Title: Common human coronaviruses seem at least as severe as influenza in patients hospitalized with acute respiratory infection: results from 8-year hospital-based surveillance in Quebec, Canada

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Summary

Common human coronaviruses were less frequent than influenza in children and adults with respiratory hospitalizations but generated significant morbidity. Length-of-stay, intensive-care admissions and case-fatality ratio in patients hospitalized with HCoV monoinfections were comparable to influenza monoinfections.

Footnote page

Conflict of interest statement

RG has received research grants from Sanofi Pasteur for an unrelated study. GDS has received investigator-initiated grants from Pfizer and received paid expert testimony from the Ontario Nurse Association, the Quebec Ministry of justice and GlaxoSmithKline (GSK). Other authors have no financial relationships or conflicts of interest relevant to this article to disclose.

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Abstract:

Background Few data exist about the role of common human coronaviruses (HCoV) in patients hospitalized for acute respiratory illness (ARI) and the severity of these infections compared to influenza.

Methods Prospective data on virus etiology of ARI hospitalizations during the peaks of 8 influenza seasons (2011-12 to 2018-19) in Quebec, Canada, was used to compare patients with HCoV to those with influenza infections; generalized estimation equations models were used for multivariate analyses.

Results We identified 340 HCoV infections which affected 11.6%(n=136) of children and 5.2%(n=204) of adults hospitalized with ARI. The majority of children (75%) with HCoV infections were also coinfected with other respiratory viruses compared to 24% of the adults (p<0.0001). No deaths were recorded in children; 5.8% of adults with HCoV monoinfection compared to 4.2% of those with influenza monoinfection died (p=0.226). The risk of pneumonia was non-significantly lower in children with HCoV than with influenza but similarly high in adults. Markers of severity (length-of-stay, intensive-care admissions and case-fatality ratio) were comparable between these infections in multivariate analyses, both in children and adults.

Conclusions In children and adults hospitalized with ARI, HCoV infections were less frequent than influenza infections, but HCoV monoinfections were as severe as influenza monoinfections.

Key words: common coronaviruses, influenza, respiratory hospitalization, children, adults, severity, case-fatality ratio, coinfections

Introduction

The emergence of novel coronaviruses associated with severe disease in different animal species has brought to attention the need to better understand characteristics of human coronaviruses (HCoV). The first human coronaviruses (HCoV) were described in the 1960s in patients with common colds (1). They were not considered highly pathogenic to humans until the outbreaks of severe acute respiratory syndrome (SARS) in 2002-03 (2), the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 (3), and recently the novel coronavirus SARS-CoV-2 associated with the current COVID-19 pandemic (4). While much attention has been focused on these highly pathogenic coronaviruses, little is known about the role of the common HCoV subtypes, despite their wide circulation in humans. Two common HCoV (the HCoV-229E (alphacoronavirus) and the HCoV-OC43 (betacoronavirus, lineage A)) were discovered in the mid-1960s, two other HCoV (the HCoV-NL63 (alphacoronavirus) and the HKU1 (betacoronavirus, lineage A)) were discovered in the mid-2000s(5,6). Along with rhinoviruses, HCoV are the most frequently identified viruses in all age categories, with HCoV more frequent that rhinoviruses in adults; acute respiratory infection (ARI) caused by these viruses are least likely to be medically attended compared to other respiratory viruses (7). Patients infected with HCoV are also less likely to be hospitalized than patients infected with other respiratory viruses (8). However, the role of common HCoV subtypes in severe infections leading to hospitalization is less known, especially in adults, as few long-term multicenter studies describing characteristics of patients hospitalized with confirmed HCoV have been published and most of them focused on children. Despite increasing awareness of the role of other respiratory viruses (ORV) in respiratory morbidity in hospitalized patients, most reports continue to focus on influenza. To our knowledge, none of them compared HCoV and influenza infections directly.

The objective of this study was to compare severe outcomes in children (<18 years) and adults hospitalized with HCoV monoinfection to those of patients hospitalized with influenza monoinfection from a prospective hospital-based surveillance during 8 years in Quebec, Canada.

Method

Study Population

The study design has been described in detail elsewhere(9). In brief, four regional hospitals (2 community, 2 academic/tertiary; all four serving both children and adults) with a catchment area of nearly 10% of the Quebec population (approximately 8.4 million) participated in the surveillance during eight influenza seasons from 2011-12 to 2018-19. All patients presenting to their emergency department with ARI were systematically swabbed during high influenza activity weeks, as part of the standard of care during the influenza season.

Eligible patients were those admitted for ≥24 hours with cough and fever/feverishness in 2011-12, and with cough or sore throat or fever/feverishness in absence of other identifiable cause starting in 2012-13. After obtaining an informed consent (signed the first 3 years and verbal in subsequent years), research nurses collected demographic and clinical details from the patient or legal representative on a standardized questionnaire and reviewed patients' charts at discharge for additional clinical information. Influenza vaccination status was self-reported, as collected by nurses in face-to-face interviews. Specimens from all eligible patients were sent to the provincial public health laboratory (LSPQ) and tested with a multiplex PCR assay.

Surveillance period

The surveillance period started when the positivity rate for influenza in respiratory specimens from the provincial hospital-based sentinel laboratory surveillance had been ≥15% for two consecutive weeks and stopped the week after this rate dropped below 15% or when the planned sample size for the season was achieved (800-1000 specimens depending on the season). During the various seasons, the surveillance period varied between 8 and 12 weeks (Supplementary Figure 1). The provincial hospital-based sentinel laboratory surveillance system includes >40 laboratories across the province of Quebec testing >100,000 respiratory specimens per year.

