

**Incidence of medically attended acute respiratory illnesses due to respiratory viruses
across the life course during the 2018/19 influenza season**

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Summary: This study provides one of the first assessments of the burden of multiple respiratory viruses during influenza season among persons aged ≥ 1 year . Influenza, hCoV, and hRV cause a substantial burden of outpatient visits in persons of all ages.

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ABSTRACT

Background: While multiple respiratory viruses circulate in humans, few studies have compared the incidence of different viruses across the life course. We estimated the incidence of outpatient illness due to 12 different viruses during November 2018 through April 2019 in a fully enumerated population.

Methods: We conducted active surveillance for ambulatory care visits for acute respiratory illness (ARI) among members of Kaiser Permanente Washington (KPWA). Enrolled patients provided respiratory swab specimens which were tested for 12 respiratory viruses using RT-PCR. We estimated the cumulative incidence of infection due to each virus overall and by age group.

Results: The KPWA population under surveillance included 202,562 individuals, of whom 2,767 (1.4%) were enrolled in the study. Influenza A(H3N2) was the most commonly detected virus, with an overall incidence 21 medically attended illnesses per 1,000 population; the next most common viruses were influenza A(H1N1) (18 per 1,000), coronaviruses (13 per 1,000), respiratory syncytial virus (RSV, 13 per 1,000), and rhinovirus (9 per 1,000). RSV was the most common cause of medically attended ARI among children aged 1-4 years; coronaviruses were the most common among adults aged ≥ 65 years.

Conclusions: Consistent with other studies focused on single viruses, we found that influenza and RSV were major causes of acute respiratory illness in persons of all ages. In comparison, coronaviruses and rhinovirus were also important pathogens. Prior to the emergence of SARS-CoV-2, coronaviruses were the second-most common cause of medically attended ARI during the 2018/19 influenza season.

Keywords: Incidence; Viruses; Influenza, Human; Coronavirus; Rhinovirus

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Introduction

Many respiratory viruses circulate in humans, and viral respiratory tract infections occur globally across the life course.[1–9] Respiratory virus infections can be associated with a wide range of illness, including asymptomatic infection, mild respiratory disease (the “common cold”), severe illness, and even death.[10–12] Despite their similarities in infection and modes of transmission, there is considerable heterogeneity in the incidence of disease due to different respiratory viruses. This includes the overall burden of disease and the age groups that are most affected by different viruses.[6,13]

One limitation to our understanding of respiratory virus epidemiology is that published studies have tended to focus on a single virus or on a handful of viruses together. Few studies (e.g. [14]) have directly compared the incidence of many viruses within the same population. Furthermore, many studies of respiratory viruses have focused on a subset of the population, such as young children or older adults (e.g. [15,16]) rather than evaluating incidence across the life course.

We conducted the present study to address these knowledge gaps. Using active surveillance for acute respiratory illness (ARI) in outpatient clinics, we estimated the burden of illness in ambulatory care settings for twelve respiratory virus species during the 2018/19 influenza season.

Methods

Study population

This study was conducted at the Washington State site of the United States Influenza Vaccine Effectiveness (US Flu VE) Network during the 2018/19 influenza season. Methods

for the Network have been described previously.[17] In brief, active surveillance for ARI in ambulatory care settings was conducted at Kaiser Permanente Washington (KPWA). Eligible patients were aged at least 6 months of age and had a cough illness of <8 days' duration. Eligible and consenting patients (or parent/guardian for minors) were interviewed for demographics, risk factors for ARI, and influenza vaccination history. Study staff collected combined nasal and oropharyngeal swabs (nasal only in children aged <2 years) for respiratory virus testing. Due to low enrollment in infants aged <1 year, the present analysis is restricted to subjects aged 1 year and older.

Laboratory methods

We extracted total nucleic acids using the Magna Pure nucleic acids extraction kit (Roche). We screened extracted nucleic acids for the presence of respiratory pathogens by TaqMan reverse transcriptase polymerase chain reaction (RT-PCR) on the OpenArray platform (Thermo). Screened viruses included adenovirus (AdV); enterovirus (EntV); human bocavirus (hBoV); human coronavirus (229E, NL63, OC43, HKU1) (hCoV); human metapneumovirus (hMPV), human parainfluenza virus (hPIV 1-4); human parechovirus (hPCV), influenza A(H1N1), A(H3N2), B, and C; respiratory syncytial virus (RSV) A and B; and rhinovirus (hRV).

