

Factors Associated With Prolonged Respiratory Virus Detection From Polymerase Chain Reaction of Nasal Specimens Collected Longitudinally in Healthy Children in a US Birth Cohort

Zheyi Teoh,^{1,2} Shannon Conrey,^{1,2} Monica McNeal,^{1,3} Allison Burrell,^{1,2} Rachel M. Burke,⁴ Claire P. Mattison,^{4,5} Meredith McMorrow,^{4,6} Natalie Thornburg,^{4,7} Daniel C. Payne,^{6,8} Ardythe L. Morrow,² and Mary Allen Staat^{1,3}

¹Division of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA ²Department of Environmental and Public Health Sciences, Division of Epidemiology, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA ³Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA ⁴Coronavirus and Other Respiratory Viruses Division, Centers for Disease Control and Prevention, Atlanta, Georgia, USA ⁵Cherokee Nation Assurance, Arlington, Virginia, USA ⁶Division of Foodborne, Waterborne, and Environmental Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Background. Respiratory viral shedding is incompletely characterized by existing studies due to the lack of longitudinal nasal sampling and limited inclusion of healthy/asymptomatic children. We describe characteristics associated with prolonged virus detection by polymerase chain reaction (PCR) in a community-based birth cohort.

Methods. Children were followed from birth to 2 years of age in the PREVAIL cohort. Weekly nasal swabs were collected and tested using the Luminex Respiratory Pathogen Panel. Weekly text surveys were administered to ascertain the presence of acute respiratory illnesses defined as fever and/or cough. Maternal reports and medical chart abstractions identified healthcare utilization. Prolonged virus detection was defined as a persistently positive test lasting ≥ 4 weeks. Factors associated with prolonged virus detection were assessed using mixed effects multivariable logistic regression.

Results. From a sub-cohort of 101 children with $\geq 70\%$ weekly swabs collected, a total of 1489 viral infections were detected. Prolonged virus detection was found in 23.4% of viral infections overall, 39% of bocavirus infections, 33% of rhinovirus/enterovirus infections, 14% of respiratory syncytial virus (RSV) A infections, and 7% of RSV B infections. No prolonged detection was found for influenza virus A or B, coronavirus 229E or HKU1, and parainfluenza virus 2 or 4 infections. First-lifetime infection with each virus, and co-detection of another respiratory virus were significantly associated with prolonged detection, while symptom status, child sex, and child age were not.

Conclusions. Prolonged virus detection was observed in 1 in 4 viral infections in this cohort of healthy children and varied by pathogen, occurring most often for bocavirus and rhinovirus/enterovirus. Evaluating the immunological basis of how viral co-detections and recurrent viral infections impact duration of virus detection by PCR is needed to better understand the dynamics of prolonged viral shedding.

Key words: birth cohort; pediatrics; prolonged detection; respiratory virus; shedding.

INTRODUCTION

Respiratory viruses contribute to a significant burden of acute respiratory infections (ARIs) in children, especially in the first years of life [1, 2]. The identification and detection of respiratory viruses during ARI episodes have improved with the widespread use of molecular-based diagnostic tests including multiplex polymerase chain reaction (PCR) platforms [3–5]. However, the interpretation of PCR-based results obtained during ARI episodes remains challenging given the potential

for asymptomatic, prolonged, and/or intermittent viral shedding seen with various respiratory viruses [6–9].

The patterns and factors impacting respiratory viral shedding are poorly understood, especially for healthy and asymptomatic children who do not present for medical care. Available studies suggest that viral shedding appears to be impacted by age, symptomatology, and presence of co-pathogens, but the strength and directionality of these findings vary [9–14]. These findings are frequently limited by their study design, as most studies perform respiratory viral testing only during ARI episodes, often with limited repeated and sequential nasal sampling. This lack of longitudinal nasal sampling further limits our ability to accurately characterize prolonged respiratory viral infections, which has implications for interpreting test results in clinical, research, and infection prevention contexts.

The Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal (PREVAIL) cohort is a Centers

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Corresponding Author: Mary Allen Staat, MD, Division of Infectious Diseases, Cincinnati Children's Hospital, 3333 Burnet Ave, Cincinnati, OH 45229. E-mail: mary.staat@cchmc.org

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for Disease Control and Prevention (CDC) sponsored birth cohort that conducted prospective community-based surveillance for endemic respiratory viruses through longitudinal weekly nasal swabs. In this study, we describe the patterns and determinants of respiratory viral shedding and prolonged viral infections among children less than 2 years of age.