Laboratory Analysis

Nasal specimens collected on flocked swabs were tested at LSPQ using the Luminex® NxTAG Respiratory Pathogen Panel assay which detects influenza A (subtypes H3 and H1), influenza B, respiratory syncytial virus (RSV) A and B, human parainfluenza viruses 1, 2, 3, and 4 (hPIV), human metapneumovirus (hMPV), common human coronaviruses (HCoV) NL63, HKU1, 229E, and OC43, enterovirus/rhinovirus (not differentiated), adenovirus, bocavirus, and 3 bacteria (M. pneumoniae, C. pneumoniae et L. pneumophila). Results of multiplex tests were faxed to participating hospitals within 24–48 hours of specimen receipt.

Statistical Analysis

Characteristics and outcomes of patients were compared by using the Fisher exact test (proportions) and the Kruskal-Wallis test for non-parametric variables (such as lengths of stay (LOS) and age). Patients with influenza and HCoV co-infections were excluded from all comparisons between HCoV infection (cases) vs influenza infection (controls).The severity of HCoV infection was assessed by comparing the following outcomes to influenza infection: pneumonia, LOS, intensive-care unit (ICU) admission and in-hospital

death. Generalized estimation equations (GEE) models with a binomial distribution and logit link were used for all outcomes with the exception of LOS. Due to the skewed LOS distribution, a negative binomial distribution with a log link was assigned to the GEE model for this outcome (10). In children, only pneumonia and LOS were assessed in the multivariate analysis due to the limited number of observations for ICU admissions and absence of deaths; models were adjusted for age (0-5 months, 6-23 months, 2-4 years, 5-17 years), sex, comorbidity (yes or no), and influenza vaccination. The influenza vaccination status was defined as: 1) vaccinated if seasonal influenza vaccination had been received ≥14 days before symptom onset, 2) not vaccinated if no vaccine had been administered or if it was received <14 days before symptom onset, 3) unknown if vaccine receipt or timing were not reported. The proportion of vaccinated individuals among influenza-negative individuals (controls) was similar across the various seasons.

In adults, models were adjusted for age (18-64, 65-74, 75-84, and ≥85 years), sex, admission from community or other institutions (long-term care facility (LTCF) or nursing home), comorbidity (chronic respiratory disease, cardiovascular disease, other comorbidity or no comorbidity), season, and influenza vaccination as fixed effect variables. Hospital was included as a random effect variable to take into account the correlation between subjects recruited at the same hospital, including those who may have been recruited in more than one season. Multivariate analyses were performed 1) by including HCoV coinfections (with viruses other than influenza) and influenza coinfections (with viruses other than HCoV) as covariates; and 2) by restricting the analysis to HCoV monoinfection and influenza monoinfection. The impact of the circulating strain of influenza was taken into account by adjusting for the season and for the receipt of influenza vaccine in the multivariate analyses. The association between HCoV subtype and severity outcomes was also explored.

Ethics

Institutional Review Board approval was obtained from all participating hospitals for the first 3 years; a waiver was obtained for the following years when the project was conducted as a surveillance project and only verbal consent was required.

Results

Among the 5,104 patients hospitalized with ARI included in the analysis, 3,539 (69.3%) were positive for at least one virus. Influenza was detected in 35.9% (n=1,831) overall (22.9%, n=268 in children <18 years and 39.7%, n=1,563 in adults) and HCoV in 6.7% (n=340) overall (11.6%, n=136 in children and 5.2%, n=204 in adults) (Table 1). Proportion of influenza detection increased from 12.3% in 0-5-month-olds to 43.8% in 5-17-year-olds; it remained at similar levels in different adult age groups (38.0% to 40.6%) (Figure 1). In contrast, the proportion of HCoV was the highest in 0-5 months (12.7%) and 6-23 months (14.5%); it decreased 2-3-fold in the next age groups (2-4 years, 5.8%; 5-17 years, 7.4%) and remained at comparable level in all examined adult age groups (4.5% to 5.9%) (Figure 1). Over eight seasons, overall detection rate ranged from 21.6% to 50.7% for influenza and from 2.7% to 10.4% for HCoV. For influenza, 85% were influenza A (59% A(H3N2), 24% influenza A(H1N1)) and 15% influenza B.

Among the 136 HCoV-infected children, 84.5% were <2-year-old, 75% (n=102) were co-infected with another virus (Table 1, Figure 1). Most (77.5%) HCoV coinfections were with one other virus but 17.6% were with two and 4.9% with three viruses. Viruses most frequently contributing to HCoV coinfections in children were: RSV (55.9%), influenza and hMPV (15.7% each), and entero/rhinoviruses (13.7%) (Supplementary Table 1, Figure 2). The most frequent HCoV coinfections by age were: HCoV/RSV in 0-5

month-olds (73.5%) and in 6-23-month-olds (50.9%); HCoV/hMPV and HCoV/influenza (33.3% each) in 2-4-year-olds; and HCoV/influenza (66.7%) in 5-17-year-old children.

