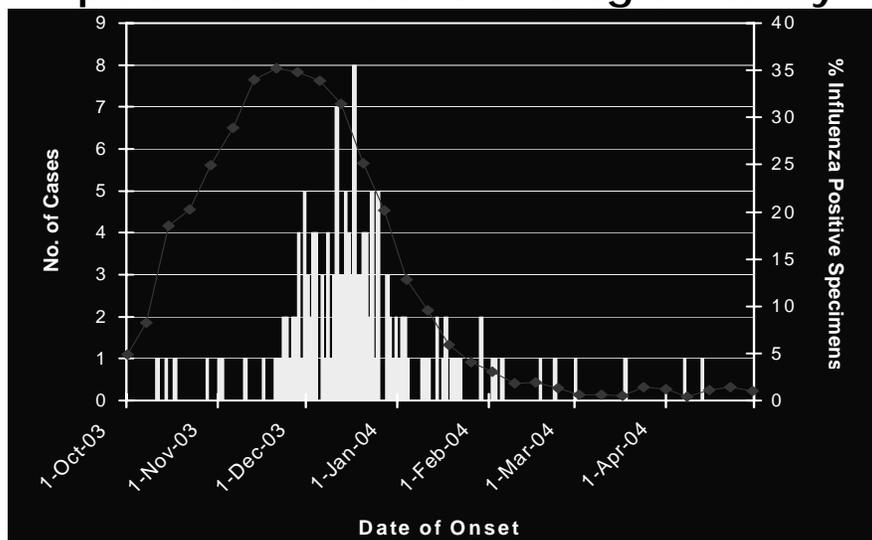
	Sole method <u>Number (%)</u>	Total <u>Number</u>
Rapid antigen/EIA	58 (38)	117
Viral Culture	17 (11)	54
RT-PCR	5 (3)	11
Fluorescent antibody (DFA, IFA)	5 (3)	25
Immunohistochemical staining	5 (3)	27
<i>Multiple methods</i>	<i>63 (41)</i>	



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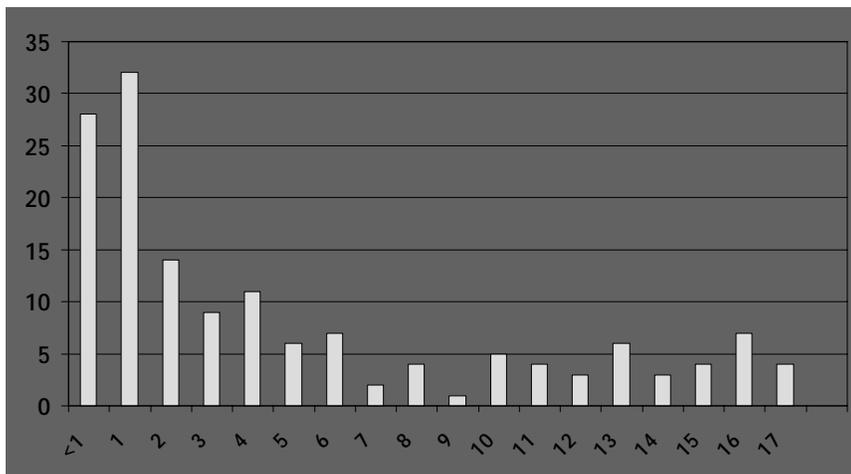
## Epidemic Curve and Virologic Activity



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## Age Distribution (n=153)



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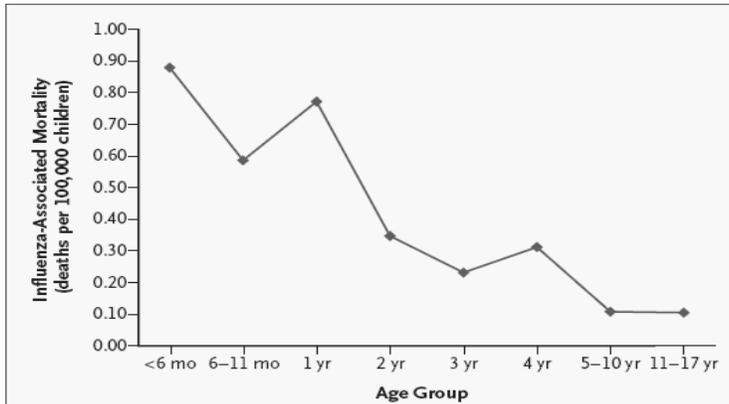
## Age-specific Mortality Rates