METHODS

The PREVAIL cohort is a longitudinal, community-based, maternal-infant birth cohort that enrolled healthy mother–infant pairs from April 2017 to July 2018 in the greater Cincinnati, OH region. Enrollment occurred on a rolling basis and children were followed from birth until 2 years of age across multiple respiratory seasons from April 2017 to July 2020. The institutional review boards at the CDC, Cincinnati Children's Hospital Medical Center, and the two enrolling birth hospitals, The Christ Hospital and University of Cincinnati Medical Center, approved this study.

Mothers over 18 years of age who were at least at 34 weeks of gestation with a healthy singleton pregnancy were eligible and provisionally enrolled. Exclusion criteria included use of illicit drugs during pregnancy, residence > 20 miles from the birth hospital, birth weight < 2500 g, severe congenital anomalies, or failure to complete their first postnatal study visit at week two. Further details on the study design and methodology including enrollment strategy and data and sample collection are described elsewhere [15].

Clinical and Biological Data Collection

Mothers were trained to collect mid-turbinate nasal swabs from their infants on a weekly basis. Nasal samples were collected at home and delivered to the study laboratory via courier. Multiplex PCR testing was performed on nasal samples using NxTAG Respiratory Pathogen Panel (Luminex Molecular Diagnostics, Toronto, Canada) which contains multiple viral targets including adenovirus, human bocavirus, endemic human coronaviruses (types 229E, HKU1, NL63, and OC43), influenza viruses (types A and B), human metapneumovirus (HMPV), parainfluenza viruses (types 1, 2, 3, and 4), rhinovirus/enterovirus, and respiratory syncytial virus (RSV) (types A and B). Viral controls along with an internal control, bacteriophage MS2 (*Emesivirus zingeri*), were ran to ensure adequate sample collection and assay validity.

Automated weekly text surveys were sent to mobile phones to ascertain the presence of respiratory symptoms including fever and cough. Reports of fever or cough triggered additional text surveys to collect the presence of additional respiratory and gastrointestinal symptoms, symptom start-date and end-date, and medically attended visits. Abstraction of medical and immunization records further identified unreported medically attended visits and medical treatments.

Outcome Definitions

A viral infection was defined as a positive viral detection from a nasal swab. The detection was considered part of the same viral infection if the same virus or viral type (when applicable) was detected in two nasal samples ≤ 30 days apart, regardless of any interval negative swabs. Prolonged virus detection was defined as a viral infection lasting 4 or more weeks.

Statistical Analysis

All analyses were performed on a sub-cohort of highly adherent participants, defined as participants who returned at least 70% of eligible samples during the study period and were followed until at least 18 months of age. Descriptive statistics using median, interquartile range, and total range were used to describe duration of virus detection. The proportion of prolonged viral infections and the median duration of virus detection seen with different respiratory viruses were compared using Fisher's exact test and Kruskal-Wallis test with Holm's corrections for multiple comparisons. A mixed effects multivariable logistic regression model was used to calculate adjusted odds ratio (aOR) and 95% confidence interval (CI) of having a prolonged virus detection, while controlling for within-subject clustering, respiratory virus type, child age, child sex, co-detection of respiratory virus, and first infection with each respiratory virus. All statistical analysis was performed using Stata/IC version 16.1 (StataCorp, College Station, Texas) and R Environment for Statistical Computing V4.2.3 (R Foundation for Statistical Computing, Vienna, Austria)

RESULTS

A total of 245 mother–infant pairs were enrolled into the cohort, of which a sub-cohort of 101 highly adherent participants were used for this analysis (Table 1). Most mothers were White (78%), married or partnered (86%), had private insurance (77%), and an annual household income of ≥\$50 000 (77%). Participants from this sub-cohort submitted a total of 9801 nasal swabs during the study period, which accounted for 71% of all nasal swabs ($n = 13\ 781$) from the full cohort. This accounted for 8595 unique weeks of follow-up and the detection of 1489 viral infections, of which 585 (39%) were symptomatic. The median nasal sample submission and text-messaging completion by participants in this sub-cohort was 91% (IQR 81–94%) and 99% (IQR 96–100%) respectively. A schematic representation of the patterns of nasal sample submission, omission, and results by participant is seen in Figure 1.