In contrast to HCoV infections, about half (54.5%) of influenza in children was detected in <2-year-olds and only 34.0% (n=91) were co-infections (Table 1, Figure 1). Most (77.2%) influenza coinfections were with one other virus; 18.2% were with two and 4.5% with three viruses. Viruses most frequently contributing to influenza coinfections in children were: entero/rhinoviruses (27.5%), followed by RSV (25.3%), bocavirus (22.0%), HCoV (17.6%) and hMPV (14.3%) (Supplementary Table 1, Figure 2). The most frequent influenza coinfections by age were: influenza/RSV coinfection in 0-5 month-olds (60.0%) and in 6-23-month-olds (21.7%); influenza /entero/rhinoviruses (22.2%) in 2-4-year-olds and influenza/HCoV (44.4%) in 5-17-year-old children.

Children with HCoV monoinfections were younger than those with influenza monoinfections (median age, 6 months vs 2 years (p<0.0001) and had half the risk of radiologically-confirmed pneumonia (11.8%, n=4 vs 22.0%, n=39), however this difference did not reach statistical significance (p=0.127)(Table 1). Overall 14.8% of children had at least one comorbidity (76% asthma), with no difference (p>0.05) across examined subgroups (Table 1). There was no difference in the LOS (median 2 days, p=0.78) and admission to ICU **(**0% vs 1.1%, p=0.70**)** in children with HCoV and influenza monoinfections (Table 1). Only 3 children with influenza (1 coinfected with entero/rhinovirus) and 4 children with HCoV (all coinfected: 2 with RSV, 1 with entero/rhinovirus and 1 with hMPV) were admitted to ICU and no deaths were recorded (Table 1). When comparing HCoV monoinfection to coinfection, there were no differences in LOS, admission to ICU and case-fatality ratio (CFR) (Table 1). Children with HCoV coinfections compared to monoinfections had almost 3 times more pneumonia (31.4%, n=32 vs 11.8%, n=4, p=0.018).

The majority of HCoV infections in adults were mono-infections (76.0% (155/204) compared to 25.0% (34/136) in children, p<0.0001) (Table 1, Figure 1). HCoV coinfections in adults involved influenza (46.9%), RSV and hMPV (22.5% each), and entero/rhinoviruses (17.3%)(Supplementary table 1, Figure 2). Most (87.8%) HCoV coinfections were with one other virus and 12.2% were with two viruses.

There was no difference in the age of adult patients with HCoV and influenza monoinfections (median age, 75 vs 74 years, p=0.34). The proportion of patients with at least one comorbidity was similar in HCoV- and influenza-monoinfected patients (84.0% vs 88.4%, p=0.16). However more patients with HCoV monoinfection had chronic respiratory disease (60.7% vs 46.9%, p=0.0013) and chronic cardiovascular disease (58.7% vs 44.9%, p=0.0059); no differences were detected for the other examined chronic conditions (Table 1). There was no difference between HCoV- and influenza-mono-infected adult patients for LOS, pneumonia, ICU admission and in-hospital mortality (Table 1). Among HCoV monoinfected patients ≥65 years, 7.4% were admitted to ICU and 7.4% died compared to 6.4% ICU admissions and 5.6% deaths in influenza-monoinfected patients (p>0.05 for both comparisons). Mortality increased with age in adults with both HCoV monoinfection (from 2.1% in 18-64-year-olds to 12.5% in ≥85-year-olds, overall 5.8%) and influenza monoinfection (from 0.7% in 18-64-year-olds to 7.9% in ≥85-year-olds, overall 4.2%). Similar increase with age was detected when coinfections were included (Supplementary table 2). Overall 5.8% of adults with HCoV monoinfection died compared to 4.2% of those with influenza monoinfection (p=0.226); there was also no difference in LOS, pneumonia, and ICU admission (all P>0.05) (Table 1). When comparing HCoV mono- to co-infection in adults, there was no difference in LOS (median 6 vs 7 days), pneumonia (37.4% vs 34.7%), ICU admission (10.3% vs 4.1%) and CFR (5.8% vs 4.1%) (all p>0.05).”

In the multivariate analyses, the LOS and frequency of pneumonia in HCoV monoinfected children were not statistically different from those in influenza monoinfected children, both when coinfections were used as a co-variate and in the analysis restricted to monoinfections (Table 2). Increasing age was associated with greater risk of pneumonia. HCoV coinfection with ORV (excluding influenza) was an independent risk factor for pneumonia (adjusted odd ratio (aOR) =2.83 (95%CI: 1.80 – 4.46)). In adults, the severity of HCoV mono-infection was not statistically different from that of influenza monoinfection as evidenced by the LOS, risk of pneumonia, ICU admission, and CFR (Table 2). Increasing age was associated with longer LOS, pneumonia and death but lower risk of ICU admission. Cardiovascular disease was associated with increased risk of ICU admission and death, decreased risk of pneumonia and shorter LOS. Coinfection with another respiratory virus (excluding influenza) was not associated with the severity of HCoV infections. Similar results were obtained when restricting the analysis to mono-infections (Table 2).

In all seasons and all age groups, the most frequently detected subtype was the HCoV-OC43 (55.6%, n=189), followed at almost equal frequencies by HKU1 (15.6%, n=53), NL63 (14.7%, n=50) and 229E (12.9%, n=44)). Four patients (1.2%) were coinfected with OC43 and HKU1. HCoV-NL63 affected less often young adults aged 18-64 years (13.6%) than HCoV-229E and HCoV-HKU1 (respectively 41.2% (p=0.027) and 45.2% (p=0.015)). HCoV-229E was associated to higher risk of pneumonia (50.0%) as compared to HCoV-HKU1 (22.6%, p=0.020 (Supplementary table 3)).

