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Title: Burden and seasonality of primary and secondary symptomatic common cold coronavirus infections in Nicaraguan children

Running Title: ccCoV burden, seasonality in Nicaragua

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Conflict of interest:

Aubree Gordon serves on an RSV vaccine scientific advisory board for Janssen Pharmaceuticals and has served on a COVID-19 scientific advisory board for Gilead Sciences. All other authors certify no potential conflicts of interests.

Author contributions: Aaron M Frutos: Conceptualization; formal analysis; methodology; validation; visualization. **Angel Balmaseda:** Data curation; project administration; resources. **Nivea Vydiswaran:** Data curation; project administration. **Mayuri Patel:** Data curation; project administration. **Sergio Ojeda:** Data curation; project administration. **Andrew Brouwer:** Formal analysis; methodology; validation; visualization. **Rebecca Tutino:** Data curation; project administration. **Shuwei Cai:** Data curation; project administration. **Kevin Bakker:** Formal analysis; methodology; validation; visualization. **Nery Sanchez:** Data curation; project

administration. **Roger Lopez:** Data curation; project administration. **Guillermina Kuan:** Data curation; project administration; resources. **Aubree Gordon**: Conceptualization; funding acquisition; methodology; project administration; resources; supervision; validation.

Ethics statement:

The institutional review boards at the Nicaraguan Ministry of Health and the University of Michigan approved these studies.

Patient consent statement: Parents/guardians of participants provided written informed consent and children 6 years and older provided verbal assent. All consenting documents and scripts were approved by institutional review boards at the Nicaraguan Ministry of Health and the University of Michigan.

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Abstract

Background: The current SARS-CoV-2 pandemic highlights the need for an increased understanding of coronavirus epidemiology. In a pediatric cohort in Nicaragua, we evaluate the seasonality and burden of common cold coronavirus (ccCoV) infection and evaluate likelihood of symptoms in reinfections.

Methods: Children presenting with symptoms of respiratory illness were tested for each of the four ccCoVs (NL63, 229E, OC43, HKU1). Annual blood samples collected before ccCoV infection were tested for antibodies against each ccCoV. Seasonality was evaluated using wavelet and GAM analyses, and age-period effects were investigated using a Poisson model. We also evaluate the risk of symptom presentation between primary and secondary infections

Results: In our cohort 2,576 children from 2011-2016, we observed 595 ccCoV infections and 107 cases of ccCoV-associated lower respiratory infection (LRI). The overall incidence rate was 61.1 per 1,000 person-years (95% CI: 56.3, 66.2). Children under two had the highest incidence of ccCoV infections and associated LRI. ccCoV incidence rapidly decreases until about age six. Each ccCoV circulated throughout the year and demonstrated annual periodicity. Peaks of NL63 typically occurred three months before 229E peaks and six months after OC43 peaks. Approximately 69% of symptomatic ccCoV infections were secondary infections. There was slightly lower risk (RR: 0.90, 95% CI: 0.83, 0.97) of LRI between secondary and primary ccCoV infections among participants under the age of 5.

Conclusions: ccCoV spread annually among children with the greatest burden among ages 0-1. Reinfection is common; prior infection is associated with slight protection against LRI among the youngest children.

Keywords: coronavirus, cohort study, global health, child health, infant health, tropical climate, Latin America

The SARS-CoV-2 pandemic underscores the need for understanding human coronavirus epidemiology. The four common cold coronaviruses (ccCoVs), NL63, 229E, OC43, and HKU1, are generally associated with upper respiratory tract infections, [1-4] but have also been associated more severe lower respiratory tract infections. [5-8] Following the detection of NL63 and HKU1 in the 2000s, OC43 is the most frequently detected globally while 229E is the least and is primarily detected among individuals with severe infections or weakened immune systems. [4,7-16] ccCoVs are split into two, genetically similar groups, alpha (NL63 and 229E) and beta (OC43 and HKU1); [2] prior work has identified cross-reactive antibodies within and between groups.[17] However, it is unclear whether immunity to one of the ccCoV, whether within alpha and beta groups or across, protects against infection with another.