The median duration of virus detection for most respiratory viruses was 1 week, except bocavirus, rhinovirus/enterovirus, and coronavirus NL63, which each had a median duration of 2 weeks (Table 2). Four viruses had a maximum detection duration of greater than 5 weeks; rhinovirus/enterovirus (39 weeks), bocavirus (33 weeks), adenovirus (14 weeks), and

Table 1. Demographics of Mother-Infant Pairs in the PREVAIL Highly Adherent Cohort (n = 101), Cincinnati, Ohio, April 2017 to July 2020

Characteristics	Highly Adherent Cohort (n = 101)
	N (%)
Maternal age	
18–24 years	7 (6.9)
25–34 years	69 (68.3)
≥ 35 years	25 (24.8)
Maternal race	
White	79 (78.2)
Non-white	22 (21.8)
Insurance	
Public	23 (22.9)
Private	78 (77.2)
Marital status	
Married/partnered	87 (86.1)
Single	14 (13.9)
Maternal education	
Less than 2 years of post-secondary education	18 (17.8)
More than 2 years of post-secondary education	83 (82.2)
Annual household income	
<US \$25 000	11 (10.9)
US \$25 000–US \$49 999	10 (9.9)
≥US \$50 000	78 (77.2)
Unknown	2 (2.0)
Infant sex	
Female	46 (45.5)
Male	55 (54.5)

human metapneumovirus (6 weeks). Prolonged virus detection was found in 23.4% of all respiratory viral infections. Bocavirus infections had the highest proportion of prolonged virus

detection (39%, n = 67/170) (Table 2). Following bocavirus, rhinovirus/enterovirus (33%, n = 235/709), coronavirus NL63 (17%, n = 8/46), RSV A (14%, n = 7/50), and adenovirus (12%, n = 16/137) infections had the highest proportion of prolonged virus detection (Figure 2).

No infections with prolonged virus detection were found for parainfluenza virus 2 or 4, influenza virus A or B, or coronavirus 229E or HKU1 infections. Abstracted medical records revealed that among the 22 children with symptomatic influenza virus infection (19 influenza virus A and 3 influenza virus B), four received anti-viral medication for their influenza virus A infection, and all four had a viral infection duration of one week.

Controlling for respiratory virus type, first-lifetime infection with each specific virus (aOR 2.30, 95% CI 1.53, 3.46), and co-detection with another respiratory virus (aOR 4.40, 95% CI 3.36, 5.76) were associated with prolonged virus detection (Table 3). Child age, sex, and presence of symptoms (fever and/or cough) were not found to be significantly associated with prolonged virus detection.

DISCUSSION

In our community-based US birth cohort of healthy children 0–2 years of age, approximately one in four (23.4%) respiratory viral infections detected by nasal PCR were positive for four or more weeks. Bocavirus and rhinovirus/enterovirus infections both had the longest median and total duration of detection as well as the highest proportion of prolonged virus detection compared to the other respiratory viruses included in this study. Prolonged virus detection varied across

