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Surveillance for Enterovirus D68 in Colorado Children Reveals Continued Circulation

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Abstract

Background—The largest, most widespread outbreak of enterovirus D68 respiratory disease occurred from August to December of 2014 in the United States with 1,153 confirmed infections in 49 states. The epidemiology of enterovirus D68 following the 2014 outbreak is unknown.

Objectives—This study seeks to describe the epidemiology of enterovirus D68 circulation amongst Colorado children from 2014–2016.

Study Design—This is a prospective observational surveillance study of enterovirus D68 infection amongst children tested for respiratory pathogens from July–October 2014–2016 at Children's Hospital Colorado (CHCO), a quaternary care children's hospital in Aurora, CO.

Results—Amongst rhinovirus/enterovirus positive respiratory specimens from intensive care unit patients, ninety-eight of 314 (31.2%) in 2014, none of 307 (0%) specimens in 2015, and 19 of 240 (7.9%) specimens in 2016 were identified as enterovirus D68. Amongst respiratory specimens from all patients during the prospective active surveillance period, none of 1469 (0%) in 2015 and 46 of 1403 (3.3%) were positive for enterovirus D68.

Conclusions—Surveillance for enterovirus D68 amongst respiratory specimens at a quaternary care children's hospital revealed a seasonal pattern of circulation in the late summer to early fall of 2014 and 2016. Continued surveillance of respiratory specimens is necessary to define the circulation pattern and understand the epidemiology of this emerging pathogen.

Keywords

enterovirus; enterovirus-D68; surveillance; respiratory disease; acute flaccid myelitis

Background

Enterovirus D68 (EV-D68) was first isolated in 1962 in California from hospitalized children with severe respiratory infections (1). Until recently, it was only associated with

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sporadic cases of respiratory disease, with only 26 cases confirmed through passive surveillance systems in the USA between 1970 and 2005 (2). Between 2008 and 2014, an increasing number of small clusters of EV-D68 respiratory disease was reported in the USA, Europe, Africa, and southeast Asia (3, 4). In late summer and early fall of 2014, however, the largest reported outbreak of EV-D68-associated severe respiratory disease occurred in the USA and Canada (5, 6). Importantly, circulation of EV-D68 in 2014 coincided with an outbreak of acute flaccid myelitis (AFM) (7, 8), with accumulating evidence suggesting a causal link between EV-D68 and AFM (9). It is not known whether the outbreak of EV-D68 in 2014 in the USA represented an isolated event or whether the virus will become endemic and periodically resurface.

Objective

This study seeks to better understand the epidemiology of EV-D68 after 2014 through prospective active surveillance of respiratory specimens from Colorado children.

Study Design

Children's Hospital Colorado (CHCO) is an academic, quaternary care hospital with a catchment of approximately 2.5 million children, primarily in the Denver metropolitan area. The CHCO Clinical Microbiology Laboratory receives respiratory specimens from outpatients and inpatients at CHCO and affiliated sites. Specimens are tested by the FilmArray® Respiratory Panel (RP) (BioFire Diagnostics, Salt Lake City, UT), a multiplex PCR that detects RVs and EVs but cannot discriminate between the two (10). During the 2014 outbreak, residuals of all RV/EV positive respiratory specimens collected in July–October 2014 from patients in our intensive care units (ICU) were sent to the CDC Polio and Picornavirus Laboratory Branch for PCR-based identification of EV-D68 (9). Thereafter, an EV-D68 specific PCR was implemented at CHCO (11) and used to detect the virus in all specimens positive for RV/EV by RP from July–October of 2015–2016, regardless of patient location. Only the first positive specimen from an individual patient was included in the case counts. Representatives of EV-D68 lineages from 2014 and 2016 were selected for genotyping using partial VP1 sequencing and compared with VP1 gene sequences in GenBank, as previously described (12).