Younger children have higher rates of symptomatic and severe illness associated with ccCoV infection compared to older children and adults. [7,10,18] By age three most children have had their first ccCoV infection and by age six, children typically have antibodies against each of the four ccCoV types. [19,20] ccCoV infections occur repeatedly throughout life, suggesting the lack of long-lasting sterilizing immunity produced by natural infection. [21] Declining antibody levels following primary ccCoV infection may explain frequent ccCoV reinfection in children.[20] The clinical significance of primary vs secondary ccCoV infections in children is not well understood.

Many large ccCoV studies lack a well-defined study population and rely on reporting from hospitals, healthcare systems, and passive surveillance networks; these studies detect and report on the epidemiology of more severe ccCoV infections. [3,6-9,11,13,14] Studies conducted in temperate locations report consistent annual seasonal peaks during winter months, similar to other common respiratory pathogens; ccCoV spread in other climates, however, does not appear to follow similar patterns and drivers of ccCoV seasonality remain unknown.[3,4,7-11,22]

Here we describe the incidence and seasonality of symptomatic ccCoV infections and evaluate risk of symptom presentation of between primary and secondary ccCoV infections in a community-based pediatric cohort in Managua, Nicaragua, from 2011-2016.

Methods

The Nicaraguan Pediatric Influenza Cohort (NPICS) is an ongoing prospective cohort study of children aged 0-14 years in Managua, Nicaragua which has a tropical, urban environment. Previous work has detailed descriptions of study protocols. [23] Briefly, children aged 0-12 were enrolled in 2011 and newborns are enrolled monthly. Parents agreed to bring enrolled children to the study health center, Health Center Sócrates Flores Vivas, at the first signs of a fever. Children age out of the cohort on their 15th birthday. This analysis uses data collected January 1, 2011-December 31, 2016.

Study personnel collected nasal and oropharyngeal swabs (oropharyngeal only if under 6 months) from participants if they met any one of the testing criteria: 1.) fever (temperature of 37.8 °C or greater) or feverishness and cough, sore throat and/or rhinorrhea; 2.) fever or feverishness and under two years old; 3.) severe respiratory symptoms (i.e., pneumonia, chest indrawing, wheezing, apnea, etc.) evaluated by a study physician; 4.) and hospitalization with respiratory symptoms or sepsis. Laboratory personnel at the University of Michigan tested samples using reverse transcriptase-polymerase chain reaction (PCR) for the four seasonal ccCoVs following the CDC protocol.[24] Respiratory symptoms are recorded from each clinic visit by study physicians as well as from symptom diaries by parents/guardians. Participants with diagnosed cases of pneumonia, bronchiolitis, bronchitis, or bronchial hyperreactivity were considered to have lower respiratory tract infections (LRI). [25]

Blood samples were collected annually from participants between February and April each year. To evaluate the frequency of secondary ccCoV infections, blood samples that were collected within one year before an ccCoV PCR+ infection were tested for IgG antibodies to the spike protein for each ccCoV via an enzyme-linked immunosorbent assay (ELISA) following previously developed protocols [26]. Results from blood samples may be paired with multiple PCR+ infections if a participant had multiple PCR+ infections within a year.

Person-time was calculated as the number days between the participants' enrollment and exit from the study. Exit dates were determined as participants' fifteenth birthday for NPICS, the day the participant withdrew from the study, or was lost to follow-up. In cases of loss-to-follow-up, the midpoint between the date of last contact with the participant and the start of the annual survey collection as the exit date was used. Participants did not contribute person time for 28 days following a PCR positive sample. Person-time was calculated for all ccCoV infections and separately for each coronavirus. To identify significant seasonal patterns, wavelet analyses with pink noise and a log +1 transformation were used. To examine if the seasonality of one ccCoV impacted the seasonality of another, a cross-wavelet analysis was conducted. Using time-series data, wavelets can be used to identify periodic signals; cross-wavelet analysis allows us to evaluate the temporal relationship between two time-series [27-29] A generalized additive model was used to identify peak months for each group and type. To calculate incidence rates, a Poisson model was used. Crude rates and rates adjusted for period and for age were calculated; age was adjusted for using B-splines; age-period provided better model fit than age-cohort, or period-cohort. Crude and fitted incidence rates were displayed using hexamaps to visualize age-period-cohort (APC) trends.[30]

To evaluate differences in symptom presentation between primary and secondary infections, symptom presentation risk was compared among those with blood samples collected within a year before a ccCoV PCR+ infection. Secondary infections were defined as PCR+ infections

following a previous PCR+ infection with the same ccCoV type or presence of type-specific IgG spike antibodies before infection. PCR+ infections in children under the age of 1 without a collected blood before infection were considered primary infections. Risk ratios were calculated from a generalized estimating equation log-binomial model adjusted for age linearly; this model was restricted to participants under the age of 5.

