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Post-mortem study of endemic human coronaviruses (HCoV-NL63, OC43, 229E and HKU-1) in deaths of children under five in low- and middle-income countries: Findings from the Child Health and Mortality Prevention Surveillance (CHAMPS) study

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ABSTRACT

Background: Endemic human coronaviruses (HCoV-229E, HKU1, NL63, and OC43) are common causes of mild or asymptomatic respiratory infections in children but are considered rare causes of death.
Methods: We evaluated pediatric deaths from January 2017 through December 2022. A panel of experts determined the cause of death (CoD) by reviewing available data, including pathological and molecular findings from minimally invasive tissue sampling (lung tissues, blood, CSF, and nasopharyngeal swabs), clinical records, and verbal autopsies.
Results: Endemic HCoV were detected in the respiratory samples of 3 % (n = 86/3357) of enrolled decedents: 1 % (n = 12/2043) of neonates, 5 % (n = 35/681) of infants and 6 % (n = 39/633) of children deaths. However, HCoVs were attributed as the CoD in only two cases — both involving young infants with underlying birth defects and severe wasting, who succumbed to polymicrobial hospital-acquired infections involving *HCoV-OC43*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. Amongst the remaining 84 decedents in whom an HCoV was detected, 82 % (n = 69/84; median Ct of 25.34; range: 15.28–36.17) were deaths attributed to other infections, including 54 % (n = 32/69; median Ct of 23.86; range: 15.28–35.2) with lower respiratory infections determined to be the CoD. The bulk of these deaths (96 %, n = 66/69) were attributed to other pathogens – *Plasmodium falciparum* (27 %, n = 19/69), *K. pneumoniae* (23 %, n = 16/69), *Streptococcus pneumoniae* (20 %, n = 14/69), *Escherichia coli* (16 %, n = 11/69) and Cytomegalovirus (10 %, n = 7/69).
Conclusion: Although endemic HCoV was identified in children who died of respiratory infections, it was rarely attributed to being in the CoD. Nevertheless, further research is warranted to explore the potential role of HCoVs in LRTI pathogenesis and their impact on facilitating more pathogenic infections.

1. Introduction

Coronaviruses (CoVs) are zoonotic RNA viruses [1] comprised of four genera, *Alphacoronaviruses, Betacoronaviruses, Gammacoronaviruses* and *Deltacoronaviruses*. In humans, the majority of CoV infections are asymptomatic but, in a small proportion, respiratory infections can present as a common cold to more severe manifestations including bronchiolitis, pneumonia and even death [2–4]. Traditionally there were four endemic human CoVs (HCoV) namely; HCoV-229E and -NL63 which are *Alphacoronaviruses* and -HKU1, and -OC43 which are *Betacoronaviruses*. In the PERCH multi-country case-control study, the attributable contribution of the endemic HCoV's to etiology of hospitalised severe pneumonia was <1 %, with the detection prevalence of HCoV being higher amongst the community controls (10 %) compared with pneumonia cases (7.5 %) [5]. However, this study included very few samples from the site of pneumonia – i.e., inside the lung – so relied on more indirect diagnostic methods. More recently, SARS-CoV-2 has transitioned to being another endemic HCoV [6,7].

It has been hypothesized that HCoV-OC43 followed a similar path as SARS-CoV-2 is currently following and that HCoV-OC43 might have caused the 1889–1891 pandemic (based on clinical manifestations and mortality curves resembling that of SARS-CoV-2 more than influenza and very limited paleoserological methods) before becoming endemic as the population developed immunity [8,9]. Other epidemic HCoVs include severe acute respiratory syndrome CoV (SARS-CoV) which emerged in 2002 followed by Middle East respiratory syndrome CoV (MERS-CoV) in 2012. HCoV-OC43, -HKU1, SARS-CoV, SARS-CoV-2 and MERS-CoV are all part of the *Betacoronavirus* genera [3].

The Child Health and Mortality Prevention Surveillance (CHAMPS) network undertakes standardised, systematic post-mortem investigation on the causes of childhood deaths in countries with high mortality rates. CHAMPS methods include post-mortem minimally invasive tissue sampling (MITS), extensive review of clinical records and verbal autopsies [10,11]. Using the CHAMPS data, we undertook an analysis on the contribution of the four traditional endemic HCoVs species (OC43, 229E, HKU1 and NL63) in the causal pathway of death in decedents aged 0 to 59 months who died between January 2017 through December 2022.