Results

For epi weeks 27–43 (July – October), the number of respiratory specimens submitted for RP during 2014, 2015, and 2016 was 1443, 1469, and 1403, respectively, of which the number and percent positive for RV/EV was 731 (50.6%), 583 (39.6%), and 540 (38.5%). The weekly distribution of EV-D68 detections from the subset of patients in the ICU from 2014 – 2016 is shown in Figure 1. Ninety-eight of 314 (31.2%) specimens in 2014 and 19 of 240 (7.9%) specimens in 2016 were positive for EV-D68. By contrast, none of 307 (0%) specimens sent from the ICU in 2015 contained EV-68. In both 2014 and 2016, the EV-D68 season encompassed epi weeks 28–41 with peak activity from weeks 34–38. In 2014, 64% of EV-D68 positive PICU patients had a history of asthma and 15% had other underlying medical conditions. In 2016, 37% of EV-D68 positive PICU patients had a history of asthma

and 26% had other underlying medical conditions (prematurity and congenital heart disease most commonly). Children positive for EV-D68 requiring PICU care trended towards being younger in 2016 compared to 2014 [5.1 (2.4–11.7) years compared to 7.3 (4.3–11.7) years; median (IQR), p value = 0.27] with similar clinical presentations consisting of increased work of breathing, cough, wheezing, and hypoxia. Intubation and ventilator support was required in 5% of PICU patients with EV-D68 in 2016 compared to 7% in 2014. During this same time frame, 12 patients (5 EV-D68 positive), 0 patients, and 1 patient (1 EV-D68 positive) were diagnosed with AFM at CHCO in 2014, 2015, and 2016 respectively.

During prospective active surveillance of all specimens submitted for RP testing, no new specimens were positive for EV-D68 in 2015. In 2016, 46 (3.3%) specimens were positive for EV-D68, including 19 (7.9%) of 240 specimens from children admitted to the ICU, 13 (2.7%) of 486 specimens from non-ICU hospitalized children, and 14 of 678 (2.1%) specimens from outpatients.

A representative subset of ten EV-D68 specimens from CHCO in 2016 all belonged to clade B3, which was similar to other circulating strains in the US in 2016 and did not contain significant amino acid changes in the capsid compared to 2014 clade B strains (personal communication, W. Allan Nix, Centers for Disease Control and Prevention Picornavirus Laboratory) (12, 13).

Discussion

The unprecedented surge in EV-D68 respiratory disease at our institution during 2014 (6) and uncertainty about its epidemiology prompted active surveillance for EV-D68 in 2015–2016. The complete absence of EV-D68 in 2015 and its resurgence in 2016 is suggestive of continued periodic circulation, similar to patterns being reported in Europe (14). The observed pattern of circulation in 2014 and 2016 may reflect the need for a new immune-susceptible birth cohort to support spread of the virus following an outbreak, or may reflect the time required for new antigenic variants to arise. Circulation in both 2014 and 2016 followed a similar pattern of late summer to early fall (July–October) seasonality, peaking August–September in Colorado. Our data also demonstrate that EV-D68 did not simply circulate once but has the potential for continued seasonal endemic circulation in the US.

We propose that surveillance of respiratory specimens from children in the ICU may serve as a surrogate marker of EV-D68 circulation in the community that may not be readily apparent. Indeed in 2016, EV-D68 continued to cause a wide spectrum of respiratory disease in children ranging from mild illnesses requiring only outpatient symptomatic care, to severe disease necessitating ICU respiratory support. Additionally, the pattern of circulation of EV-D68 observed in this study temporally correlated with spikes in AFM cases reported throughout the US in 2014 and 2016, further supporting the hypothesis that EV-D68 is a cause of AFM (15).

This is a single-center, three-year surveillance study which may not be generalizable to other regions of the US and observed patterns may not be predictive of future circulation. The use of clinically collected respiratory specimens underestimates overall incidence and likely

reflects the more severe end of the spectrum of disease, as our institution discourages sampling in cases where testing would not change management. Specimens from PICU patients were used for consistent comparison between all years, as retrospective non-PICU specimens were unavailable for testing in 2014 as in 2015 and 2016.

In summary, during the past three years EV-D68 demonstrated continued seasonal circulation in 2014 and 2016 associated with a wide spectrum of respiratory illnesses and neurologic disease. Our data indicate that EV-D68 is an emerged pathogen with the potential for sustained endemic transmission in the US. Enhanced surveillance for EV-D68 in respiratory specimens is needed to better understand the epidemiology of this pathogen with significant public health implications.

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Highlights

- Aug–Oct 2014: enterovirus D68 caused a large outbreak of respiratory disease in CO.
- 2015: enterovirus D68 did not circulate in CO or the US.
- Aug–Oct 2016: enterovirus D68 circulated in CO at lower levels compared to 2014.
- Continued enterovirus D68 surveillance is needed to better understand its epidemiology.
- Respiratory specimens are an important component of enterovirus surveillance efforts.

Figure 1.
RV/EV and EV-D68 positive respiratory specimens from children admitted to the intensive care unit by year and epi week