We used R version 4.1.1 to create figures as well as conduct the wavelet, GAM, and incidence analyses. All other analyses occurred in SAS version 9.4 (SAS Institute Inc.).

Results

From 2011-2016 there were 2,576 NPICS participants who contributed 7,309 person-years. On average about 3% of participants withdrew from the study or were lost to follow-up per year (range 2-6%) and over the 6 years there were six deaths (Figure S1). Approximately 50% of participants were female. There were between 1,436 and 1,776 active participants each month. (Figure S2).

Study personnel collected 9,018 respiratory samples of which 8,803 (97.6%), had sufficient sample remaining to test all four ccCoVs. 610 (6.8%) were positive for ccCoVs. We detected 595 distinct coronavirus infections and 28 ccCoV coinfections (sample positive for two or more

ccCoVs) among 476 participants. OC43 was the most common ccCoV detected (n=323; 52.9%) followed by NL63 (n=163; 26.7%), 229E (n=86; 14.1%), and HKU1 (n=69; 11.3%) (Table 1). There were 107 cases of ccCoV-associated LRI and 23 hospitalizations.

There was no clear season to ccCoV circulation, with cases presenting in every month of the study period. (Figure 1). NL63, 229E, and OC43 circulated annually throughout the study period. NL63 generally peaked in the last six months of the year, but there was no identified general peak month for the other ccCoVs (Figure 2 & Figure S4). Cross-wavelet analysis indicated that 229E generally peaks occur three months before NL63; we also found that NL63 and OC43 peaks occurred approximately 6 months apart from 2011-2013 but shifted to three-months apart from 2014-2015 (Figure S5).

Overall incidence of symptomatic ccCoV infection was 61.1 per 1,000 person-years (95% CI: 56.3, 66.2). Incidence was highest among the youngest participants and sharply decreased with increasing age. The incidence rate among those aged 4 (63.9, 95% CI: 47.7, 85.5) was less than a third of the rate among those less than one year old (217.4, 95% CI: 183.6, 257.6) and the rate among those aged 8 (22.0.3, 95% CI: 13.3, 36.5) is about a third of the rate among those aged 4. This age pattern is similar for each ccCoV type (Figure 3). Incidence rates between males and females were similar (Table S1). ccCoV-associated lower respiratory infection (LRI) incidence was 8.9 per 1,000 person-years (95% CI: 7.2, 11.0). LRI incidence was also highest among the

youngest participants, with all ccCoV-associated LRI incidence following a similar age pattern as symptomatic infection incidence (Figure 4). There was also no difference in ccCoV-associated LRI incidence by sex (Table S1).

Although it has been shown that people are repeatedly infected with ccCoVs, we hypothesized that the breadth of immunity would increase as children accumulate exposures to the same type, resulting in a decrease in the incidence of cases. APC analysis suggests that incidence declines sharply until around age six when incidence rates decline more slowly (Figure 5 & Figure S6). At age six, ccCoV incidence is less than 30% of infant ccCoV incidence. Symptomatic infections are relatively uncommon in individuals older than 10 years old. Periods that had higher incidence for a specific ccCoV (ex. NL63 in 2013, HKU1 in 2015) had higher incidence among all participants, including older children (Figure S7). Compared to others, cohorts with lower incidence at under one year of age old (ex. NL63 and 2011 cohort, OC43 and 2013 cohort) had generally higher incidence at age one.

To determine whether an infection was a primary or secondary ccCoV infection we tested 406 blood samples that were collected within one year before 434/595 (72.9%) ccCoV PCR+ infections. 108/161 (67%) of PCR+ infections without a blood sample collected within one year were among participants less than one year old. Overall, most children experiencing an infection had had at least one prior ccCoV infection. OC43 antibodies were detected most frequently

(n=316, 77.8%) then NL63 (n=286, 70.4%), HKU1 (n=278, 68.5%) and 229E (n=257, 63.3%). 300 infections (69.1%) occurred in participants who had preexisting antibodies against the infecting ccCoV type, ranging from 73.5% of OC43 infected participants to 63.1% of 229E acute infections (Table 2). Seropositivity was over 50% for each ccCoV for those aged 2 and older (Figure S3).