<u>Age group</u>	<u>N (%)</u>	<u>Deaths/100,000</u> <u>(95% CI)</u>
<6 months	18 (12)	0.88 (0.52-1.39)
6 - 23 months	43 (28)	0.71 (0.51-0.96)
2 - 4 years	35 (23)	0.30 (0.20-0.42)
5 - 17 years	57 (37)	0.11 (0.08-0.14)
<b>All ages</b>	<b>153 (100)</b>	<b>0.21 (0.18-0.24)</b>



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**Figure 2. Influenza-Associated Mortality Rates According to Age Group — United States, 2003–2004 Season.**

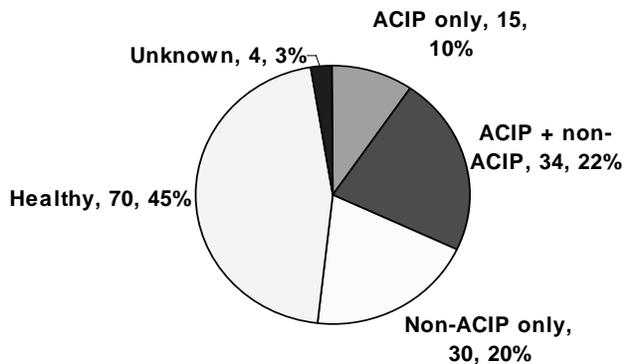
Bhat N et al. Influenza-associated deaths among children in the United States, 2003-04. *N Engl J Med* 2005;24:2559-67



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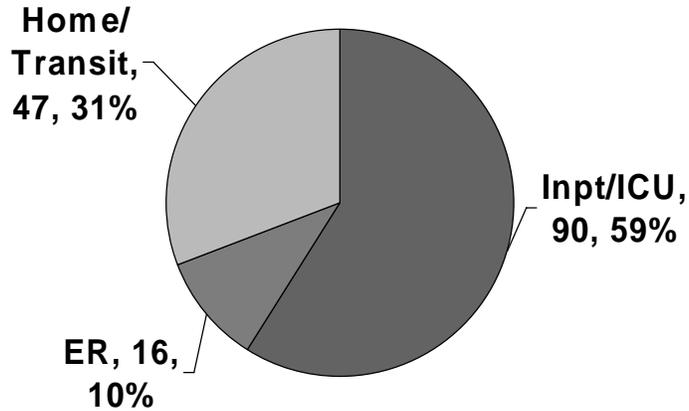
## Underlying Health Status



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## Location at Time of Death (n=153)



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## Reported Clinical & Autopsy Diagnoses -1

	Clinical only	Autopsy only	Both	Total (n=146)
Pneumonia	26	29	16	71
Pneumonitis	1	10	2	13
Bronchiolitis	1	10	--	11
ARDS	9	1	--	10
Croup	6	--	--	6
Tracheitis/ bronchitis	--	27	--	27
Sepsis	32	6	5	43
Shock	30	1	2	33



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## Reported Clinical and Autopsy Diagnoses - 2

	Clinical only	Autopsy only	Both	Total (n=146)
Encephalopathy/encephalitis	8	2	3	13
Stroke	4	1	1	6
Seizures	14	--	--	14
Myo/pericarditis	1	5	--	6
Myocardial infarction	--	2	--	2
Myositis/rhabdomyolysis	4	1	--	5
DIC	15	2	1	18
Hemophagocytosis	1	1	1	3



\*On review, 9 met the case definition for probable or suspected influenza-associated encephalopathy

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Table 4. Bacterial Coinfections in 24 Children with Fatal Influenza — United States, 2003–2004 Season.\*