Discussion

To our knowledge, this 8-year prospective study reports one of the largest series of HCoV-confirmed hospitalized pediatric and adult patients. HCoV infection was less frequent than influenza infection in

patients hospitalized with acute respiratory illness, and occurred more frequently as a co-infection compared to influenza, both in children (75% vs 34%) and in adults (24% vs 10%). The severity of HCoV monoinfection was comparable to influenza monoinfection, both in children and in adults.

The study was conducted during the peak of influenza seasons and was therefore not designed to quantify the proportional burden of each respiratory virus. HCoV has a winter seasonal distribution with year-to-year and subtype variations (11–14). Consequently, the proportion of HCoV detected in this study may not be representative of the entire winter season or of the relative burden of each HCoV subtype. Nevertheless, our results are comparable to other studies in patients hospitalized for ARI, where HCoV was detected in 2.1% - 5.7% in overall population (12,15–17) and 3.2% to 11.8% in adult patients (13,18,19). Similar to our study, the detection of HCoV in hospitalized children decreased with increasing age, from 14% in children <2 years (20) to 11% in children <3 years (21) , 7.6% in children <5 years (14), and 4.3% to 5.5% in children <18 years (11,22,23). Our observation that HCoV-OC43 was the most often detected subtype (56%) both in the pediatric and adult population is also similar to findings elsewhere (12–14,17,20–22,24).

The important number of HCoV coinfections, especially in children, limited the number of HCoV and influenza monoinfections and consequently the power to detect significant differences between the two monoinfections. Also, there was insufficient sample size to assess ICU admission and deaths in children. In adults, LOS, the frequency of pneumonia, ICU admission and CFR in patients with HCoV monoinfections were not statistically different from influenza monoinfections. It is difficult to compare these results to other studies since no study compared directly HCoV to influenza. In one study from Southern Brazil conducted during one season (2012-2013), the CFR was 9% among the 34 HCoV-infected

patients (all ages included) compared to 6% in 410 patients infected with ORV, including 38 with influenza(25). Few data describing HCoV severity in hospitalized patients exists in the literature. One study reported that younger age (<2 years) and presence of comorbidity were associated with severity in hospitalized children <18 years with ARI, but this population was mostly Latino/Hispanic, publically insured, and under active surveillance for respiratory illness(26) , and as such not representative of the general pediatric population. The frequency of ICU admissions in patients ≥65 years in our study (7.1%) was lower than in the study of Walsh et al where only 2 HCoV subtypes (OC43 and 229 HCoV) were detected (14.1%), while the case-fatality ratio (7.2%) was higher than in that study (4.2%)(13). Variability in these results might be a reflection of the population included in each study, patient management strategies or the differences in the distribution or detection of HCoV subtypes which may be associated with different degrees of severity. It is of note that in our study the proportion of adult patients admitted from LTCF was comparable between patients with influenza monoinfection (11.2%) and HCoV (9.7%) monoinfection. This is in line with other studies reporting significant morbidity associated with HCoV in LTCF residents, with a clinical picture often mimicking influenza (27,28).

The proportion of HCoV coinfections in children (75%) and in adults (24%) in our study is at the upper limit of what was reported in children (36%-78%) (11,14,21,22) and similar to the findings in adults (25%-26%) (13,25). The role of coinfections in increasing respiratory infections severity remains unclear(29,30). This may be explained by different viral combinations across seasons, age groups, specific populations, geographical region, specific viral or host interactions, or different criteria of severity. In our study, HCoV coinfection with ORV (excluding influenza) was associated with greater risk for pneumonia compared to HCoV infection alone. A greater severity (longer LOS and greater risk of pneumonia/bronchiolitis diagnosis) was also reported in children <5 years coinfected with HCoV and ORV compared to HCoV alone(14) ; and a higher risk of ICU admission in children <3 years coinfected

with HCoV and rhinovirus C compared to other respiratory infections(21). In the context of the current COVID-19 pandemic, it seems important to understand the role of coinfections. In a recent review and meta-analysis of patients hospitalized with COVID-19 during the early period of the pandemic (1 January 2020 to 17 April 2020), the pooled proportion of patients hospitalized with COVID-19 and also co-infected with another respiratory virus was 3% (varying between 0% and 25%), with RSV and influenza A being most frequent (31). This review however did not assess the association between coinfections and the severity of COVID-19, a topic that will be especially relevant during the coming winter season.

There was a higher proportion of patients with chronic respiratory and chronic cardiovascular disease in adults with HCoV compared with those with influenza. Cardiovascular disease and chronic respiratory disease were also identified as risk factors for severe COVID-19 in a recent estimation based on data from 188 countries(32). Cardiovascular disease was associated with increase in the incidence and in the severity of SARS-CoV in general and SARS-CoV-2 in particular(33). Some hypotheses have been proposed in relation to the angiotensin-converting enzyme 2 (ACE2), one of the receptors of SARS-CoV and SARS-CoV-2 on the human host cell surface (including the heart and human alveolar epithelial cells)(34,35). The specific underlying conditions associated with increased severity of COVID-19, as well as the underlying mechanisms for increased susceptibility and severity in some patients are yet to be established(33). The comorbidity differences detected between patients with common HCoV and influenza in our study suggest that there may be differences in the risk factors associated with HCoV (and potentially with SARS-CoV-2) as compared to influenza and there is a need to assess the underlying health conditions specific for COVID-19 in order to identify individuals most at-risk.

