Epidemiology of Symptomatic Respiratory Viral Codetections Among Children and Adults in the Cascadia Community-Based Cohort, 2022-2024

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Abstract

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Background: Respiratory virus codetection, or the concurrent presence of multiple viruses in a single host, can complicate diagnoses and may influence clinical severity. This study examined the burden and clinical impact of viral codetections in a community-based U.S. cohort, focusing on eight common respiratory pathogens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza virus (Flu), respiratory syncytial virus (RSV), and others.

Methods: We conducted a secondary analysis of data from the CASCADIA study, a prospective cohort of 3,500 participants aged 6 months to 50 years, followed from June 2022 to March 2024. Illness episodes with single vs. multiple virus detections at illness onset were compared in terms of demographic and clinical characteristics. Multivariable logistic regression models were used to assess the association between codetection and illness severity outcomes, including extended

symptom duration, medically attended illness, and absenteeism. Analyses were conducted both overall and stratified by involved viral pathogens and age groups.

Results: Among 8,908 symptomatic illness episodes, 9.6% involved codetection. Codetections were most frequent in children aged 5-11 years, while single detections were more common in adults. Overall, codetection was not significantly associated with illness severity. However, in children, codetection was linked to higher odds of extended symptoms (aOR: 1.27; 95% CI: 1.06–1.53) and medical visits (aOR: 1.53; 95% CI: 1.17–1.99). A positive, though non-significant, association was observed with absenteeism in adults.

Conclusion: Although most associations between codetection and illness severity were not statistically significant, some patterns suggest potential links to more severe outcomes, particularly in pediatric populations. Further research is needed to better understand viral interactions and their influence on clinical trajectories over time.

Keywords: Codetection, coinfection, respiratory viruses, illness severity, community-based study.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has highlighted the urgent need to better understand the epidemiology of respiratory viral infections. Among various infectious diseases, acute respiratory tract infections (ARIs) have long contributed significantly to global morbidity, mortality, and workforce loss.[1,2] During the COVID-19 pandemic, respiratory infections emerged as the second leading cause of death worldwide.[3] Prior to the pandemic, in 2019, the age-standardized incidence, mortality, and disability-adjusted life years (DALYs) due to respiratory infections in the United States were approximately 340,000, 14, and 385 per 100,000 population, respectively.[1] Upper respiratory infections accounted for the majority of incident cases, while lower respiratory infections represented the highest proportion of respiratory infection-related deaths and DALYs.[1]

Many viral pathogens are associated with ARIs, with the most commonly implicated being severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza virus (Flu), and respiratory syncytial virus (RSV).[4,5] Other frequently encountered viral pathogens include human rhinovirus (HRV), human coronavirus (HCoV), parainfluenza viruses (HPIV), human metapneumovirus (HMPV), enterovirus (EV), and adenovirus (AdV).[6,7]

Multiple respiratory viruses may infect the same individual concurrently, potentially leading to positive, negative, or neutral virus-virus interactions.[8,9] The terms coinfection and codetection are often used interchangeably to describe the concurrent presence of multiple respiratory viruses. Codetection refers to the detection of more than one respiratory virus in a single clinical specimen, which does not necessarily indicate active infection.[10–12] Residual viral RNA or DNA from prior infections with viruses known for prolonged shedding, such as adenovirus or rhinovirus,[13–15] may be detected even when not contributing to current illness.

Coinfection, on the other hand, implies simultaneous active infection and replication of two or more pathogens contributing to clinical symptoms.[10–12] While codetection does not always equate to coinfection,[11] it can serve as a useful proxy for exploring potential virus-virus interactions, especially in the absence of confirmatory methods to establish active replication or concurrent disease processes.

The simultaneous presence of multiple respiratory viruses often complicates both diagnosis and patient management and may be associated with worse clinical outcomes. Prior studies have linked this pattern to an increased likelihood of fever, prolonged symptom duration, higher pediatric intensive care unit admission rates, and more severe bronchiolitis.[16–20] Residual pathology from a previously acquired infection may also influence the risk, frequency, or severity of illness among codetected cases.[10,11] Although most existing studies have been limited to small-scale or hospital-based settings,[16,19,21–23] these findings underscore the importance of understanding viral coinfection patterns at a broader population level, even though untangling such interactions is challenging due to the large number of respiratory viruses and the many infections that go undetected.[24,25]

To address current gaps in literature, this study aimed to assess the burden of concurrent respiratory viral infections using codetection data from a community-based study in the United States. Additionally, we sought to investigate the impact of viral codetection on the severity of symptomatic illness episodes involving eight respiratory viruses: SARS-CoV-2, influenza A/B, RSV A/B, HRV/EV, HCoV, HPIV, HMPV, and AdV. We hypothesized that codetection with two or more viral pathogens would be associated with worse clinical outcomes, as reflected by longer symptom duration, increased likelihood of medically attended illness, and greater disruption to daily activities, such as work and school absenteeism.

METHODS

Study Design and Setting

This secondary analysis utilized data from the CASCADIA study, a community-based prospective cohort study investigating respiratory infections among 3,500 unique participants aged 6 months to 50 years in parts of the Pacific Northwest (Washington (WA) and Oregon (OR), USA).[26] CASCADIA study sites included the University of Washington (Seattle, WA) and the Kaiser Permanente Northwest (KPNW) Center for Health Research (Portland, OR).[26] CASCADIA participant enrollment began in June 2022, with follow-up concluding in March 2024.[26]

Data Collection

CASCADIA collected survey data at multiple time points (enrollment, weekly, monthly, and semi-annually), along with respiratory specimens, to monitor COVID-like illness (CLI) and gather relevant epidemiological information.[26] This analysis specifically included data from enrollment survey, weekly online symptoms survey, and home nasal swab results.

Enrollment and Symptom Survey

At enrollment, participants or their parent/guardian completed a baseline survey on demographic characteristics, household context, as well as various aspects of participants' health including vaccination history. Active CLI surveillance began within one week of enrollment. Participants were assigned or selected a preferred weekday for routine communication for the weekly Symptom & Swabbing Survey and nasal swab specimen collection. If symptoms indicative of an acute illness were reported (marked as day 0), participants were prompted to complete a detailed Infection/Illness Onset Survey, which captured symptom type and onset date.[26] Follow-up assessments were conducted 7 and 14 days after symptom onset through short surveys (1-Week

and 2-Week Post-Illness Follow-up Surveys). These surveys gathered updates on symptom persistence, recovery status, health care utilization, and disruptions to daily life, including work or school absenteeism.

Respiratory Specimen

Anterior nares nasal swabs (TINY RHINOstic) were collected from all CASCADIA participants.[26] Respiratory specimens were obtained under four main conditions: (1) weekly from all participants regardless of symptoms to detect SARS-CoV-2, RSV, and influenza; (2) when CLI symptoms were reported; (3) following a positive result from external testing; and (4) serially, every three days for three weeks after a SARS-CoV-2-positive PCR result.[26] A subset of these specimens underwent multiplex (open array) testing for multiple respiratory pathogens, including SARS-CoV-2, influenza, RSV, HRV, enterovirus (EV), seasonal coronavirus (HCoV), parainfluenza virus (HPIV), human metapneumovirus (HMPV), and adenovirus (AdV).

Study Population

CASCADIA participants of all ages were eligible in this analysis if they completed an enrollment survey, experienced at least one symptomatic illness episode throughout the study period, and provided at least one nasal swab by March 31, 2024. Only illness episodes with a positive swab for one or more of the following viral pathogens were included in this analysis: SARS-CoV-2, influenza A/B, RSV A/B, HRV/EV[1], HCoV, HPIV, HMPV, or AdV.

[1] Rhinovirus and enterovirus are grouped together in this analysis due to their close phylogenetic relationship; both are classified as distinct species within the Enterovirus genus (family Picornaviridae).

Variables

Primary Exposure

The primary exposure of interest in this study was codetection status. Codetection was defined as the concurrent detection of two or more respiratory viruses from a single nasal swab collected during one acute illness episode. In contrast, single detection referred to one virus being detected. An illness episode was defined as a period when the participant reported at least one symptom and had one positive swab. Distinct episodes were identified by a new symptom onset occurring >30 days after the prior episode for the same individual. To isolate the effects of coinfection from those of prior illnesses, or secondary infections occurring in the weeks following primary infection, only the first swab of each illness episode was included in this analysis.

Outcomes

Three primary outcomes were used in this analysis to serve as proxies for illness severity: extended symptom period, medically attended illness, and absenteeism.