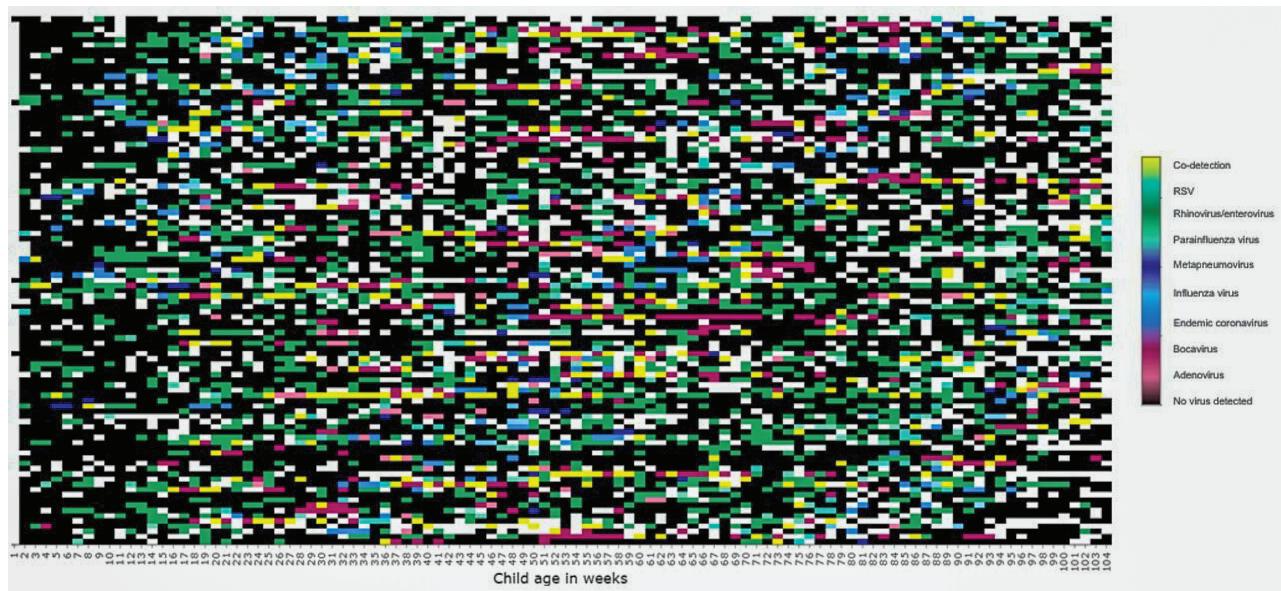


Figure 1. Heat map illustrating the results of submitted nasal swabs in the PREVAIL cohort (n = 101), by subject (y-axis) and child age in weeks (x-axis).

Table 2. Duration of Respiratory Viral Infections and Proportion of Prolonged Viral Detection in PREVAIL Cohort (n = 101), by Respiratory Virus

Pathogen ^a	Viral Infections, n	Prolonged Detection, n (%)	Infection Duration in Weeks		
			Median	IQR	Maximum
Bocavirus	170	67 (39)	2	1–6	33
Rhinovirus/Enterovirus	709	235 (33)	2	1–5	39
Coronavirus NL63	46	8 (17)	2	1–3	5
RSV A	50	7 (14) ^b	1 ^c	1–2	5
Adenovirus	137	16 (12) ^b	1 ^{c,d}	1–2	14
HMPV	49	5 (10) ^b	1 ^{c,d}	1–1	6
Parainfluenza virus 1	20	2 (10)	1	1–1	5
RSV B	43	3 (7) ^b	1 ^{c,d}	1–1	4
Coronavirus OC43	59	3 (5) ^b	1 ^{c,d}	1–2	4
Parainfluenza virus 3	66	2 (3) ^b	1 ^{c,d}	1–1	5
Coronavirus 229E	10	0 (0)	1	1–1	3
Coronavirus HKU1	49	0 (0) ^b	1 ^{c,d}	1–1	3
Influenza virus A	25	0 (0) ^b	1 ^{c,d}	1–1	2
Influenza virus B	4	0 (0)	1	1–1.5	2
Parainfluenza virus 2	17	0 (0) ^b	1 ^{c,d}	1–1	2
Parainfluenza virus 4	35	0 (0) ^b	1 ^{c,d}	1–1	2
Total	1489	348 (23.4)			

^aOrdered by % of viral infections that are prolonged, in descending order.^bSignificantly different from proportion of prolonged bocavirus and rhinovirus/enterovirus infections using Fisher's exact test ($p < .05$).^cSignificantly different from median duration of bocavirus shedding using Kruskal-Wallis ($p < .05$).^dSignificantly different from median duration of rhinovirus/enterovirus shedding using Kruskal-Wallis ($p < .05$).

other types and subtypes of the same respiratory virus, with greater than 10% of coronavirus NL63 and parainfluenza virus 1 infections having prolonged virus detection, while no prolonged episodes of viral detection were found among coronavirus 229E and HKU1 or parainfluenza virus 2 and 4 infections.