The main limit of our study is the recruitment done only during peak weeks of influenza seasons which may have contributed to an underestimation of overall HCoV contribution to hospitalizations and inaccurate estimation of the relative contribution of each HCoV subtype. However, this limitation does not impact the analysis of comparative outcome severity between influenza and HCoV. Second, the total number of HCoV and influenza infections in the overall population were not available. If the proportion of mild cases is higher among patients with HCoV than in patients with influenza, the analyses including only hospitalized patients would overestimate the overall severity of HCoV vs influenza. As such, the results of this study apply only to hospitalized patients. Third, the sample size for some of the severity outcomes, especially in children, was limited mainly due to the important proportion of coinfections. However, the number of patients with HCoV in our study (n=340) including both pediatric and adult populations during 8 years is, to our knowledge, one of the largest published to date. Most of the published studies describing hospitalized patients had a smaller sample size, with the number of patients hospitalized for ARI ranging from 294 for all ages(17), to 96 in seniors (13) and to 489 in children (22). Also, many of them did not test systematically for ORV or used a limited number of viral targets and therefore some described HCoV infections may in fact have been coinfections with other viruses. In addition, these studies did not compare outcomes of HCoV-infected patients to influenza-infected patients.

In conclusion, our data suggest that in patients with respiratory hospitalizations, HCoV infection are less frequent than influenza but generate significant morbidity. HCoV monoinfections are not less severe than influenza monoinfections in children and in adults.

