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Human parainfluenza virus circulation, United States, 2011–2019

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ABSTRACT

Background: Human parainfluenza viruses (HPIVs) cause upper and lower respiratory tract illnesses, most frequently among infants and young children, but also in the elderly. While seasonal patterns of HPIV types 1–3 have been described, less is known about national patterns of HPIV-4 circulation.
Objectives: To describe patterns of HPIVs circulation in the United States (US).
Study design: We used data from the National Respiratory and Enteric Virus Surveillance System (NREVSS), a voluntary passive laboratory-based surveillance system, to characterize the epidemiology and circulation patterns of HPIVs in the US during 2011–2019. We summarized the number of weekly aggregated HPIV detections nationally and by US census region, and used a subset of data submitted to NREVSS from public health laboratories and several clinical laboratories during 2015–2019 to analyze differences in patient demographics.
Results: During July 2011 - June 2019, 2,700,135 HPIV tests were reported; 122,852 (5 %) were positive for any HPIV including 22,446 for HPIV-1 (18 %), 17,474 for HPIV-2 (14 %), 67,649 for HPIV-3 (55 %), and 15,283 for HPIV-4 (13 %). HPIV testing increased substantially each year. The majority of detections occurred in children aged ≤ 2 years (36 %) with fluctuations in the distribution of age by type.
Conclusions: HPIVs were detected year-round during 2011–2019, with type-specific year-to-year variations in circulation patterns. Among HPIV detections where age was known, the majority were aged ≤ 2 years. HPIV-4 exhibited an annual fall-winter seasonality, both nationally and regionally. Continued surveillance is needed to better understand national patterns of HPIV circulation.

1. Background

Human parainfluenza viruses (HPIVs) are enveloped, single-stranded RNA viruses in the *Paramyxoviridae* family with four antigenically distinct types known to infect humans: HPIV-1, HPIV-2, HPIV-3, and HPIV-4 [1]. HPIVs can cause a range of upper and lower respiratory tract illnesses including bronchitis, bronchiolitis, laryngotracheobronchitis (croup), and pneumonia [2]. HPIVs are the second most common cause of acute respiratory illness-related hospitalizations in children < 5 years of age, second only to respiratory syncytial virus (RSV). HPIVs account for approximately 7 % of all hospitalizations for fever, acute respiratory illness (ARI), or both [3]. Co-infections of HPIV and other respiratory viruses are common and may lead to more complicated and prolonged disease course, especially among children [1,3].

Clinical presentation can vary by type; HPIV-1 and HPIV-2 commonly cause croup and cold-like symptoms and HPIV-3 is more often associated with bronchiolitis and pneumonia [4]. HPIV-4 is less well-characterized, as it has been less commonly included in respiratory virus diagnostic panels, but has been suggested to have a similar clinical presentation as HPIV-3 [3,5,6]. Infants, young children, the elderly, and those that are immunocompromised are at higher risk for severe HPIV illness. In healthy adults, HPIV illness is usually limited to mild upper respiratory track symptoms [6].

In the United States, HPIVs typically circulate seasonally with variations in annual prevalence. HPIV-1 peaks in the fall of odd-numbered years, HPIV-2 peaks in the fall of even-numbered years, and HPIV-3 peaks annually in the spring and early summer, when HPIV-1 and HPIV-2 are not present [1,4,7–8,9]. HPIV-4 seasonal patterns are less well-described; the few studies that assessed HPIV-4 focused on solitary outbreaks of HPIV-4 or were limited to countries outside the United States [10–16]. Available studies that have documented patterns of