2. Material and method

Deaths, stillbirth to children <60 months of age, were enrolled from CHAMPS catchment areas in seven countries, six in Africa and one in South Asia – Baliankani, Bangladesh; Harar and Kersa, Ethiopia; Siaya and Kisumu, Kenya; Bamako, Mali; Manhiça, Mozambique; Bombali, Sierra Leone; and Soweto, South Africa. Detailed selection criteria and description of each site has been published previously [10]. Death notifications were received from health facilities situated within the catchment area of each site and from deaths occurring within the community. CHAMPS staff approached families of the deceased for eligibility screening and informed consent was obtained for the MITS procedure, verbal autopsy and clinical abstraction. Deaths were eligible for inclusion into the CHAMPS study if the child resided within the catchment area of each site and if notification of death occurred within 24 h of death or within 72 h if post-mortem refrigeration occurred.

Using aseptic techniques, biopsy needles were used to collect tissue samples from lung, liver, and brain [11]. Peripheral blood, cerebrospinal fluid (CSF), rectal swab, and a combined oropharyngeal/nasopharyngeal (NP) swab were also collected. Custom TaqMan Array Cards (ThermoFisher Scientific, Waltham, MA, USA) were designed to detect 116 pathogens (including HCoV-OC43, 229E, HKU1, NL63 and MERS) in lung tissue, blood, CSF, rectal, and NP swabs [11,12]. Histopathology examination was conducted on lung, liver, and brain tissues. All clinical records from deceased children and maternal records where applicable were used for data abstraction and caregivers were interviewed within 4 weeks of the death using a standard verbal autopsy form. All data for each case were reviewed by Determination of Cause of Death (DeCoDe) panels, which were convened at each site at regular intervals. These panels consisted of a multidisciplinary team—including pediatricians, pathologists, microbiologists, epidemiologists, and public health specialists—with relevant expertise in child health and mortality review [13]. Using World Health Organization (WHO) recommended guidelines and CHAMPS protocols, the panels reviewed clinical, laboratory, and pathological findings to determine the causal pathway to death. A structured algorithm was applied to assign the underlying, intermediate, and immediate causes of death. Differences in opinion were resolved through consensus; cases for which consensus could not be achieved

[1] The CHAMPS Consortium is listed under the acknowledgements.

were classified as undetermined.

This analysis focused on deaths in liveborn children up to 59 months of age where any of the endemic HCoV species was detected in respiratory samples (lung biopsy or nasopharyngeal swab samples) from January 2017 through December 2022. Semiquantitative results for HCoV were reported based on the cycle threshold value (Ct value) from the custom TaqMan Array Cards, and a Ct value >37 in either replicate was regarded as a negative test. **Descriptive analyses were performed using counts and percentages to summarise outcomes. Cycle threshold values were analysed using medians, ranges, and Student's *t*-tests, as appropriate. All analyses were performed using Stata version 18.0, and p-values <0.05 were considered statistically significant.** Detection of SARS-CoV-2 in CHAMPS deaths is being analysed and reported separately in a dedicated manuscript focused on COVID-19-related mortality.

3. Results

Overall, HCoV was detected in 3 % (n = 86/3 357) of enrolled decedents: 1 % (n = 12/2043) of neonates (<28 days of age), 5 % (n = 35/681) of infants (28 days to less than 12 months) and 6 % (n = 39/633) of children deaths (12 months to less than 60 months); Fig. 1A. The sites of HCoV detection included only the nasopharyngeal swab in 55 cases, concurrently from lung tissue and nasopharyngeal swab in 25 cases and only in lung tissue in six cases. Of the 86 decedents in whom HCoV was identified, one was infected with HCoV-43 and HCoV-HKU1 (both *betacoronaviruses*), four (5 %) were infected with both an *Alpha* and a *Betacoronavirus*, 43 % (n = 37) were infected with an *Alphacoronavirus*