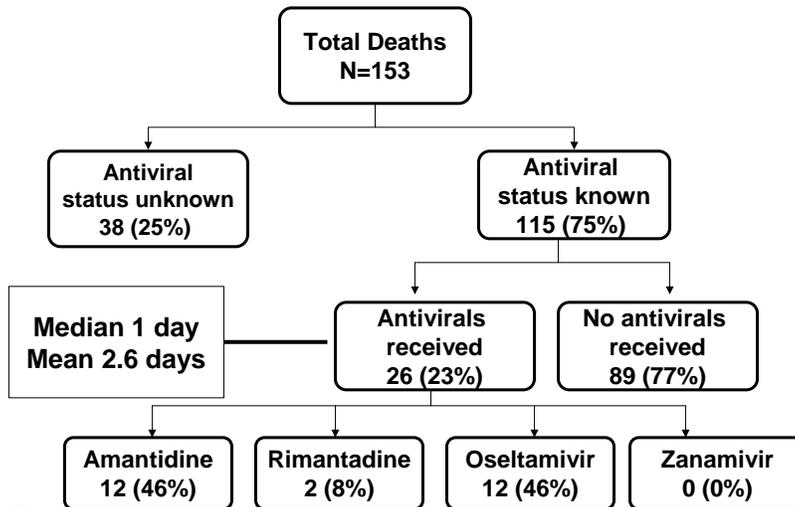
Bacterial Agent	No. of Children
<i>Staphylococcus aureus</i>	11
Methicillin-resistant	6
Methicillin-susceptible	1
Unknown sensitivity	4
<i>Staphylococcus</i> , species not specified	1
<i>Streptococcus pneumoniae</i> †	2
Group A streptococcus	3
<i>Bordetella pertussis</i> ‡	1
<i>Haemophilus influenzae</i>	4
Nontypeable	2
Type a	1
Type b	1
<i>Pseudomonas aeruginosa</i>	1
<i>Enterococcus faecalis</i>	1
<i>Neisseria meningitidis</i>	1
<i>Mycoplasma pneumoniae</i> §	1



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## Antiviral Medication Use



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## Limitations

- Request for case reports was made near the peak of the season in December
- Passive surveillance
- Variations in testing practices, clinical, and pathologic diagnoses
- Incomplete medical records
- Limited information for non-hospitalized cases
- Lack of comparable data, from prior and subsequent seasons



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## Pediatric Influenza Mortality Reporting System

- Lab-confirmed pediatric influenza-associated death became a nationally notifiable condition in June 2004
  - Reporting began October 2004
  - Data reported weekly in MMWR Table 1 and weekly influenza update
- Fewer data elements collected in 2-page reporting form



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## Pediatric Influenza Mortality Reporting System

- 47 cases reported from 18 states during the 2004-05 season
  - 1 received oseltamivir
- 45 cases from 14 states during 2005-06
  - 3 received oseltamivir, 1 rimantadine
- 71 cases from 26 states during 2006-07
  - 3 received oseltamivir, 1 unknown antiviral



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# Influenza-Associated Acute Encephalopathy in Children – United States, 2003-04 Influenza Season



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## Background

- Influenza-associated encephalopathy (IAE) is an uncommon complication of influenza
- Can result in serious neurologic sequelae
- IAE most commonly reported in young Japanese children
  - 148 Japanese cases reported during 1998-99
  - 25 U.S. cases identified during 1999-2003



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# Enhanced Surveillance Methods

- Surveillance period
  - September 28, 2003 - May 22, 2004
- Case definition
  - U.S. resident
  - <18 years of age
  - Febrile illness
  - Laboratory-confirmed Influenza virus infection
  - Altered mental status



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# Case Classification

## Probable

- Altered mental status >24 hours

And

- Onset of altered mental status within 5 days of fever onset

And

- No other cause for altered mental status identified



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# Case Classification

## Suspect

- Duration of altered mental status unknown

Or

- Altered mental status  $\geq$  24 hours, but unable to rule out another cause

Or

- Altered mental status < 24 hours, or other cause for altered mental status identified

And Status Epilepticus

Or Objective findings of cerebral inflammation (CT, MRI, EEG, CSF)



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# Results 2003-04 Season

- 42 IAE cases reported from 22 states
  - 22 Probable
  - 20 Suspect
- 20 Males (48%)
  - Probable: 54% Male
  - Suspect: 40% Male



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## Results 2003-04 Season

- **White**
  - Probable: 9 (50%)
  - Suspect: 12 (67%)
- **Black**
  - Probable: 6 (33%)
  - Suspect: 6 (33%)
- **Asian**
  - Probable: 3 (17%)
  - Suspect: 0