Source population

To estimate the population-based incidence of respiratory viruses, we followed the process previously developed for influenza incidence in this population.[5,18] We identified the source cohort at risk for ARI and potentially eligible for US Flu VE Network enrollment based on membership in KPWA's integrated group practice. The source cohort consisted of

members aged at least 1 year of age as of September 1st 2018 whose primary care provider was at a medical center where study recruitment occurred. We used KPWA administrative healthcare databases to characterize all members of the source cohort, including those enrolled in the US Flu VE Network, by age, receipt of 2018/19 influenza vaccine, and number of medical encounters for ARI (defined by International Classification of Diseases, Version 10 [ICD-10] codes).

Statistical analyses

We estimated the cumulative incidence of medically-attended respiratory virus infections by extrapolating the number of virus-positive illnesses among US Flu VE Network enrollees to the source population, as previously described.[5,18] We estimated sampling weights for each US Flu VE Network enrollee relative to the source population, based on joint stratification by age group, receipt of 2018/19 influenza vaccine, and number of ARI medical encounters (0, 1, ≥ 2) during 2018/19. Network enrollees with zero ARI encounters (i.e. those who were not assigned an ARI ICD-10 code at their enrollment visit) were assigned a sampling weight of 1.0. Using the sampling weights, we estimated the total number of ambulatory care visits for each virus individually and for any detected virus in the source cohort. We calculated confidence limits by bootstrapping samples from the source population and the US

Flu VE Network enrollees. To avoid double-counting events for persons co-infected with multiple viruses, we grouped all co-infections into a single category for incidence estimation, and estimated the virus-specific incidence of disease using only persons with a single detected virus. We did not calculate incidence for viruses with less than 10 detections without co-infection.

We assumed that seasonal respiratory virus circulation occurred between November 2018 and April 2019. Our surveillance ran from November 18 2018 through April 20 2019. We upweighted our incidence estimates to account for weeks with missing surveillance. For this, we calculate the proportion of total respiratory virus infections detected by regional surveillance during periods of US Flu Network enrollment, and multiplied our burden estimates by the inverse of this proportion.

Results

The source cohort consisted of 202,562 individuals, of whom 46% received the 2018/19 influenza vaccine and 14% had at least one ambulatory care visit for ARI (Table 1). We enrolled 2,767 patients (1.4% of the source cohort) in the US Flu VE Network. Compared to the source cohort, Network enrollees were more likely to be aged <10 years and to have received the 2018/19 influenza vaccine.

We detected 2,059 respiratory viruses among 1,860 (67.2%) unique US Flu VE Network enrollees. Influenza A viruses were the most commonly detected, with 441 (15.9%) of

enrollees having influenza A(H3N2) and 348 (12.6%) influenza A(H1N1) (Supplemental Table 1). The third most common virus detected overall was hCoV (297 enrollees, 10.7%). The least common viruses were hPCV (2 detected, 0.07%), influenza B (13 detected, 0.5%), and hBoV (21 detected, 0.8%). Detected viruses peaked on the week of March 4 2019, corresponding to the peak of influenza A (H3N2) activity (Supplemental Figure 1).

Co-infections occurred in 179 (9.6%) of the 1,860 persons with detected viruses. Co-infection was most common for hPCV (both detections had co-infection), hBoV (66.7%), AdV (50.9%), and influenza C (41.2%). Co-infection was least common for influenza A(H1N1) (8.6%) influenza A(H3N2) (10.2%), and RSV B (11.1%) (Supplemental Table 1). When considering infections with only a single virus isolated, hCoV was the third-most common virus in ambulatory care visits for ARI in 2018/19, behind only influenza A(H3N2) and A(H1N1).

The cumulative incidence of medically attended illness for any of the targeted viruses between November and April was 100 visits per 1,000 population (95% CI, 97 to 103). In other words, 10% of the population aged 1 year and older sought medical care due to infection with one of these viruses. Incidence was highest among the youngest children (385 per 1,000, 95% CI 314 to 465 in children aged 1-2 years) and declined to a low of 81 per 1,000 (95% CI, 69 to 92) among adults aged 31-49 years before increasing among older adults and seniors (Table 2). For individual viruses, incidence ranged from 21 per 1,000 (95% CI, 19 to 23) for influenza A(H3N2) to 0.7 (95% CI, 0.3 to 1.1) for influenza B (Figure 1). We

did not estimate incidence for hBoV or hPCV, as they had less than 10 detected infections without co-infection.