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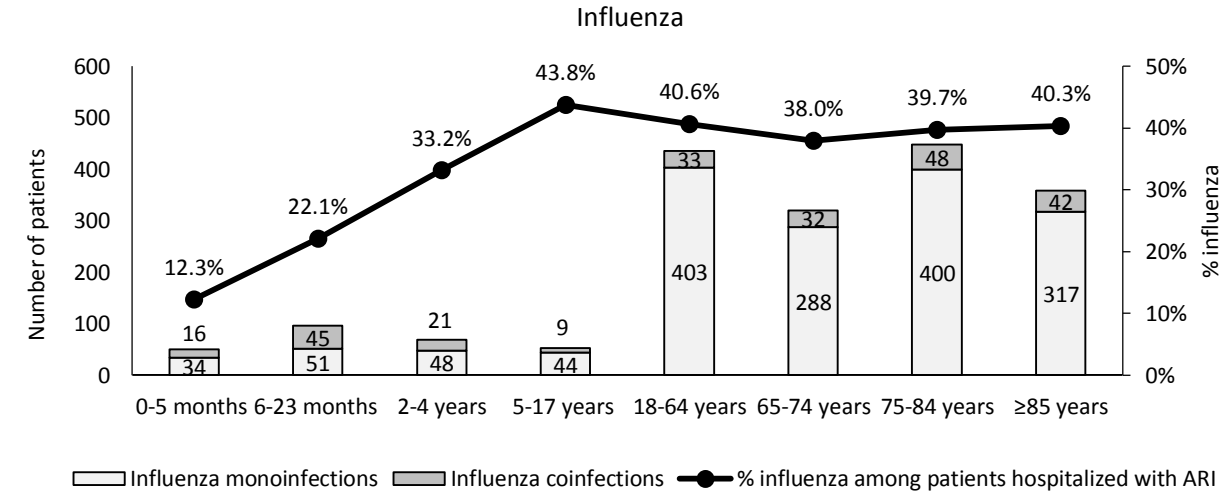
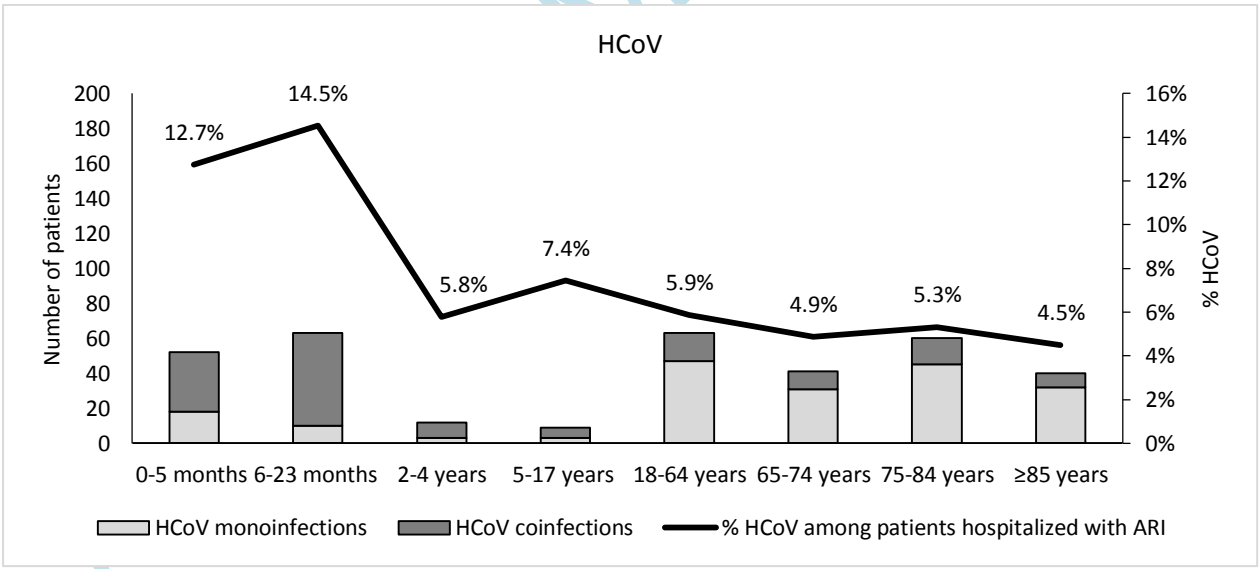
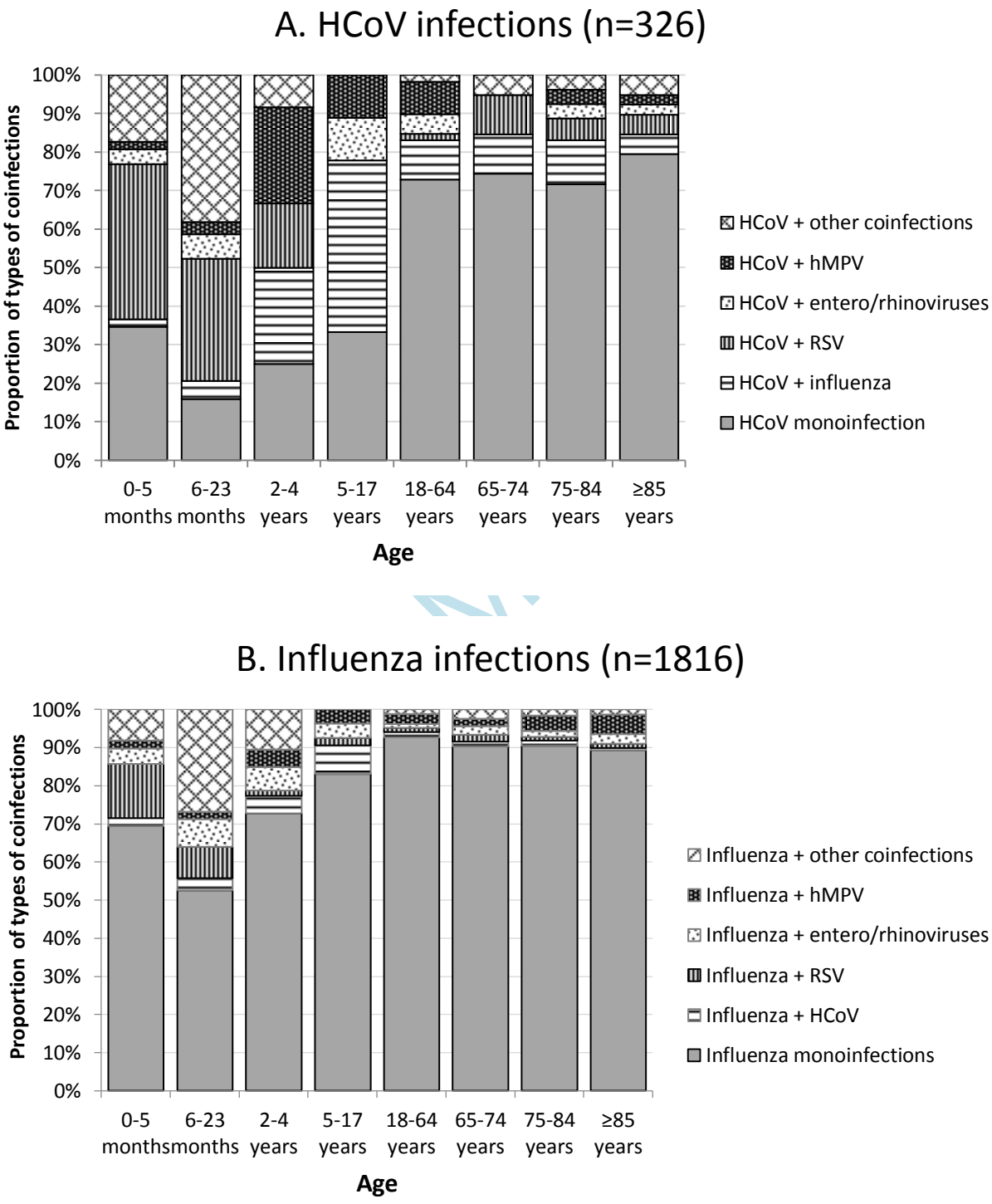
Figure 1 Number of patients hospitalized with influenza and HCoV mono- and coinfections and proportion of influenza and HCoV detection among patients admitted with acute respiratory infection during the peak of influenza seasons, Quebec 2011-12 to 2018-19





HCoV-common human coronavirus; ARI: acute respiratory infections; Influenza coinfections: coinfections with any other respiratory virus, including HCoV; HCoV coinfections: coinfections with any other respiratory virus, including influenza

Figure 2 Distribution of different types of coinfections in patients hospitalized with acute respiratory infections



Abbreviations: HCoV= human coronavirus; hMPV=human metapneumovirus; RSV= respiratory syncytial virus

Note: presented are monoinfections and pairs of viruses; infections with 3 or more viruses are included in the "HCoV+other coinfections" and "Influenza+other coinfections" category