Between RSV and influenza virus, two viruses associated with severe illness and hospitalizations, 11% of RSV infections had prolonged virus detection compared to none of the influenza virus infections, including those who received anti-viral treatment. Several other prospective cohorts have

described viral detection and shedding patterns seen with RSV and influenza virus [10, 11, 16, 17], but prolonged virus detection is often underreported due to the lack of repeated nasal sampling. While prolonged virus detection is a well-described phenomenon with immunocompromised children [18], the extent of prolonged virus detection for viruses such as RSV seen in our cohort of healthy children supports the need to further evaluate the kinetics and patterns of shedding in healthy children of different ages. We found that first-lifetime infection with each specific respiratory virus, and infections with multiple viral co-detections were associated

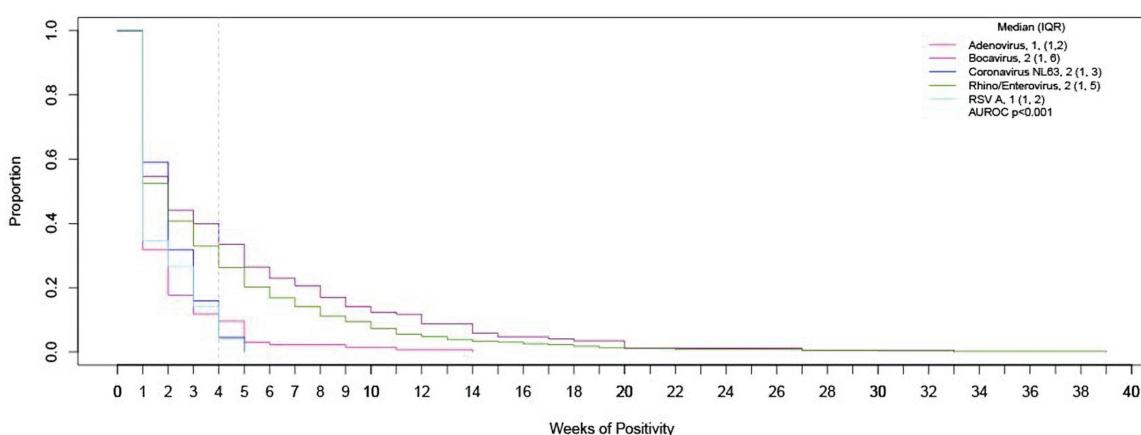


Figure 2. Time to negativity for respiratory viruses with the highest proportion of prolonged viral detection (>10%). Proportion of respiratory viral infection by weeks of positivity using Kaplan-Meier survival analysis. Dashed line represents 4 weeks of positivity. Abbreviations: IQR, interquartile range.

Table 3. Factors Associated With Prolonged Viral Detection in the PREVAIL Cohort Using a Mixed Effects Logistic Regression Model

	Viral Infections, n	Prolonged Infections, n (%)	aOR ^a	95% CI		p
Child age						
<6 months	285	79 (28)	reference			
6–12 months	426	114 (27)	1.44	0.99	2.08	0.06
13–18 months	389	81 (21)	1.01	0.66	1.54	0.97
19–24 months	389	74 (19)	0.94	0.63	1.41	0.76
Child sex						
Male	856	190 (22)	reference			
Female	633	158 (25)	1.06	0.81	1.40	0.67
Presence of ARI ^b						
Asymptomatic	904	224 (25)	reference			
Symptomatic	585	124 (21)	1.04	0.78	1.40	0.77
First-lifetime infection with each respiratory virus						
First infection	673	125 (19)	reference			
Not first infection	816	223 (27)	0.43	0.29	0.65	<0.001
Co-detection of other viruses						
No	961	157 (16)	reference			
Yes	528	191 (36)	4.40	3.36	5.76	<0.001

^aAdjusted odds ratio (aOR) calculated using a mixed effect multivariate logistic regression model controlling for within-subject clustering, type of virus, child age category, child sex, the presence of symptoms, first-lifetime infection with each respiratory virus, and presence of additional viral infection.

^bDefined by the presence of maternally reported fever and/or cough.

Bold signifies a p < 0.05.

with prolonged virus detection, while child age, sex, and presence of fever or cough were not. Longer virus detection with a first-time infection with each respiratory virus has also been described with other viruses such as bocavirus and endemic coronavirus [7, 11, 19], but viral co-detection has not been consistently associated with longer virus detection [9]. This may result from the varying interaction seen between different viral-viral combinations and different timing of viral acquisition [20]. While we were able to capture a large number of infections with viral co-detections, we had insufficient power to study specific viral-viral combinations or how the timing of viral acquisition impacts the presence of prolonged virus detection.