The age distribution of subjects with detected viruses varied between viruses (Supplemental Figure 2). Virus-specific incidence was heterogeneous across age groups (Figure 2). Among individual viruses, RSV A and RSV B were the most common causes of medically attended ARI among children aged 1-2 years (52 and 55 cases per 1,000, respectively), followed by hRV (33 per 1,000). Co-infections were most common in this age group, with an incidence of 120 cases per 1,000.

Outside of early childhood, influenza A(H3N2) and influenza A(H1N1) tended to have the highest incidence, followed by hCoV. Among seniors, multiple pathogens contributed an approximately similar burden of disease of between 11 and 18 cases per 1,000 population: hCoV, hMPV, influenza A(H1N1), influenza A(H3N2), RSV B, and hRV. hCoV caused the highest incidence (18 cases per 1,000 population) of medically attended ARI among seniors.

Discussion

The 2018/19 influenza season in Washington State was dominated by influenza A viruses, with an early wave of A(H1N1) infections followed by a later wave of A(H3N2) viruses, and unusually low circulation of influenza B viruses.[19] In this context, we found that 10% of the population had a medically attended respiratory virus infection between November

2018 and April 2019. Care-seeking for respiratory viruses was as high as 38% among children aged 1-2 years.

Consistent with prior studies,[6,20–22] we found that RSV was the most common pathogen among young children, with a combined incidence RSV A and B of over 100 per 1,000 in children aged 1-2 years and nearly 60 per 1,000 in children aged 2-4 years. Also consistent with prior studies,[23,24] influenza A viruses were the most common pathogen causing ARI when considering all age groups together. In this study the combined incidence of influenza A viruses was 39 cases per 1,000 persons. This is higher than previous studies in this population, which found incidence of influenza A viruses ranging from 8 to 26 cases per 1,000.[5,18], and may be attributed to the unusual 2018/19 season, which saw intensive circulation of both influenza A subtypes. In contrast, the incidence of influenza B (0.7 per 1,000) was substantially lower than seen in those prior studies (range, 2 to 17 per 1,000), consistent with regional surveillance data.[19]

Influenza C is being increasingly recognized as a contributor to the burden of respiratory illness in humans.[25,26] During 2018/19, we found that 0.7% of ARI ambulatory care had influenza C as the only virus detected. The cumulative incidence of influenza C as the only detected virus was estimated as 1.2 cases per 1,000 population, which was higher than influenza B and comparable to the burden due to AdV (1.5 per 1,000) and EntV (1.3 per 1,000) as solo pathogens.

Prior studies frequently found hCoV among persons with ARI, particularly those with mild illness.[27–29] This study provides one of the first population-based estimates of the incidence of medically attended disease due to hCoV. We found that, prior to the emergence of SARS-CoV-2, human coronaviruses were important contributors to the burden of ARI in this population, second only to influenza A viruses, with an overall incidence of 13 cases per 1,000 population during 2018/19. hRV was also a common cause of medically attended illness in persons of all ages. Among those aged 2 years or older, the incidence of hRV varied between 7 and 14 cases per 1,000.

Several limitations of this study should be considered. First, our surveillance definition required all US Flu VE Network enrollees to have ARI with cough. Our study thus excluded ARI patients that presented for care without a cough, and should be considered a lower bound for the total burden of disease in ambulatory care settings due to these viruses. Second, this study only covers a single influenza season, which was somewhat atypical in terms of circulating viruses. Both the absolute and the relative contribution of respiratory viruses to the burden of ARI may be different in other years. Third, due to the primary goals of the US Flu VE Network, enrollment was restricted to children aged ≥ 6 months, and given low enrollment of patients aged 6-11 months this analysis excluded patients aged < 1 year, among whom the burden of respiratory virus infection is high. Finally, this study was conducted among members of a pre-paid health care/insurance provider, who may have different illness thresholds for seeking care

than other populations. The absolute incidence of medically attended illness may be different in other populations. An additional caveat is that this study measured incidence among persons seeking ambulatory medical care; the relative prevalence of illness due to these viruses in the community or in inpatient settings may be different.

This study provides one of the first assessments of the contribution of a wide range of respiratory viruses to disease among children, adults, and seniors during periods of influenza circulation. Many viruses have been known to cause respiratory illness among young children; this study shows that viruses such as influenza, hCoV, and hRV also cause a substantial burden of disease among persons of all ages.