Extended symptom period was defined as persistence of at least one ARI or CLI symptoms (e.g., fever, cough, fatigue, etc.) reported on the 7-day follow-up survey. Symptom types were also grouped into gastrointestinal (nausea/vomiting, diarrhea), respiratory (cough, shortness of breath, sore throat, nasal congestion/runny nose), and systemic (fever, fatigue, muscle or body aches, headache, loss of taste or smell, chest pressure, and blue-tinged skin).

Medically attended illness was defined by any reported care-seeking behavior (e.g., urgent care, hospital/emergency department, telehealth, or other). Care-seeking behavior was reported on the 14-day follow-up survey (2-Week Post-Infection/Illness Follow-up Survey).

Absenteeism, or work/school absenteeism, was also measured on day 14 after illness onset. Absenteeism was defined as reported absence from work, school, or usual activities due to illness.

Other covariates

To investigate predictors of illness severity, several other covariates describing the demographic and other characteristics of study participants were included in analyses. These covariates included age category at enrollment (6 months-1 year; 2-4 years; 5-12 years; 13-17 years; 18-49 years), sex assigned at birth (male; female), race/ethnicity (American Indian/Alaskan Native; Asian; Black/African American; Native Hawaiian/Pacific Islander; White; Multiple/Other), and Hispanic ethnicity (yes; no). We also accounted for daycare, school, or job attendance status, self-reported overall health at enrollment (poor/fair; good/very good; excellent), and the presence of self-reported comorbidities (asthma; chronic obstructive pulmonary disease (COPD); hypertension; immunocompromised; and other comorbidities). History of COVID-19 and influenza vaccination, as well as smoking status (non-smoker; e-cigarette/cigarette/marijuana use), were also included. Household-level characteristics incorporated into the analysis were household density (living alone; 2-4 people; 5 or more people) and number of children in the household (no children; one child; 2-4 children; 5 or more children).

Statistical Analysis

Descriptive Statistics

Descriptive statistics were reported to summarize the demographic, household, and clinical characteristics of participants across illness episodes, comparing single detection vs. codetection on day 0 (illness onset). All categorical variables were described using counts and percentages. Additional descriptive analyses were also performed to illustrate symptom patterns at illness onset, to examine the distribution of viral detection types (single vs. codetection) by pathogen, and to identify which viral respiratory codetection pairs were most frequently detected in the community.

Multivariable Analysis

Multivariable logistic regression was conducted to assess the association between codetection and illness severity (extended symptom period, medically attended illness, and absenteeism). Six separate models were constructed for each of the clinical outcomes. The primary model compared all illness episodes with codetection to those with single detection. Additional models were used to study subsets of illness episodes, including the COVID-19 positive episodes, influenza-positive episodes, and RSV-positive episodes. SARS-CoV-2, influenza, and RSV were selected as a priori for additional analysis due to their clinical relevance and their role in the current global burden of respiratory disease. We also constructed two separate models to study illness episodes among pediatric participants (children aged 6 months-17 years) and adult participants (18-50 years) separately.

All analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing) in RStudio 2024.12.0+467 (RStudio, Inc; Boston, MA). Odds ratios (ORs) estimates and 95% confidence intervals (CIs) were reported for each fitted multivariable logistic regression model. Both unadjusted and adjusted odds ratio estimates were provided for the primary model comparing codetection to single detection across illness severity outcomes. For the remaining models, odds ratio estimates were adjusted for the potential confounders, including age, daycare/school/job attendance status, any comorbidity (yes/no), as well as COVID-19 and influenza vaccination history.

Due to the nature of rhinovirus, which is prone to prolonged shedding and potential residual detection from previous illness episodes, a sensitivity analysis was also performed to compare illness severity in codetection and single detection after excluding rhinovirus/enterovirus cases.

Ethical Approval of the Primary Study

The CASCADIA study protocol was approved by the Kaiser Permanente Inter-regional Institutional Review Board (IRB), with reliance from the University of Washington and Seattle Children's Research Institute.[26]

RESULTS

Illness Characteristics

A total of 8908 illness episodes were observed from June 2022-May 2024. A total of 2919 enrolled participants had at least one episode of acute viral respiratory illness. Among these symptomatic illness episodes, 8052 (90.4%) had single viral detection on their first swab, while 856 (9.6%) had codetection (i.e., multiple viruses detected). Of those with codetection, 804 (93.9%) had two viruses detected, 49 (5.7%) had three, and 3 (0.4%) had more than three viruses detected. Among codetection cases, the highest proportion was observed in children aged 5-11 years (32.2%), while among single detection cases, adults aged 18-50 years accounted for the largest share (38.6%) (Table 1). However, when looking within age groups, the highest proportion of codetections relative to single detections was found among infants aged 6 months-1 year (26.2%), followed by children aged 2-4 years (18.0%) (Supplementary Table 1). Older children and adults had notably lower proportions of codetections within their respective groups, particularly those aged 12-17 years (5.2%) and 18-50 years (5.2%), suggesting codetection was more common among younger children.

Codetection status did not differ substantially by sex, race/ethnicity, COVID-19 or influenza vaccination history, smoking status, household density, or number of children in the household (Table 1). Across codetected illness episodes, the highest proportion was observed in

individuals attending school (40.7%), followed by those in daycare (28.0%). Across single detection episodes, individuals with jobs (32.3%) were nearly as frequent as those attending school (42.5%). Within the daycare group, 24.5% of illness episodes involved codetection, the highest proportion across attendance categories (Supplementary Table 1). Comorbidities such as asthma, hypertension, and other chronic conditions were more frequently reported among individuals with single detection than those with codetection.

When categorized by symptom group, respiratory symptoms on day 0 or illness onset were nearly universal across all symptomatic illness episodes (95.8%), with a slightly higher prevalence among those with codetection (97.4%) compared to single detection (95.5%) (Supplementary Table 1a). Systemic symptoms, such as fatigue and muscle aches, were slightly more prevalent among single detections (47.1%) than codetections (38.6%). Gastrointestinal (GI) symptoms were less common overall and reported at similar frequencies between single detection and codetection cases. Within codetection cases, respiratory symptoms alone were more commonly reported than symptoms classified in the multiple symptom group.

Overall, congestion or runny nose was the most commonly reported symptom across all groups, particularly among codetection cases. Among pathogen-specific patterns (Figure 1), codetections involving severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respiratory syncytial virus (RSV), and adenovirus (AdV) were frequently associated with broader symptom profiles, including both respiratory and systemic symptoms. Among children, RSV and human metapneumovirus (HMPV) infections were notably associated with higher proportions of respiratory symptoms, regardless of detection type (Supplementary Figure 1a).

The frequencies of single and multiple viral detections for the eight viral pathogens are shown in Supplementary Table 1b. Single detections were most frequent among SARS-CoV-2-

positive cases (91.1%). Of 684 adenovirus cases, 331 (48.4%) were single detections, while 353 (51.6%) were codetected with other viral pathogens, making AdV the viral pathogen with the highest ratio of codetection to single detection. Notably, among 453 illness episodes with RSV A/B-positive swabs, 114 (25.2%) were codetected, resulting in a higher codetection-to-single detection ratio compared to episodes with SARS-CoV-2- or Influenza A/B-positive swabs. For other virus-positive swabs, single detections remained dominant, including HRV/EV (86.5%), HCoV (80.2%), HPIV (74.4%), and HMPV (74.6%).

Figure 3 presents a heat map of viral codetection pair frequencies among illness episodes. Diagonal cells represent single detections, while off-diagonal cells represent codetections between viral pairs. Overall, codetection patterns varied by virus, with human rhinovirus/enterovirus (HRV/EV) being the most frequently codetected virus across multiple combinations. Among RSV-positive swabs, 12.1% were codetected with HRV/EV. Similar patterns were observed among HCoV-, HPIV-, and AdV-positive illnesses, with 9.8%, 9.4%, and 27.8% codetected with HRV/EV, respectively. AdV also showed relatively high codetection frequencies with seasonal coronavirus (HCoV) at 5.7%, and human parainfluenza virus (HPIV) at 4.2%.

Clinical Severity Outcomes

Among all illness episodes, 2,989 (33.6%) participants were still experiencing symptoms on day 7, as reported in the one-week post-illness follow-up survey. This included 318 codetection episodes (37.5% of all codetections) and 2,671 single detection episodes (33.2% of all single detections). Out of 8,909 illness episodes, 779 sought various forms of clinical care, including clinic visits, emergency department visits, urgent care visits, or telehealth consultations. Only 22%

of illness episodes (1,966 cases) reported absence from work, school, or usual activities due to illness, based on the two-week post-illness follow-up survey.

