

Supplementary Appendix

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Web-only supplement

The Under-recognized Burden of Influenza Illness in Young Children

Short title: The Under-recognized Burden of Influenza Illness in Children

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Methods:

Sites were selected through a competitive grant review process by an external review board. The surveillance population had similar age and gender distribution as the U.S. population, but more white (65% versus 58%) and black (23% versus 14%) children, and fewer Hispanic children (6% versus 19%).(1)

Laboratory Samples

The nasal and throat swabs were combined in a tube of veal-infusion broth transport medium, kept on ice and delivered within 1-2 hours to the local research laboratory. Aliquots of each specimen were inoculated onto primary rhesus monkey kidney cells and incubated at 35°C. Viruses were identified by cytopathic effect and hemadsorption. All cultures negative at 10 days were screened by immunofluorescent assay.(2;3)

In 2000-2001, sample aliquots were collected in lysis buffer, frozen at -70°C, and shipped in batches to the CDC for RNA extraction and reverse transcription polymerase chain reaction assays (RT-PCR).(4) From 2001-2004 each site performed its own RT-PCR assays. The laboratory methods used in Nashville and Rochester were similar to

those used at the CDC laboratory.(3) Cincinnati used the commercially available multiplex assay (Hexaplex Prodesse, Inc., Milwaukee, WI) to capitalize on local laboratory expertise.(5) Quality assurance activities verified similar detection across sites (data not shown).

All inpatient samples and outpatient samples from 2003-2004 had both viral cultures and RT-PCR performed, while outpatient samples from 2002-2003 were tested by RT-PCR alone.

Influenza season

Although the influenza seasons were defined by site, they encompassed the same weeks during these study years and the peak influenza activity overlapped across sites and with national surveillance data.(6) This definition included 100% and 92% of all identified influenza cases in 2002-2003 in Nashville and Rochester, and 100%, 99%, and 98% of all identified influenza cases in 2003-2004 in Nashville, Rochester and Cincinnati, respectively.

Population-based hospitalization rates

Enrolled and non-enrolled children were comparable by gender. The weighting accounted for significant age differences between enrolled and non-enrolled children by site and study year.

National Estimates of ARI visits

We calculated the mean rates and 95% confidence intervals of all ARI visits for the 13-week influenza season in outpatient clinics and EDs by age group using the National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS).(7) ARI visits had an ICD-9 diagnosis for an ARI (see footnote of **Table 1**). These surveys collect nationally representative data about the utilization and diagnoses for outpatient visits in the U.S. NAMCS collects data from a randomly selected 1-week sample of clinic visits to physicians outside a hospital setting. We evaluated all ARI visits to primary care physicians. Similarly, NHAMCS collects data from a 4-week sample of visits to hospital-based clinics and EDs; we evaluated all ARI visits to hospital-based pediatric clinics and EDs.(8) These datasets were combined accounting for the complex survey sampling designs.

References

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- (3) Weinberg GA, Erdman DD, Edwards KM et al. Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. *J Infect Dis* 2004;189:706-710.
- (4) Erdman DD, Weinberg GA, Edwards KM et al. GeneScan reverse transcription-PCR assay for detection of six common respiratory viruses in young children hospitalized with acute respiratory illness. *J Clin Microbiol* 2003;41:4298-4303.
- (5) Kehl SC, Henrickson KJ, Hua W, Fan J. Evaluation of the Hexaplex assay for detection of respiratory viruses in children. *J Clin Microbiol* 2001;39:1696-1701.

- (6) Centers for disease Control and Prevention. Flu Activity: Reports and Surveillance Methods in the United States. (Accessed January 26, 2006 at <http://www.cdc.gov/flu/weekly/fluactivity.htm>.)
- (7) Estimate means, totals, ratios, and proportions for survey data. In: Survey Data Reference Manual Release 8. College Station, TX: Stata Press, 2003.
- (8) National Center for Health Statistics. NAMCS and NHAMCS. (Accessed June 30, 2005, at <http://www.cdc.gov/nchs/about/major/ahcd/ahcd1.htm>.)