Table 1 Characteristics of patients hospitalized with respiratory infections, influenza and HCoV infections and coinfections during the peaks of influenza seasons, Quebec 2011-12 to 2018-19

	All respiratory hospitalizations	Influenza			HCoV			HCoV + Influenza
		All	Mono-infections	Co-infections with any virus[a]	All	Mono-infections	Co-infections with any virus[a]	
TOTAL	5,104	1,831	1,585	246	340	189	151	39
Children	1,171	268 (14.6)	177	91	136 (40.0)	34	102	16
Sex (% female)	546 (46.6)	124 (46.3)	86 (69.4)	38 (30.7)	54 (39.7)	13 (38.2)	41 (40.2)	5 (31.3)
Age 0-5 months (%)	408 (34.8)	50 (18.7)	**34 (19.2)**	16 (17.6)	52 (38.2)	**18 (52.9)**[b]	34 (33.3)	2 (12.5)
6-23 months (%)	434 (37.1)	96 (35.8)	**51 (28.8)**	45 (49.5)	63 (46.3)	**10 (29.4)**	53 (52.0)	7 (43.8)
2-4 years (%)	208 (17.8)	69 (25.8)	**48 (27.1)**	21 (23.1)	12 (8.8)	**3 (8.8)**	9 (8.8)	3 (18.8)
5-17 years (%)	121 (10.3)	53 (19.8)	**44 (24.9)**	9 (9.9)	9 (6.6)	**3 (8.8)**	6 (5.9)	4 (25.0)
Comorbidity (%)	173 (14.8)	54 (20.2)	34 (19.2)	20 (22.0)	23 (16.9)	3 (8.8)	20 (19.6)	6 (37.5)
Influenza vaccine[c] (%)	133 (11.8)	29 (11.3)	14 (8.2)	15 (17.4)	13 (10.0)	3 (9.1)	10 (10.3)	2 (13.3)
LOS in days, median (IQR)	2; 2-3	2; 2-3	2; 2-3	2; 2-3	2; 2-3	2; 2-3	2.5; 2-4	3; 2-4
Pneumonia[d] (%)	356 (30.4)	67 (25.0)	39 (22.0)	28 (30.8)	36 (26.5)	4 (11.8)	32 (31.4)	3 (18.8)
ICU (%)	23 (2.0)	3 (1.1)	2 (1.1)	1 (1.1)	4 (2.9)	0 (0.0)	4 (3.9)	0 (0.0)

Death (%)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adults	3,933	1,563 (85.4)	1,408	155	204 (60.0)	155	49	23
Sex (% female)	2179 (55.4)	874 (55.9)	783 (55.6)	91 (58.7)	108 (52.9)	80 (51.6)	28 (57.1)	11 (47.8)
Age 18-64 years (%)	1,073 (27.3)	436 (27.9)	403 (28.6)	33 (21.3)	63 (30.9)	47 (30.3)	16 (32.7)	6 (26.1)
65-74 years (%)	842 (21.4)	320 (20.5)	288 (20.5)	32 (20.7)	41 (20.1)	31 (20.0)	10 (20.4)	6 (26.1)
75-84 years (%)	1,128 (28.7)	448 (28.7)	400 (28.4)	48 (31.0)	60 (29.4)	45 (29.0)	15 (30.6)	7 (30.4)
85+ years (%)	890 (22.6)	359 (23.0)	317 (22.5)	42 (27.1)	40 (19.6)	32 (20.7)	8 (16.3)	4 (17.4)
Comorbidity (%)	3,368 (85.6)	1,310 (83.8)	1,183 (84.0)	127 (81.9)	181 (88.7)	137 (88.4)	44 (89.8)	20 (87.0)
Chronic respiratory disease[e] (%)	2,015 (51.2)	721 (46.1)	**660 (46.9)**	61 (39.4)	120 (58.8)	**94 (60.7)** [b]	26 (53.1)	10 (43.5)
Chronic cardiovascular disease[e] (%)	1,824 (46.4)	709 (45.4)	**632 (44.9)**	77 (49.7)	112 (54.9)	**91 (58.7)** [b]	21 (42.9)	11 (47.8)
Diabetes[e] (%)	1,151 (29.3)	465 (29,8)	420 (29.8)	45 (29.0)	60 (29.4)	43 (27.7)	17 (34.7)	8 (34.8)
Chronic renal disease[e] (%)	761 (19.4)	298 (19.1)	271 (19.3)	27 (17.4)	44 (21.6)	34 (21.9)	10 (20.4)	4 (17.4)
Other chronic disease[e] (%)	221 (5.6)	85 (5.4)	79 (5.6)	6 (3.9)	13 (6.4)	8 (5.2)	5 (10.2)	2 (8.7)
Influenza vaccine[c] (%)	1597 (49.1)	578 (43.5)	**510 (43.0)**	68 (48.2)	91 (51.7)	**70 (52.2)** [b]	21 (50.0)	9 (50.0)
Admitted from LTCF	388 (9.9)	174 (11.1)	157 (11.2)	17 (11.0)	21 (10.3)	15 (9.7)	6 (12.2)	5 (21.7)
Pregnancy (%)	26 (0.7)	22 (1.4)	19 (1.4)	3 (1.9)	1 (0.5)	0 (0.0)	1 (2.0)	1 (4.4)
LOS in days, median IQR	6; 3-11	6; 3-11	6; 3-10	6; 3-11	6; 3-10.5	6; 3-10	7; 4-12	7; 5-16

