What Have We Learned About Influenza Deaths in Children and How Can We Do Better?

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Bhat et al[1] reported in the *New England Journal of Medicine* that there were 153 influenza-associated deaths among children in the United States during the 2003–2004 influenza season, a somber reminder of the impact of influenza on children. Nearly half of the children that died had no underlying medical conditions and the highest mortality rates were seen in the youngest children. The conclusions of that paper were that "high priority should be given to improvements in influenza-vaccine coverage and improvements in the diagnosis and treatment of influenza to reduce childhood mortality from influenza."

Since this initial report, the Centers for Disease Control and Prevention have continued to periodically report their findings from the passive "Influenza-Associated Pediatric Mortality Surveillance System."[2–4] More than a decade later, 6 additional influenza seasons are characterized in this issue of *Pediatrics*, with nearly identical findings.[5] On average each year in the United States, >100 children die of laboratory-confirmed influenza. Nearly 50% of these fatalities are in children who were previously healthy with no underlying medical conditions, the mortality remains the highest in the youngest children, and those that died are most often unvaccinated. Both group A β-hemolytic *Streptococcus* and methicillin-resistant *Staphylococcus aureus* (MRSA) are the most commonly detected bacteria and are associated with rapid demise. The important role of MRSA in influenza-related mortality had been previously published.[6] In contrast to earlier reports, authors of the current article report that coinfections with respiratory syncytial virus (RSV) and influenza were detected in 24 of the fatalities and the diagnosis of bronchiolitis was made in 22 of the deaths. However, there are limitations in the data collected by this passive surveillance system. The system does not comprehensively capture data on biomarkers like C-reactive protein and procalcitonin, radiology and imaging reports, positive bacterial culture results from the blood and pleural fluid, antibiotic susceptibilities on isolated bacteria, and details of treatment with antibiotics and antiviral agents.

These reports raise many critical questions. Why are children continuing to die of influenza? What additional data are needed for clinicians to distinguish between those patients who die and those who do not? Are there biomarkers that could predict disease severity? What is the pathogenesis of rapid demise, often before presentation to the medical care system? Can it be better managed? Are there clues in patients who would benefit from immediate antibiotic use? What are the characteristics of the pneumonia reported in a number of the children? How did the radiographs look, and did they provide information helpful for management? How many of the patients who died had been placed on antibiotics before presentation or death? What are the best antibiotics to prescribe? What

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are the resistance patterns of the detected bacteria? Did the percent of MRSA decrease over the time of the study? The codetection of both RSV and influenza is intriguing. Were the children first infected with RSV and then influenza? What would have happened if the patients with high-risk medical conditions were more promptly treated with antiviral agents?

In an attempt to provide additional answers to these questions, children with severe influenza infection without underlying medical conditions were enrolled in the Pediatric Influenza Study. A total of 358 US children with laboratory-confirmed influenza admitted to 38 PICUs from November 2008 to April 2016 were studied.[7] Children who were enrolled underwent rigorous diagnostic testing, extensive clinical phenotyping, and sequencing of specific genetic markers that had been associated with fatal influenza in adults.[8] No specific genetic markers associated with death were identified, but this report demonstrated the ability of a network of pediatric providers to collect data and samples in a collaborative manner in children who were severely ill to improve our understanding of the problem. Such studies should continue and expand.

Although questions remain, there are important lessons from the report by Shang et al.[5] First, many children are not receiving the recommended influenza vaccines, with >70% of the children who died not immunized. This must be improved. Second, although maternal influenza vaccinations were not captured in the surveillance system, authors of randomized clinical trials and observational studies strongly support the impact of maternal influenza vaccination on influenza prevention in infants.[9,10] Current data reveal that only one-third of pregnant women are immunized with influenza vaccine this season. This must be widely implemented. Third, the thoughtful and judicious use of antibiotics in patients with bacterial and influenza coinfections should always be considered. Studies on predictive biomarkers and severity criteria should continue. Finally, the prompt use of neuraminidase inhibitor antiviral agents in patients with underlying medical conditions and in those that are hospitalized should be implemented. Both the Centers for Disease Control and Prevention and the American Academy of Pediatrics Committee on Infectious Diseases endorse this policy that is supported by effectiveness data recently summarized in the literature.[11] Although antiviral drugs work best when treatment is started within 2 days of illness onset, clinical benefit has also been observed when treatment is initiated later. We can only hope that when the data are published at the end of the next decade, we will see a reduction in fatalities in children with influenza.

ABBREVIATIONS

MRSA: methicillin-resistant *Staphylococcus aureus*
RSV: respiratory syncytial virus

REFERENCES

1. Bhat N, Wright JG, Broder KR, et al; Influenza Special Investigations Team. Influenza-associated deaths among children in the United States, 2003-2004. *N Engl J Med*. 2005;353(24):2559–2567
2. Cox CM, Blanton L, Dhara R, Brammer L, Finelli L. 2009 pandemic influenza A (H1N1) deaths among children—United States, 2009-2010. *Clin Infect Dis*. 2011;52(suppl 1):S69–S74
3. Peebles PJ, Dhara R, Brammer L, Fry AM, Finelli L. Influenza-associated mortality among children - United States: 2007-2008. *Influenza Other Respir Viruses*. 2011;5(1):25–31
4. Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004-2012. *Pediatrics*. 2013;132(5):796–804
5. Shang M, Blanton L, Olsen SJ, Fry AM, Brammer L. Influenza-associated pediatric deaths in the United States, 2010–2015. *Online J Public Health Inform*. 2017;9(1):e077
6. Finelli L, Fiore A, Dhara R, et al. Influenza-associated pediatric mortality in the United States: increase of *Staphylococcus aureus* coinfection. *Pediatrics*. 2008;122(4):805–811
7. Randolph AG, Yip WK, Allen EK, et al; Pediatric Acute Lung Injury and Sepsis Investigators Network Pediatric Influenza Investigators. Evaluation of IFITM3 rs12252 association with severe pediatric influenza infection. *J Infect Dis*. 2017;216(1):14–21
8. Everitt AR, Clare S, Pertel T, et al; GenISIS Investigators; MOSAIC Investigators. IFITM3 restricts the morbidity and mortality associated with influenza. *Nature*. 2012;484(7395):519–523
9. Madhi SA, Nunes MC, Cutland CL. Influenza vaccination of pregnant women and protection of their infants. *N Engl J Med*. 2014;371(24):2340
10. Poehling KA, Szilagyi PG, Staat MA, et al; New Vaccine Surveillance Network. Impact of maternal immunization on influenza hospitalizations in infants. *Am J Obstet Gynecol*. 2011;204(6, suppl 1):S141–S148
11. Malosh RE, Martin ET, Heikkinen T, Brooks WA, Whitley RJ, Monto AS. Efficacy and safety of oseltamivir in children: systematic review and individual patient data meta-analysis of randomized controlled trials [published online ahead of print November 23, 2017]. *Clin Infect Dis*. doi:10.1093/cid/cix1040

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