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## Results 2003-04 Season

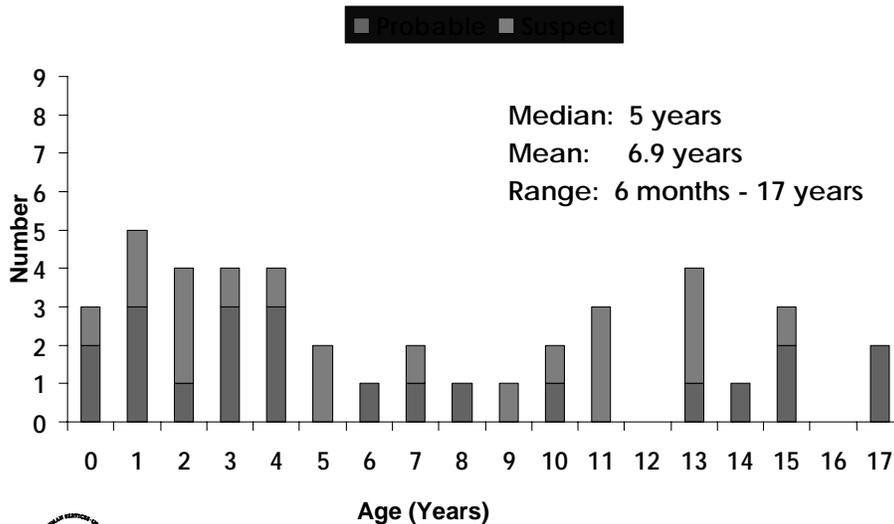
- **Ethnicity information available for some probable and suspect cases**
  - 6 Hispanic (23%)
- **Probable: N=13**
  - 1 Hispanic (8%)
- **Suspect: N=13**
  - 5 Hispanic (38%)



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## Age Distribution (N=42)



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## Underlying High Risk Medical Conditions

- 42 Suspect and Probable Cases
  - 27 had no prior medical conditions
  - 15 had at least 1 chronic medical conditions
    - 7 Probable
    - 8 Suspect
    - 5 had a condition for which ACIP recommended influenza immunization for the 2003-04 influenza season



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## Specific High Risk Medical Conditions

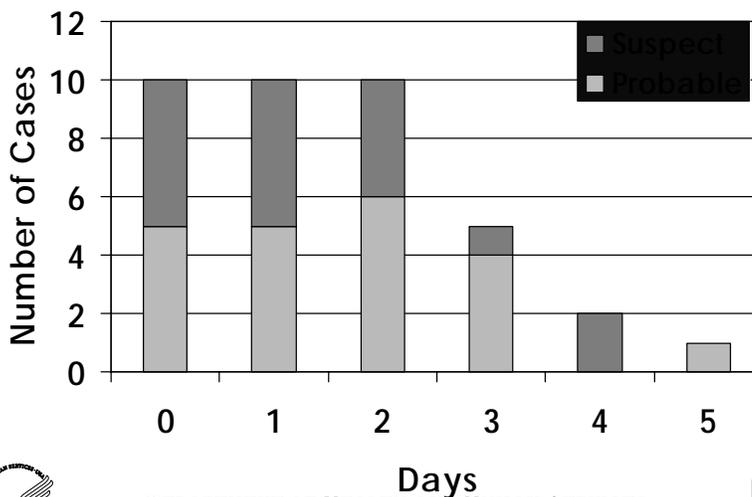
- Chronic GI: 1
- Arthritis: 1
- Chronic lung disease: 1
- Cerebral palsy: 2
- Seizure disorder: 2
- ENT abnormality: 2
- Asthma: 3
- Developmental delay: 6



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## Time from fever to onset of encephalopathy



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## Clinical Presentation - 1

- 33 (78%) presented with altered mental status
  - Duration: median 3 days (range 1-31) among 28 patients with available data
- 20 (48%) Seizures: 9 Probable & 11 Suspect
  - 8 Status Epilepticus: 3 Probable & 5 Suspect
  - 16 Multiple seizures: 8 Probable & 8 Suspect



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## Clinical Presentation - 2

- 17 (40%) Movement Disorder/Ataxia
  - 8 Probable
  - 9 Suspect
- Decreased strength/Flaccid weakness
- Hypotonicity/Hypertonicity
- Slow movements
- Unable to hold trunk/head properly



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## Neuroimaging Studies - 1

- 26 children had an MRI
  - 17 (65%) Abnormal
    - 11 Abnormal
  - 17 Probable
    - 11 Abnormal
  - 9 Suspect
    - 6 Abnormal
- Abnormalities included
  - Cerebral edema (most common)
  - Evidence of infarct
  - Tonsillar herniation
  - Focal cerebritis