Results from multivariable analyses (Tables 3-5) showed that codetection was not significantly associated with extended symptom duration (aOR: 1.15; 95% CI: 0.98–1.36) or absenteeism (aOR: 1.07; 95% CI: 0.89–1.29), after adjusting for age, daycare/school/job attendance, comorbidities, and vaccination history. However, it was associated with an estimated 38% higher odds of medically attended illness compared to single detection (aOR: 1.38; 95% CI: 1.08–1.75).

When stratified by virus type (Table 6), codetection was not significantly associated with any of the three clinical severity outcomes among episodes positive for SARS-CoV-2, influenza A/B, or RSV. In age-stratified analyses (Table 7), codetection was associated with higher odds of extended symptom duration (aOR: 1.27; 95% CI: 1.06–1.53) and medically attended illness (aOR: 1.53; 95% CI: 1.17–1.99) among pediatric participants but showed no significant associations among adults. For absenteeism, no statistically significant differences were observed between codetection and single detection groups in either age group.

A sensitivity analysis was conducted excluding all HRV/EV-associated cases to assess whether the associations between codetection and outcome severity were influenced by the high proportion of HRV/EV-positive episodes (Table 8). Among non-HRV/EV illness episodes, 110 codetection cases and 1510 single detection cases experienced an extended symptom period. A total of 30 non-HRV/EV codetection cases sought various clinical care, while 77 non-HRV/EV codetection cases reported missing school, work, or usual activities. After excluding all HRV/EV-positive illness episodes, codetection was not significantly associated with extended symptoms

(aOR: 1.27; 95% CI: 0.93–1.72), care-seeking (aOR: 0.92; 95% CI: 0.58–1.41), or work/school absenteeism (aOR: 0.97; 95% CI: 0.70–1.34).

DISCUSSION

Viral Codetection Pattern

In this study, we analyzed data from a two-year prospective community-based cohort of individuals aged 6 months to 49 years in the United States to assess the burden of concurrent respiratory viral infections (codetections) and their impact on the clinical severity of symptomatic illness episodes involving eight respiratory pathogens: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza virus (Flu), respiratory syncytial virus (RSV), human rhinovirus/enterovirus (HRV/EV), human coronavirus (HCoV), parainfluenza viruses (HPIV), human metapneumovirus (HMPV), and adenovirus (AdV). Codetections were identified in nearly 10% of symptomatic respiratory illness episodes, higher than the 3-8% range reported in earlier studies.[27–29]

Most codetections occurred among pediatric participants (aged 6 months to 17 years), with the highest proportion observed among children aged 5-11 years. This pattern is consistent with findings from smaller-scale or hospital-based studies.[27,30–32] A study of hospitalized patients in Brazil reported that 65.8% of viral codetections occurred in children aged 0-12 years.[31] Similarly, primary care and hospital-based studies in Spain and France also reported higher codetection rates among young children, with a median age of 3 years.[27,32]

These findings are not unexpected, as respiratory viruses pose a greater threat to pediatric populations due to their developing immune systems and smaller airways, which can increase susceptibility to severe infection.[31,33] In our study, codetections were also more common among

children attending daycare and school, reflecting higher risk of exposure to circulating respiratory viruses in these types of settings. Prior research has consistently shown that child-centered settings such as daycares and schools are sites of intensive respiratory virus transmission, due to close contact, and use of shared equipment.[34] However, as demonstrated during the COVID-19 pandemic,[35] implementing infection prevention and control (IPAC) measures (e.g., mask-wearing and vaccination) can effectively reduce transmission in these settings, highlighting that such environments need not pose unavoidable risks.

Among the codetected cases identified in our study, the majority presented with respiratory symptoms only, rather than symptoms spanning multiple groups (i.e., combinations of gastrointestinal, respiratory, and systemic symptoms). This finding aligns with prior literature noting that common symptoms across various viral infections include sore throat, nasal congestion, rhinorrhea or runny nose, and cough.[28,36,37] Systemic symptoms such as muscle pain and headache have frequently been described as typical responses to viral infections.[36] Previous studies have noted that headache is more commonly associated with influenza, whereas its absence has been linked to RSV and HMPV infections.[28] The lower proportion of headache, as well as other systemic and gastrointestinal symptoms, reported in our study may be explained by the lower frequency of certain pathogen detections, such as influenza, in this cohort.

In terms of specific viral pathogens, HRV/EV emerged as the most frequently codetected virus in our analysis. This is likely due to its high prevalence in the community and its capacity for prolonged viral shedding in some cases. HRV consists of over 100 serotypes across species A–C (now reclassified as enteroviruses) and is recognized as a leading cause of the common cold.[38] In pediatric populations, HRV is among the most frequently detected viruses in respiratory admissions to pediatric intensive care units.[39] However, HRV can also be associated with mild or

even asymptomatic infection, particularly in healthy young children, while still resulting in extended viral shedding duration.[14] Among immunocompetent adults, HRV shedding typically lasts 1-2 weeks, whereas shedding durations of 28 days or more have been reported in immunocompromised individuals.[13] Other studies have documented the persistence of the same HRV strain for up to 3 months in healthy infants, although prolonged presence beyond 30 days is less common in healthy older children and adults.[15]

Adenovirus also showed a high codetection-to-single detection ratio in our study, which may similarly be attributed to its prolonged shedding characteristics. Prior studies have reported adenovirus shedding durations ranging from 54 to 95 days.[40,41] The higher percentage of AdV codetection in our findings is also consistent with data from previous study, where human adenovirus (HAdV) was detected in 1,136 cases (6.1%), and 56.9% of these involved codetection with at least one other respiratory virus.[42]

We also observed that RSV A/B-positive illness episodes had a greater codetection-to-single detection ratio compared to those positive for SARS-CoV-2 or influenza A/B. Although SARS-CoV-2 detections were more frequent overall, RSV A/B-positive cases showed a higher percentage of codetection in our analysis. This may reflect the fact that most codetections in our study occurred in children, and that RSV is one of the most prevalent pathogens detected in pediatric populations, alongside HRV and AdV.[43]

Codetection involving SARS-CoV-2 and influenza viruses was relatively infrequent in our study. This observation may reflect potential viral interference, where infection with one virus inhibits replication or transmission of another, or the dominance of these viruses when present, limiting opportunities for concurrent infections.[44,45] It is also possible that temporal differences in the circulation of these viruses in the community reduced the likelihood of overlapping infections.

These findings are consistent with other studies reporting codetections of SARS-CoV-2 with other respiratory viral pathogens.[46]

Viral Codetection and Outcome Severity

Overall, our assessment of the association between viral codetection and outcome severity aligned with our initial hypotheses. When stratified by the primary pathogens investigated in the CASCADIA study (i.e., SARS-CoV-2, influenza, and RSV), the odds of extended symptom duration, medically attended illness, and work/school absenteeism did not differ meaningfully between single-virus and codetection cases. This may be attributed to the relatively small number of codetection cases within these pathogen-specific subsets, potentially due to viral interference or differences in seasonal circulation.[29,44–46]

Age-stratified analyses revealed that codetection was significantly associated with higher odds of both extended symptom duration and medically attended illness among children, but not with absenteeism. These findings are consistent with previous studies in pediatric populations, which reported that children with viral codetection had higher odds of presenting symptoms such as cough and rhinorrhea compared to those with single-virus infections, although both symptoms are commonly observed in respiratory illness.[47] Regarding care-seeking behavior, the same study showed that children infected with both influenza and RSV had a higher probability of hospitalization than those with influenza alone,[47] which may reflect the patterns of medically attended illness observed in our analysis. This is consistent with previous studies that have also reported a significant association between viral codetections and increased illness severity in children.[48] In terms of absenteeism, prior research similarly found that the duration of children's absence from daycare or school, as well as parental work absence, did not significantly differ by

type of respiratory virus.[49] However, the same study reported that viral-bacterial codetections were associated with longer parental work absence compared to viral infections alone.[49]

Among adults, work or school absenteeism showed a positive but non-significant association with codetection, indicating that adults with viral codetection were somewhat more likely to report absenteeism compared to those with single-virus detections. In contrast, the direction of association for extended symptoms and medically attended illness was negative, suggesting that codetection in adults was not linked to increased severity for these outcomes in our data. Previous studies have reported that viral-viral coinfections in adults were associated with higher rates of intensive care unit (ICU) admission and use of invasive mechanical ventilation compared to single-virus infections.[50] In addition, 60-day all-cause mortality was significantly greater among coinfected adults than among those with mono-infections.[50] These trends were not reflected in our analysis, possibly due to the milder illness episodes captured in our community-based cohort, and the cohort of healthy adults who were primarily parents/guardians to young children, who often do not have time to seek care for themselves. Other explanations for the lack of statistically significant findings may include the reliance on a single swab collected at illness onset (day 0), which may not capture the full window of viral coinfection, and the use of self-reported outcomes such as symptom persistence after 7 days, care-seeking behavior, and absenteeism, which may introduce recall or reporting bias.