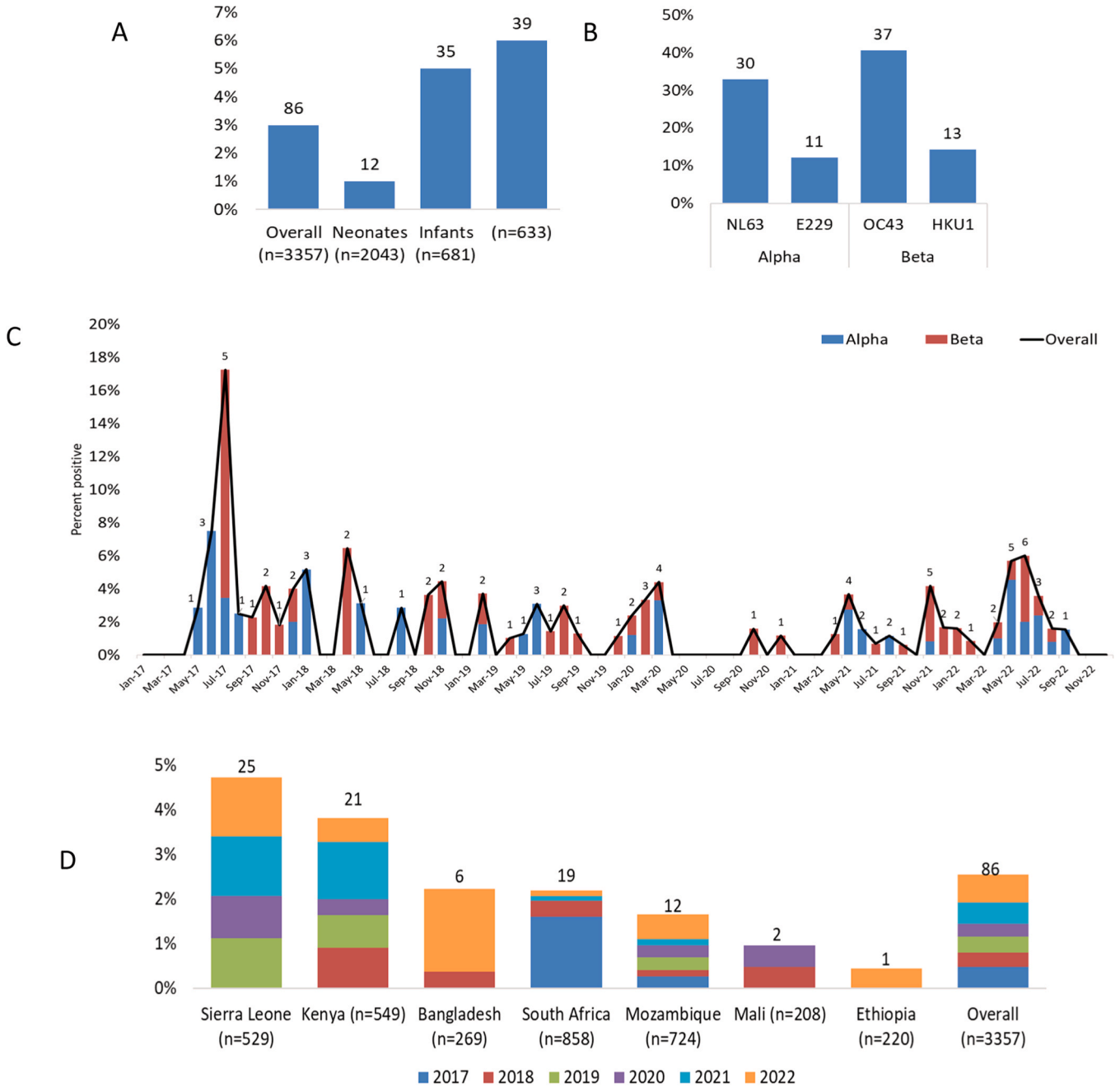


Fig. 1. The combined prevalence of HCoV, AlphaCoV endemic species (NL63 and E229) and *Beta*HCoV endemic species (OC43 and HKU1) between January 2017 and December 2022 (Panel B), by age category (Panel A), across all CHAMPS study sites (Panel C) and by each individual site (Panel D). The percent positivity among tested CHAMPS deaths is indicated on the vertical axis and the actual case count is indicated above each positive bar.

and 51 % (n = 44) with a *Betacoronavirus*. HCoV-OC43 accounted for the majority of the infections (43 %, n = 37) followed by HCoV-NL63 (35 %, n = 30), HCoV-HKU1 (15 %, n = 13) and HCoV-229E (13 %, n = 11); Fig. 1B. Similar distributions of *Beta* and *Alpha*CoV species were observed regardless of whether HCoV was detected in the NP swab or the lung biopsy sample. Regardless of genera, HCoV's were detected throughout the year without any real evidence of year-on-year seasonality; Fig. 1C. There was little difference in the prevalence of HCoV by geographic site, being identified in 3 % of decedents in Sierra Leone (n = 25/730) and Kenya (n = 22/765), 2 % (n = 20/1144) in South Africa, 1 % in Mozambique (n = 14/1173) and Bangladesh (n = 6/559) compared with 0.6 % (n = 2/327) in Mali and 0.2 % (n = 1/532) in Ethiopia; Fig. 1D. No deaths tested positive for MERS-CoV.