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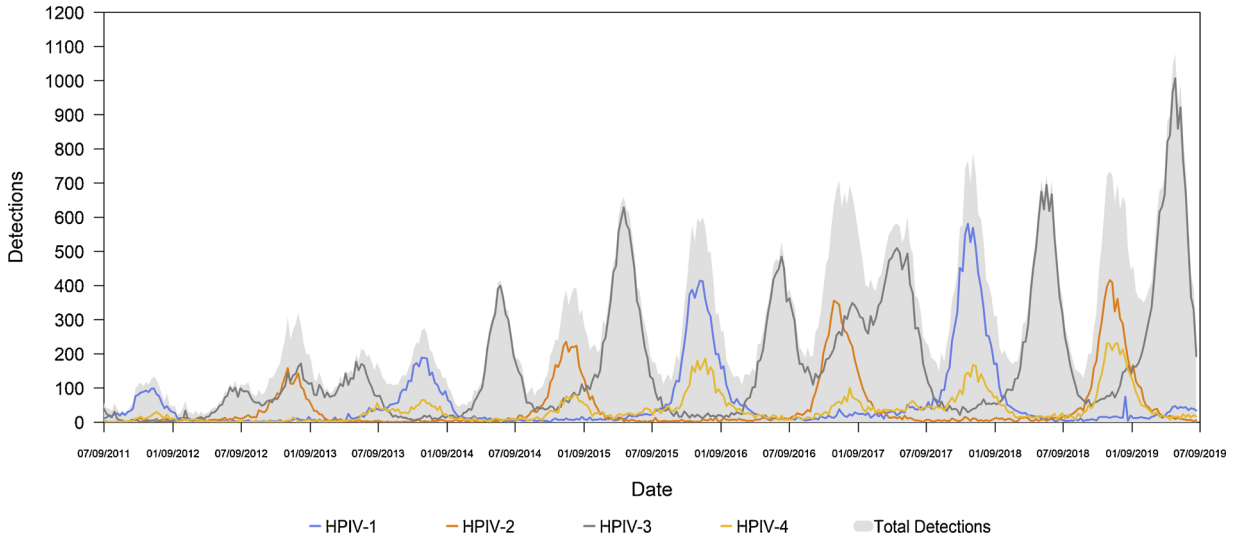

Fig. 1. Human Parainfluenza Virus (HPIV) Circulation, National Enteric and Respiratory Virus Surveillance System, United States, 2011–2019.

HPIV-4 circulation have reported conflicting findings, suggesting that HPIV-4 peaks either in the fall of odd-numbered years or annually following HPIV-3 peaks [6,7]. However, these studies reflect regional or local circulation and are not necessarily representative of national HPIV-4 circulation patterns.

2. Objectives

We aimed to characterize the epidemiology and describe patterns of HPIV 1–4 circulation in the United States during 2011–2019 using data available from the National Respiratory and Enteric Virus Surveillance System (NREVSS).

3. Study design

NREVSS is a voluntary passive laboratory-based surveillance system that collects weekly aggregate specimen data on respiratory and enteric viruses, including HPIVs, from participating U.S. laboratories. From 2011–2019, approximately 500 laboratories reported to NREVSS including state and local public health laboratories (PHLs), reference laboratories, and clinical hospitals. For NREVSS, laboratories report on a weekly basis the aggregated total number of tests performed and the number of positive tests determined in the previous week by either of three categories of detection methods; molecular diagnostic assays, virus antigen detection, and viral isolation by culture. The diagnostic method reported from each laboratory varies by surveillance year and by virus. The NREVSS surveillance year begins in July and ends in June of the following year in order to first capture the onset followed by the offset of most respiratory viruses within a 12-month period. A surveillance week was defined as a seven day period lasting from Sunday through Saturday.

Data are submitted to NREVSS either directly from clinical, state, and local PHLs or indirectly by larger hospital networks or public health jurisdictions. Laboratories reporting directly voluntarily report to the NREVSS data submission portal and include weekly aggregated tests and positive detections of pathogens surveyed.

Additionally, NREVSS receives data electronically via two mechanisms by which PHLs and non-commercial labs report surveillance data to the Centers for Disease Control and Prevention (CDC): the Public Health Laboratory Interoperability Project (PHLIP) and the Public Health Lab Information System replacement (PHLIS2). PHLIP, a partnership between the Association of Public Health Laboratories, CDC, PHLs, and standard organizations, streamlines the data submission process by electronically sending specimen-level data including basic patient demographics and co-infections if detected [17,18]. Of the 14 NREVSS-participating laboratories reporting through PHLIP/PHLIS2 at the time of analysis, 11 were PHLs, two were military health research centers and one was a clinical lab. Ten of the 11 participating laboratories had more than 80 % of data available and were included in the analysis. Once received, the specimen-level data is then aggregated and entered directly into the NREVSS platform with the aggregate number of tests performed and positive detections summarized by virus and surveillance week.