Given the large proportion of HRV/EV codetected cases in our dataset, we conducted sensitivity analyses excluding HRV/EV-positive illness episodes to evaluate whether these codetections substantially influenced our overall findings. The attenuated associations observed after excluding HRV/EV suggest that this viral pathogen plays a meaningful role in shaping the clinical severity of codetection episodes and should be considered in future analyses of viral

interactions. Previous studies have similarly emphasized the importance of including HRV/EV in assessments of viral codetection.[20]

Strengths and Limitations

The interpretation of our findings should be considered in the context of the study's strengths and limitations. Our study features a large sample size and systematic follow-up from a community-based cohort. It helps fill a gap in the literature by providing results from a broader community cohort, whereas similar previous studies have often focused on smaller community or hospital- and clinic-based settings. Our study also featured high retention and intensive follow-up among children and adults. Regular weekly symptom monitoring, timely swab collection, detailed baseline demographic information, and documentation of the impact of respiratory illness on absenteeism and healthcare-seeking behavior all contribute to the richness of the dataset. The use of multiplex PCR testing for a wide range of respiratory pathogens also provides important insights into concurrent viral interactions. In terms of analysis, our stratification by age and virus adds nuance to codetection research, allowing for more granular interpretation of potential effects.

Notwithstanding these strengths, there are several limitations that should be considered in future analysis. Most of the outcome variables in this study, including symptom persistence after seven days, care-seeking behavior, and work or school absenteeism, were self-reported through follow-up surveys. As a result, these data are subject to potential misclassification and recall bias. Another limitation is that multipathogen testing was conducted only among symptomatic participants, which limits our ability to assess the burden in asymptomatic individuals.

In terms of codetection classification, our study relied on a single swab collected at day 0 or illness onset. While this approach helped standardize the timing of testing across episodes, it may not capture the full duration or dynamic interactions of viruses over the course of illness.

Implications for Future Research

It may be important for future research to incorporate viral load measurements or genomic sequencing to help distinguish active coinfections from incidental detections and to better interpret the clinical relevance of codetected pathogens. Longitudinal or time-varying analyses are also needed to more fully characterize the clinical trajectories of codetection and to explore the temporal dynamics of viral interactions, including the effects of coinfection and viral interference.

Furthermore, future studies may also need to consider virus-bacteria codetections in addition to virus-virus interactions when evaluating the impact of codetection on illness severity. Previous studies have noted that respiratory illnesses often involve virus-bacteria codetections, which may contribute significantly to disease progression.[51–53] While our analysis provides baseline evidence for the association between viral codetection and outcome severity, understanding these more complex interactions may be critical to improving diagnostic, prevention, and treatment strategies for respiratory infections.

CONCLUSION

In this community-based cohort study, approximately 1 in 10 symptomatic respiratory illness episodes involved more than one virus, with codetections most frequently observed in children. Although most associations between codetection and illness severity were not statistically significant, several showed trends in the expected direction, suggesting that codetection may increase the likelihood of more severe illness, particularly in pediatric cases. Further research is needed to better understand how multiple viruses interact over time and how these interactions may influence clinical outcomes.

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APPENDIX

Table 1. Individual and household characteristics stratified by type of viral detection among symptomatic illness episodes.[a]

	Total (%)	Single Detection (%)	Codetection (%)
Individual Characteristics*			
Age category (at enrollment)			
6mo-1years	530 (5.9)	391 (4.9)	139 (16.2)
2-4 years	1158 (13.0)	950 (11.8)	208 (24.3)
5-11 years	2744 (30.8)	2468 (30.7)	276 (32.2)
12-17years	1161 (13.0)	1105 (13.7)	56 (6.5)
18-50 years	3275 (36.8)	3106 (38.6)	169 (19.7)
Sex assigned at birth			
Male	3799 (42.6)	3410 (42.3)	389 (45.4)
Female	5055 (56.7)	4598 (57.1)	457 (53.4)
Race/Ethnicity			
American Indian/Alaskan Native	30 (0.3)	29 (0.4)	1 (0.1)
Asian	541 (6.1)	484 (6.0)	57 (6.7)
Black/African American	114 (1.3)	108 (1.3)	6 (0.7)
Native Hawaiian/Pacific Islander	12 (0.1)	11 (0.1)	1 (0.1)
White	6804 (76.4)	6188 (76.9)	616 (72.0)
Multiple/Other	1367 (15.3)	1200 (14.9)	167 (19.5)
Hispanic			
No	8079 (90.7)	7320 (90.9)	759 (88.7)
Yes	716 (8.0)	634 (7.9)	82 (9.6)
Daycare/school/job attendance status			
No daycare/school/job	1237 (13.9)	1134 (14.1)	103 (12.0)
Daycare	978 (11.0)	738 (9.2)	240 (28.0)
School	3767 (42.3)	3419 (42.5)	348 (40.7)
Job	2745 (30.8)	2598 (32.3)	147 (17.2)
Job and school	79 (0.9)	74 (0.9)	5 (0.6)
Overall health (self-reported)			
Poor/fair	157 (1.8)	147 (1.8)	10 (1.2)
Good/very good	4230 (47.5)	3915 (48.6)	315 (36.8)
Excellent	4481 (50.3)	3958 (49.2)	523 (61.1)
Comorbidities (self-reported)			
Asthma	1205 (13.5)	1127 (14.0)	78 (9.1)
COPD	23 (0.3)	23 (0.3)	0 (0.00)
Hypertension	285 (3.2)	275 (3.4)	10 (1.2)
Immunocompromised	118 (1.3)	114 (1.4)	4 (0.5)
Other comorbidities[b]	1414 (15.9)	1334 (16.6)	80 (9.3)
Any comorbidities (self-reported)			
No	6552 (73.6)	5836 (72.5)	716 (83.6)
Yes[c]	2356 (26.4)	2216 (27.5)	140 (16.4)
Vaccine history			
COVID-19	8637 (97.0)	7816 (97.1)	821 (95.9)
Influenza	8572 (96.2)	7751 (96.3)	821 (95.9)
Smoking status			
Non-smoker	4134 (46.4)	3924 (48.7)	210 (24.5)
E-cigarette/cigarette/marijuana	288 (3.2)	274 (3.4)	14 (1.6)

Household Characteristics			
Household density			
Lives alone	30 (0.3)	28 (0.3)	2(0.2)
2-4 people	6797 (76.3)	6176 (76.7)	621 (72.5)
5+ people	2017 (22.6)	1792 (22.3)	225 (26.3)
Number of children			
No children	132 (1.5)	128 (1.6)	4 (0.5)
1 child	2274 (25.5)	2051 (25.5)	223 (26.1)
2-4 children	6382 (71.6)	5766 (71.6)	616 (72.0)
5+ children	56 (0.6)	51 (0.6)	5 (0.6)

[a]Percentages of missing data are not shown since variable missingness was <5%. A total of 2919 participants reported at least 1 illness episode. Out of 8908 illness episodes, 856 are associated with multiple virus detection in one swab (codetection), and 8052 are associated with single detection on day 0.

[b]Other comorbidities included sleep apnea, heart disease, congenital heart disease, heart failure, down syndrome, diabetes (high blood sugar), liver condition, weak or failing kidneys, cancer or malignancy, arthritis, stroke, deep vein thrombosis (DVT) or pulmonary embolism (PE), sickle cell disease or thalassemia, depression, anxiety, or thyroid issues. No participants reported any other health issues.

[c]Participants are categorized as having any comorbidities ("Yes") if they reported at least one of the following conditions: asthma, COPD, hypertension, immunocompromised status, sleep apnea, heart disease, congenital heart disease, heart failure, down syndrome, diabetes (high blood sugar), liver condition, kidney disease or failure, cancer or malignancy, arthritis, stroke, deep vein thrombosis (DVT) or pulmonary embolism (PE), sickle cell disease or thalassemia, depression, anxiety, or thyroid disorders.

[*]Comorbidities were self-reported at enrollment. Age, sex, race, smoking status, and vaccine history data were also obtained from the enrollment survey.