Of these 86 decedents who tested positive for an HCoV, only two cases, both infants from South Africa, had an HCoV (OC43) attributed to being in the causal chain to death. The first child died at 3 months of age, had an underlying congenital heart defect (Tetralogy of Fallot) and was severely under-weight (weight for age Z score: −5.43). The immediate CoD in the deceased was hospital acquired *Klebsiella pneumoniae* sepsis, with a polymicrobial pneumonia caused by *Acinetobacter baumannii* and HCoV-OC43 listed as a comorbid factor leading to the death. The second child died at 29 days of age and also had an inherited skin disorder (*Epidermolysis bullosa*) and was severely under-weight (weight for age Z score: −4.52). The immediate CoD was polymicrobial pneumonia caused by *S. aureus, K. pneumoniae, A. baumannii* and HCoV-OC43.

In the remaining 84 decedents in whom HCoV was detected but was not included as the agent causing death, 81 % (n = 69) were in children who died due to infectious causes, of which 54 % (n = 32/69) had lower respiratory tract infections. The HCoV median cycle threshold in the non-infectious CoD was 29.94 (range: 18.53–39.48), while in the infectious CoD it was 25.34 (range: 15.28–36.17; p = 0.067) and 23.86 (range: 15.28–35.2; p = 0.051) in the decedents that dies due to a LRTI. In decedents with an infectious disease in the causal pathway to death (n = 69), the most commonly identified pathogens attributed as causing the death were *Plasmodium falciparum* (27 %, n = 19/69), *Klebsiella pneumoniae* (23 %, n = 16/69), *Streptococcus pneumoniae* (20 %, n = 14/69), *Escherichia coli* (16 %, n = 11/69) and Cytomegalovirus (10 %, n = 7/69). No appreciable differences were observed in the distribution of these pathogens when comparing CoV-positive and CoV-negative cases. Among decedents in whom LRTI was included in the causal pathway to death and in whom HCoV was identified (n = 32), the etiology of the LRTI was attributed to *K. pneumoniae* (41 %; n = 13), *S. pneumoniae* (38 %; n = 12) and cytomegalovirus (19 %; n = 6). Three of the LRTI-related deaths had no pathogen attributed as the CoD, even though HCoV was detected in the lung tissues or NP swabs at high genomic viral loads (two HCoV-NL63 at 15.2 Ct and 16.3 Ct and HCoV-HKU1 at 23.8 Ct). Two of these cases were childhood deaths (16 months and 27 months of age), both of which were severely malnourished (underlying CoD) with LRTI as the immediate CoD. The third case was a neonatal death where LRTI was included as the only CoD.

4. Discussion

Of more than 3000 evaluated childhood deaths, HCoV was determined to have caused only two deaths, even though HCoV was detected in 3 % of all decedents and 6 % of decedents older than 12 months of age. Both HCoV-associated deaths were in young infants with severe congenital birth disorders and malnutrition which could have predisposed the infants to the fatal HCoV polymicrobial pneumonia events. The association between severe HCoV infections and congenital defects has been described [2,3,14,15]. Notably, both deaths were in severely malnourished and thus likely immunocompromised infants infected with *Betacoronavirus* genera, which is from the same genera as SARS-CoV-2 [16,17]. Several studies have shown that SARS-CoV-2 (also a *Betacoronavirus*) can cause fatal infections in children, with a study in South Africa showing that 12 % of childhood deaths occurring during a peak in SARS-CoV-2 infections were attributed to SARS-CoV-2. Further, similar to the HCoV associated deaths in this study, over 55 % of the SARS-CoV-2 associated deaths also showed evidence of invasive bacterial disease [18].

The limited role of HCoV in childhood death in this study aligns with many other studies that have found HCoVs are commonly present in asymptomatic children or those with mild disease [2,4,5,19–22]. Thus, highlighting that detection does not infer causality, especially for diseases such as pneumonia where sampling the site of infection, namely the lung, is very difficult and invasive. For these reasons, pneumonia etiology studies, including the PERCH study, generally rely on sampling the nasopharynx in order to determine the etiology of the disease. These specimens however cannot differentiate between common colonisers of the upper respiratory tract and the causative agent of the pneumonia episode. Further, the detectability of viral pathogens, including HCoV's, is known to be limited to a short window during the acute phase of infection. Therefore, in cases where death occurred days or weeks after the initial illness, post-mortem sampling may have missed viral infections due to the natural decline in viral load over time. This limitation is particularly relevant for HCoV's, which exhibit transient shedding patterns, further complicating detection during later stages of infection [23,24].