We characterized the circulation of HPIVs by surveillance week from July 2011 – June 2019. We analyzed tests determined by molecular diagnostic assays as they were the most prevalent test type reported (encompassing approximately 75 % of HPIV detections) and limited to laboratories that reported at least one HPIV test and one detection during the analysis period. The total number of weekly positive HPIV detections were summarized both nationally and by US census regions, as testing for HPIV occurred throughout the year. The US census regions are divided into Northeast, Midwest, West, and South [19].

For 2015–2019, using available PHLIP and PHLIS2 data, we analyzed gender and age differences among the four HPIV types. Using the Chi Square Test, associations were considered significant at $P < 0.05$. Lastly, the frequency and percentage of HPIV co-detections were assessed with the following viruses: RSV, respiratory adenovirus, influenza A/B, human metapneumovirus, rhinovirus/enterovirus, and coronavirus. Analyses were completed using SAS 9.4 (SAS Institute, Cary, NC).

4. Results

During July 2011 - June 2019, 2,714,135 HPIV tests were reported to NREVSS from 288 laboratories, encompassing 49 states in the U.S. Among these reported HPIV tests, 122,852 (5 %) were positive for any HPIV: 22,446 for HPIV-1 (18 %), 17,474 for HPIV-2 (14 %), 67,649 for HPIV-3 (55 %), and 15,283 for HPIV-4 (13 %). Overall, HPIV testing increased substantially each year (Supplemental Fig. 1). From July 2011 to June 2012, 100,971 HPIV tests were reported to NREVSS, increasing to 536,527 HPIV tests during July 2017- June 2019. The seasonal distribution and annual prevalence of HPIV by type varied considerably. HPIV-1 rose mainly in the summer and peaked in the fall of odd numbered years (2011, 2013, 2015, and 2017) and declined in the spring of the following year. In contrast, HPIV-2 peaked in the fall of even numbered years (2012, 2014, 2016, and 2018), declining in the spring of the following year. HPIV-3 peaked annually in summer