Supplementary Table 1. Distribution of viral detection status (single vs. codetection) within individual and household characteristic subgroups among symptomatic illness episodes.[a]

	Total (%)	Single Detection (%)	Codetection (%)
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2-4 children	6382 (71.6)	5766 (90.3)	616 (9.7)
5+ children	56 (0.6)	51 (91.1)	5 (8.9)

[a]Percentages of missing data are not shown since variable missingness was <5%. A total of 2919 participants reported at least 1 illness episode. Out of 8908 illness episodes, 856 are associated with multiple virus detection in one swab (codetection), and 8052 are associated with single detection on day 0.

[b]Other comorbidities included sleep apnea, heart disease, congenital heart disease, heart failure, down syndrome, diabetes (high blood sugar), liver condition, weak or failing kidneys, cancer or malignancy, arthritis, stroke, deep vein thrombosis (DVT) or pulmonary embolism (PE), sickle cell disease or thalassemia, depression, anxiety, or thyroid issues. No participants reported any other health issues.

[c]Participants are categorized as having any comorbidities ("Yes") if they reported at least one of the following conditions: asthma, COPD, hypertension, immunocompromised status, sleep apnea, heart disease, congenital heart disease, heart failure, down syndrome, diabetes (high blood sugar), liver condition, kidney disease or failure, cancer or malignancy, arthritis, stroke, deep vein thrombosis (DVT) or pulmonary embolism (PE), sickle cell disease or thalassemia, depression, anxiety, or thyroid disorders.

[*]Comorbidities were self-reported at enrollment. Age, sex, race, smoking status, and vaccine history data were also obtained from the enrollment survey.

Supplementary Table 1a. Symptoms characteristics by type of viral detection among symptomatic illness episodes.[a]

	Total (%)	Single Detection (%)	Codetection (%)
Symptom group			
Gastrointestinal symptoms [b]	896 (10.1)	818 (10.2)	78 (9.1)
Respiratory symptoms [c]	8535 (95.8)	7701 (95.6)	834 (97.4)
Systemic symptoms [d]	4126 (46.3)	3796 (47.1)	330 (38.6)
Multiple symptom groups [e]			
Gastrointestinal only	71 (0.8)	68 (0.8)	3 (0.4)
Respiratory only	4560 (51.2)	4066 (50.5)	494 (57.7)
Systemic only	213 (2.4)	198 (2.5)	15 (1.8)
Multiple symptom group	4054 (45.5)	3711 (46.1)	343 (40.1)
ARI[f] and CLI[g] symptoms			
Fever	1706 (19.2)	1541 (19.1)	165 (19.3)
Cough	4864 (54.6)	4338 (53.9)	526 (61.4)
Shortness of breath/difficulty breathing	516 (5.8)	479 (5.9)	37 (4.3)
Fatigue	2685 (30.1)	2483 (30.8)	202 (23.6)
Muscle or body aches	1390 (15.6)	1304 (16.2)	86 (10.0)
Headache	2190 (24.6)	2052 (25.5)	138 (16.1)
Loss of taste or smell	294 (3.3)	277 (3.4)	17 (2.0)
Sore throat	3742 (42.0)	3483 (43.3)	259 (30.3)
Congestion or runny nose	7142 (80.2)	6439 (80.0)	703 (82.1)
Nausea or vomiting	555 (6.2)	506 (6.3)	49 (5.7)
Diarrhea	482 (5.4)	446 (5.5)	36 (4.2)
Persistent pain/pressure in the chest	91 (1.0)	85 (1.1)	3 (0.4)
Pale, gray, or blue-colored skin, lips, or nail beds	26 (0.3)	25 (0.3)	1 (0.1)
Other	186 (2.1)	168 (2.1)	18 (2.1)

[a]Symptoms were recorded on the day of acute illness onset (day 0).

[b]Gastrointestinal (GI) symptoms consisted of nausea or vomiting, and diarrhea.

[c]Respiratory symptoms consisted of cough, shortness of breath, sore throat, and nasal congestion/runny nose.

[d]Systemic symptoms consisted of fever, fatigue, muscle or body aches, headache, loss of taste or smell, chest pressure, and blue-tinged skin.

[e]A total of 10 illness episodes included single non-categorized symptoms (e.g., phlegm, hand-foot-and-mouth disease, eye discharge/pink eye, rash, stomachache [distinct from nausea/diarrhea], numbness, sneezing, and scratchy throat) and were not assigned to the defined symptom categories.