By age 5, 96.7% of symptomatic infections were type-specific secondary infections (range 95.0% to 100.0% by type). Indeed, for the most common types, OC43 and NL63, 54.6% and 67.7%, of symptomatic infections are secondary infections by age 2; for 229E and HKU1 only 14.3% and 36.4% are secondary infections by age 2. We then examined the severity of primary versus secondary ccCoV infections, adjusted for age. Because almost all ccCoV symptomatic infections were secondary infections by age 5, we limited this analysis to participants under the age of 5. The risk of ccCoV-associated LRI was lower among secondary infections compared to primary infections (RR: 0.90, 95% CI: 0.83, 0.97). We found that the risk of cough (RR: 1.12, 95% CI: 1.04, 1.20) and rhinorrhea (RR: 1.13, 95% CI: 1.06, 1.2) were slightly higher among those with secondary infections compared to primary infections. We found no difference in risk of measured fever, congestion, or hospitalization by serostatus prior to infection (Table 3).

Discussion

This study investigates the burden and seasonality of symptomatic ccCoV infections in a community-based pediatric cohort. This study is the longest running pediatric cohort in Central or South America that has evaluated the burden of ccCoV infections. Like other studies in non-temperate locations, we observed ccCoV infections throughout the year, [22,31-34] with alternating spread of different ccCoV types. While there was no distinct ccCoV season in Managua, Nicaragua, each ccCoV type exhibited annual periodicity. We found that the two alpha coronaviruses, 229E and NL63, peaks generally do not occur at the same time. Other studies in temperate locations found that while NL63 and 229E did spread at the same time, years with a high prevalence of 229E coincided with low levels of NL63. [9,35] These results may indicate the presence of short-term, sub-group specific cross-reactive immunity.[36-42]

Consistent with other respiratory infections and previous research, younger children had a higher incidence of symptomatic ccCoV infections and ccCoV-associated LRI than older children, especially within the first two years of life. [3,7,9-12,43] We note a clear pattern of rapidly decreasing incidence of symptomatic infection until about age six at which point nearly all infections are secondary. Additionally, ccCoV reinfection is very common among children; [20] we found that by age five, almost all symptomatic infections were secondary, not primary infections. Among those under five years of age, there was slightly lower risk of ccCoV-associated LRI for secondary infections compared to primary infections after adjusting for age. Similarly, frequent reinfection with SARS-CoV-2 has also been observed among children. [44] In a household transmission study,

infection-induced immunity was not associated with protection against SARS-CoV-2 infection for children. [45] These findings suggest that while protection against ccCoV-associated LRI develops following a primary infection, protection against symptomatic infections wanes quicker early in life,[20] but may build, lasting longer, over several exposures.

We also observed some years that had high ccCoV type-specific incidence rates across all ages. We expect that ccCoV type-specific genetic diversity, frequently detected among children [46], may explain these high incidence years. Additionally, birth cohorts that experienced lower rates of symptomatic infections for a particular ccCoV type as infants, had higher rates of symptomatic illness at age one compared to other cohorts; this was likely a result of both annual ccCoV spread and an absence of type-specific immunity acquired before the one year of age.

The main strength of this study is the size and duration of the prospective cohort. With over 9,000 respiratory samples collected and over 7,000 person years, we observed almost 600 ccCoV infections, exclusively among children. The six years of data provides sufficient power to evaluate seasonality statistically, identify annual periodicity, as well as evaluate the frequency of repeat ccCoV infections. The consistent cohort age structure and limited loss-to-follow-up allowed us to identify age-period-cohort trends of symptomatic ccCoV illness.

We do note some limitations in this study. Respiratory swabs were only collected when a participant presented at the clinic with symptomatic illness, thus likely missing some mild cases and underestimating the true incidence of both ccCoV infections and the frequency of reinfections in the population. However, testing participants' blood samples for ccCoV antibodies, did reveal that the majority of symptomatic ccCoV infections were reinfections. Additionally, we did not examine genetic variation in ccCoVs which may help to explain seasonal variation as well as the frequency of reinfections.