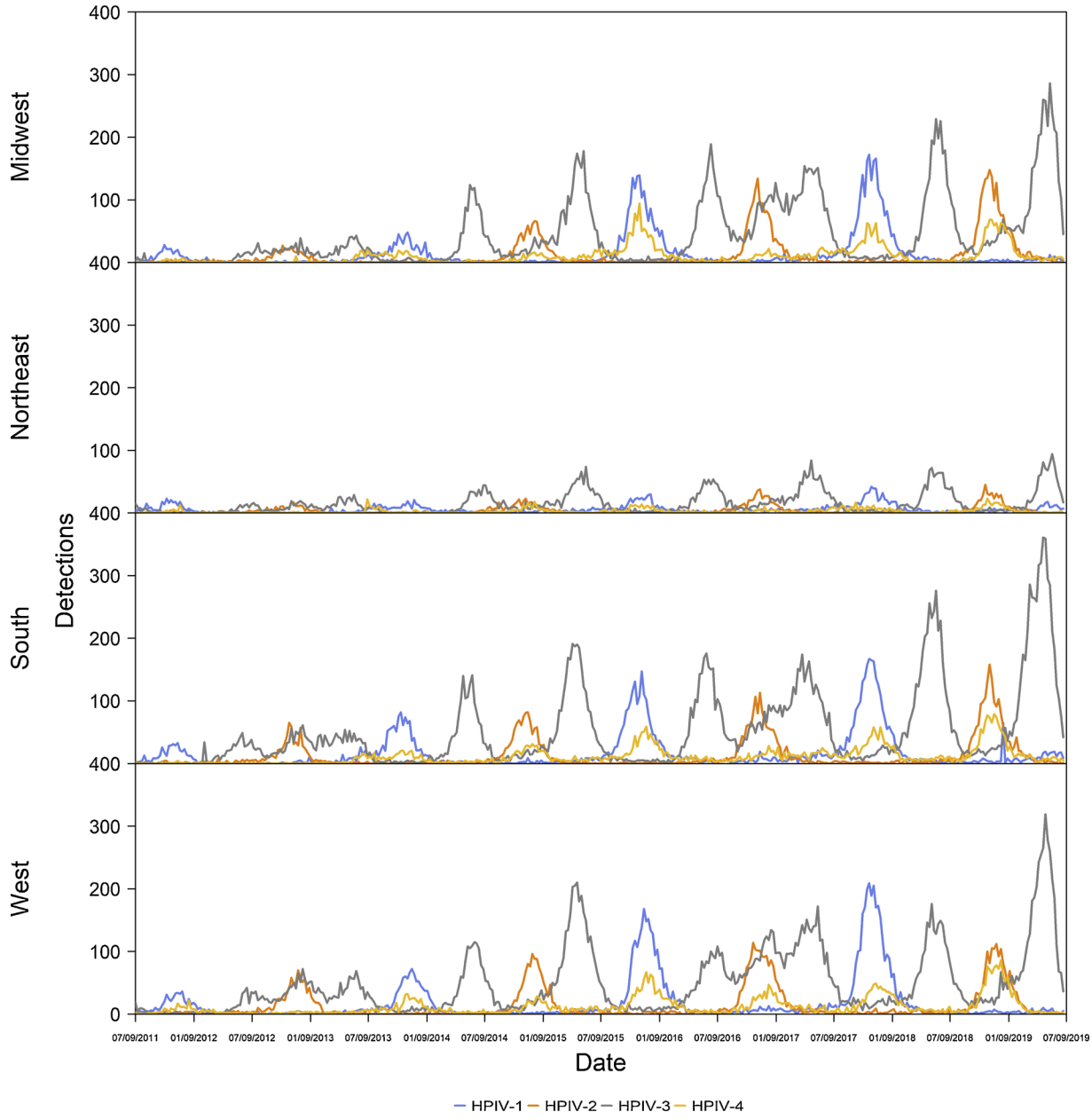

Fig. 2. Human Parainfluenza Virus (HPIV) Circulation, National Enteric and Respiratory Virus Surveillance System, United States Census Regions, 2011–2019.

months and declined in the fall of the same reporting year. During 2012 and 2016, smaller HPIV-3 peaks were also observed during fall months. HPIV-4 was most commonly seen during the fall, peaking in winter of each year (Fig. 1). Each geographic region had a similar distribution of HPIV detections and seasonal patterns to what was observed nationally (Fig. 2).

During 2015–2019, 71,419 specimens tested for HPIV were submitted to NREVSS through PHLIP/PHLIS2. Of those tested, 2717 (4 %) were positive for any HPIV: 2675 tests detected a single HPIV type and 42 tests detected two or more HPIV types. Overall, there were 2765 positive HPIV detections: 593 were HPIV-1 (21 %), 475 were HPIV-2 (17 %), 1312 were HPIV-3 (47 %), and 385 were HPIV-4 (14 %). Among specimens with at least a single HPIV detection, 2618 (96 %) had complete gender and age data, 79 (3 %) had only age data available, and 20 (1 %) had only gender data available. HPIV was predominantly detected among younger age groups, specifically in children two years or younger (36 %). The median age was seven years with a range from 0 to 102 years. The largest proportion of detections were reported among those ≤2 years for all types, notably HPIV-1 (32 %), HPIV-2 (26 %), HPIV-3 (41 %), and HPIV-4 (37 %) (Fig. 3). By gender, 1353 were male (51 %); males significantly predominated for HPIV-2 only.

Of the 2717 positive HPIV tests submitted to PHLIP, 2009 (74 %) were also tested for RSV, respiratory adenovirus, influenza A/B, human metapneumovirus, rhinovirus/enterovirus, and four coronavirus subtypes: 229E, OC43, NL63, and HKU1. Although 1383 (69 %) reported a single HPIV detection, 7 (0.3 %) reported two or more HPIV types, and 619 (31 %) reported HPIV co-detections with other respiratory viruses. The most common co-detections with other respiratory viruses were rhinovirus/enterovirus (56 %) and influenza (20 %) (Supplemental Table 1).