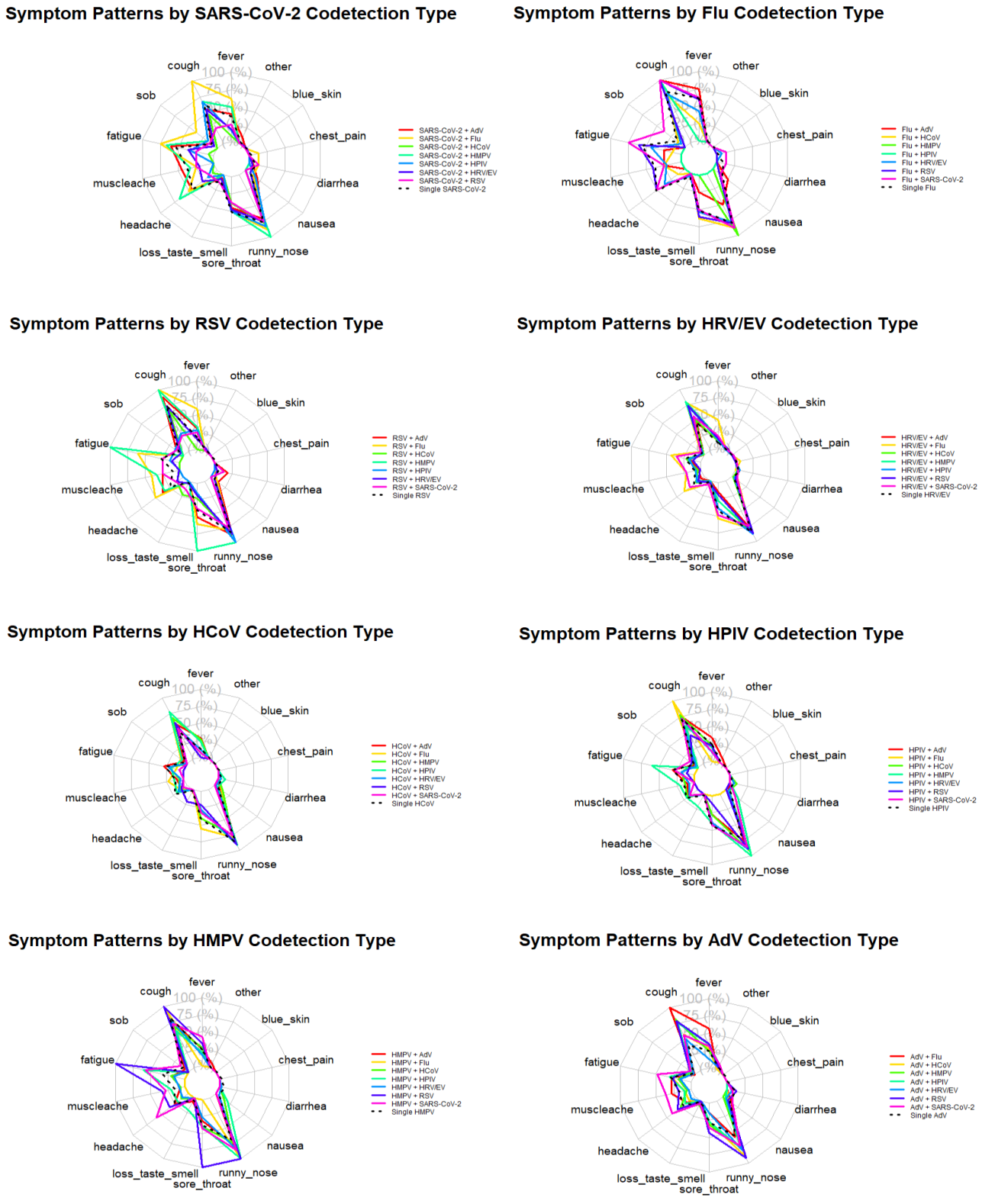
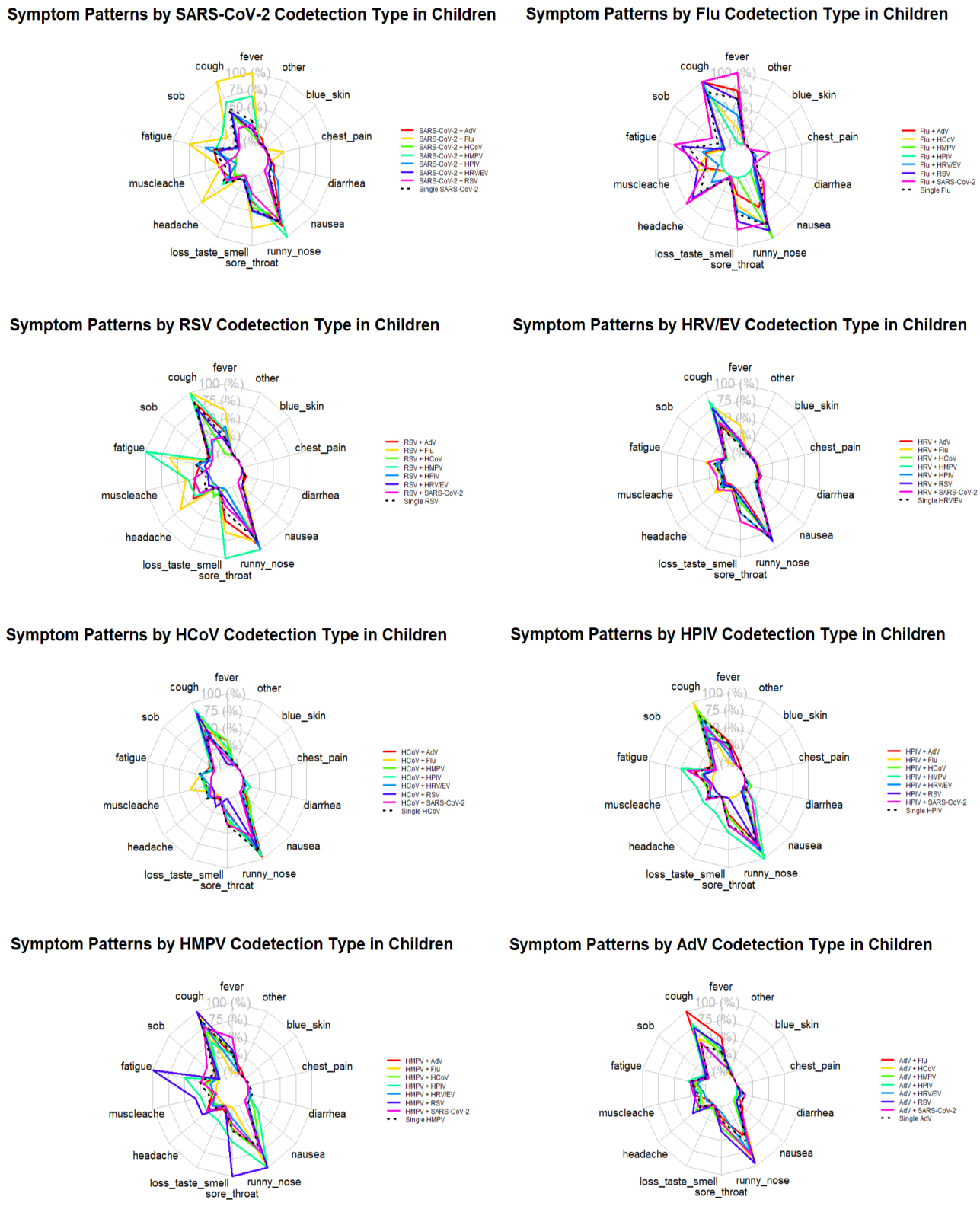
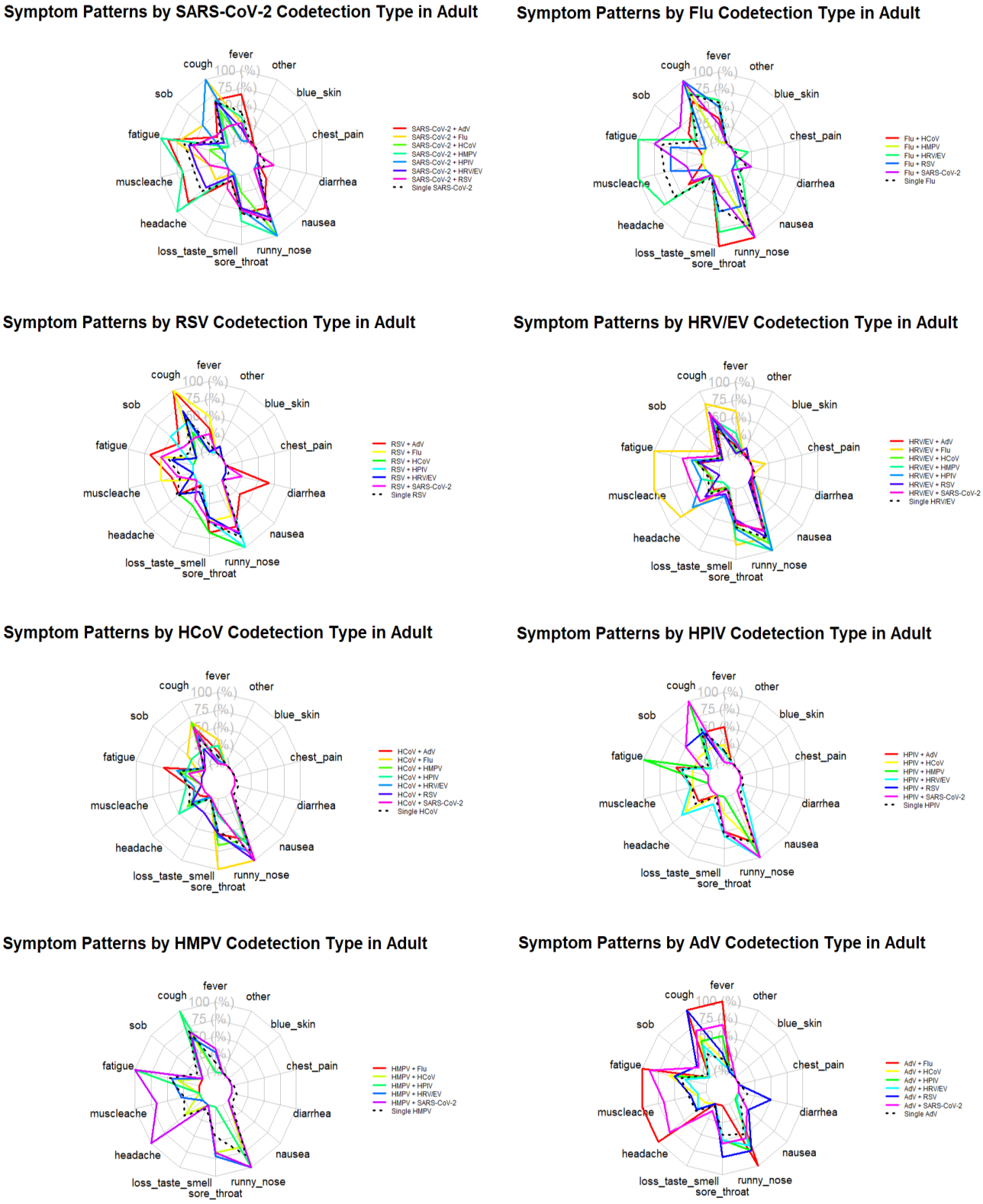


Figure 1. Symptom prevalence by type of viral detection among symptomatic illness episodes. *Proportions of symptomatic illness episodes reporting each symptom on day 0, stratified by viral detection type and by pathogen.* Abbreviations: SARS-2 = Severe Acute Respiratory Syndrome Coronavirus 2; Flu = Influenza A/B; RSV = Respiratory Syncytial Virus A/B; HRV/EV = Human Rhinovirus/Enterovirus; HCov = Human Seasonal Coronavirus; HPIV = Human Parainfluenza Virus, HMPV = Human Metapneumovirus; AdV = Adenovirus.



Supplementary Figure 1a. Symptom prevalence by type of viral detection among symptomatic illness episodes in children. *Proportions of symptomatic illness episodes reporting each symptom on day 0, stratified by viral detection type and by pathogen.*

Abbreviations: SARS-2 = Severe Acute Respiratory Syndrome Coronavirus 2; Flu = Influenza A/B; RSV = Respiratory Syncytial Virus A/B; HRV/EV = Human Rhinovirus/Enterovirus; HCov = Human Seasonal Coronavirus; HPIV = Human Parainfluenza Virus, HMPV = Human Metapneumovirus; AdV = Adenovirus.



Supplementary Figure 1b. Symptom prevalence by type of viral detection among symptomatic illness episodes in adult. *Proportions of symptomatic illness episodes reporting each symptom on day 0, stratified by viral detection type and by pathogen.*

Abbreviations: SARS-2 = Severe Acute Respiratory Syndrome Coronavirus 2; Flu = Influenza A/B; RSV = Respiratory Syncytial Virus A/B; HRV/EV = Human Rhinovirus/Enterovirus; HCov = Human Seasonal Coronavirus; HPIV = Human Parainfluenza Virus, HMPV = Human Metapneumovirus; AdV = Adenovirus.