Although ccCoV infections occur repeatedly throughout childhood, our understanding of coronavirus epidemiology in early life is limited. We show that ccCoV infections spread continuously throughout the year in a pediatric population in Nicaragua, with frequent reinfections; however, history of prior infection did convey protection against ccCoV-associated LRI among those under five. Future research should focus on the early-life development of coronavirus immunity to, the contributions of viral evolution and immunity to coronavirus reinfections and immune correlates of protection against coronaviruses.

Figure 1: Monthly ccCoV PCR+ Infections by Type, 2011-2016

Symptomatic ccCoV infections over time. Dashed line represents monthly sum of all ccCoV PCR+ infections during the study period

A: NL63 PCR+ infections, B: 229E PCR+ infections, C: OC43 PCR+ infections, D: HKU1 PCR+ infections

Figure 2: Wavelet Analysis by ccCoV Type

Wavelet analysis conducted separately by ccCoV type to identify type-specific periodicity. Red represents dominant periods and the area circled in black lines represent significant periodicity. Only the area within the light grey semi-circle (the wavelet cone of influence) can be interpreted.

A: NL63 wavelet analysis, B: 229E wavelet analysis, C: OC43 wavelet analysis, D: HKU1 wavelet analysis

Figure 3: ccCoV Incidence Rates by Age, Type

Incidence rates (per 1,000 person-years) of PCR+ ccCoV infections for all ccCoV infections and by type using one year age groups. Shaded area represents 95% confidence intervals.

A: All ccCoV, B: NL63, C: 229E, D: OC43, E: HKU1

Figure 4: ccCoV-Associated Lower Respiratory Infection Incidence Rates by Age, Type

Incidence rates (per 1,000 person-years) of PCR+ ccCoV-associated lower respiratory infections (LRI) for all ccCoV infections and by type using one year age groups. Shaded area represents 95% confidence intervals.

A: All ccCoV-associated LRI, B: NL63-associated LRI, C: 229E-associated LRI, D: OC43-associated LRI, E: HKU1-associated LRI

Figure 5: ccCoV Incidence Rate Hexamaps

Visualizing ccCoV incidence rates (per 1,000 person-years) by type as a function of age, calendar year, and birth year. Hexamaps with incidence rates from raw data are presented on the

left within each ccCoV type's panel. Predicted incidence rates from age-period model are presented on the right within each ccCoV type's panel.

A: NL63, B: 229E, C: OC43, D: HKU1

Figure S1: Participant Enter-Exit by Year

Flow chart represent total active participants in January for each year from 2011-2016 with total number of participants entering (enrolled, re-enrolled) and exiting (aged out, withdrawn, or deaths) the cohort.

Figure S2: Participation by Age, Month

Total number of monthly active participants in the cohort over the study period by age groups.

Figure S3: ccCoV Seropositivity by Age, Type

Proportion of participants with ccCoV-antibodies before ccCoV PCR+ infection by one year age groups and type.

A: NL63, B: 229E, C: OC43, D: HKU1

Figure S4: Generalized Additive Model Analysis for Peak Month by ccCoV Type

Analysis uses month as the predictive variable for time series data for each ccCoV type. Dotted lines represent 95% confidence intervals. If confidence intervals at the peaks overlap with confidence intervals of the trough, there is no significant peak month.

A: NL63, B: 229E, C: OC43, D: HKU1

Figure S5: Cross-wavelet Analysis

Cross-wavelet analysis of two ccCoV types to evaluate temporal relationship. White arrows pointing up at a period of 1 year represent a three-month lag between the first list ccCoV type and the second. Arrows pointing to the left at a period of 1 year represent a six-month lag between types.

A: 229E-NL63, B: OC43-NL63

Figure S6: Age-period Incidence Model- Age Effects

Predicted rate ratios by age from age-period model by ccCoV type. Black line represents predicted rate ratios for all ccCoV infections for comparison.

A: NL63, B: 229E, C: OC43, D: HKU1

Figure S7: Age-period Incidence Model- Period Effects

Predicted rate ratios by year from age-period model by ccCoV type. 2011 is the reference category. Black points and confidence intervals represent predicted rate ratios for all ccCoV infections for comparison.

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