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Potential Conflicts of Interest

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Table 1: Characteristics of the source population and of United States Influenza Vaccine Effectiveness Network enrollees, 2018/19

Characteristic	Source population	US Flu VE* Network enrollees	Percent of Source population enrolled
Total population	202,562	2,767	1.4%
Age group			
1-2 years	1,455 (0.7%)	92 (3.3%)	6.3%
2-4 years	4,622 (2.3%)	160 (5.8%)	3.5%
5-9 years	7,586 (3.7%)	229 (8.3%)	3.0%
10-17 years	12,321 (6.1%)	213 (7.7%)	1.7%
18-30 years	35,607 (17.6%)	345 (12.5%)	1.0%
31-49 years	57,446 (28.4%)	641 (23.2%)	1.1%
50-64 years	43,645 (21.5%)	566 (20.5%)	1.3%

65+ years	39,880 (19.7%)	521 (18.8%)	1.3%
Vaccinated	92,535 (45.7%)	1,674 (60.5%)	1.8%
ARI visits			
0	173,997 (85.9%)	456 (16.5%)	0.3%
1	19,728 (9.7%)	1,413 (51.1%)	7.2%
2 or more	8,837 (4.4%)	898 (32.5%)	10.2%

* United States Influenza Vaccine Effectiveness

Table 2: Overall and age-specific incidence of medically attended acute respiratory illness with any detected virus, 2018/19

Age group	Estimated incidence	Lower confidence limit	Upper confidence limit
1 year	385	312	457
2-4 years	263	218	307
5-9 years	164	130	198
10-17 years	120	98	142
18-30 years	84	69	98
31-49 years	81	69	92
50-64 years	89	76	101
65 years and older	107	90	123
All ages	100	97	103

FIGURE LEGENDS

Figure 1: Overall incidence of medically attended illness per 1,000 population due to 12 respiratory viruses, 2018/19. Coinfection includes all illnesses with more than one detected virus.

Figure 2: Age-specific incidence of medically attended illness due to 12 respiratory viruses per 1,000 population, 2018/19

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Figure 1

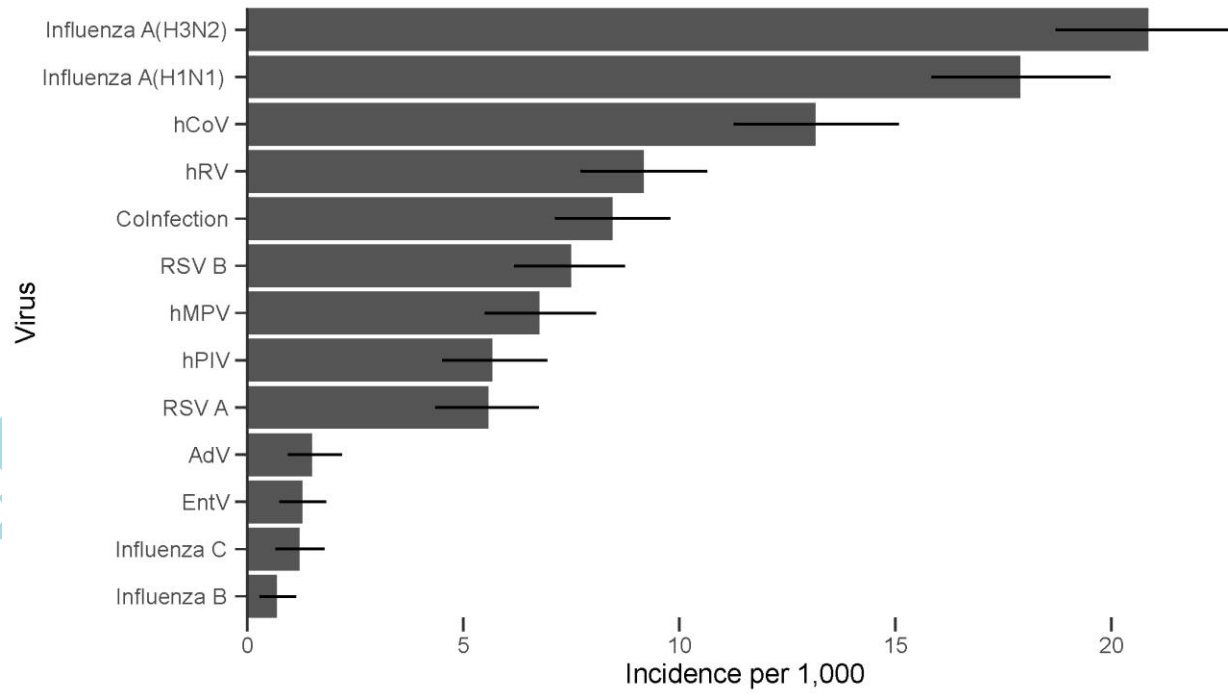


Figure 2