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## Neuroimaging Studies - 2

- 11 Children only had CT scan
  - 3 Probable
    - 1 Abnormal
  - 8 Suspect
    - 3 Abnormal
- All 4 abnormal CTs showed cerebral edema
  - 2 with herniation



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## Diagnostic Testing

- **31 (71%) Cerebrospinal Fluid Studies**
  - 18 Probable cases
    - 7 with  $> 5$  WBCs/mm<sup>3</sup>
    - Range 8-69 cells
  - 13 Suspect cases
    - 1 with  $> 5$  WBCs/mm<sup>3</sup> (13 cells)
- **Influenza CSF Cultures (N=17)**
  - 1 positive (Suspect case)



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## Antiviral Treatment

- **20 Received antivirals**
  - 10 Probable
    - 10 Oseltamivir
    - 1 Rimantadine
  - 10 Suspect
    - 4 Oseltamivir
    - 5 Amantadine
    - 1 Rimantadine



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## Antiviral Treatment: Timing

- Before neurological symptoms
  - 0 probable, and 1 suspect case
- Day of development of neurological symptoms
  - 2 probable, and 5 suspect cases
- After development of neurological symptoms
  - 8 probable, and 4 suspect cases



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## Outcomes

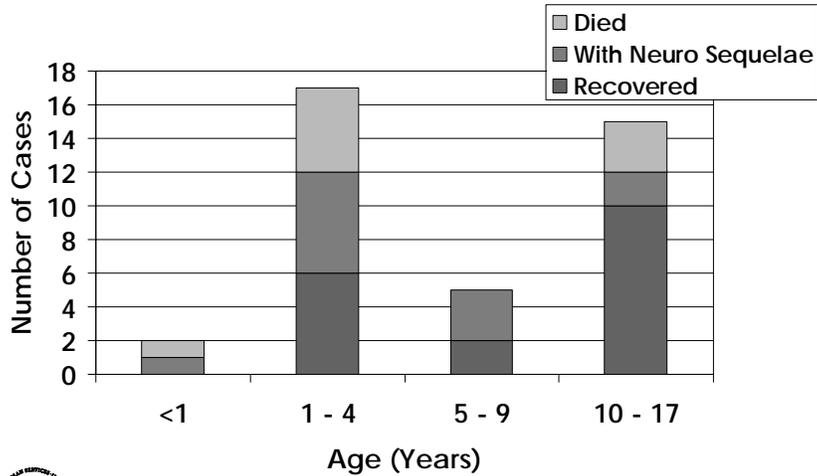
- 19 recovered without neurologic sequelae: 10 Probable and 8 Suspect cases
- 13 recovered with chronic neurologic sequelae: 8 Probable and 5 Suspect cases
- 7 died: 4 Probable and 3 Suspect cases
- Status unknown for 3 Suspect cases



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## Outcomes by Age



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## Limitations

- Passive surveillance
- May have missed cases
- Selection or referral bias
- Differential reporting by states
- Timing of surveillance
- Limited clinical data
- No national system to collect data on laboratory-confirmed cases



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## Summary

- At least 42 IAE cases occurred
  - 22 Probable
  - 20 Suspect
- Asian-Americans were not prominent
- 50% were <5 years old, but older children also affected
- 20 had severe outcomes, including death or chronic neurologic sequelae



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## Acknowledgments

- State and Local Health Departments
- CSTE
- EOC
- EPO
- Vivek Shinde
- Anna Likos
- Tim Uyeki
- Karen Broder
- Michael Greenberg
- Drew Posey
- Niranjana Bhat
- Erin Murray
- Alicia Postema
- Laura Podewils
- Scott Harper
- Keiji Fukuda
- Ermias Belay
- Marc Fischer
- Stephanie Schrag
- Scott Harper
- Matt Kuehnert
- Cynthia Whitney
- David Shay
- Tonya Farris
- James Sejvar
- Sherif Zaki
- Wun-Jun Shieh
- Chris Paddock
- Jeanette Guarner
- Mitesh Patel
- Alexander Klimov
- Kathryn Teates
- Thea Fischer
- Cynthia Whitney
- Stephanie Schrag
- Matt Kuehnert
- Brittany Baughman
- Michelle Oberlin
- Melissa Amundson
- Jeevan Sekhar
- Tonya Farris
- Irene Shui
- James Sejvar
- Craig Borkowf



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