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Enterovirus D68 Reemerges Globally as a Severe Pathogen Targeting Children

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In the late summer and early fall of 2014, U.S. pediatric emergency rooms were filled with children presenting with acute onset of severe respiratory distress.⁽¹⁾ Many developed respiratory insufficiency and/or failure and were admitted to the pediatric intensive care unit (PICU). Cases were initially reported in Missouri and Illinois where most had positive PCR tests for rhinovirus/enterovirus (RV/EV) from respiratory secretions; subsequent testing of samples by the U.S. Centers for Disease Control and Prevention (CDC) identified Enterovirus D68 (EV-D68) as the most common pathogen. ⁽²⁾ EV-D68 spread within weeks to encompass 49 U.S. states and Canada ⁽³⁾ with outbreaks reported in Europe ⁽⁴⁾ and Asia ⁽⁵⁾. Although 1,152 U.S. cases would be virologically confirmed by CDC as EV-D68 by December 2014, speculation is that millions could have been infected because available testing was so limited.⁽¹⁾

EV-D68 is an atypical enterovirus. Most enteroviruses flourish in the pH and temperature of the gastrointestinal tract.⁽⁶⁾ EV-D68 behaves similarly to rhinovirus flourishing in the upper and lower respiratory tract. The anxiety generated by the rapidity of spread of EV-D68 and severity of presentation reminded clinicians of the 2009 H1N1 influenza A pandemic.⁽⁷⁾ In this issue of *Pediatric Critical Care Medicine*, Dr. Rao and colleagues report results of a retrospective comparison of 97 pediatric EV-D68 cases admitted to the Children's Hospital Colorado PICU during the 2014 outbreak to 68 children with 2009 H1N1 admitted to their PICU during that pandemic.⁽⁸⁾ Patients testing positive for RV/EV during the 2014 outbreak who tested negative at the CDC for EV-D68 (n=86) were included as a second comparison group. Standard use of multiplex viral PCR testing over the years in children with respiratory illness admitted to the PICU enabled full capture of their cohort and allowed them to make a valid comparison.

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In brief, children admitted to the PICU with EV-D68 were more likely to have bronchospasm and present with an exacerbation of reactive airways disease whereas 2009 H1N1 presented more commonly as pneumonia. Because of this, use of bronchodilators and steroids was markedly higher in children with EV-D68. EV-D68 had a shorter prodrome and the PICU course of children with EV-D68 was also shorter; only a small percentage of children with EV-D68 were intubated although use of CPAP/BiPAP was common. Acute respiratory distress syndrome (ARDS) was diagnosed in 24% of those with 2009 H1N1 but only 3% of those with EV-D68. None of the children with EV-D68 died compared to 12% (N=8) of those with 2009 H1N1. Compared to children positive for other RV/EV strains, children with EV-D68 were older (median age 7 years), more likely to have an asthma history, more likely to be treated with bronchodilators, magnesium and steroids, and less likely to be intubated.

In September 2014, the U.S. CDC began investigating cases of acute flaccid paralysis of unclear etiology presenting similar to poliomyelitis (9); poliovirus is also a human enterovirus. EV-D68 was identified in the respiratory secretions of some of these patients but not in the spinal fluid, thus, a direct link was not possible. Many patients did not recover full function. Limited ability to test for EV-D68, and the rapidity of onset and offset of this global outbreak limited our understanding. A systematic review of 70 reports of smaller outbreaks since EV-D68 first emerged in California in 1962 reveals EV-D68 to be a potential emerging pathogen.(10) Multiple clades of EV-D68 now exist worldwide.(11) International calls for increased public health surveillance for EV-D68 and other emerging pathogenic viruses have been raised.(3,9) Children are often the most severely affected by emerging viral pathogens and the most severe cases are treated in the PICU. Therefore, clusters of PICU cases can be the canary offering advance warning of a national epidemic.

Development of an international PICU surveillance network to identify and test for severe emerging pathogens could advance our understanding of their pathophysiology, hasten development of treatments, and ultimately, save lives. What would it take to do this? As a first step, with funding from the CDC Influenza Division, in 2013 the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network developed a group of 39 U.S. PICUs poised to collect clinical data during an outbreak of a novel influenza or emerging viral pathogen called the Pediatric Intensive Care Influenza and Emerging Severe Pathogens (PICFlu-ESP) Subgroup. A single institutional review board (IRB) was set up across institutions and 24/39 sites agreed to rely on it. Web-based data collection forms were developed in a modular fashion, facilitating rapid modifications based on pathogen and clinical characteristics. The plan was for data to be sent to government collaborators to provide real-time tracking of the outbreak like was done during the 2009 pandemic.(7) Waiver of consent was approved by the IRBs for data collection in the event that a national emergency was declared by a government agency.

Although promising, the EV-D68 outbreak revealed some gaps in the PICFlu-ESP Subgroup's surveillance model. Because consent is waived, samples from patients are not collected under the current IRB approved protocol unless they are for clinical purposes. Systematic viral testing and banking of respiratory samples for further evaluation is a prerequisite for confirming the pathogen and evaluating genetic drift. Funding was also an

issue; contracts for payment to support data collection take time and must be done in advance to capture a rapidly emerging pathogen that rises and falls within months. Even if site contracts were in place, government funds would need to be available and quickly released. Given the inability to predict when outbreaks will occur, a more optimal approach may be to perform ongoing viral surveillance in sentinel PICUs. Until then, PICUs like that of Rao and colleagues (8), that routinely perform viral multiplex testing and bank respiratory samples provide a valuable resource.

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