Supplementary Table 1b. Distribution of viral detection type (single vs. codetection) by pathogen among symptomatic illness episodes.

	Total (%)	Single Detection (%)	Codetection (%)
Viral Pathogens			
SARS-CoV-2	1554 (17.4)	1416 (91.1)	138 (8.9)
Influenza A/B	417 (4.7)	356 (85.4)	61 (14.6)
RSV A/B	453 (5.1)	339 (74.8)	114 (25.2)
Rhinovirus/enterovirus[a]	4513 (50.7)	3902 (86.5)	611 (13.5)
Seasonal coronavirus	1239 (13.9)	994 (80.2)	245 (19.8)
Parainfluenza virus	620 (7.0)	461 (74.4)	159 (25.6)
Human metapneumovirus	339 (3.8)	253 (74.6)	86 (25.4)
Adenovirus	684 (7.7)	331 (48.4)	353 (51.6)

[a]Rhinovirus and enterovirus are grouped together in this analysis due to their close phylogenetic relationship; both are classified as distinct species within the *Enterovirus* genus (family *Picornaviridae*).
*Abbreviations: SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; RSV = Respiratory Syncytial Virus.

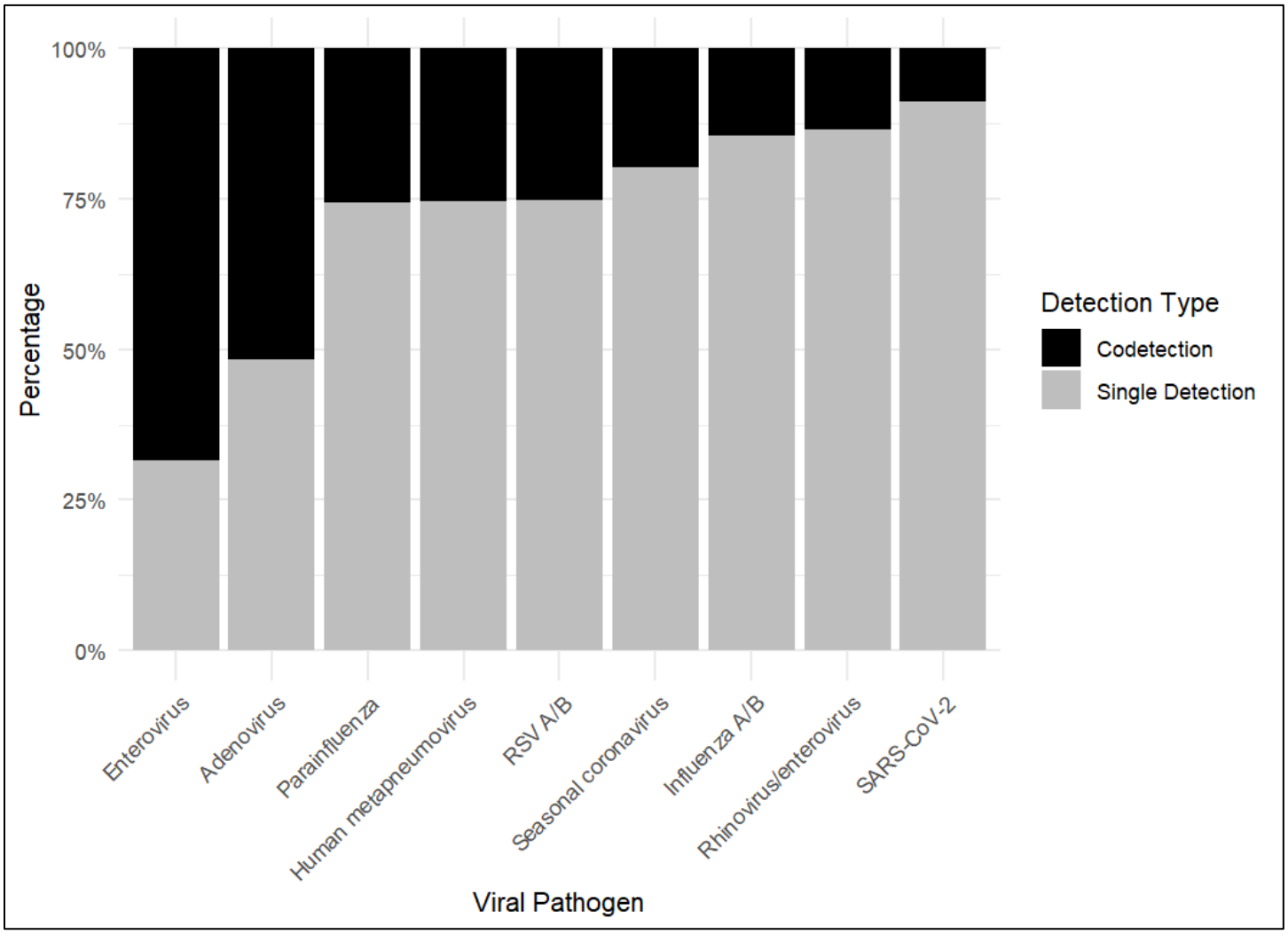


Figure 2. Proportion of single and codetection cases by viral pathogen among symptomatic illness episodes. *Each bar shows the percentage of symptomatic illness episodes with single-virus detection (light grey) versus codetection (black) for each viral pathogen.* Abbreviations: SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; RSV = Respiratory Syncytial Virus.

Table 2. The number of viral respiratory coinfection pairs among symptomatic illness episodes.[a]

Viral Pairs[b]	SARS-2	Flu	RSV	HRV/EV	HCoV	HPIV	HMPV	AdV
SARS-2	1416							
Flu	6	356						
RSV	7	10	339					
HRV/EV	72	25	55	3902				
HCoV	11	8	8	121	994			
HPIV	6	1	5	71	22	461		
HMPV	6	2	2	32	15	5	253	
AdV	20	4	16	190	39	29	16	331

[a]Each row represents a unique pair of viruses detected concurrently in the same symptomatic episode. Single detection for each type is highlighted in black.

[b]A total of 804 episodes (93.9%) had two viruses detected, 49 episodes (5.7%) had three, and 3 episodes (0.4%) had more than three viruses detected.

*Abbreviations: SARS-2 = Severe Acute Respiratory Syndrome Coronavirus 2; Flu = Influenza A/B; RSV = Respiratory Syncytial Virus A/B; HRV/EV = Human Rhinovirus/Enterovirus; HCov = Human Seasonal Coronavirus; HPIV = Human Parainfluenza Virus, HMPV = Human Metapneumovirus; AdV = Adenovirus.

Viral Pairs	SARS-2	Flu	RSV	HRV/EV	HCoV	HPIV	HMPV	AdV
SARS-2	91.1%	0.4%	0.5%	4.6%	0.7%	0.4%	0.4%	1.3%
Flu	1.4%	85.4%	2.4%	6.0%	1.9%	0.2%	0.5%	1.0%
RSV	1.5%	2.2%	74.8%	12.1%	1.8%	1.1%	0.4%	3.5%
HRV/EV	1.6%	0.6%	1.2%	86.5%	2.7%	1.6%	0.7%	4.2%
HCoV	0.9%	0.6%	0.6%	9.8%	80.2%	1.8%	1.2%	3.1%
HPIV	1.0%	0.2%	0.8%	11.5%	3.5%	74.4%	0.8%	4.7%
HMPV	1.8%	0.6%	0.6%	9.4%	4.4%	1.5%	74.6%	4.7%
AdV	2.9%	0.6%	2.3%	27.8%	5.7%	4.2%	2.3%	48.4%

Figure 3. Heat map of viral codetection pair frequencies by pathogen among 8908 acute illness episodes with codetection swab results on day 0. *Each row represents the proportion of illness episodes in which the virus listed in the row header was detected. The cells show the percentage of those episodes that were either single detections (diagonal cells) or codetections with another virus (off-diagonal cells). For example, among all SARS-CoV-2-positive episodes, 91.1% had SARS-CoV-2 detected alone, 0.4% were codetected with influenza virus, 0.5% were detected with RSV and 4.3% were codetected with HRV/EV.*

Abbreviations: SARS-2 = Severe Acute Respiratory Syndrome Coronavirus 2; Flu = Influenza A/B; RSV = Respiratory Syncytial Virus A/B; HRV/EV = Human Rhinovirus/Enterovirus; HCov = Human Seasonal Coronavirus; HPIV = Human Parainfluenza Virus, HMPV = Human Metapneumovirus; AdV = Adenovirus.