5. Discussion

Increased availability of multiplex molecular testing and the expansion of panels to include HPIV-4 as a target has contributed to the

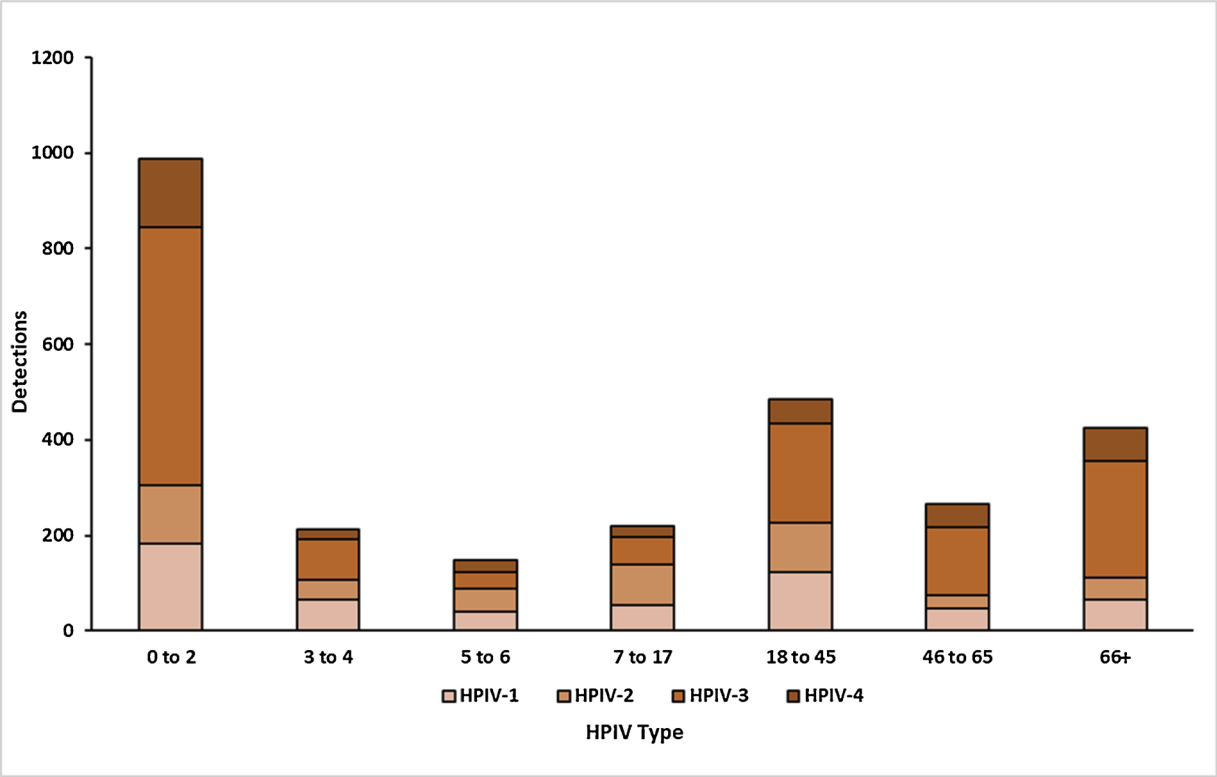

Fig. 3. Age Distribution of Human Parainfluenza Viruses (HPIVs) Reported through the Public Health Laboratory Interoperability Project, 2015–2019.

more comprehensive characterization of HPIV-4 circulation in the US according to NREVSS. We found that nationally, HPIV-4 exhibited a unique circulation pattern, with a winter peak occurring annually. Previously published descriptions of HPIV-4 circulation have been conflicting, finding either a biennial peak in the fall of odd-numbered years or a peak in the winter of each year [6,7]. These studies were limited in geographic scope, focusing on local circulation patterns which may explain the difference in conclusions.