Better characterization of viral detection and shedding has numerous clinical implications, as highlighted by the SARS-CoV-2 pandemic, where our understanding of the dynamics of SARS-CoV-2 shedding was used for infection prevention and isolation strategies, organ transplant allocation, as well as timing of medical procedures [21–23]. Misattributing a positive molecular test to an active viral infection, rather than the result of prolonged virus detection, could lead to the unnecessary continuation of transmission-based precautions as well as unnecessary delays in medical and surgical procedures. The literature that characterizes prolonged virus detection due to respiratory viruses besides SARS-CoV-2, especially non-influenza virus and RSV infections, remains lacking. Understanding how various biological factors, beyond respiratory virus type, contribute to prolonged virus detection is integral for clinicians and researchers to understand why some infections are detectable by PCR-based assays for one week while others for weeks to

months. This information may ultimately help clinicians better interpret a positive or negative respiratory viral test, which can be challenging in patients who are asymptomatic or lack attributable respiratory symptoms.

In contrast to most existing studies that describe respiratory viral shedding, our cohort collected longitudinal, weekly nasal samples regardless of respiratory symptoms. Longitudinal weekly sampling better characterizes infections with intermittent shedding, compared with studies that ceased sample collection once one or two negative swabs resulted [6, 9]. This allows us to better discriminate and define prolonged virus detection seen with different respiratory viral infections, which lacks standardization across different cohorts and studies. Unlike studies that focus on symptomatic or severe respiratory viral infections, our study included healthy children in the community with a diverse range of respiratory viral infections including asymptomatic infections, symptomatic but non-medically attended infections, and infections requiring emergency department evaluation or hospitalization [24].

There are several limitations to consider when interpreting our results. While prolonged shedding has been described for rhinoviruses [9, 12, 25], we were unable to differentiate between rhinovirus and enterovirus and between different rhinovirus types (A, B, and C) given the use of our multiplex respiratory assay and the lack of genomic sequencing. Consequently, we may have overestimated the proportion of prolonged viral detection seen with rhinovirus/enterovirus infections, especially since re-infections with different rhinovirus types can occur [26, 27]. Nevertheless, prolonged viral detection was found in approximately one in seven non-rhinovirus/enterovirus viral infections

(14.5%) in our cohort; first-time infection and co-detections remained significantly associated with prolonged viral detection without the inclusion of rhinovirus/enterovirus infections (**Supplementary Table 1**). The use of PCR without viral culture prevents us from discriminating between prolonged virus detection from viable viral shedding versus viral remnants. While our definition for what constitutes a viral infection is consistent with other methodologically similar cohorts with weekly viral sampling [12], without daily nasal sampling, we may still under-capture episodes where intermittent shedding occurs. In addition, the use of a multiplex respiratory assay prevents us from discriminating between infections from different viral strains of the same respiratory virus. The use of genomic sequencing would better discriminate these infections, although few large cohorts have used sequencing methods for the evaluation of viral shedding, emphasizing the need for future cohort studies that incorporate viral sequencing [28, 29].

In conclusion, the overall prevalence of prolonged virus detection in our US community cohort of healthy children was 23.4%, occurring most commonly with bocavirus, rhinovirus/enterovirus, coronavirus NL63, and RSV A infections. Biological factors such as viral co-detections and first life-time viral infection were associated with prolonged virus detection. Employing genomic sequencing and evaluating the immunological basis between viral-viral interaction and recurrent infections will allow us to better understand mechanisms that contribute to prolonged virus detection, and hence, the interpretation of a respiratory nasal swab result.

Supplementary Data

Supplementary materials are available at the Journal of The Pediatric Infectious Diseases Society online (<http://jpids.oxfordjournals.org>).

Author Contributions

Z. T. and M. A. S. conceptualized this study. Z. T. and S. C. assisted with data curation. Z. T. and S. C. performed formal analysis. M. A. S. acquired financial support for the project. A. L. M. and M. A. S. were responsible for conducting the research and investigation process. D. C. P., A. L. M., and M. A. S. were responsible for development and design of methodology. A. B. and M. A. S. were responsible for project administration. M. A. S. was responsible for provision of resources. Z. T. and S. C. were responsible for software programming. D. C. P., A. L. M., and M. A. S. provided oversight and supervision. Z. T. and S. C. were responsible for validation. Z. T. and S. C. conducted data visualization. Z. T. wrote the original draft. All authors reviewed and edited the manuscript.

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Data availability. Data may be available upon request from the authors and permission of the Centers for Disease Control and Prevention.

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