Table 3. Unadjusted and adjusted odds ratios for the association between codetection status and extended symptom period.[a]

	Extended symptom period		uOR (p)	95% CI	aOR (p)	95% CI
	No	**Yes**				
Codetection status						
Single detection	3894	2671	Ref.		Ref.	
Codetection	368	318	1.26 (0.004)	1.08, 1.48	1.15 (0.088)	0.98, 1.36
Age category (at enrollment)						
6mo - 1years	217	206			Ref.	
2-4 years	517	450			0.90 (0.380)	0.71, 1.14
5-11 years	1442	863			0.63 (0.001)	0.48, 0.83
12-17years	622	328			0.56 (0.001)	0.41, 0.75
18+ years	1452	1124			0.94 (0.705)	0.69, 1.28
D/S/J Attendance Status*						
No D/S/J	618	410			Ref.	
Daycare	398	402			1.45 (0.001)	1.17, 1.80
School	1960	1182			1.25 (0.028)	1.03, 1.52
Job	1214	934			0.99 (0.935)	0.80, 1.23
Job and school	45	19			0.65 (0.134)	0.36, 1.13
Any comorbidity						
No	3236	2146			Ref.	
Yes	1026	843			1.27 (0.001)	1.13, 1.43
COVID-19 vaccine history						
No	61	63			Ref	
Yes	4153	2883			0.71 (0.067)	0.49, 1.03
Influenza vaccine history						
No	98	77			Ref	
Yes	4116	2869			0.93 (0.665)	0.68, 1.28

[a]Extended symptom period was defined as having any new or remaining symptoms on day 7 of illness or as reported during the 1 Week Post Infection/Illness Follow-up Survey.
*Daycare/school/job attendance status.

Table 4. Unadjusted and adjusted odds ratios for the association between codetection status and medically attended illness.[a]

	Medically attended illness		uOR (p)	95% CI	aOR (p)	95% CI
	No	**Yes**				
Codetection status						
Single detection	5595	679	Ref.		Ref.	
Codetection	569	100	1.45 (0.001)	1.15, 1.81	1.38 (0.008)	1.08, 1.75
Age category (at enrollment)						
6mo - 1years	349	57			Ref.	
2-4 years	797	136			1.01 (0.963)	0.72, 1.43
5-11 years	2005	194			0.56 (0.008)	0.37, 0.86
12-17years	833	66			0.44 (0.001)	0.27, 0.72
18+ years	2153	324			0.83 (0.450)	0.52, 1.34
D/S/J Attendance Status*						
No D/S/J	878	97			Ref.	
Daycare	653	127			1.59 (0.006)	1.14, 2.23
School	2719	265			1.32 (0.105)	0.95, 1.85
Job	1806	272			1.12 (0.508)	0.81, 1.58
Job and school	54	9			1.52 (0.280)	0.67, 3.12
Any comorbidity						
No	4667	500			Ref.	
Yes	1497	279			1.82 (0.001)	1.51, 2.18
COVID-19 vaccine history						
No	113	10			Ref.	
Yes	5972	759			2.52 (0.030)	1.19, 6.50
Influenza vaccine history						
No	142	15			Ref.	
Yes	5943	754			1.12 (0.674)	0.67, 2.02

[a] Medically attended illness includes any clinical encounter such as outpatient clinic visit, emergency department visit, urgent care visit, or telehealth consultation related to the illness episode.
*Daycare/school/job attendance status.

Table 5. Unadjusted and adjusted odds ratios for the association between codetection status and absenteeism.[a]

	Absenteeism		uOR (p)	95% CI	aOR (p)	95% CI
	No	Yes				
Codetection status						
Single detection	4508	1766	Ref.		Ref.	
Codetection	496	200	1.09 (0.340)	0.91, 1.29	1.07 (0.440)	0.89, 1.29
Age category (at enrollment)						
6mo - 1years	314	92			Ref.	
2-4 years	649	284			1.53 (0.003)	1.16, 2.03
5-11 years	1569	630			1.52 (0.010)	1.11, 2.11
12-17years	664	235			1.32 (0.113)	0.94, 1.88
18+ years	1756	721			0.82 (0.328)	0.55, 1.22
D/S/J Attendance Status*						
No D/S/J	780	195			Ref.	
Daycare	532	248			1.59 (0.001)	1.24, 2.04
School	2150	834			1.21 (0.092)	0.97, 1.52
Job	1422	656			2.51 (0.001)	1.89, 3.36
Job and school	45	18			1.79 (0.052)	0.97, 3.16
Any comorbidity						
No	3722	1445			Ref.	
Yes	1255	521			1.06 (0.376)	0.93, 1.21
COVID-19 vaccine history						
No	91	32			Ref.	
Yes	4817	1914			1.09 (0.692)	0.72, 1.68
Influenza vaccine history						
No	103	54			Ref.	
Yes	4805	1892			0.74 (0.089)	0.52, 1.05

[a]Absenteeism, or work/school absenteeism, was defined as absence from work, school, or usual activities due to illness, as reported on day 14 during the 2 Week Post Infection/Illness Follow-up Survey.
*Daycare/school/job attendance status.

Table 6. Adjusted odds ratios for associations of coinfection compared to mono-infection on measures of clinical severity, stratified by the selected illness type (SARS-CoV-2, Influenza, RSV)

	Extended symptom period			Medically attended illness			Absenteeism		
	Mono.	**Co.**	**aOR [95% CI]**	**Mono.**	**Co.**	**aOR [95% CI]**	**Mono.**	**Co.**	**aOR [95% CI]**
Overall[a]	2671	318	1.15 [0.98-1.36]	679	100	1.38 [1.08, 1.75]	1766	200	1.07 [0.89, 1.29]
SARS-2	464	51	1.32 [0.83-2.10]	158	12	0.69 [0.34, 1.33]	467	51	0.80 [0.50, 1.27]
Flu A/B	145	24	1.05 [0.55, 2.03]	51	7	0.81 [0.31, 1.88]	126	17	0.77 [0.38, 1.51]
RSV A/B	146	45	0.87 [0.52, 1.45]	49	11	0.58 [0.26, 1.21]	80	23	0.86 [0.47, 1.53]

*aORs were adjusted for age, daycare/school/job attendance status, comorbidities, and vaccination history.
**Abbreviations: Mono. = single viral detection; Co. = codetection; aOR = adjusted odds ratio; SARS-2 = Severe Acute Respiratory Syndrome Coronavirus 2; Flu = Influenza A/B; RSV = Respiratory Syncytial Virus.

Table 7. Adjusted odds ratios for associations of coinfection compared to mono-infection on measures of clinical severity, stratified by the selected populations (pediatric (<18 years) vs. adult (18+)).

	Extended symptom period			Medically attended illness			Absenteeism		
	Mono.	**Co.**	**aOR [95% CI]**	**Mono.**	**Co.**	**aOR [95% CI]**	**Mono.**	**Co.**	**aOR [95% CI]**
Overall[a]	2671	318	1.15 [0.98-1.36]	679	100	1.38 [1.08, 1.75]	1766	200	1.07 [0.89, 1.29]
Pediatric	1599	266	1.27 [1.06-1.53]	370	85	1.53 [1.17, 1.99]	1087	158	1.05 [0.86, 1.29]
Adult	1072	52	0.84 [0.58, 1.20]	309	15	0.94 [0.52, 1.59]	679	42	1.17 [0.79, 1.71]

*aORs were adjusted for age, daycare/school/job attendance status, comorbidities, and vaccination history.
**Abbreviations: Mono. = single viral detection; Co. = codetection; aOR = adjusted odds ratio; Pediatric = Illness episodes from individual aged <18 years; Adult = Illness episodes from individual aged 18+ years.

Table 8. Sensitivity analysis for the adjusted odds ratios and 95% confidence intervals of coinfection compared to mono-infection on three measures of clinical outcome, excluding all cases of rhinovirus (HRV).

	Extended symptom period	Medically attended illness	Absenteeism
Non-HRV/EV Mono.	1402	439	1070
Non-HRV/EV Co.	93	25	63
aOR (95% CI) *	1.27 [0.93, 1.72]	0.92 [0.58, 1.41]	0.97 [0.70, 1.34]

*aORs were adjusted for age, daycare/school/job attendance status, comorbidities, and vaccination history.
**Abbreviations: HRV/EV = Human Rhinovirus/Enterovirus; Mono. = single viral detection; Co. = codetection; aOR = adjusted odds ratio.