HPIV-1, 2, and 3 were also characterized by distinct circulation patterns. Biennial peaks of HPIV-1 were seen in the winter of odd-numbered years, with a steady decline in the following spring as described in prior studies [1,6,20,21]. Biennial peaks of HPIV-2 were discernable during the winter of even-numbered years. Our analysis of national-level data demonstrates that peaks of these two serotypes were distinct, occurring in alternating-year cycles during the fall of each respective year. HPIV-3 peaks were typically seen annually during the spring and summer, with smaller peaks in the fall occurring at irregular intervals, as previously noted [1,3,6,20]. We noted no substantial differences among regions in seasonal circulation of HPIV, as noted elsewhere [1,3,8].

Among those with demographic characteristics and co-detections data available, these factors varied by HPIV type. While children ≤ 2 years accounted for the largest proportion of HPIV detections of all types, the distribution of detections by age was highly variable in our study. Approximately 37 % of HPIV-4 detections were among children ≤ 2 years, similar to other HPIV types.

While HPIV detections may peak during influenza season, we found that HPIV testing continues throughout the year (Supplemental Fig. 1). This year-round testing trend indicates that the circulation patterns observed were not merely an artifact of testing practices such as increased testing for influenza.

Our study is subject to several limitations. First, NREVSS is a passive laboratory-based surveillance system that receives voluntary reports from participating laboratories. As a result, certain laboratories or regions of the US may be overrepresented or underrepresented in the analysis. NREVSS cannot be used to determine prevalence or incidence of infection because reports represent virus detections but not the number of patients testing positive. PHLIP data represent a subset of NREVSS data, limiting our assessment of age and gender of HPIV detections. Molecular panel tests, which contain HPIV, are more frequently ordered among children than adults in NREVSS, which may have affected the age distribution [22]. Additionally, these data include only a limited pool of clinical and sociodemographic factors including information on comorbidities, racial/ethnic background, or clinical course of infection, which limited the ascertainment of clinical associations among the HPIV types. Future studies should explore these other factors. Lastly, while HPIV testing increased over time, this increase may not be representative of viral activity, but a result of increased availability of multiplex molecular panels which contain HPIV targets. Despite these limitations, data collected through NREVSS provides a comprehensive understanding of HPIV trends in the US. The extensive laboratory network routinely reporting to NREVSS allows us to identify circulation patterns and monitor year-to-year changes in HPIV types, including HPIV-4.

Although the epidemiology and clinical presentation of HPIV types 1–3 are well documented, less is known about HPIV-4. Historically, HPIV-4 has been rarely reported due to the non-specific clinical manifestations of HPIV-4 illness, as well as the difficulty in accessibility of laboratory diagnostics used for HPIV-4 detection [1,16]. The increased use of multiplex RT-PCR respiratory panels with HPIV-4 included has aided in the increased testing, recognition, and reporting of respiratory viruses owing to ease of use in clinical settings and high sensitivity and specificity of the assays [17].

Broader testing for HPIV allows for the characterization of national and regional patterns of circulation and improved understanding of the epidemiology associated with the four HPIV types. The increased characterization of HPIVs is especially important as HPIVs are responsible for a substantial proportion of respiratory illnesses, particularly in young children. Increased use of panels that include HPIVs and improved surveillance can provide a more conclusive characterization

of the epidemiology of HPIVs in the US, in support of development of future vaccines and antivirals [23,24].

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Ethics approval

Data collected for the National Respiratory and Enteric Virus Surveillance System has been approved by Centers for Disease Control and Prevention as routine public health surveillance.

Prior presentations of data

This work has not been previously presented.

Note regarding author affiliation

Calli Taylor is now a contracting agent with the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

CRediT authorship contribution statement

Nicholas P. DeGroote: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Amber K. Haynes:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - review & editing. **Calli Taylor:** Software, Resources, Data curation. **Marie E. Killerby:** Conceptualization, Resources, Data curation, Writing - review & editing, Visualization. **Rebecca M. Dahl:** Methodology, Software, Resources, Data curation, Writing - review & editing. **Desiree Mustaquim:** Resources, Writing - review & editing. **Susan I. Gerber:** Conceptualization, Supervision, Writing - review & editing. **John T. Watson:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare no potential conflicts of interest

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jcv.2020.104261.

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