Pneumonia[e] (%)	1,608 (40.9)	548 (35.1)	487 (34.6)	61 (39.4)	75 (36.8)	58 (37.4)	17 (34.7)	9 (39.1)
ICU (%)	385 (9.8)	134 (8.6)	127 (9.0)	7 (4.5)	18 (8.8)	16 (10.3)	2 (4.1)	0 (0.0)
Death (%)	231 (5.9)	63 (4.0)	59 (4.2)	4 (2.6)	11 (5.4)	9 (5.8)	2 (4.1)	0 (0.0)

HCoV- common human coronaviruses; LOS-length of stay; IQR-interquartile range; ICU-intensive care unit; LTCF-long-term care facility

[a] Including Influenza and HCoV coinfections

[b] **In bold**, significant difference ($p<0.05$) between HCoV and influenza monoinfections; Fisher exact test used to compare proportions and Kruskal-Wallis test used to compare LOS between mono and coinfections

[c] Influenza vaccination in those with known vaccination status and timing

[d] Radiologically confirmed pneumonia among those with a pulmonary radiography

[e] Categories are not mutually exclusive

TABLE 2 Results of regression models estimating the risk of different severity outcomes in patients hospitalized with HCoV infections compared to influenza infections (reference) in adults and children, Quebec 2011-12 to 2018-19

		HCoV vs influenza[a]		
OUTCOME	No[a]	Crude OR/RR (95%CI)	Adjusted OR/RR(95%CI)	Adjustment variables[b]
Children				
Length of stay[c]				
HCoV and influenza coinfections included as co-variate	372	1.12 (0.96, 1.30)	1.12 (0.94, 1.32)	**Age**; sex; **year**; comorbidity; coinfection[e]; vaccination
Restricted to mono-infections	211	0.90 (0.67, 1.20)	0.90 (0.60, 1.36)	Age; sex; **year**; comorbidity**; vaccination**
Pneumonia[d]				
HCoV and influenza coinfections included as co-variate	372	1.11 (0.68, 1.82)	1.08 (0.69, 1.69)	**Age**; sex; **year**; comorbidity; **coinfection[e]**; **vaccination**
Restricted to mono-infections	211	0.47 (0.16, 1.42)	Not available	Adjusted model did not converge
Adults				
Length of stay[c]				
HCoV and influenza coinfections included as co-variate	1719	1.04 (0.91, 1.18)	1.07 (0.89, 1.29)	**Age**; sex; **year**; **admitted from LTCF**; **comorbidity**; coinfection[e]; influenza vaccination
Restricted to mono-infections	1561	1.02 (0.89, 1.18)	1.05 (0.89, 1.25)	**Age**; sex; **year**; **admitted from LTCF**; **comorbidity;**

				influenza vaccination
Pneumonia[d]				
HCoV and influenza coinfections included as co-variate	1720	1.08 (0.78, 1.48)	1.14 (0.75, 1.71)	**Age**; **sex**; **year**; **admitted from LTCF**; **comorbidity**; coinfection[e]; **influenza vaccination**
Restricted to mono-infections	1562	1.14 (0.81, 1.61)	1.17 (0.76, 1.81)	**Age**; **sex**; **year; admitted from LTCF**; comorbidity**; influenza vaccination**
ICU admission[d]				
HCoV and influenza coinfections included as co-variate	1721	1.16 (0.69, 1.95)	0.96 (0.55, 1.68)	**Age**; **sex**; **year**; admitted from LTCF; **comorbidity**; coinfection[e]; influenza vaccination
Restricted to mono-infections	1563	1.16 (0.67, 2.01)	0.98 (0.57, 1.69)	**Age**; **sex**; **year**; admitted from LTCF; **comorbidity;** influenza vaccination
In-hospital death[d]				
HCoV and influenza coinfections included as co-variate	1721	1.52 (0.78, 2.93)	1.42 (0.92, 2.17)	**Age**; sex; **year**; admitted from LTCF; **comorbidity**; coinfection[e]; influenza vaccination
Restricted to mono-infections	1563	1.41 (0.68, 2.90)	1.27 (0.83, 1.95)	**Age**; sex; **year;** admitted from LTCF; **comorbidity;** influenza vaccination

Abbreviations: HCoV- common human coronaviruses; OR-odds ratio; RR-risk ratio for LOS; ICU-intensive care unit, LTCF-long-term care facility

[a] 39 patients with coronavirus-influenza coinfection where excluded from the analyses

[b] Variables **in bold** are those associated with outcome at p<0.05; Categories are as follows: Age - 6-23 months, 2-4 years, 5-17 years (children) and 18-64 years, 65-74 years, 75-84 years and 85+ years (adults); admitted from - community-dwelling and long-term care facility/other; comorbidity in in children - presence or absence; comorbidity in adults - no comorbidity, cardiovascular disease, chronic respiratory disease, both cardiovascular and respiratory disease and other comorbidity (obesity, diabetes, chronic renal disease, immunodefficiency or neurological disease; influenza vaccination -vaccinated, not vaccinated and unknown vaccination status or timing;

[c] Generalized Estimating Equations with exchangeable correlation matrix for hospital of recruitment and negative binomial distribution and log link

[d] Generalized Estimating Equations with exchangeable correlation matrix for hospital of recruitment, binomial distribution and logit link

[e] coinfection other than HCoV/influenza