In this study, we report on the detection of HCoV in NP and lung biopsy samples and found that HCoV detection together with high genomic loads was commonly detected in decedents that died of infectious causes (median Ct of 25.3) and more specifically pneumonia (median Ct of 23.9). Heimdal et al. [22] also reported an association of high genomic loads of HCoV (<28Ct) in children hospitalised with respiratory tract infections compared with healthy children and in a study of bronchoalveolar lavage (BAL) fluid specimens, Garbino et al. [25] found that 5 % of severe respiratory infections in immunocompromised adults were due to HCoV.

While the detection of HCoV, especially in lung biopsy samples, and at high genomic viral loads in the children that died of infectious causes provides evidence that HCoVs might contribute to more childhood deaths than previously reported, DeCoDe panel members attributed these deaths to more likely and highly pathogenic organisms including *Plasmodium falciparum, Klebsiella pneumoniae, Streptococcus pneumoniae* and cytomegalovirus. Whether this attribution is correct or incorrectly influenced by convention thinking that HCoV is not a highly pathogenic organisms is unclear. Polymicrobial infections with HCoV do seem to occur and might complicate the course of the disease, resulting in a more severe outcome. In the PERCH study it was found that *S. pneumoniae* co-infections with HCoV were associated with more severe disease outcomes and death [4]. Further, in a large (39,836 children) randomized, double-blinded, placebo-controlled clinical trial looking at the efficacy of a 9-valent pneumococcal conjugate vaccine, the data suggested that pneumococcal co-infections likely played a role in the development of severe HCoV associated hospitalisations [26]. Similarly, many other studies have documented that virus-bacteria co-infections can lead to increased morbidity and mortality [4,27–29].

In conclusion, HCoV was rarely detected during post-mortem examinations of deaths in children aged <5 years, and when it was detected, it was attributed as a contribution factor to death in only 2 of 86 cases — both of whom had underlying medical conditions. Thus, it appears that HCoVs are a rare cause of death in children, although the accuracy of this estimate depends on the judgments of expert panels, which may be influenced by existing clinical biases. Additionally, while most of the HCoV detections were in childhood deaths who had other pathogens that are well known causes of severe illness attributed as the cause of death, studies are required to determine whether HCoV infections might contribute to more severe disease especially in immunocompromised children with complicated medical courses. Linking CHAMPS data to other data on HCoV infections is needed to better quantify the burden of HCoV and its role in deaths.

CRediT authorship contribution statement

Cynthia G. Whitney: Writing – review & editing, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Soter Ameh:** Methodology, Investigation. **Portia C. Mutevedzi:** Investigation, Data curation. **J. Anthony G. Scott:** Methodology, Investigation, Funding acquisition, Conceptualization. **Shabir A. Madhi:** Writing – review & editing, Methodology, Funding acquisition, Data curation, Conceptualization. **Julius Ojulong:** Methodology, Investigation. **Quique Bassat:** Writing – review & editing, Data curation, Conceptualization. **Ikechukwu Udo Ogbuanu:** Methodology, Investigation, Funding acquisition. **Karen L. Kotloff:** Project administration, Methodology, Investigation. **James Bunn:** Methodology, Investigation. **Mohammad Zahid Hossain:** Methodology, Investigation, Data curation. **Emily S. Gurley:** Investigation, Data curation, Conceptualization. **Victor Akelo:** Methodology, Investigation, Data curation, Conceptualization. **Nega Assefa:** Methodology, Investigation. **Afruna Rahman:** Methodology, Investigation, Data curation. **Jeanie du Toit:** Writing – review & editing, Methodology, Investigation. **Dickens Onyango:** Methodology, Investigation, Conceptualization. **Zelalem Teklemariam Kidanemariam:** Methodology, Investigation. **Clayton Onyango:** Methodology, Investigation. **Joseph Oundo:** Methodology, Investigation. **Elisio G. Xerinda:** Methodology, Investigation, Data curation. **Rosauro Varo:** Methodology, Investigation, Data curation. **Muntasir Alam:** Methodology, Investigation, Data curation. **Vicky Baillie:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Natalia Rakislova:** Methodology, Investigation, Data curation. **Dianna M. Blau:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Shams El Arifeen:** Data curation, Conceptualization. **Ziyaad Dangor:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis. **Sana Mahtab:** Methodology, Investigation, Data curation. **Samba O. Sow:** Methodology, Investigation. **Adama Mamby Keita:** Methodology, Investigation. **Milagritos D. Tapia:** Methodology, Investigation. **Inacio Mandomando:** Methodology, Investigation, Data curation. **Marcelino Garrine:** Methodology, Investigation, Data curation.

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Declaration of Competing Interest

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the U.S. Centers for Disease Control and Prevention.

Data availability

CHAMPS data are open access and datasets are available for download or request on www.champshealth.org.

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